SPONSOR:	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.	
COMPOUND NAME:	MK-1439, Tablet	
INDICATION:	Antiviral treatment for HIV-1 infection	
PROTOCOL TITLE:	A 2-Part, Open-Label, Single-Dose Study to Investigate the Influence of Hepatic Insufficiency on the Pharmacokinetics of MK-1439	
TRIAL IDENTIFIERS:	Protocol Number:	MK-1439 019
	Clinical Phase:	1
TRIAL CENTERS:	Multicenter – 2 sites [redacted], MD [redacted], USA [redacted], MD [redacted], USA	
DESIGN:	**STUDY DESIGN:** This was a 2-part, non-randomized, open-label, single-dose study to compare the pharmacokinetics of MK-1439 in subjects with moderate hepatic insufficiency (based on the Child-Pugh classification) to healthy matched control subjects in Part 1. The effect of mild hepatic impairment on MK-1439 pharmacokinetics was not assessed since a clinically meaningful increase in MK-1439 exposure was not observed in subjects with moderate hepatic impairment. Therefore, Part 2 of the study was not conducted. Eight (8) subjects with moderate hepatic insufficiency (a score of 7 to 9, on the Child-Pugh scale) and 8 healthy matched control subjects were enrolled. Each subject received a single oral dose of 100 mg MK-1439 on Day 1. **DIAGNOSIS/INCLUSION CRITERIA:** **Part 1**: Male and female subjects with moderate hepatic insufficiency (a score of 7 to 9 on the Child-Pugh scale) and male and female healthy matched control subjects (mean demographics of the subjects with moderate hepatic insufficiency: mean age [± 15 years] and mean weight [± 20%]) between 18 and 75 years of age, inclusive, and body mass index (BMI) ≥ 19 and ≤ 40 kg/m^2 at the screening visit were eligible to enter the study. A similar number of males and females were enrolled in the moderate hepatic insufficiency and healthy matched control subject groups.	

<table>
<tr><td>DESIGN (Continued):</td><td colspan="2">DIAGNOSIS/INCLUSION CRITERIA (Continued):
<u>Part 1 (Continued):</u> At least 4 subjects with moderate hepatic insufficiency were required to have a score of at least 2 on one of the laboratory parameter values on the Child-Pugh scale. Female subjects could not be pregnant and females of childbearing potential were required to use appropriate birth control methods for specified time periods.
<u>Part 2:</u> Not conducted.</td></tr>
<tr><td></td><td>Actual duration of main phase:</td><td>Hepatic subjects:
7 weeks from screening to follow-up
Healthy subjects:
6 weeks from screening to follow-up</td></tr>
<tr><td>OBJECTIVES:</td><td colspan="2">Primary:
Part 1:
To compare the plasma concentration-time profile and pharmacokinetics (e.g., AUC0-∞, AUC0-24, Cmax, C24, Tmax, CL/F, Vz/F, and apparent terminal t½) after single dose administration of 100 mg MK-1439 to subjects with moderate hepatic insufficiency with that of healthy (mean) matched (age and weight) control subjects.
Part 2:
To compare the plasma concentration-time profile and pharmacokinetics (e.g., AUC0-∞, AUC0-24, Cmax, C24, Tmax, CL/F, Vz/F, and apparent terminal t½) after single dose administration of 100 mg MK-1439 to subjects with mild hepatic insufficiency with that of healthy control subjects from Part 1.
Secondary:
Part 1:
To evaluate the safety and tolerability of MK-1439 in subjects with moderate hepatic insufficiency and in healthy subjects after single dose administration of 100 mg MK-1439. Following a review of the safety and pharmacokinetic data from Part 1, a decision was to be made regarding the initiation of Part 2.
Part 2:
To evaluate the safety and tolerability of MK-1439 in subjects with mild hepatic insufficiency after single dose administration of 100 mg MK-1439.</td></tr>
<tr><td>ESTIMATIONS:</td><td colspan="2">Primary:
Part 1:
The GMR AUC0-∞ and Cmax of MK-1439 after single dose administration in subjects with moderate hepatic insufficiency, to that observed in healthy (mean) matched control subjects will be estimated.</td></tr>
</table>

ESTIMATIONS (Continued):	**Part 2:** The GMR AUC0-∞ and Cmax of MK-1439 after single dose administration in subjects with mild hepatic insufficiency, to that observed in healthy control subjects will be estimated.	
TREATMENT GROUPS:	Moderate Hepatic	Single oral dose of 100 mg MK-1439 following an overnight fast. 8 Subjects
	Healthy Subjects	Single oral dose of 100 mg MK-1439 following an overnight fast. 8 Subjects

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

Clinical Supplies Dispensed to Subjects

Bulk Product Description	**Manufacturing Lot Number**
OCT MK-1439 100 mg	[redacted]

ENDPOINTS AND DEFINITIONS:	**Primary Endpoints**	**Pharmacokinetics:** Blood samples for the determination of single-dose plasma MK-1439 pharmacokinetics were collected from each subject at predose and selected time points over 144 hours postdose on Day 1 for subjects with moderate hepatic insufficiency, and at predose and selected time points over 72 hours postdose on Day 1 for healthy matched control subjects. Plasma MK-1439 concentrations were summarized using the following pharmacokinetic parameters: AUC0-∞, AUC0-24, Cmax, C24, Tmax, CL/F, Vz/F and apparent terminal t½. The primary pharmacokinetic endpoints included AUC0-∞ and Cmax for MK-1439 in plasma.	
	Secondary Endpoints	**Safety:** The safety and tolerability of MK-1439 was assessed by clinical evaluation, including vital signs (heart rate and blood pressure), medical history, physical examination, 12-lead electrocardiograms (ECGs), and laboratory safety tests (hematology, blood chemistry, and urinalysis) obtained at prespecified time points. Subjects were also monitored for adverse events throughout the study.	
DATABASE LOCK:	05-AUG-2014	**TRIAL STATUS:**	01-Apr-2014 to 23-May-2014

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

SUBJECT DISPOSITION:	**Moderate Hepatic**	**Healthy Control**
ENTERED: Total	8	8
Male N (age range)	6 (54 to 64 yrs)	6 (44 to 63 yrs)
Female N (age range)	2 (54 to 61 yrs)	2 (58 to 59 yrs)
COMPLETED:	8	8
DISCONTINUED: Total	0	0
Adverse event	0	0
Other	0	0

ANALYSIS DECSRIPTION:	**Primary Analysis - Pharmacokinetics** To address the primary hypothesis, individual AUC0-∞ values of MK-1439 after a single-dose administration of 100 mg MK-1439 to subjects with moderate hepatic insufficiency and healthy matched control subjects were natural log-transformed and evaluated with an analysis of covariance model (ANCOVA). The ANCOVA model contained a categorical factor for population (moderate hepatic insufficiency subjects, healthy matched control subjects) and continuous covariates age and weight, and the interactions between population and covariates. All non-significant interactions were dropped from the final model. A 90% confidence interval (CI) for the AUC0-∞ ratio of the geometric least-squares means (moderate hepatic insufficiency subjects/healthy matched control subjects) was computed from the above model. These confidence limits were exponentiated to obtain a CI for the true geometric mean AUC0-∞ ratio (moderate hepatic insufficiency subjects/healthy matched control subjects). Cmax, C24, and AUC0-24 were analyzed in a similar fashion to AUC0-∞.
ANALYSIS POPULATION AND TIME POINT DESCRIPTION:	The "Per-Protocol" analysis population consisted of the subset of 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. Compliance covers such considerations as exposure to treatment, availability of measurements, and absence of major protocol violations. This population was used for the pharmacokinetic analyses. All 16 subjects completed MK-1439 dosing and were included in the analysis of the pharmacokinetics of MK-1439.

SUMMARY:	**Pharmacokinetics:** Results of the analyses of the single-dose plasma pharmacokinetics of MK-1439 following the administration of 100 mg MK-1439 in subjects with moderate hepatic insufficiency and in healthy matched control subjects are summarized in the table below. The administration of 100 mg MK-1439 to subjects with moderate hepatic insufficiency resulted in similar exposures relative to those in healthy matched control subjects, with GMRs [90% CIs] of 0.99 [0.72, 1.35], 0.93 [0.74, 1.18], 0.90 [0.66, 1.24] and 0.99 [0.74, 1.33] in AUC0-∞, AUC0-24, Cmax, and C24, respectively. The observed median Tmax, geometric mean apparent terminal t½, geometric mean CL/F, and Vz/F values were similar between the subjects with moderate hepatic insufficiency compared to the healthy matched control subjects, respectively.

Statistical Comparison of Plasma Pharmacokinetics of MK-1439 Following a Single Oral Dose of 100 mg MK-1439 Administered to Subjects With Moderate Hepatic Insufficiency and Healthy Matched Control Subjects

MK-1439 Pharmacokinetic Parameter	Moderate Hepatic			Healthy Subjects			Moderate Hepatic / Healthy Subjects		
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	rMSE[†]
AUC0-∞[‡] (µM•hr)	8	53.9	(41.5, 70.0)	8	54.6	(42.1, 71.0)	0.99	(0.72, 1.35)	0.329
AUC0-24[‡] (µM•hr)	8	28.5	(23.4, 34.8)	8	30.6	(25.1, 37.3)	0.93	(0.74, 1.18)	0.251
Cmax[‡] (nM)	8	1850	(1420, 2420)	8	2050	(1570, 2680)	0.90	(0.66, 1.24)	0.338
C24[‡] (nM)	8	842	(658, 1080)	8	847	(662, 1080)	0.99	(0.74, 1.33)	0.310
CL/F[§] (L/hr)	8	4.37	38.5	8	4.29	22.5			
Vz/F[§] (L)	8	113	38.8	8	112	23.1			
Tmax[‖] (hr)	8	2.00	(1.00, 6.00)	8	2.50	(1.00, 3.00)			
Apparent terminal t½[§] (hr)	8	17.97	30.81	8	18.12	30.53			

Treatment: Single oral dose of 100 mg MK-1439 following an overnight fast.
Moderate Hepatic: Subjects with a score of 7 to 9 on the Child-Pugh scale enrolled in Part 1 of the study.
Healthy Subjects: Healthy subjects matched to the mean of moderate insufficiency subjects for age (± 15 years), gender, and weight (± 20%).
[†]rMSE calculated by taking the square root of the residual variance component from the PROC MIXED outputs.
[‡]Back-transformed least squares means and confidence intervals from the ANCOVA model containing a fixed-effects term for population (hepatic insufficient or healthy normal) and age and weight as covariates performed on natural log-transformed values.
Interaction terms between the covariates and population were not significant for all pharmacokinetic parameters and therefore dropped from the final model.
[‖]Median (min, max) reported for Tmax.
[§]Geometric Mean and Percent Geometric Coefficient of Variation reported for Apparent terminal $t_{½}$, CL/F and Vz/F.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio between treatment populations.

ANALYSIS DECSRIPTION:	**Secondary Analysis – Safety:** Incidence of the number of subjects with adverse events were descriptively summarized and listed by population. A summary of the incidence of the number of subjects with drug-related adverse event was descriptively summarized by population. Since no meaningful changes in individual values for laboratory safety tests, ECGs, and vital signs were observed, summary statistics and plots over time were not provided.
ANALYSIS POPULATION AND TIME POINT DESCRIPTION:	The "All Patients As Treated" population consisted of all subjects who received at least 1 dose of the investigational drug. This population was used for assessments of safety and tolerability. All 16 subjects, 8 subjects with moderate hepatic insufficiency and 8 healthy matched control subjects, were included in the evaluation of safety.
SUMMARY:	Single-dose administration of 100 mg MK-1439 in subjects with moderate hepatic insufficiency and in healthy matched control subjects was generally well tolerated in this study. No serious adverse events, pregnancies, events of clinical interest (ECIs), subject discontinuation due to an adverse events, or deaths occurred in this study. Seven (7) subjects (43.8%) reported a total of 7 adverse events. Four (4) subjects with moderate hepatic insufficiency (50.0%) reported a total of 4 adverse events and 3 healthy subjects (37.5%) reported a total of 3 adverse events. The most common adverse event was headache (2 subjects overall, 12.5%). A total of 6 adverse events were considered related to study drug. Two (2) healthy control subjects (25.0%) reported 1 episode each of drug-related headache and 4 subjects (50.0%) with moderate hepatic insufficiency reported 1 drug-related adverse event each (postural dizziness, somnolence, dry mouth, and vomiting). All adverse events were mild in intensity, transient in nature, and resolved by study completion. No clinically meaningful relationships were observed for changes in clinical laboratory values, vital signs, or electrocardiogram (ECG) safety parameter values as a function of treatment. Subjects with hepatic insufficiency had some abnormalities in laboratory safety parameter values at prestudy that were consistent with their disease state (e.g., aspartate aminotransferase [AST], alanine aminotransferase [ALT], prothrombin time [PT], hemoglobin/hematocrit, red blood cell counts [RBCs], and/or platelets), and a single 100 mg MK-1439 dose did not appear to have any impact on these laboratory parameter values.

CONCLUSIONS:	1. The administration of a single dose of 100 mg MK-1439 to subjects with moderate hepatic insufficiency results in similar exposure to that in healthy matched control subjects (AUC0-∞ and Cmax), indicating that moderate hepatic insufficiency does not affect the pharmacokinetics of MK-1439. 2. Single-dose administration of 100 mg MK-1439 in subjects with moderate hepatic insufficiency and in healthy matched control subjects is generally well tolerated.
REPORT DATE:	Final: 21-Jan-2015

SPONSOR:	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.	
COMPOUND NAME:	MK-1439 (Doravirine), Tablet	
INDICATION:	Antiviral treatment for HIV-1 infection	
PROTOCOL TITLE:	An Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics of MK-1439 (Doravirine) in Subjects With Severe Renal Impairment	
TRIAL IDENTIFIERS:	Protocol Number:	MK-1439-051
	Clinical Phase:	1
	EudraCT Number:	Not Applicable
	US IND Number:	112,796
TRIAL CENTERS:	This trial was conducted at 2 centers in the United States: [redacted] USA [redacted] USA	
DESIGN:	**STUDY DESIGN:** This was an open-label, single-dose, renal impairment study to compare the pharmacokinetics (PK) of doravirine in subjects with severe renal impairment to that in healthy mean matched control subjects [control subjects were matched to the mean age (± 10 years) and weight (± 10 kg) of subjects with renal impairment]. Sixteen (16) adult, male and female subjects were enrolled, 8 with severe renal impairment and 8 healthy matched control subjects. On Day 1, subjects received a single oral dose of 100 mg doravirine following an overnight fast. **DIAGNOSIS/INCLUSION CRITERIA:** Male and female subjects ≥ 18 and ≤ 75 years of age, with a body mass index (BMI) ≥ 18.5 and ≤ 40 kg/m^2 at the prestudy (screening) visit, having a clinical diagnosis of severe renal impairment with baseline estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2 based on eGFR (estimated by the Modification of Diet in Renal Disease [MDRD] equation), not requiring hemodialysis, and healthy matched control subjects who met all the inclusion and none of the exclusion criteria were selected for the study.	

DESIGN (CONTINUED):	Planned duration of main phase:	4.5 weeks from screening to Day 4 (healthy matched control subjects) or Day 5 (severe renal impairment subjects) postdose. 6 weeks from screening to follow-up for all subjects.
OBJECTIVES:	**Primary:** To evaluate the plasma PK (e.g., AUC0-∞, AUC0-last, Cmax, C24, Tmax, apparent terminal t½, CL/F, and Vz/F) of a single oral dose of 100 mg doravirine in subjects with severe renal impairment compared to healthy matched control subjects. **Secondary:** To evaluate the safety and tolerability of doravirine in subjects with severe renal impairment.	
ESTIMATION:	**Primary:** In subjects with severe renal impairment, plasma PK (AUC0-∞, Cmax, and C24) of doravirine following a single 100 mg doravirine oral dose were estimated and compared to those observed in healthy mean matched control subjects.	
TREATMENT GROUPS: (POPULATION)	Severe Renal Impairment	Single oral dose of 100 mg doravirine following an overnight fast 8 subjects
	Healthy Matched Control	Single oral dose of 100 mg doravirine following an overnight fast 8 subjects

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	[redacted]

ENDPOINTS AND DEFINITIONS:	**Primary Endpoints**	**Pharmacokinetics** Doravirine AUC0-∞, AUC0-last, Cmax, C24, Tmax, apparent terminal t½, CL/F, and Vz/F.
	Secondary Endpoints	**Safety** Safety endpoints included all types of adverse events (AEs), physical examinations, vital signs, 12-lead electrocardiograms (ECGs), and clinical laboratory values (hematology, serum chemistry, and urinalysis).

DATABASE LOCK:	30-Jun-2016	**TRIAL STATUS:**	01-Feb-2016 to 25-May-2016

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

Disposition of Subjects

	Severe Renal Impairment	Healthy Matched Control	Total
	N (%)	**N (%)**	**N (%)**
Subjects in Population	8	8	16
Completed	8 (100.0)	8 (100.0)	16 (100.0)
Discontinued	0 (0.0)	0 (0.0)	0 (0.0)

Treatment: Single oral dose of 100 mg MK-1439 following an overnight fast
Severe Renal Impairment: Subjects with eGFR values < 30 (mL/min/1.73 m²) and not on dialysis
Healthy Matched Control: Healthy subjects with eGFR values ≥ 80 (mL/min/1.73 m²) and matched to mean age (± 10 years) and weight (± 10 kg) of subjects with severe renal impairment
Each subject is counted only once for Study Disposition based on the latest corresponding disposition record.

Summary of Characteristics of Subjects With Severe Renal Impairment and Healthy Mean Matched Control Subjects

	Severe Renal Impairment Subjects		Healthy Matched Control Subjects	
	N	**(%)**	**N**	**(%)**
Subjects in population	8		8	
Gender				
Female	2	(25.0)	3	(37.5)
Male	6	(75.0)	5	(62.5)
Age (yr)				
19 to 49	0	(0.0)	0	(0.0)
50 to 59	4	(50.0)	4	(50.0)
60 to 69	4	(50.0)	4	(50.0)
Mean	60.8		60.0	
SD	6.3		5.5	
Median	60.0		59.5	
Range	51 to 69		52 to 69	
Race				
Black	3	(37.5)	1	(12.5)
White	5	(62.5)	7	(87.5)
Ethnicity				
Hispanic or Latino	3	(37.5)	5	(62.5)
Non-Hispanic and Non-Latino	5	(62.5)	3	(37.5)
Height (cm)				
Mean	170.94		172.50	
SD	9.355		6.985	
Range	155.2 to 184.0		160.4 to 181.2	
Weight (kg)				
Mean	90.86		90.93	
SD	17.409		6.086	
Range	71.1 to 128.1		81.6 to 98.3	
BMI (kg/m^2)				
Mean	31.20		30.58	
SD	5.663		1.608	
Range	21.3 to 37.8		27.6 to 33.4	

Severe Renal Impairment: Subjects with eGFR values < 30 (mL/min/1.73 m²) and not on dialysis
Healthy Matched Control: Healthy subjects with eGFR values ≥ 80 (mL/min/1.73 m²) and matched to mean age (± 10 years) and weight (± 10 kg) of subjects with severe renal impairment
Age is calculated from the date of first dosing.
BMI = Body mass index

ANALYSIS DESCRIPTION:	**Primary Analysis – Pharmacokinetics** An analysis of covariance (ANCOVA) model was used for the analysis of doravirine natural log-transformed AUC0-∞, Cmax, and C24 after a single dose administration of 100 mg doravirine to subjects with severe renal impairment and healthy matched control subjects. The ANCOVA model contained a categorical factor for population (severe renal impairment, healthy matched control) and continuous covariates for age and BMI. A two-sided 90% confidence interval (CI) for the mean differences of AUC0-∞, Cmax, and C24 of doravirine in the log-scale (severe renal impairment - healthy matched control) was calculated based on the above model. These CIs were exponentiated to obtain CIs for the geometric mean ratio (GMR) (severe renal impairment/healthy matched control) for AUC0-∞, Cmax, and C24 of doravirine. A 95% CI was constructed for the geometric means (GM) of doravirine AUC0-∞, Cmax, and C24 by population (severe renal impairment and healthy matched control subjects).
ANALYSIS POPULATION AND TIME POINT DESCRIPTION:	*Per-Protocol* – This population consisted of the subset of 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. Compliance covered such considerations as exposure to treatment, availability of measurements and absence of major protocol deviations. This population was used for the PK analyses. All 16 subjects (8 with severe renal impairment and 8 as healthy matched control subjects) completed the study and were included in the PK analyses.
SUMMARY:	**Pharmacokinetics:** The statistical comparison and summary statistics of plasma doravirine PK following the administration of a single oral dose of 100 mg doravirine to subjects with severe renal impairment and to healthy mean matched control subjects are summarized in the following table. A single oral dose of doravirine resulted in higher AUC0-∞ and C24 in subjects with severe renal impairment compared to those in healthy matched control subjects, with GMRs (90% CIs) of 1.43 (1.00, 2.04) and 1.38 (0.99, 1.92), respectively. Similarly, higher AUC0-last GM was observed in subjects with severe renal impairment. Doravirine Cmax was slightly lower in subjects with severe renal impairment compared to that in healthy matched control subjects, with the GMR (90% CIs) of 0.83 (0.61, 1.15). The median Tmax of doravirine was comparable in both treatment populations. The observed apparent terminal t½ GM was longer in subjects with severe renal impairment (25.02 hours) compared to that in healthy matched control subjects (16.69 hours). The GM apparent clearance was 3.53 L/hr in subjects with severe renal impairment versus 5.38 L/hr in healthy matched control subjects, while the GM apparent volume of distribution was comparable in both treatment populations.

Statistical Comparison and Summary Statistics of Plasma MK-1439 Pharmacokinetics Following the Administration of a Single Oral Dose of 100 mg MK-1439 to Subjects with Severe Renal Impairment and Healthy Mean Matched Control Subjects

	Severe Renal Impairment			Healthy Matched Control			Severe Renal Impairment / Healthy Matched Control		
Pharmacokinetic Parameter	**N**	**GM**	**95% CI**	**N**	**GM**	**95% CI**	**GMR**	**90% CI**	**rMSE[†]**
AUC0-∞[‡] (µM•hr)	8	64.5	(47.4, 87.8)	8	45.1	(33.2, 61.4)	1.43	(1.00, 2.04)	0.398
AUC0-last[§] (µM•hr)	8	60.5	56.3	8	41.0	29.9			
Cmax[‡] (nM)	8	1580	(1210, 2080)	8	1900	(1450, 2500)	0.83	(0.61, 1.15)	0.354
C24[‡] (nM)	8	943	(710, 1250)	8	684	(515, 908)	1.38	(0.99, 1.92)	0.367
Tmax[‖] (hr)	8	2.00	(0.50, 4.00)	8	1.50	(0.50, 6.00)			
Apparent terminal t½[§](hr)	8	25.02	36.4	8	16.69	26.1			
CL/F[§] (L/hr)	8	3.53	63.9	8	5.38	32.8			
Vz/F[§] (L)	8	127	40.9	8	129	28.3			

Treatment: Single oral dose of 100 mg MK-1439 following an overnight fast
Severe Renal Impairment: Subjects with eGFR values < 30 (mL/min/1.73 m^2) and not on dialysis
Healthy Matched Control: Healthy subjects with eGFR values ≥ 80 (mL/min/1.73 m^2) and matched to mean age (± 10 years) and weight (± 10 kg) of subjects with severe renal impairment
[†]rMSE: Square root of conditional mean squared error (residual error) from the ANCOVA model. rMSE*100% approximates the between-subject %CV on the raw scale.
[‡]Back-transformed least-squares mean and confidence interval from linear mixed-effect model performed on natural log-transformed values.
[§]Geometric mean and geometric percent coefficient of variation calculated as 100 x sqrt(exp(s^2) - 1), where s^2 is the observed variance on the natural log-scale. Reported for AUC0-last, apparent terminal t½, CL/F, and Vz/F.
[‖]Median (minimum, maximum) reported for Tmax.
GM = Geometric mean; GMR = Geometric mean ratio; CI = Confidence interval

ANALYSIS DESCRIPTION:	**Secondary Analysis - Safety** Incidence of the number of subjects with AEs was descriptively summarized and listed by population. A summary of the incidence of the number of subjects with drug-related AEs was descriptively summarized by population. Since no meaningful changes in individual laboratory safety values, ECGs, and vital signs were observed, summary statistics were not provided.
ANALYSIS POPULATION AND TIME POINT DESCRIPTION:	*All Subjects as Treated Population* - All subjects who received at least 1 dose of the investigational drug were included in the analysis population. This population was used for assessments of safety and tolerability. All 16 subjects were included in the evaluation of safety.

SUMMARY:	Administration of a single oral dose of doravirine 100 mg was generally well tolerated in the male and female subjects with severe renal impairment and healthy matched control subjects. Three (3, 19%) subjects reported 1 mild postdose adverse experience (AE) each, including 2 (25%) subjects with severe renal impairment and 1 (13%) healthy matched control subject. One (1) AE of mild nausea in a subject with severe renal impairment was considered by the Investigator as related to study drug. All AEs were resolved by the end of the study. No subject was discontinued due to an AE and no serious AEs (SAEs), events of clinical interest (ECIs), or deaths were reported. No clinically meaningful relationships were observed for differences between clinical laboratory values, vital signs, or ECG safety parameter values as a function of treatment.
CONCLUSIONS:	1. Severe renal impairment had a modest, but not clinically meaningful effect on the PK of a 100 mg dose of doravirine. Specifically, the AUC0-∞ and C24 of doravirine were higher in subjects with severe renal impairment compared to those in healthy matched control subjects, with GMRs (90% CIs) of 1.43 (1.00, 2.04) and 1.38 (0.99, 1.92), respectively. In addition, the Cmax of doravirine was slightly lower in subjects with severe renal impairment compared to that in healthy matched control subjects, with a GMR (90% CI) of 0.83 (0.61, 1.15). 2. Administration of a single 100 mg oral dose of doravirine was generally well tolerated in the male and female subjects with severe renal impairment and healthy matched control subjects.
REPORT DATE:	Final: 11-Nov-2016

SPONSOR:	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.	
COMPOUND NAME:	Doravirine (MK-1439)	
INDICATION:	HIV-1 Infection	
PROTOCOL TITLE:	A Study to Evaluate the Effect of Multiple Doses of Ritonavir on the Single Dose Pharmacokinetics of Doravirine (MK-1439)	
m	Protocol Number:	002
	Clinical Phase:	1
	EudraCT Number:	20[redacted]-002722-48
TRIAL CENTERS:	[redacted], BELGIUM	
DESIGN:	This was an open-label, fixed-sequence, 2-period study in eight (8) healthy young male subjects 18 to 50 years of age to evaluate the safety, tolerability, and pharmacokinetic (PK) profile of a single oral dose of MK-1439 (hereafter referred to as doravirine) co-administered with ritonavir. In Period 1, all subjects received a single oral dose of 50 mg of doravirine. There was a washout period of at least 7 days between study drug administration in Period 1 and the first dose of study drug in Period 2. In Period 2, the same subjects received 100 mg of ritonavir twice daily (b.i.d.) for 20 days. On Day 14, all subjects received the morning (AM) dose of ritonavir in combination with a single oral dose of 50 mg doravirine.	
	Duration of study:	Approximately 10 weeks
Objectives	<u>Primary</u> 1. To evaluate the safety and tolerability of multiple, twice-daily, oral doses of ritonavir co-administered with a single oral dose of doravirine. 2. To evaluate the effect of co-administration of ritonavir and doravirine on the plasma PK profile of doravirine (e.g., C24, AUC0-inf, Cmax, Tmax, and apparent t1/2).	
Hypotheses	<u>Primary</u> 1. The co-administration of ritonavir with a single oral dose of doravirine is sufficiently safe and well tolerated, based on an assessment of clinical and laboratory adverse experiences, to permit continued clinical investigation. 2. Multiple-dose administration of ritonavir prior to and co-administered with a single oral dose of doravirine does not substantially affect the C24 of doravirine, i.e., the true C24 geometric mean ratio (GMR) (doravirine + ritonavir / doravirine) lies within the interval (0.50, 2.00).	

Treatments groups	Period 1	50 mg doravirine single dose Day 1, n=8
	Period 2	100 mg b.i.d. ritonavir Days 1 – 20 and 50 mg doravirine single dose on Day 14, n=8

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) 10mg	[redacted]
Norvir (ritonavir) 100 mg film coated tablet (FCT) (Manufacturer: Abbott Laboratories; Lot Number #[redacted]; Expiry Date: [redacted] 20[redacted]) was supplied by the sponsor locally. OCT = oral compressed tablet	

Endpoints and definitions	Primary endpoint	**Safety** Adverse Events (AEs), laboratory safety tests (hematology, chemistry, and urinalysis), 12-lead electrocardiograms (ECG), and vital signs (VS).
		Pharmacokinetics Doravirine C24
	Secondary endpoint	**Pharmacokinetics** Doravirine AUC0-inf, Cmax, Tmax, and apparent t1/2
Database lock	[redacted]-20[redacted]	Trial status [redacted]-20[redacted] to [redacted]-20[redacted]
RESULTS AND ANALYSIS:	All safety analyses were performed according to the protocol. For PK analyses, the protocol stated that harmonic mean and jack-knife standard deviations would be provided for apparent t1/2. Instead, geometric mean (GM) and percent geometric coefficient of variation (GCV%) 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

	All Subjects	
	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	29.4	
SD	9.7	
Median	26.0	
Range	21 to 46	
Race		
White	8	(100.0)
Ethnicity		
Not Hispanic Or Latino	8	(100.0)

Disposition of Subjects

	All Subjects	
	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.		

Analysis description	**Primary Analysis – Safety** 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	All subjects who received at least one dose of the investigational drug were included in the assessment of safety and tolerability. All 8 subjects were included in the evaluation of safety and tolerability.
Summary	Doravirine was generally well tolerated by healthy adult male subjects when administered alone or in combination with ritonavir. Across both treatment periods, 8 subjects (100%) were reported to have a total of 22 treatment-emergent AEs (TEAEs). Five (5) subjects (62%) reported 11 TEAEs which were considered by the Investigator to be drug-related; 4 subjects following treatment with ritonavir, and 2 subjects following treatment with ritonavir + doravirine. All AEs were mild in intensity with the exception of one unrelated AE of headache, which was considered to be of moderate intensity. All of the AEs were of limited duration and all resolved by the end of the study, with the exception of two unrelated AEs, lipoma and urticaria, which were not resolved and were continuing at the end of the study. The most common AE was headache which was reported by 3 (37.5%) subjects. No other AE was reported by more than 1 subject. There were no serious AEs (SAEs), events of clinical interest (ECIs), or deaths reported during the study and no subjects discontinued due to an AE. There were no clinically meaningful trends for changes in clinical safety laboratories, VSs or ECGs as a function of treatment.
Analysis description	**Primary Analysis: Pharmacokinetics** The plasma doravirine PK values (AUC0-inf, Cmax and C24) were natural log transformed prior to analysis and evaluated in the linear mixed effects model with treatment as a fixed effect and subject as a random effect, separately. A two-sided 90% confidence interval (CI) for the GMR (doravirine + ritonavir / doravirine alone) was generated separately for doravirine AUC0-inf, Cmax, and C24 from the model. The 90% CI for the GMR of doravirine C24 was compared against the pre-specified bound of (0.50, 2.00). If the 90% CI fell within (0.50, 2.00), then it would be claimed that the multiple-dose administration of ritonavir prior to, and co-administered with a single oral dose of doravirine, does not substantially affect the C24 of doravirine.
Analysis population and time point description	All subjects who complied 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. All 8 subjects were included in the assessment of PK.

Summary	**PK** The GMR (90% CI) of doravirine C24 for the doravirine + ritonavir / doravirine alone comparison was 2.91 (2.33, 3.62). Since the 90% CI for GMR of doravirine C24 fell outside of the pre-specified interval of (0.50, 2.00), it indicated that the co administration of multiple-dose of ritonavir substantially affected doravirine C24. The GMRs (90% CI) of doravirine AUC0-inf and Cmax for the doravirine + ritonavir / doravirine alone comparison were 3.54 (3.04, 4.11) and 1.31 (1.17, 1.46), respectively.

Statistical Comparison of Plasma Pharmacokinetics of MK-1439 Following the Administration of a Single Oral Dose of 50 mg MK-1439 Alone and Co-administered on Day 14 of Twice Daily Administration of 100 mg Ritonavir for 20 Days in Healthy Adult Subjects

Pharmacokinetic Parameters	MK-1439 Alone			MK-1439 + Ritonavir			MK-1439 + Ritonavir / MK-1439 Alone		
	n	GM	95 % CI	n	GM	95 % CI	GMR	90 % CI	rMSE ¶
AUC0-inf (μM•hr)†	8	20.8	(17.5, 24.6)	8	73.5	(62.0, 87.1)	3.54	(3.04, 4.11)	0.159
C24 (nM)†	8	322	(266, 390)	8	935	(772, 1130)	2.91	(2.33, 3.62)	0.231
Cmax (nM)†	8	963	(825, 1120)	8	1260	(1080, 1470)	1.31	(1.17, 1.46)	0.118
Tmax (hr)‡	8	3.50	(2.00, 5.00)	8	5.00	(1.00, 16.00)			
Apparent t 1/2 (hr)§	8	13.97	(10.59)	8	35.16	(12.27)			

MK-1439 Alone: A single oral dose of 50 mg MK-1439 administered on Day 1 in Period 1.

MK-1439 + Ritonavir: 100 mg ritonavir twice daily on Days 1-20 co-administered with a single oral dose of 50 mg MK-1439 on Day 14 in Period 2.

† Back-transformed least squares mean and confidence interval from linear 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.

¶ rMSE: Square root of conditional mean square error (residual error) from the linear mixed-effect model. When multiplied by 100 approximates the within-subject % CV on the raw scale.

GM = Geometric Mean, GMR = Geometric Mean Ratio, CI = Confidence Interval, CV=Coefficient of Variation.

CONCLUSIONS:	1. Single dose doravirine administered alone or concomitantly with multiple doses of ritonavir is generally well tolerated. 2. Administration of multiple doses of ritonavir 100 mg b.i.d with a single 50 mg dose of doravirine increases the plasma C24 of doravirine by approximately 2.9-fold. Doravirine AUC0-inf and Cmax were also increased by 3.5-fold and 1.3-fold, respectively.
REPORT DATE:	[redacted]-20[redacted]

SPONSOR:	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.	
COMPOUND NAME:	Doravirine (MK-1439)	
INDICATION:	Treatment of HIV-1 infection	
PROTOCOL TITLE:	A Study to Evaluate the Effect of Multiple Doses of Tenofovir on the Single-Dose Pharmacokinetics of MK-1439	
TRIAL IDENTIFIERS:	Protocol Number:	003
	Clinical Phase:	1
	EudraCT Number:	Not applicable
	IND Number:	112,796
TRIAL CENTERS:	[redacted], MD, [redacted] USA	
DESIGN:	This was an open-label, 2-period, fixed-sequence study in eight young healthy male subjects. In Period 1, all subjects received a single oral dose of 100 mg MK-1439 (hereafter refered to as doravirine). There was a washout period of at least 7 days from the first dose of doravirine in Period 1 to the start of Period 2. In Period 2, the same subjects received a single daily dose of 300 mg tenofovir disoproxil fumarate (TDF) for 18 days with coadminstration of a single dose of 100 mg doravirine on Day 14.	
	Duration of study:	The duration of the study was approximately 9 weeks per subject.

Objectives	<u>Primary</u> 1. To evaluate the safety and tolerability of multiple doses of tenofovir disoproxil fumarate coadministered with a single dose of doravirine. 2. To evaluate the effect of coadministration of tenofovir disoproxil fumarate and doravirine on the plasma pharmacokinetic (PK) profile of doravirine (e.g., $AUC_{0-\infty}$, C_{24hr}, C_{max}, T_{max}, and apparent $t_{1/2}$).	
Hypotheses	<u>Primary</u> 1. The co-administration of tenofovir disoproxil fumarate with a single oral dose of doravirine is sufficiently safe and well tolerated, based on an assessment of clinical and laboratory adverse experiences, to permit continued clinical investigation. 2. Multiple-dose administration of tenofovir disoproxil fumarate prior to and co-administered with a single oral dose of doravirine does not substantially impact doravirine pharmacokinetics (i.e., the true C_{24hr} geometric mean ratio (doravirine + tenofovir disoproxil fumarate/doravirine) is greater than 0.50, and the true AUC_{0-24hr} geometric mean ratio (doravirine + tenofovir disoproxil fumarate/doravirine) is less than 2.00).	
Treatments groups	Period 1: Doravirine alone	100 mg doravirine Day 1, N=8
	Period 2: TDF + co-administration of doravirine	300 mg TDF on Days 1-18 and 100 mg doravirine on Day 14, N=8

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]
Tenofovir Disoproxil Fumarate 300mg (lot number [redacted]; expiration date [redacted]-20[redacted]; Gilead) was supplied by the investigator.	

Endpoints and definitions	Primary endpoints	**Safety** Adverse experiences (AEs), laboratory safety tests, electrocardiograms (ECG), and vital signs (VS). **Pharmacokinetics** Doravirine C_{24hr}, $AUC_{0-\infty,}$ C_{max}, T_{max}, and apparent $t_{1/2}$.	
Database lock	[redacted]-20[redacted]	Trial status	[redacted]-20[redacted] to [redacted]-20[redacted]
RESULTS AND ANALYSIS:	All analyses for safety were performed according to the protocol. One subject was discontinued on Day 11 of the study. Available PK data before the discontinuation for this subject were included in the PK analysis, and all data from the other 7 subjects were included in the PK analysis. For PK analyses, the protocol stated that harmonic mean and jack-knife standard deviations would be provided for apparent $t_{1/2}$. Instead, geometric mean (GM) and percent geometric coefficient of variation (GCV%) were provided, in order to be consistent with reporting done in other studies. Additionally, true $AUC_{0-\infty}$ geometric mean ratio was evaluated and replaced AUC_{0-24hr} as stated in the primary hypothesis of the protocol. The statistical analysis plan (SAP) was not affected, since the SAP pre-specified the primary hypothesis test for $AUC_{0-\infty}$, instead of AUC_{0-24hr}.		

Subject Characteristics

	All Subjects	
	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	44.3	
SD	4.8	
Median	46.0	
Range	36 to 50	
Race		
Black Or African American	6	(75.0)
White	2	(25.0)
Ethnicity		
Not Hispanic Or Latino	8	(100.0)

Disposition of Subjects

	All Subjects	
	n	(%)
Subjects in population	8	
Trial Disposition		
Completed	7	(87.5)
Discontinued	1	(12.5)
Adverse Event	1	(12.5)
Each subject is counted once for Trial Disposition based on the latest corresponding disposition record.		

Analysis description	**Primary Analysis - Safety** 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. Summary statistics and plots were generated for the change from baseline values in the VS, 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 VS were also computed.
Analysis population and time point description	All subjects who received at least one dose of the investigational drugs were included in the assessment of safety and tolerability. All eight (8) subjects were included in the assessment of safety and tolerability.
Summary	Doravirine was generally well tolerated when administered alone or in combination with TDF. Across both treatment periods, three (3) of the 8 subjects (37.5 %) reported a total of ten (10) treatment-emergent clinical AEs, four (4) of which were considered by the Investigator to be 'possibly' or 'probably' drug related. All of the AEs were mild in intensity, of limited duration and all resolved by the end of the study. The most common AE was headache which was reported by two (2) subjects. No other AE was reported by more than one (1) subject. One subject (AN72) was discontinued by the Investigator on Day 11, Period 2 of the study due to onset of ascending colonic diverticulitis on Day 10, Period 2, which was considered definitely not related to study drug. There were no serious AEs, events of clinical interest (ECIs), or deaths reported during the study and no clinically meaningful trends for changes in clinical safety laboratories, VSs or ECGs as a function of treatment.

Analysis description	**Primary Analysis**: Pharmacokinetics The plasma doravirine PK ($AUC_{0-\infty}$, C_{max} and C_{24hr}) were natural-log transformed prior to analysis and evaluated in separate linear mixed effects models having treatment as a fixed effect and subject as a random effect. A two-sided 90% confidence interval (CI) for the geometric mean ratio (GMR) (doravirine + TDF / doravirine alone) was generated separately for doravirine $AUC_{0-\infty}$, C_{max}, and C_{24hr} from the model. The lower bound of the 90% CI for the GMR of doravirine C_{24hr} was compared against the pre-specified bound 0.50, and the upper bound of the 90% CI for the GMR of doravirine $AUC_{0-\infty}$ was compared against the pre-specified bound 2.00. If the upper bound of the 90% CI of doravirine $AUC_{0-\infty}$ was less than 2.00, and the lower bound of the 90% CI of doravirine C_{24hr} was greater than 0.50, then it would be concluded that multiple-dose administration of TDF prior to and co-administered with a single oral dose of doravirine does not substantially impact doravirine PK.
Analysis population and time point description	The PK analysis population included the subset of 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. Compliance covered such considerations as exposure to treatment, availability of measurements and absence of major protocol deviations. Eight (8) subjects received at least one dose of doravirine. However, one subject was discontinued on Day 11, Period 2 of the study. Available PK data before the discontinuation for this subject and all data from the other seven (7) subjects were included in the PK analysis.

Summary	**Pharmacokinetics** GMR (90% CI) of doravirine $AUC_{0-\infty}$ and C_{24hr} (doravirine + TDF / doravirine alone) was 0.95 (0.80, 1.12) and 0.94 (0.78, 1.12), respectively. As the upper bound of the 90% CI of doravirine $AUC_{0-\infty}$ was less than 2.00 and the lower bound of the 90% CI of doravirine C_{24hr} was greater than 0.50, the primary hypothesis, that the multiple-dose administration of TDF prior to and co-administered with a single oral dose of doravirine does not substantially impact doravirine PK, was supported. GMR (90% CI) of doravirine C_{max} (doravirine + TDF / doravirine alone) was 0.80 (0.64, 1.01). Median (minimum, maximum) reported T_{max} for doravirine + TDF and doravirine alone were 3.0 (0.98, 7.92) and 2.5 (0.50, 4.98), respectively. For apparent $t_{1/2}$, GM (GCV%) for doravirine + TDF and doravirine alone were 15.39 (24.98%) and 14.42 (24.66%), respectively.

Statistical Comparison of Plasma Pharmacokinetics of MK-1439 Following the Administration of a Single Oral Dose of 100 mg MK-1439 Alone or Co-administered on Day 14 of Once-Daily Administration of 300 mg Tenofovir Disoproxil Fumarate for 18 Days in Healthy Adult Subjects

Pharmacokinetic	MK-1439 Alone			MK-1439 + tenofovir disoproxil fumarate			MK-1439 + tenofovir disoproxil fumarate / MK-1439 Alone		
Parameters	N	GM	95 % CI	N	GM	95 % CI	GMR	90 % CI	rMSE [†]
$AUC_{0-\infty}$ [‡] (µM•hr)	8	35.3	(27.5, 45.3)	7	33.4	(25.9, 43.2)	0.95	(0.80, 1.12)	0.162
C_{24hr} [‡] (nM)	8	584	(463, 738)	7	547	(430, 697)	0.94	(0.78, 1.12)	0.171
C_{max} [‡] (nM)	8	1630	(1210, 2190)	7	1310	(965, 1780)	0.80	(0.64, 1.01)	0.216
T_{max} [§] (hr)	8	2.50	(0.50, 4.98)	7	3.00	(0.98, 7.92)			
Apparent $t_{1/2}$ [‖] (hr)	8	14.42	(24.66)	7	15.39	(24.98)			

MK-1439 Alone: A single oral dose of 100 mg MK-1439 administered on Day 1 in Period 1.

MK-1439 + tenofovir disoproxil fumarate: 300 mg tenofovir disoproxil fumarate once-daily (QD) on Days 1-18 co-administered with a single oral dose of 100 mg MK-1439 on Day 14.

[†] rMSE: Square root of conditional mean square error (residual error) from the linear mixed-effect model. When multiplied by 100 approximates the within-subject % coefficient of variation (CV) on the raw scale.

[‡] Back transformed least square 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 $t_{1/2}$.

GM = Geometric least square mean; GMR = Geometric least square mean ratio; CI = Confidence interval.

CONCLUSIONS:	1. Multiple doses of TDF coadministered with a single dose of doravirine were generally well tolerated. 2. Following multiple doses, TDF did not have a clinically meaningful effect on the single-dose PK of doravirine.
PUBLICATION(S):	Publications are in [16.1.11] and [16.1.12].
REPORT DATE:	[redacted]-20[redacted]

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC
MK-1439,Tablets
Antiviral treatment for HIV-1 infection

CLINICAL STUDY REPORT SYNOPSIS

PROTOCOL TITLE/NO.: A Study to Assess the Effects of Multiple Oral Doses of Ketoconazole on the Single-Dose Pharmacokinetics of MK-1439 in Healthy Subjects **#010**

INVESTIGATOR/STUDY CENTER: [redacted], MD, [redacted]

PUBLICATION(S): None

PRIMARY THERAPY PERIOD: [redacted]-20[redacted] through [redacted]-20[redacted]. The frozen file date was [redacted]-20[redacted]. **CLINICAL PHASE:** I

DURATION OF TREATMENT:
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.

OBJECTIVE:
Primary: To assess the effect of multiple doses of ketoconazole, a strong CYP3A4 and P-gp inhibitor, on the single-dose plasma pharmacokinetic profile of MK-1439 (AUC0-∞, Cmax, Tmax, C24 and apparent terminal t½).

HYPOTHESIS:
Primary: The effect of multiple doses of ketoconazole on the single-dose plasma pharmacokinetic profile of MK-1439 will be estimated.

STUDY DESIGN:
This was an open-label, 2-period, fixed-sequence study to assess the effect of multiple doses of ketoconazole on the single-dose plasma pharmacokinetic profile of MK-1439. Ten (10) healthy adult non-tobacco using male and female subjects 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 (2 x 200 mg tablets) QD for 10 days, with co-administration of a single oral dose of 100 mg MK-1439 (1 x 100 mg tablet) on Day 2. There was a 7 day washout between the single oral dose administration of Period 1 and the first oral dose administration of Period 2. The total duration of the study (from screening to follow-up) was approximately 6 weeks.

SUBJECT DISPOSITION:

ENTERED: Total	10
Male (N, age range)	8 (22 to 50 yrs)
Female (N, age range)	2 (48 to 49 yrs)
COMPLETED:	10
DISCONTINUED: Total	0
Clinical adverse experience	0
Laboratory adverse experience	0
Other	0

DOSAGE/FORMULATION NOS.: In Period 1, a 100 mg dose of MK-1439 was administered as 1 x 100 mg tablet on Day 1. In Period 2, 400 mg doses of ketoconazole were administered as 2 x 200 mg tablets QD for 10 days with co-administration of a 100 mg dose of MK-1439 on Day 2.

Drug	Potency	Formulation No.	Dosage Form	Control No.
MK-1439	100 mg	[redacted]	Tablet	[redacted]
Ketoconazole†	200 mg	NA	Tablet	NA

†Ketoconazole (manufactured by Mylan Pharmaceuticals Inc.) was purchased by the Investigator. The lot number was [redacted]; expiration date [redacted]-20[redacted].

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC MK-1439,Tablets Antiviral treatment for HIV-1 infection	**CLINICAL STUDY REPORT SYNOPSIS**

DIAGNOSIS/INCLUSION CRITERIA:
Healthy adult non-smoking male and female subjects of non-childbearing potential, between 19 and 50 years of age, inclusive, with a body mass index (BMI) ≥ 18.5 and ≤ 32.0 kg/m^2.

EVALUATION CRITERIA:
PHARMACOKINETICS: Blood samples for determination of MK-1439 concentrations were collected at predose and at specified time points over 72 hours in Period 1 following a single oral dose of 100 mg MK-1439 on Day 1 and over 216 hours in Period 2 following the co-administration of multiple oral doses of 400 mg ketoconazole QD for 10 days and a single oral dose of 100 mg MK-1439 on Day 2.
SAFETY: Safety was monitored 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: The pharmacokinetic parameters (AUC0-∞, C24, and Cmax) were natural log (ln)-transformed and analyzed with a linear mixed-effects model with a fixed-effect term for treatment. An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlation between the 2 treatment measurements within the same subject via the REPEATED statement in SAS® PROC MIXED. Back-transformed inferential results were reported for pharmacokinetic parameters. The 90% confidence intervals (CIs), based on the t-distribution, were generated for the geometric mean ratios (GMRs, MK-1439 + Ketoconazole/MK-1439 Alone) for AUC0-∞, C24, and Cmax of MK-1439. The geometric means and corresponding 95% CIs were also provided. Summary statistics were provided for Tmax and apparent terminal t½.
Safety: The safety and tolerability of a single dose of MK-1439 administered alone, and in combination with multiple doses of ketoconazole, were evaluated by clinical assessment of adverse experiences and other safety measurements. Incidence of the number of subjects with adverse experiences was descriptively summarized and listed by 3 treatment segments (MK-1439 Alone, Ketoconazole Alone, and MK-1439 with Ketoconazole). Since laboratory safety tests, ECGs, and/or vital signs were not deemed clinically significant, the safety parameters were not summarized for each treatment.

RESULTS:
PHARMACOKINETICS:
The following table presents the statistical comparison of the pharmacokinetics of MK-1439 in healthy male and female subjects following a single dose of 100 mg MK-1439 alone or co-administered with multiple doses of 400 mg ketoconazole.

The MK-1439 AUC0-∞ GMR (MK 1439 + ketoconazole/MK-1439 alone) (90% CI) for the comparison of a single dose of 100 mg MK-1439 co-administered with multiple doses of 400 mg ketoconazole versus a single dose of 100 mg MK-1439 alone was 3.06 (2.85, 3.29). The Cmax and C24 GMRs (MK 1439 + ketoconazole/MK-1439 alone) (90% CI) were 1.25 (1.05, 1.49) and 2.75 (2.54, 2.98), respectively.

The median peak MK-1439 concentration was delayed by 1 hour when MK-1439 was co-administered with ketoconazole with a median value of 3 hours. A wider range of Tmax values was observed when MK-1439 was administered with ketoconazole (1.00 - 24.00 hours). The geometric mean apparent terminal t½ was 15.23 hours when MK-1439 was administered alone and 32.37 hours when MK-1439 was co-administered with multiple oral doses of ketoconazole.

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC
MK-1439,Tablets
Antiviral treatment for HIV-1 infection

CLINICAL STUDY REPORT SYNOPSIS

RESULTS (Continued):
PHARMACOKINETICS (Continued):

Statistical Comparisons of Plasma Pharmacokinetics of MK-1439 Following the Administration of a Single Oral Dose of 100 mg MK-1439 Alone and Following the Administration of a Single Oral Dose of 100 mg MK-1439 With Multiple Oral Doses of 400 mg Ketoconazole in Healthy Adult Subjects

	MK-1439 Alone			MK-1439 + Ketoconazole			MK-1439 + Ketoconazole/ MK-1439 Alone		
Pharmacokinetic Parameter	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	Pseudo Within Subject %CV‡
AUC0-∞† (μM•hr)	10	29.88	(26.61, 33.56)	10	91.47	(76.36, 109.56)	3.06	(2.85, 3.29)	8.77
Cmax† (nM)	10	1402.12	(1160.00, 1694.77)	10	1759.00	(1460.93, 2117.89)	1.25	(1.05, 1.49)	21.24
C24† (nM)	10	429.51	(382.57, 482.21)	10	1180.14	(991.41, 1404.80)	2.75	(2.54, 2.98)	9.79
Tmax§ (hr)	10	2.00	(1.00, 6.00)	10	3.00	(1.00, 24.00)			.
Apparent terminal t½‖ (hr)	10	15.23	28.09	10	32.37	12.54			.

MK-1439 Alone: Single oral dose of 100 mg MK-1439 (1 x 100 mg tablet) on Day 1 of Period 1 following an overnight fast (Reference).
MK-1439 + Ketoconazole: Multiple oral doses of 400 mg ketoconazole (2 x 200 mg tablets) QD for 10 consecutive days in Period 2 and a single oral dose of 100 mg MK-1439 (1 x 100 mg tablet) on Day 2 following an overnight fast (Test).
†Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.
‡Pseudo Within-Subject %CV = $100*\mathrm{Sqrt}((\sigma_A^2 + \sigma_B^2 - 2*\sigma_{AB})/2)$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
§Median (min, max) reported for Tmax.
‖ Geometric arithmetic mean and percent geometric coefficient of variation reported for apparent terminal t½.
GM = Geometric least-squares mean; GMR = Geometric least-squares mean ratio; CI = Confidence interval

SAFETY:
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. No deaths, serious adverse experiences, laboratory adverse experiences, or pregnancies were reported during the study, and no subject discontinued because of an adverse experience. One subject (Subject AN 0006) experienced 2 episodes of mild papular rash which the Investigator considered to be related to MK-1439 only. Overall, 6 subjects reported a total of 18 adverse experiences, 13 of which were considered drug-related (6 related to MK-1439 only, 5 related to ketoconazole only, and 2 related to both MK-1439 and ketoconazole). All adverse experiences were mild in intensity, and resolved prior to the end of the study. The most common adverse experiences reported in this study were nausea, rhinorrhoea, and sinus congestion, each reported in ≥ 2 subjects. There were no consistent treatment-related changes in laboratory, vital signs, or ECG safety parameters.

CONCLUSIONS:

- 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-∞ GMR (MK-1439 + ketoconazole/MK-1439 alone) and 90% CI 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.

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC
MK-1439, Tablets
Antiviral treatment for HIV-1 infection

CLINICAL STUDY REPORT SYNOPSIS

PROTOCOL TITLE/NO.: 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 #011

INVESTIGATOR/STUDY CENTER: [redacted], MD, [redacted]

PUBLICATION(S): None

PRIMARY THERAPY PERIOD: 13-Apr-2013 through 25-Jun-2013. The frozen file date was 06-Aug-2013.

CLINICAL PHASE: I

DURATION OF TREATMENT:
For Treatment A (Period 1), subjects received a single oral dose of 100 mg MK-1439 on Day 1. For Treatment B (Period 2), subjects received a single oral dose of 600 mg rifampin co-administered with a single oral dose of 100 mg MK-1439 on Day 1, and for Treatment C (Period 2), subjects received single oral doses of 600 mg rifampin administered once daily (QD) for 15 days (Days 4 to 18) and co-administered with a single oral dose of 100 mg MK-1439 on Day 17. Although this study was dosed in 2 periods, and the protocol describes 2 treatments, for presentation of pharmacokinetic and safety data, the single-dose administration of MK-1439 alone, the co-administration of MK-1439 with a single dose of rifampin on Day 1, and the co-administration of multiple doses of rifampin with a single dose of MK-1439 on Day 17, were presented as the first, second, and third treatments, respectively. There was a washout of at least 7 days between dosing in Period 1 and the first dose in Period 2.

OBJECTIVES:
Objective 1 (single-dose rifampin): To evaluate the effect of co-administration of a single dose of rifampin on the plasma pharmacokinetic profile of MK-1439 (e.g., AUC0-∞, Cmax, Tmax, C24hr, t½ and CL/F).
Objective 2 (multiple-dose rifampin): To evaluate the effect of co-administration of multiple doses of rifampin on the plasma pharmacokinetic profile of MK-1439 (e.g., AUC0-∞, Cmax, Tmax, C24hr, t½ and CL/F).

HYPOTHESES:
Hypothesis 1 (single-dose rifampin): Single-dose administration of rifampin co-administered with a single oral dose of MK-1439 does not substantially affect the AUC0-∞ and C24hr of MK-1439 compared to a single oral dose of MK-1439 alone; that is, the true AUC0-∞ and C24hr geometric mean ratios (GMRs) (MK-1439 + rifampin/MK-1439 alone) are within (0.50, 2.00).
Hypothesis 2 (multiple-dose rifampin): C24hr of MK-1439 is > 54 nM when a single oral dose of 100 mg MK-1439 is co-administered with multiple doses of rifampin.
Estimation (multiple-dose rifampin): The true GMR of AUC0-∞ and C24hr of MK-1439 (administered alone and in the setting of multiple-dose rifampin co-administration) will be estimated.

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC
MK-1439, Tablets
Antiviral treatment for HIV-1 infection

CLINICAL STUDY REPORT SYNOPSIS

STUDY DESIGN:
This was an open-label, 2-period, fixed-sequence study to assess the effects of single and multiple doses of rifampin on the single-dose pharmacokinetics of MK-1439. Eleven (11) healthy non-tobacco using male adult subjects were enrolled in this study. For Treatment A (Period 1), subjects received a single oral dose of 100 mg MK-1439 on Day 1. For Treatment B (Period 2), subjects received a single oral dose of 600 mg rifampin co-administered with a single oral dose of 100 mg MK-1439 on Day 1. For Treatment C (Period 2), subjects received multiple oral doses of 600 mg rifampin QD for 15 days (Days 4 to 18) co-administered with a single oral dose of 100 mg MK-1439 on Day 17. The washout period was at least 7 days between dosing in Period 1 and first dosing in Period 2. The total duration of the study (from screening to follow-up) was approximately 12 weeks.

SUBJECT DISPOSITION:

ENTERED: Total	11
Male (N, age range)	11 (22 to 52 yrs)
Female (N)	0
COMPLETED:	10
DISCONTINUED: Total	1
Clinical adverse experience	0
Laboratory adverse experience	0
Other	1[†]

[†]One (1) subject, Subject AN 0010, was discontinued on Day 17 of Period 2 due to a failed drug screen at check-in on Day 16, Period 2.

DOSAGE/FORMULATION NOS.: In Period 1, a 100 mg dose of MK-1439 was administered as 1 x 100 mg tablet on Day 1. In Period 2, 600 mg doses of rifampin were administered as 2 x 300 mg capsules QD on Day 1 and Days 4 to 18, with co-administration of a 100 mg dose of MK-1439 on Days 1 and 17.

Drug	Potency	Formulation No.	Dosage Form	Control No.
MK-1439	100 mg	[redacted]	Tablet	[redacted]
Rifampin[†]	300 mg	NA	Capsule	NA

[†]Rifampin (a product of West-ward Pharmaceutical Corp.) was purchased by the Investigator. The lot number was [redacted]; expiration date Oct-2014.

DIAGNOSIS/INCLUSION CRITERIA:
Healthy, non-tobacco using adult males (weighing at least 52 kg) between 19 and 55 years of age, with a body mass index (BMI) between 18.5 and 32.0 kg/m^2.

EVALUATION CRITERIA:
PHARMACOKINETICS: Blood samples for the determination of plasma MK-1439 were obtained predose and at specified time points for 72 hours in Period 1 following a single oral dose of 100 mg MK-1439 on Day 1 (Treatment A). In Period 2, blood samples for the determination of plasma MK-1439 following a single oral dose of 100 mg MK-1439 co-administered with a single oral dose of 600 mg rifampin on Day 1 (Treatment B) were obtained predose and at specified time points for 72 hours postdose. On Days 4 to 18 of Period 2, 600 mg doses of rifampin were administered daily with a single oral dose of 100 mg MK-1439 co-administered on Day 17 (Treatment C). Blood samples for the determination of plasma MK-1439 were obtained at predose on Day 17 until 48 hours postdose (Day 19) in Period 2. The plasma pharmacokinetic parameters (AUC0-∞, Cmax, C24hr, Tmax, CL/F, and apparent terminal t½) were calculated for each treatment.

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC MK-1439, Tablets Antiviral treatment for HIV-1 infection	**CLINICAL STUDY REPORT SYNOPSIS**

EVALUATION CRITERIA (Continued):

SAFETY: Safety was monitored through physical examination, vital signs, electrocardiograms (ECGs), adverse events and clinical laboratory tests.

STATISTICAL PLANNING AND ANALYSIS:

METHODS:

Pharmacokinetics: The pharmacokinetic parameters (AUC0-∞, C24hr, and Cmax) were natural log (ln)-transformed and analyzed with a linear mixed-effects model with a fixed-effect term for treatment (MK-1439 Alone, MK-1439 + SD Rifampin and MK-1439 + MD Rifampin). An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlation between the treatment measurements within the same subject via the REPEATED statement in SAS PROC MIXED. The Kenward and Roger adjustment was used to calculate the denominator degrees of freedom for the fixed effects (DDFM=KR). A 90% confidence interval (CI) was constructed for the difference of a single dose (SD) of MK-1439 (Period 1, Day 1) with and without co-administration of a SD of rifampin (Period 2, Day 1) in least-squares means (LS means) on the ln-scale for AUC0-∞. Exponentiating the ln-scale 90% CI provided a 90% CI for the AUC0-∞ GMR (SD MK-1439 + SD Rifampin/MK-1439 Alone). The same analysis was done for C24hr and Cmax.

A 90% CI (equivalent to a one-sided alpha of 0.05) for the C24hr mean value when a single oral dose of 100 mg MK-1439 was co-administered with multiple doses of rifampin was also calculated. If the lower bound of the 90% CI was greater than 54 nM, then Hypothesis 2 was satisfied.

A 90% CI was constructed for the difference of SD MK-1439 (Period 1, Day 1) with and without co-administration of multiple doses (MD) of rifampin (Period 2, Day 17) in LS means on the ln-scale for AUC0-∞. Exponentiating the ln-scale 90% CI provided a 90% CI for the AUC0-∞ GMR (SD MK-1439 + MD Rifampin/MK-1439 Alone). The same analysis was done for C24hr and Cmax.

RESULTS:

PHARMACOKINETICS:

The table below presents the statistical comparison of the plasma pharmacokinetics of MK-1439 in healthy male subjects following the administration of a single oral dose of 100 mg MK-1439 alone or co-administered with a single oral dose of 600 mg rifampin.

Since the GMRs and 90% CIs for MK-1439 AUC0-∞ and C24hr (MK-1439 + SD rifampin/MK-1439 alone) were within (0.50, 2.00), the hypothesis that single-dose administration of rifampin co-administered with a single oral dose of MK-1439 does not substantially affect the AUC0-∞ and C24hr of MK-1439 compared to a single oral dose of MK-1439 alone was supported. The GMRs (MK-1439 + SD rifampin/MK-1439 alone) and 90% CIs for AUC0-∞ and C24hr were 0.91 (0.78, 1.06) and 0.90 (0.80, 1.01), respectively. The GMR (MK-1439 + SD rifampin/MK-1439 alone) and 90% CI for Cmax were 1.40 (1.21, 1.63).

The observed median Tmax of MK-1439 was 1 hour earlier when MK-1439 was co-administered with a single oral dose of rifampin (median Tmax = 2.00 hours) than when MK-1439 was administered alone (median Tmax = 3.00 hours). The observed geometric mean CL/F of MK-1439 was comparable following MK-1439 with (7.09 L/hr) or without (6.44 L/hr) a single oral dose of rifampin. However, the geometric mean apparent terminal t½ was 5.50 hours when MK-1439 was co-administered with a single oral dose of rifampin, compared to 18.60 hours when MK-1439 was administered alone.

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC
MK-1439, Tablets
Antiviral treatment for HIV-1 infection

CLINICAL STUDY REPORT SYNOPSIS

RESULTS (Continued):
PHARMACOKINETICS (Continued):

Statistical Comparisons of Plasma Pharmacokinetics of MK-1439 Following the Administration of a Single Oral Dose of 100 mg MK-1439 With or Without the Co-administration of a Single Oral Dose of 600 mg Rifampin in Healthy Adult Subjects

Pharmacokinetic Parameter	MK-1439 Alone			MK-1439 + SD Rifampin			MK-1439 + SD Rifampin/ MK-1439 Alone		Pseudo Within Subject %CV[‖]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC0-∞[†] (µM•hr)	11	36.5	(26.7, 49.8)	11	33.1	(28.2, 38.9)	0.91	(0.78, 1.06)	19.441
Cmax[†] (nM)	11	1540	(1230, 1920)	11	2160	(1890, 2470)	1.40	(1.21, 1.63)	19.164
C24hr[†] (nM)	11	511	(360, 725)	11	459	(347, 608)	0.90	(0.80, 1.01)	15.131
CL/F[§] (L/hr)	11	6.44	48.9	11	7.09	24.2			
Tmax[‡] (hr)	11	3.00	(1.00, 6.00)	11	2.00	(1.00, 6.00)			
Apparent terminal t½[§] (hr)	11	18.60	44.52	11	5.50	18.93			

MK-1439 Alone: Single oral dose of 100 mg MK-1439 (1 x 100 mg tablet) on Day 1 of Period 1.
MK-1439 + SD Rifampin: Single oral dose of 100 mg MK-1439 (1 x 100 mg tablet) co-administered with a single oral dose of 600 mg rifampin (2 x 300 mg capsules) on Day 1 of Period 2.
[†]Back-transformed least squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.
[‡]Median (Minimum, Maximum) reported for Tmax.
[§]Geometric mean and geometric coefficient of variation reported for CL/F and apparent terminal t½.
[‖]Pseudo Within-Subject %CV = 100*sqrt ($\sigma^2_A + \sigma^2_B - 2*\sigma_{AB}$)/2), where σ^2_A and σ^2_B are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
GM = Geometric least-squares mean; GMR = Geometric least-squares mean ratio; CI = Confidence interval.

The table below presents the statistical comparison of the plasma pharmacokinetics of MK-1439 in healthy male subjects following the administration of a single oral dose of 100 mg MK-1439 alone or co-administered with multiple oral doses of 600 mg rifampin.
The lower bound of the 90% CI for C24hr was 12.4 nM when a single oral dose of MK-1439 is co-administered with multiple oral doses of rifampin; therefore, the hypothesis that the C24hr of MK-1439 is > 54 nM when a single oral dose of 100 mg MK-1439 is co-administered with multiple doses of rifampin, was not met.
The GMRs (MK-1439 + MD rifampin/MK-1439 alone) and 90% CIs for MK-1439 AUC0-∞, C24hr, and Cmax for the comparison of a single oral dose of 100 mg MK-1439 co-administered with multiple oral doses of 600 mg rifampin versus a single oral dose of 100 mg MK-1439 alone were 0.12 (0.10, 0.15), 0.03 (0.02, 0.04), and 0.43 (0.35, 0.52), respectively.
The observed median Tmax of MK-1439 was 1 hour earlier when MK-1439 was co-administered with multiple oral doses of rifampin (median Tmax = 2.00 hours) than when MK-1439 was administered alone (median Tmax = 3.00 hours). The geometric mean CL/F of MK-1439 was 51.6 L/hr following MK-1439 co-administered with multiple oral doses of rifampin, compared to 6.44 L/hr following MK-1439 alone. The geometric mean apparent terminal t½ was 6.30 hours when MK-1439 was co-administered with multiple oral doses of rifampin, compared to 18.60 hours when MK-1439 was administered alone.

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC
MK-1439, Tablets
Antiviral treatment for HIV-1 infection

CLINICAL STUDY REPORT SYNOPSIS

RESULTS (Continued):

PHARMACOKINETICS (Continued):

Statistical Comparisons of Plasma Pharmacokinetics of MK-1439 Following the Administration of a Single Oral Dose of 100 mg MK-1439 With or Without the Co-administration of Multiple Oral Doses of 600 mg Rifampin in Healthy Adult Subjects

Pharmacokinetic Parameter	MK-1439 Alone			MK-1439 + MD Rifampin				MK-1439 + MD Rifampin/ MK-1439 Alone		Pseudo Within Subject %CV[‖]
	N	GM	95% CI	N	GM	95% CI	90% CI	GMR	90% CI	
AUC0-∞[†] (μM•hr)	11	36.5	(26.7, 49.8)	10	4.47	(3.87, 5.15)	(3.98, 5.01)	0.12	(0.10, 0.15)	28.078
Cmax[†] (nM)	11	1540	(1230, 1920)	10	661	(562, 778)	(579, 755)	0.43	(0.35, 0.52)	24.702
C24hr[†] (nM)	11	511	(360, 725)	10	16.4	(11.6, 23.2)	(12.4, 21.7)	0.03	(0.02, 0.04)	39.388
CL/F[§] (L/hr)	11	6.44	48.9	10	51.6	19.6				
Tmax[‡] (hr)	11	3.00	(1.00, 6.00)	10	2.00	(0.50, 3.04)				
Apparent terminal t½[§] (hr)	11	18.60	44.52	10	6.30	40.12				

MK-1439 Alone: Single oral dose of 100 mg MK-1439 (1 x 100 mg tablet) on Day 1 of Period 1.
MK-1439 + MD Rifampin: Multiple oral doses of 600 mg rifampin QD on Day 4 to 18 of Period 2, with a single oral dose of 100 mg MK-1439 (1 x 100 mg tablet) co-administered on Day 17 of Period 2.
[†]Back-transformed least squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.
[‡]Median (Minimum, Maximum) reported for Tmax.
[§]Geometric mean and geometric coefficient of variation reported for CL/F and apparent terminal t½.
[‖]Pseudo Within-Subject %CV = 100*sqrt ($\sigma^2_A + \sigma^2_C - 2*\sigma_{AC}$)/2), where σ^2_A and σ^2_C are the estimated variances on the log scale for the 2 treatment groups, and σ_{AC} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
GM = Geometric least-squares mean; GMR = Geometric least-squares mean ratio; CI = Confidence interval.
Subject AN 0010 was dropped on Day 17 of Period 2 due to failed Period 2 Day 16 check-in drug screen.

SAFETY:
MK-1439 was generally well tolerated when administered alone or co-administered with single or multiple oral doses of rifampin in healthy adult male subjects. No deaths, serious adverse experiences or laboratory adverse experiences were reported and no subject discontinued because of an adverse experience. Six (6) subjects reported a total of 19 clinical adverse experiences, 1 of which was considered drug-related by the Investigator (increased appetite, considered related to rifampin only). All adverse experiences were of mild intensity and resolved by the end of the study. During rifampin home dosing in Period 2, Subject AN 0009 took one of the rifampin dose 10 hours late and then took the next dose as scheduled, which was considered by the Investigator to have met the criteria to be considered an overdose of study medication; this overdose of study medication was not associated with any clinical symptoms or abnormal laboratory results and was considered to be a non-serious event of clinical interest (ECI). There were no consistent treatment-related changes in laboratory, vital signs, or ECG safety parameters.

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC MK-1439, Tablets Antiviral treatment for HIV-1 infection	**CLINICAL STUDY REPORT SYNOPSIS**

CONCLUSIONS:

- Single-dose co-administration of rifampin with a single oral dose of MK-1439 results in a ~40% increase in Cmax but no clinically relevant effect on the AUC0-∞ and C24hr of MK-1439, suggesting that MK-1439 may be a weak substrate for OATP1B1 and OATP1B3 uptake transporters or that weak inhibition of P-gp may occur at the gut wall. Modulation of OATP1B1 and OATP1B3 are not likely to have clinically meaningful effects on the pharmacokinetics of MK-1439. Multiple-dose co-administration of rifampin with a single oral dose of MK-1439 results in a significant reduction in MK-1439 which is likely due to CYP3A4 induction.
- When MK-1439 is co-administered with multiple oral doses of rifampin, MK-1439 AUC0-∞ and C24hr are decreased 88% and 97%, respectively, confirming that MK-1439 is a sensitive CYP3A4 substrate.
- The C24hr of MK-1439 is < 54 nM when a single oral dose of 100 mg MK-1439 is co-administered with multiple oral doses of rifampin, suggesting that the clinical efficacy of MK-1439 may be reduced when co-administered chronically with rifampin or other strong CYP3A4 inducers.

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC
MK-1439, Tablet
Antiviral treatment for HIV-1 infection

CLINICAL STUDY REPORT SYNOPSIS

PROTOCOL TITLE/NO.: A Study to Assess the Effects of Multiple Oral Doses of MK-1439 on the Single-Dose Pharmacokinetics of an Oral Contraceptive (Ethinyl Estradiol and Levonorgestrel) in Healthy Adult Female Subjects #012

INVESTIGATOR/STUDY CENTER: [redacted], MD, [redacted]

PUBLICATION(S): None

PRIMARY THERAPY PERIOD: [redacted]-20[redacted] through [redacted]-20[redacted]. The frozen file date was [redacted]-20[redacted].

CLINICAL PHASE: I

DURATION OF TREATMENT:
In Period 1, subjects received a single dose of Nordette®-28 (0.03 mg ethinyl estradiol [EE]/0.15 mg levonorgestrel [LNG]) alone on Day 1 (Treatment A). In Period 2, subjects received 100 mg of MK-1439 once-daily (QD) for 17 consecutive days, starting on Day 1, and co-administered with a single oral dose of Nordette®-28 (0.03 mg EE/0.15 mg LNG) on Day 14 (Treatment B). There was a washout of at least 7 days between the Nordette®-28 dose in Period 1 and the first dose of MK-1439 in Period 2. The duration of the study from screening to the last follow-up was approximately 9.5 weeks.

OBJECTIVES:
Primary: To assess the effect of multiple doses of MK-1439, on the single-dose pharmacokinetic profile of the oral contraceptive (OC) components, EE and LNG, (AUC0-last, AUC0-∞, Cmax, Tmax, and apparent terminal t½) after a single dose of Nordette®-28 or generic equivalent (EE 0.03 mg/LNG 0.15 mg).
Secondary: To assess the safety and tolerability of the co-administration of MK-1439 and OCs in healthy adult female subjects.

HYPOTHESIS:
Primary: The plasma AUC0-∞ and Cmax of EE and LNG after co-administration of Nordette®-28 with multiple-dose administration of MK-1439 (100 mg per day for 17 days) are not substantially altered compared with administration of a single dose of Nordette®-28 alone. That is, the true geometric mean ratios (GMRs) (EE + MK-1439/EE alone or LNG + MK-1439/LNG alone) for AUC0-∞ and Cmax of EE and LNG are contained within (0.80, 1.25).

ENDPOINTS:
Pharmacokinetics: The primary pharmacokinetic endpoints are AUC0-∞ and Cmax for EE and LNG administered with and without MK-1439. The pharmacokinetic parameters AUC0-last, Tmax and apparent terminal t½, as appropriate, for EE and LNG were also computed.
Safety: Safety endpoints are all types of adverse events, physical examinations, vital signs (heart rate and blood pressure), 12-lead ECGs, and laboratory safety tests (hematology, serum chemistry, and urinalysis).

STUDY DESIGN:
This was an open-label, 2-period, fixed-sequence study investigating the effect of multiple doses of MK-1439 on the single-dose pharmacokinetics of a monophasic combination of EE/LNG (Nordette®-28) in healthy female subjects. Twenty (20) healthy, non-tobacco using, postmenopausal or oophorectomized, adult female subjects 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. The term 'OC' is used throughout the CSR and refers specifically to Nordette®-28; 0.03 mg/EE/0.15 mg LNG.

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC
MK-1439, Tablet
Antiviral treatment for HIV-1 infection

CLINICAL STUDY REPORT SYNOPSIS

SUBJECT DISPOSITION:

ENTERED: Total	20
Female (N, age range)	20 (42 to 65 yrs)
COMPLETED:	19
DISCONTINUED: Total	1
Clinical adverse event	1
Laboratory adverse event	0
Other	1[†]

[†]One (1) subject (AN 0006) was discontinued from the study by the Investigator due to the nonserious adverse event (determined by the Investigator as not related to study drug) of elevated blood pressure prior to Day 4 dosing of Period 2.

DOSAGE/FORMULATION NOS.:
In Period 1 (Treatment A), a single oral dose of 0.03 mg EE/0.15 mg LNG (1 Nordette®-28 tablet) was administered on Day 1. In Period 2 (Treatment B), multiple oral doses of 100 mg MK-1439 (1 x 100 mg tablet) was administered QD for 17 consecutive days (Days 1 to 17), and a single oral dose of 0.03 mg EE/0.15 mg LNG (1 Nordette®-28 tablet) on Day 14.

Drug	Potency	Formulation No.	Dosage Form	Control No.
MK-1439	100 mg	[redacted]	Tablet	[redacted]
Nordette®-28 (levonorgestrel & ethinyl estradiol)[†]	0.15 mg/0.03 mg	NA	Tablet	NA

[†]Nordette®-28 (levonorgestrel and ethinyl estradiol) (manufactured by TEVA WOMEN'S HEALTH, INC) was purchased by the Investigator. The lot number was [redacted]; expiration date [redacted]-20[redacted].

DIAGNOSIS/INCLUSION CRITERIA:
Healthy, non-smoking adult oophorectomized or postmenopausal females ≥ 18 and ≤ 65 years of age, weighing a minimum of 45 kg and having a body mass index (BMI) ≥ 18.5 and ≤ 32.0 kg/m^2 at the prestudy visit were eligible for the study.

EVALUATION CRITERIA:
PHARMACOKINETICS: Blood samples for determination of plasma EE and LNG were obtained at predose and specified time points for 96 hours postdose in Period 1 following a single oral dose of OC 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 OC co-administered on Day 14 were obtained at predose and specified time points for 96 hours 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 OC alone on Day 1 in Period 1 and following multiple oral doses of MK-1439 for 17 days with a single dose of OC co-administered on Day 14 in Period 2.
SAFETY: Physical examinations, vital signs, laboratory safety tests, and electrocardiogram (ECG) measurements were obtained at specified times. Subjects were monitored for adverse events throughout the study.

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC
MK-1439, Tablet
Antiviral treatment for HIV-1 infection

CLINICAL STUDY REPORT SYNOPSIS

STATISTICAL PLANNING AND ANALYSIS:

METHODS:

Pharmacokinetics: Individual AUC0-∞ and Cmax EE and LNG values were natural log-transformed prior to analysis and evaluated separately using a linear mixed-effects model with a fixed effect term for treatment. An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlation between the 2 treatment measurements within each subject via the REPEATED statement in SAS PROC MIXED. The Kenward and Roger adjustment was used to calculate the denominator degrees of freedom for the fixed effects (DDFM=KR).

The hypothesis was addressed by comparing AUC0-∞ and Cmax of EE and LNG values from administration of OC + MK-1439 to those obtained from administration of OC alone. A 2-sided 90% confidence interval (CI) for the true mean difference (OC + MK-1439 minus OC alone) for each parameter on the log scale was computed from the model. The 90% CI was then exponentiated to obtain the 90% CI for the true GMR (OC + MK-1439/OC alone) for each parameter. If all four 90% CIs for the true GMRs were within (0.80, 1.25), then the primary hypothesis that the plasma AUC0-∞ and Cmax of EE and LNG after co-administration of OC with multiple-dose administration of MK-1439 are not substantially altered compared with administration of a single dose of OC alone was to be supported.

AUC0-last was analyzed in similar fashion. The other pharmacokinetic parameters (Tmax and apparent terminal t½) were summarized using descriptive statistics.

Safety: The safety and tolerability of OC administered alone, MK-1439 administered alone, and OC in combination with MK-1439 were evaluated by clinical assessment of adverse events and other safety measurements. Incidence of the number of subjects with adverse events were descriptively summarized and listed by treatment. Since there were no consistent or clinically significant changes in laboratory safety tests, vital signs, or ECG safety parameters, summary statistics were not provided.

RESULTS:

PHARMACOKINETICS:

The table below presents the statistical comparison of the pharmacokinetics of EE and LNG in healthy female subjects following a single dose of OC alone or co-administered with multiple doses of 100 mg MK-1439. The EE AUC0-∞ GMR (90% CI) for the comparison of a single dose of OC alone co-administered with multiple doses of 100 mg MK-1439 versus a single dose of OC alone was 0.98 (0.94, 1.03). The EE Cmax GMR (OC + MK-1439/OC alone) (90% CI) was 0.83 (0.80, 0.87). The LNG AUC0-∞ GMR (90% CI) for the comparison of a single dose of OC alone co-administered with multiple doses of 100 mg MK-1439 versus a single dose of OC alone was 1.21 (1.14, 1.28). The LNG Cmax GMR (OC + MK-1439/OC alone) (90% CI) was 0.96 (0.88, 1.05). Of the 4 assessed GMRs and 90% CIs, only the 90% CI for LNG AUC0-∞ fell slightly outside of the pre-specified upper bound (i.e., upper confidence limit of 1.28). Nonetheless, as not all four 90% CIs for the true GMRs were within (0.80, 1.25), the primary hypothesis that the plasma AUC0-∞ and Cmax of EE and LNG after co-administration of Nordette-28 with multiple-dose administration of MK-1439 (100 mg per day for 17 days with co-administration of Nordette-28 on Day 14) are similar compared with single-dose administration of Nordette-28 alone is not supported.

The median peak EE concentration occurred at 1.50 hours in both treatments (OC + MK-1439 and OC alone). The median peak LNG concentration was 1.51 hours when OC was co-administered with MK-1439 and 1.27 hours when OC was administered alone. The arithmetic mean apparent terminal t½ for EE was similar following OC co-administered with multiple doses of MK-1439 and OC alone, 18.75 and 18.64 hours, respectively. The arithmetic mean apparent terminal t½ for LNG was 42.96 hours when OC was co-administered with multiple oral doses of MK-1439 and 37.66 hours when OC was administered alone.

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC
MK-1439, Tablet
Antiviral treatment for HIV-1 infection

CLINICAL STUDY REPORT SYNOPSIS

RESULTS (Continued):
PHARMACOKINETICS (Continued):

Statistical Comparison of Plasma Pharmacokinetics of Ethinyl Estradiol and Levonorgestrel Following the Administration of Nordette®-28 Alone and Nordette®-28 + MK-1439 in Healthy Adult Female Subjects

	Nordette®-28 Alone (Reference)			Nordette®-28 + MK-1439 (Test)			Nordette®-28 + MK-1439/ Nordette®-28 Alone		
Ethinyl Estradiol Pharmacokinetic Parameter	**N**	**GM**	**95% CI**	**N**	**GM**	**95% CI**	**GMR**	**90% CI**	**Pseudo Within Subject %CV‡**
AUC0-∞† (pg•hr/mL)	20	845.66	(758.43, 942.92)	19	832.32	(750.20, 923.43)	0.98	(0.94, 1.03)	7.916
AUC0-last† (pg•hr/mL)	20	804.58	(718.50, 900.97)	19	790.22	(708.49, 881.38)	0.98	(0.94, 1.03)	8.440
Cmax† (pg/mL)	20	66.03	(59.09, 73.78)	19	55.12	(49.30, 61.63)	0.83	(0.80, 0.87)	8.255
Tmax‖ (hr)	20	1.50	(1.00, 2.00)	19	1.50	(1.00, 3.00)			
Apparent terminal t½§ (hr)	20	18.64	17.47	19	18.75	16.61			
Levonorgestrel Pharmacokinetic Parameter	**N**	**GM**	**95% CI**	**N**	**GM**	**95% CI**	**GMR**	**90% CI**	**Pseudo Within Subject %CV‡**
AUC0-∞† (ng•hr/mL)	20	37.72	(30.77, 46.23)	19	45.59	(36.39, 57.12)	1.21	(1.14, 1.28)	10.099
AUC0-last† (ng•hr/mL)	20	31.52	(25.35, 39.18)	19	36.32	(28.64, 46.05)	1.15	(1.10, 1.21)	7.991
Cmax† (ng/mL)	20	2.57	(2.13, 3.09)	19	2.47	(2.02, 3.01)	0.96	(0.88, 1.05)	15.792
Tmax‖ (hr)	20	1.27	(1.01, 4.05)	19	1.51	(0.51, 6.00)			
Apparent terminal t½§ (hr)	20	37.66	31.16	19	42.96	34.34			

Nordette®-28 Alone: Single oral dose of 0.03 mg EE/0.15 mg LNG (1 x 0.03 mg/0.15 mg tablet) on Day 1 (Period 1) following an overnight fast (Reference)
Nordette®-28 + MK-1439: 100 mg MK-1439 (1 x 100 mg tablet) qd for 17 days and a single oral dose of 0.03 mg EE/0.15 mg LNG (1 x 0.03 mg/0.15 mg tablet) on Day 14 (Period 2) following an overnight fast (Test)
†Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.
‡Pseudo Within-Subject %CV = $100*\mathrm{Sqrt}((\sigma_A^2 + \sigma_B^2 - 2\sigma_{AB})/2)$, where σ_A^2 and σ_B^2 are the estimated variances on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
‖Median (min, max) reported for Tmax.
§Geometric mean and percent geometric coefficient of variation (GCV), reported for apparent terminal t½. The GCV is calculated in the natural log-scale with the equation: $100 \times \mathrm{sqrt}(\exp(s^2) - 1)$, where s^2 is the observed variance on the natural log-scale.
GM = Geometric least-squares mean; GMR = Geometric least-squares mean ratio; CI = Confidence interval
Subject AN 0006 was discontinued prior to receiving Treatment B (Nordette®-28 + MK-1439) and is not included in the pharmacokinetic and statistical analysis for Period 2.

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC
MK-1439, Tablet
Antiviral treatment for HIV-1 infection

CLINICAL STUDY REPORT SYNOPSIS

RESULTS (Continued):

SAFETY:

The concomitant administration of multiple oral doses of 100 mg MK-1439 with a single oral dose of OC (Nordette®-28; 0.03 mg EE/0.15 mg LNG) was generally safe and well-tolerated by the healthy female subjects in this study. No deaths, serious clinical or serious laboratory adverse events, events of clinical interest, or pregnancies were reported during the study. Overall, 12 (60%) subjects reported a total of 27 postdose clinical adverse events and 1 subject (5%) reported 1 postdose laboratory adverse event. Three (3, 15%) subjects overall reported a single drug-related clinical adverse event of mild intensity including nervousness (related to Nordette®-28 + MK-1439), oral herpes (related to MK-1439 only), and erythematous rash (related to MK-1439 only). One (1, 5%) subject experienced a laboratory clinical adverse (red blood cells in urine) experience of mild intensity considered related to Nordette®-28 with MK-1439. All adverse events were transient in duration and resolved. One (1) subject was discontinued from the study by the Investigator due to the clinical adverse event of increased blood pressure prior to Day 4 in Period 2 (during administration of MK-1439 alone, prior to Nordette®-28 administration) that was of mild intensity and considered not related to MK-1439 or Nordette®-28. There were no consistent treatment-related differences in laboratory, vital signs, or ECG safety parameters.

CONCLUSIONS:

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.

SPONSOR:	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.	
COMPOUND NAME:	MK-1439	
INDICATION:	Human immunodeficiency virus type 1 (HIV-1)	
PROTOCOL TITLE:	A 2-way Steady State Interaction Study of MK-1439 and Dolutegravir	
TRIAL IDENTIFIERS:	Protocol Number:	016
	Clinical Phase:	1
	IND number:	112,796
TRIAL CENTERS:	[redacted]	
DESIGN:	The trial was an open-label, 3-period, fixed sequence trial designed to evaluate the steady state pharmacokinetics, safety, and tolerability of a 7-day once daily dosing of MK-1439 alone and with co-administered dolutegravir in healthy male and female subjects. This trial was conducted in conformance with Good Clinical Practices (GCP). Twelve (12) subjects participated in 3 treatment periods to complete with 10 evaluable subjects.	
	Planned duration: Planned duration of run-in phase: Planned duration of extension phase:	Approximately 4 weeks Not applicable Not applicable
OBJECTIVES	**Primary:** 1) To assess the effect of MK-1439 at steady state on the plasma pharmacokinetics (area under the consentration-time curve over the dosing interval at steady state [AUC0-24hr], maximum concentration [Cmax], time corresponding to occurrence of Cmax [Tmax], concentration at 24 hours post-dose [C24hr]) of dolutegravir when co-administered to steady state. 2) To assess the effect of dolutegravir at steady state on the plasma pharmacokinetics (AUC0-24hr, Cmax, Tmax, C24hr) of MK-1439 when co-administered to steady state. **Secondary:** 1) To assess the safety and tolerability of MK-1439 and dolutegravir when co-administered to steady state.	

HYPOTHESES	**Primary:** 1) The steady state plasma C24hr of dolutegravir is not substantially altered by the co-administration of MK-1439. That is, the true geometric mean ratio (GMR) (dolutegravir + MK-1439)/dolutegravir alone for C24hr of dolutegravir is greater than 0.25. 2) The steady state plasma AUC0-24hr and C24hr of MK-1439 are not substantially altered by the co-administration of dolutegravir. That is, the true GMR (MK-1439 + dolutegravir)/MK-1439 alone for AUC0-24hr of MK-1439 is less than 2.0 and the true GMR (MK-1439 + dolutegravir)/MK-1439 alone for C24hr of MK-1439 is greater than 0.5.
Treatment periods	**Treatment (N = 12)**
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

Product Name	Product Potency	Dosage Form	Lot-No.
MK-1439	100 mg	Tablet	[redacted]
Dolutegravir	50 mg	Tablet	[redacted]

Endpoints and definitions	**Primary endpoints:** Pharmacokinetic: Primary pharmacokinetic endpoints included AUC0-24hr, Cmax, Tmax and C24hr for both MK-1439 and dolutegravir. Safety: Primary safety endpoints included all types of adverse events (AEs), in addition to laboratory safety tests, electrocardiograms (ECGs) and vital signs.
Database lock	[redacted]-20[redacted] Trial status [redacted]-20[redacted] to [redacted]-20[redacted]
RESULTS AND ANALYSIS:	

Subject Baseline Characteristics (All-Subjects-As-Treated Population)

Statistic	Gender	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)
n		12	12	12	12
Mean (SD)		32.5 (5.76)	169.6 (12.75)	81.53 (14.755)	28.15 (2.663)
Range (min - max)		23 - 42	147 - 189	51.9 – 99.5	21.6 – 31.8
Female	6 (50%)				
Male	6 (50%)				

BMI = body mass index; max = maximum; min = minimum; SD = standard deviation

Subject Disposition (All-Subjects-As-Treated Population)	
	Overall N = 12
Enrolled	12 (100.0%)
Completed	11 (91.7%)
Discontinued	1 (8.3%)
Other*	1 (8.3%)
All-Subjects-As-Treated Population	12 (100.0%)
Per-Protocol Population	11 (91.7%)

* Subject AN0005 permanently discontinued at the Principal Investigator's discretion as a result of a positive cotinine test at admission to Period 2
NOTE: All available pharmacokinetic data was used for the statistical assessment of the pharmacokinetic hypotheses.

Analysis description	**Primary Analysis** The pharmacokinetic parameters (AUC0-24hr, Cmax, and C24hr) for dolutegravir and MK-1439 were natural log-transformed prior to analysis and evaluated separately using a linear mixed effects model with fixed effects terms for treatment. An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlation between the treatment measurements within each subject via the REPEATED statement in SAS PROC MIXED. Kenward and Roger's method was used to calculate the denominator degrees of freedom for the fixed effects (DDFM = KR). Hypothesis 1 was addressed by comparing dolutegravir C24hr from administration of dolutegravir + MK-1439 to those obtained from administration of dolutegravir alone. A two-sided 90% confidence interval (CI) for the true mean difference (dolutegravir + MK-1439 minus dolutegravir alone) for dolutegravir C24hr on the log scale was computed from the above linear-mixed effect model. The 90% CI was then exponentiated to obtain the 90% CI for the true GMR (dolutegravir + MK-1439/dolutegravir alone) for dolutegravir C24hr. If the lower limit of the 90% CI of dolutegravir C24hr is greater than 0.25, then the primary hypothesis #1 was supported. Hypothesis 2 was addressed by comparing MK-1439 AUC0-24hr and MK-1439 C24hr from administration of dolutegravir + MK-1439 to those obtained from administration of MK-1439 alone. A two-sided 90% CI for the true mean difference (dolutegravir + MK-1439 minus MK-1439 alone) for MK-1439 AUC0-24hr and MK-1439 C24hr on the log scale was computed from the above linear-mixed effect model. The 90% CIs were exponentiated to obtain the 90% CIs for the true GMRs (dolutegravir + MK-1439/MK-1439 alone) for MK-1439 AUC0-24hr and MK-1439 C24hr. If the upper limit of the 90% CI of MK-1439 AUC0-24hr is less than 2.0, and the lower limit of the 90% CI of MK-1439 C24hr is greater than 0.5, then the primary hypothesis #2 was supported. The within-subject variability was also estimated using the square root of the residual error from the linear model.
Analysis population and time point description	The primary analysis was conducted on the Per-Protocol population, consisting of the subset of subjects who complied with the protocol sufficiently to ensure that these data likely exhibited the effects of treatment, according to the underlying scientific model.

Summary	**Hypothesis 1:** For dolutegravir pharmacokinetic parameters, the GMRs for AUC0-24hr, C24hr and Cmax were 1.36, 1.27 and 1.43, respectively, with corresponding 90% CIs of [1.15, 1.62], [1.06, 1.53], and [1.20, 1.71]. The results support the hypothesis that the steady state plasma C24hr of dolutegravir is not substantially altered by the co-administration of MK-1439, as the 90% CI for the true GMR (dolutegravir + MK-1439)/dolutegravir alone) for C24hr of dolutegravir lies completely above 0.25. The median Tmax was identical for dolutegravir administered with MK-1439 (1.50 hours) compared with dolutegravir administered alone (1.50 hours). **Hypothesis 2:** For MK-1439 pharmacokinetic parameters, the GMRs for AUC0-24hr, C24hr and Cmax were 1.00, 0.98 and 1.06, respectively, with corresponding 90% CIs of [0.89, 1.12], [0.88, 1.09], and [0.88, 1.28]. The results support the hypothesis that steady state plasma AUC0-24hr and C24hr of MK-1439 are not substantially altered by the co-administration of dolutegravir, as the 90% CI for the true GMR (MK-1439 + dolutegravir)/MK-1439 alone for AUC0-24hr of MK-1439 lies completely below 2.0 and the 90% CI for the true GMR (MK-1439 + dolutegravir)/MK-1439 alone for C24hr of MK-1439 lies completely above 0.5. The median Tmax for MK-1439 with and without co-administration of dolutegravir were comparable at 1.50 hours (MK-1439 alone) and 2.00 hours (MK-1439 + dolutegravir).
Analysis description	**Secondary Analysis** Adverse events and concomitant medication were captured throughout the trial. Laboratory parameters (clinical chemistry, hematology, and urinalysis), vital signs (blood pressure [BP], heart rate [HR] etc.) and ECGs were assessed at designated time points during the trial.
Analysis population and time point description	The secondary analysis was conducted on the All-Subjects-As-Treated population, consisting of all subjects who received at least one dose of the investigational product.

Summary	Eleven (11) of the 12 enrolled subjects were dosed as per protocol. Subject AN0005 received 50 mg dolutegravir once daily for 7 days in Period 1 before being permanently discontinued at Principal Investigator discretion due to a positive cotinine test at admission to Period 2. Healthy male and female subjects between the ages of 23 and 42 (inclusive) years tolerated 7-day multiple dosing of MK-1439 alone and in combination with 7-day multiple dosing of dolutegravir during the trial well. No deaths, other serious clinical or laboratory AEs, events of clinical interest, or pregnancies were reported and no subjects were discontinued from the trial due to safety reasons. In total, 5 AEs were reported by 4 subjects. None of these events were considered related to the investigational product. All reported AEs were considered mild in intensity. Apart from two subjects (AN0008 and AN0010) who experienced constipation, all other reported AEs (myalgia, musculoskeletal stiffness, and follicular conjunctivitis) were isolated events occurring in individual subjects. Some laboratory, vital sign and ECG assessments fell outside the normal range, however, none were considered of clinical significance and no meaningful relationship to treatment was identified.

Statistical Summary of Dolutegravir Pharmacokinetics Following Multiple Dose Administration with and without MK-1439

	Dolutegravir alone			Dolutegravir + MK-1439			Dolutegravir + MK-1439/Dolutegravir alone		Pseudo Within Subject
Parameter	**N[1]**	**GM**	**95% CI**	**N[1]**	**GM**	**95% CI**	**GMR**	**90% CI**	**CV (%)[2]**
AUC0-24hr (h·ng/mL)	12	42900	(37000, 49600)	11	58500	(48600, 70500)	1.36	(1.15, 1.62)	22.0
C24h (ng/mL)	12	1010	(844, 1220)	11	1290	(1010, 1650)	1.27	(1.06, 1.53)	23.7
Cmax (ng/mL)	12	3070	(2590, 3640)	11	4400	(3810, 5070)	1.43	(1.20, 1.71)	23.9
Tmax (h)[3]	12	1.50	(0.50, 3.02)	11	1.50	(1.00, 3.00)			

Period 1 - 50 mg dolutegravir QD for 7 days, Period 2 - 200 mg MK-1439 QD for 7 days, Period 3 - 50 mg dolutegravir and 200 mg MK-1439 QD for 7 days
Linear mixed effects model with fixed effects terms for treatment was utilized.
An unstructed variance-covariance matrix was assumed for the mixed model analysis.
Geometric means (GM), ratio of geometric means (GMR), and their confidence intervals (CI) are shown on the original scale of measurement.
[1] 'N' represents the number of subjects exposed to each treatment.
[2] Pseudo Within-Subject coefficient of variation (CV) was calculated as 100*sqrt[(sA2 + sC2 - 2sAC)/2], where sA2 and sC2 are the estimated variances on the log scale for the two treatments, and sAC is the corresponding estimated covariance.
[3] Reports the median value, minimum and maximum.

Statistical Summary of MK-1439 Pharmacokinetics Following Multiple Dose Administration with and without Dolutegravir

Parameter	MK-1439 alone			Dolutegravir + MK-1439			Dolutegravir + MK-1439/MK-1439 alone		Pseudo Within Subject CV (%)[2]
	N[1]	GM	95% CI	N[1]	GM	95% CI	GMR	90% CI	
AUC0-24hr (nM·h)	11	47600	(40100, 56400)	11	47600	(39700, 57100)	1.00	(0.89, 1.12)	14.4
C24h (nM)	11	993	(797, 1240)	11	975	(753, 1260)	0.98	(0.88, 1.09)	14.1
Cmax (nM)	11	3540	(2900, 4330)	11	3760	(3080, 4590)	1.06	(0.88, 1.28)	24.5
Tmax (h)[3]	11	1.50	(0.52, 3.02)	11	2.00	(0.50, 3.00)			

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 and 200 mg MK-1439 once daily for 7 days
Linear mixed effects model with fixed effects terms for treatment was utilized.
An unstructured variance-covariance matrix was assumed for the mixed model analysis.
Geometric means (GM), ratio of geometric means (GMR), and their confidence intervals (CI) are shown on the original scale of measurement.
[1] 'N' represents the number of subjects exposed to each treatment.
[2] Pseudo Within-Subject coefficient of variation (CV) was calculated as 100*sqrt[(sA2 + sC2 - 2sAC)/2], where sA2 and sC2 are the estimated variances on the log scale for the two treatments, and sAC is the corresponding estimated covariance.
[3] Reports the median value, minimum and maximum.

Summary of Adverse Events (All-Subjects-As-Treated Population)

	Period 1	Period 2	Period 3
	50 mg dolutegravir (N = 12) n (%) E	200 mg MK-1439 (N = 11) n (%) E	50 mg dolutegravir + 200 mg MK-1439 (N = 11) n (%) E
All Adverse Events	2 (16.7%) 2	1 (9.1%) 2	1 (9.1%) 1
Related Adverse Events	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0
Mild Adverse Events	2 (16.7%) 2	1 (9.1%) 2	1 (9.1%) 1
Moderate Adverse Events	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0
Severe Adverse Events	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0
Life Threatening or Disabling Adverse events	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0
Deaths	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0
Other Serious Adverse Events	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0
Adverse Events Leading to Discontinuation	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0

N = Number of subjects exposed; n = number of subjects with treatment-emergent adverse events;
E = number of adverse events

CONCLUSIONS:	1. The steady state C24hr of dolutegravir is not decreased by co-administration with multiple doses of MK-1439; AUC0-24hr, Cmax and C24hr increased ~36, 43, and 27%, respectively. 2. Steady state AUC0-24hr and C24hr of MK-1439 are not altered by co-administration with multiple doses of dolutegravir. 3. Multiple dosing (once daily for 7 days) of MK-1439 alone and in combination with multiple dosing (once daily for 7 days) of dolutegravir was generally well tolerated during the trial.
PUBLICATION(S):	None
REPORT DATE:	[redacted]-20[redacted]

SPONSOR:	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.	
COMPOUND NAME:	MK-1439, Tablet	
INDICATION:	Antiviral treatment for HIV-1 infection	
PROTOCOL TITLE:	An Open-label, Multiple-Dose Study to Investigate the Effect of Switching From Efavirenz Therapy to MK-1439 on the Pharmacokinetics of MK-1439	
TRIAL IDENTIFIERS:	Protocol Number:	MK-1439-020
	Clinical Phase:	1
TRIAL CENTER:	[redacted], MD [redacted] USA	
DESIGN:	**STUDY DESIGN:** This was an open-label, 3-period, fixed-sequence, multiple-dose study to investigate the effect of switching from efavirenz therapy to MK-1439 on the pharmacokinetics of MK-1439. Twenty (20) healthy male and female subjects were enrolled. In Period 1, subjects received multiple oral doses of 100 mg MK-1439 once daily (QD) from Days 1 to 5. In Period 2, subjects received multiple oral doses of 600 mg efavirenz QD from Days 1 to 14. In Period 3, subjects received multiple oral doses of 100 mg MK-1439 QD from Days 1 to 14. There was a 7-day washout between the last dose of MK-1439 in Period 1 and the first dose of efavirenz in Period 2. There was no washout between Periods 2 and 3. **DIAGNOSIS/INCLUSION CRITERIA:** Adult healthy non-smoking male or female subjects (non-childbearing potential) ≥ 19 and ≤ 55 years of age, with a body mass index (BMI) ≥ 18.5 and ≤ 32.0 kg/m^2 at the screening visit, were eligible to enter the study.	
	Actual duration of main phase:	7 weeks from screening to Day 15 of Period 3 9 weeks from screening to follow-up

OBJECTIVES:	**Primary:** To evaluate the effect of efavirenz on the single dose MK-1439 pharmacokinetics (e.g., AUC0-24, Cmax, and C24) when switching from efavirenz treatment to MK-1439 treatment. **Secondary:** 1. To evaluate the effect of efavirenz on the multiple-dose pharmacokinetics of MK-1439 (AUC0-24, Cmax, and C24) when switching from efavirenz treatment to MK-1439 treatment. 2. To describe the time course of efavirenz concentrations following discontinuation of efavirenz. 3. To evaluate the safety and tolerability of MK-1439. 4. To evaluate the safety and tolerability of efavirenz.	
HYPOTHESES (ESTIMATIONS):	**Primary:** The AUC0-24, Cmax, and C24 of MK-1439 obtained on the first day of administration following cessation of efavirenz (Period 3, Day 1) will be estimated and compared to that of a single dose of MK-1439 without efavirenz pretreatment (Period 1, Day 1). **Secondary:** 1a. The AUC0-24, Cmax, and C24 of MK-1439 obtained following multiple-dose administration when initiated after cessation of efavirenz dosing (Period 3, Day 14) will be estimated and compared to that of multiple doses of MK-1439 without efavirenz pretreatment (Period 1, Day 5). 1b. C24 will be estimated for MK-1439 on Days 1 - 14 of Period 3 following cessation of efavirenz. 2. In Period 3, efavirenz concentrations will be estimated prior to dosing of MK-1439 on Days 1-14 and on the morning of Day 15 (e.g., 24 hours after the MK-1439 dose on Day 14).	
TREATMENT GROUPS:	Period 1 (Treatment A)	Subject received multiple oral doses of 100 mg MK-1439 (1 x 100 mg tablet) QD from Days 1 to 5 20 subjects
	Period 2 (Treatment B)	Subject received multiple oral doses of 600 mg efavirenz (1 x 600 mg tablet) QD from Days 1 to 14. 19 subjects

TREATMENT GROUPS (Continued):	Period 3 (Treatment C)	Subject received multiple oral doses of 100 mg MK-1439 (1 x 100 mg tablet) QD from Days 1 to 14. 17 subjects

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

Clinical Supplies Dispensed to Subjects

Bulk Product Description	**Manufacturing Lot Number**
Tablet MK-1439 100 mg Tablet Sustiva® (efavirenz) 600 mg	[redacted]
Sustiva® (efavirenz) 600 mg (lot number [redacted]; expiration date [redacted]-20[redacted]; Bristol-Myers Squibb) was supplied by the Investigator.	

ENDPOINTS AND DEFINITIONS:	**Primary Endpoints**	**Pharmacokinetics** Blood samples for the determination of single-dose (Day 1) plasma MK-1439 pharmacokinetics were collected from each subject at predose and selected time points over 24 hours postdose on Day 1 of Period 1, and at predose and selected time points over 24 hours postdose on Day 1 of Period 3. Plasma MK-1439 concentrations were summarized on Day 1 of Periods 1 and 3, using the following pharmacokinetic parameters: AUC0-24, Cmax, C24, and Tmax. The primary pharmacokinetic endpoints included AUC0-24, Cmax, and C24 for single-dose MK-1439 with or without efavirenz pretreatment.

ENDPOINTS AND DEFINITIONS (Continued):	**Secondary Endpoints:**	**Pharmacokinetics** Blood samples for the determination of multiple-dose plasma MK-1439 pharmacokinetics were collected from each subject at predose on Days 1 - 5 and selected time points over 24 hours postdose on Day 5 of Period 1. In Period 3, blood samples were collected at predose (prior to MK-1439 administration) on Days 1 – 14, at 24 hours post Day 14 dose (Day 15), and at selected time points over 24 hours postdose on Day 14. Plasma MK-1439 concentrations were summarized on Day 5 of Period 1 and Day 14 of Period 3 using the following pharmacokinetic parameters: AUC0-24, Cmax, C24, and Tmax. The secondary pharmacokinetic endpoints included AUC0-24, Cmax, and C24 for multiple-dose MK-1439 administered with or without efavirenz pretreatment. Blood samples for the determination of plasma efavirenz concentrations were collected from each subject at predose on Day 1 of Period 2 and at predose (prior to MK-1439 administration) on Days 1 - 14 of Period 3 and 24 hours post Day 14 dose (Day 15) of MK-1439 in Period 3. Plasma efavirenz concentrations were summarized as the pharmacokinetic parameter Cefv, to evaluate the time course of efavirenz plasma concentrations following efavirenz discontinuation. A blood sample for determination of CYP2B6 genotype was collected at predose on Day 1 of Period 1. Additionally, a blood sample for future biomedical research was collected at predose on Day 1 of Period 1 and archived.
	Secondary Endpoints	**Safety** The safety and tolerability of MK-1439 and efavirenz 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 experiences throughout the study.
DATABASE LOCK:	[redacted]-20[redacted]	**TRIAL STATUS:** [redacted]-20[redacted] to [redacted]-20[redacted]

RESULTS AND ANALYSIS:	All analyses for pharmacokinetics and safety were performed according to the protocol. The following 3 deviations occurred which were deemed not to have a clinically significant impact on the results of the study: • According to the protocol [16.1.1], in Period 3 (Treatment C), subjects were to receive 100 mg MK-1439 (1 x 100 mg tablet) at Hour 0 on the morning of Day 1, following an overnight fast, and 100 mg MK-1439 (1 x 100 mg tablet) administered every 24 hours for 13 more days (within +/- 1 hour of dosing time on Day 1). On Day 7 of Period 3, Subject AN 0018 dosed 1 hour, 59 minutes, 53 seconds late, a deviation of 59 minutes, 53 seconds outside of the allowed +/- 1 hour window. • According to the protocol [16.1.1], blood samples for the determination of MK-1439 and efavirenz were to be collected from all subjects and processed according to Appendices 4 and 5 of the protocol [16.1.1], respectively, at scheduled time points as delineated in Tables 9-1 and 9-2. For 1 subject, the 1.5-hour sample collected for MK-1439 pharmacokinetics on Day 5 of Period 1 could not be identified during sample reconciliation and was considered missing due to a blood processing error. • On Day 15 of Period 3, the 336-hour samples collected for efavirenz assay for 2 subjects were possibly switched according to the results of the pharmacokinetic analysis and deemed questionable. There were no corresponding raw data to verify sample identity. The plasma efavirenz Cefv analyses were performed with and without these samples and yielded similar results. Additional minor protocol deviations occurred but were deemed not to have a clinically significant impact on the results of the study.

SUBJECT DISPOSITION:	ENTERED: Total	20
	Male N (age range)	17 (21 to 53 yr)
	Female N (age range)	3 (43 to 53 yr)
	COMPLETED:	17
	DISCONTINUED: Total	3
	Adverse experience	2[†]
	Other	1[††]
	[†]Two (2) subjects were discontinued by the Sponsor due to adverse events (papular rash and maculo-papular rash). [††]One (1) subject withdrew for personal reasons.	

ANALYSIS DECSRIPTION:	**Pharmacokinetics** Analysis of Variance, Ratios, and Confidence Intervals Primary Estimation: The pharmacokinetics of MK-1439 (AUC0-24, Cmax, and C24) on the first day of administration following cessation of efavirenz dosing (Day 1 of Period 3), and following a single dose of MK-1439 without efavirenz pretreatment (Day 1 of Period 1), were natural log (ln)-transformed prior to analysis and analyzed with a linear mixed-effects model with a fixed-effect term for treatment period. An unstructured covariance matrix was used to allow for unequal treatment period variances and to model the correlation between different treatment period 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. Back-transformed summary statistics and inferential results were reported for pharmacokinetic parameter values. The 90% confidence intervals (CIs), based on the t-distribution, were generated from the above mixed-effects model for the geometric least-squares means ratios (GMRs) (Day 1 of Period 3/Day 1 of Period 1) for MK-1439 Cmax, AUC0-24, and C24. Ninety-five percent (95%) CIs were also generated from the above mixed-effects model for the geometric least-squares means (GMs) by treatment period for MK-1439 Cmax, AUC0-24, and C24. Secondary Estimations: The pharmacokinetics of multiple doses of MK-1439 (Cmax, AUC0-24, and C24) when initiated after cessation of efavirenz dosing (Day 14 of Period 3) and following multiple doses of MK-1439 without efavirenz pretreatment (Day 5 of Period 1) were ln-transformed prior to analysis and analyzed with the same linear mixed-effects model as described above. The 90% CIs, based on the t-distribution, were generated from the above mixed-effects model for the GMRs (Day 14 of Period 3/Day 5 of Period 1) for MK-1439 Cmax, AUC0-24, and C24. Ninety-five percent (95%) CIs were also generated from the above mixed-effects model for the GMs by treatment period for MK-1439 Cmax, AUC0-24, and C24. C24 of MK-1439 on Days 1 - 14 of Period 3 was ln-transformed and analyzed based on a linear mixed-effects model with day as a categorical fixed effect and subject as a random effect. A two-sided 90% CI from Days 1 - 14 of Period 3 for the GM of C24 was constructed. In Period 3, Cefv prior to MK-1439 dosing on Days 1 - 14 and on the morning of Day 15 (i.e., 24 hours after the MK-1439 dose on Day 14) were analyzed in a similar fashion as MK-1439 C24 mentioned directly above. The analysis was done with and without slow metabolizers (CYP2B6*6/*6), with the primary analysis excluding slow metabolizers.

ANALYSIS POPULATION AND TIME POINT DESCRIPTION:	*Per-Protocol* – This population consisted of the subset of 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. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of major protocol violations. This population was used for the pharmacokinetic analyses. All 20 subjects completed dosing of 100 mg MK-1439 on Day 1 of Period 1 and were included in the analysis of the single-dose pharmacokinetics of MK-1439 preceding efavirenz pretreatment. Nineteen (19) subjects completed dosing of 100 mg MK-1439 QD on Days 2 - 5 of Period 1 and were included in the analysis of the multiple-dose pharmacokinetics of MK-1439 preceding efavirenz pretreatment. Seventeen (17) subjects completed dosing of 100 mg MK-1439 on Day 1 of Period 3 and were included in the analysis of the single-dose pharmacokinetics of MK-1439 following efavirenz pretreatment. Seventeen (17) subjects completed dosing of 100 mg MK-1439 QD on Days 2 to 14 of Period 3 and were included in the analysis of the multiple-dose pharmacokinetics of MK-1439 following efavirenz pretreatment, and in the analysis of C24 on Days 1 - 14 of Period 3. Seventeen (17) subjects completed dosing of 600 mg efavirenz QD for 14 days in Period 2. However, since 1 subject was determined to be a slow metabolizer (CYP2B6*6/*6) and since Cefv values for 2 subjects in Period 3 were questionable, 14 subjects were included in the primary analysis of Cefv. Secondary Cefv analyses were performed including the slow metabolizer but excluding the questionable Cefv values for the 2 subjects (N = 15) and also excluding the slow metabolizer but including the questionable Cefv values (N = 16).
SUMMARY:	**Pharmacokinetics:** Results of the analyses of the single-dose plasma pharmacokinetics of MK-1439 following the single-dose administration of 100 mg MK-1439 with or without pretreatment with 600 mg efavirenz QD in healthy adult subjects are summarized in the following table. The administration of a single dose of MK-1439 following efavirenz pretreatment (Day 1 of Period 3) resulted in a 62% (GMR [90% CI] of 0.38 [0.33, 0.45]), 35% (GMR [90% CI] of 0.65 [0.58, 0.73]), and 85% (GMR [90% CI] of 0.15 [0.10, 0.23]) reduction in AUC0-24, Cmax, and C24, respectively, compared to that following administration of a single dose of MK-1439 without efavirenz pretreatment (Day 1 of Period 1). The median Tmax of MK-1439 following single-dose MK-1439 post efavirenz pretreatment was 1.50 hours versus 2.00 hours following single dose MK-1439 without efavirenz pretreatment.

Statistical Comparison and Summary Statistics of MK-1439 Plasma Pharmacokinetics Following Single-Dose Administration of 100 mg MK-1439 With or Without Pretreatment of 600 mg Efavirenz QD in Healthy Adult Subjects

MK-1439 Pharmacokinetic Parameter	SD MK-1439			SD MK-1439 + Efavirenz			SD MK-1439 + Efavirenz/ SD MK-1439		Pseudo Within Subject %CV[†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC0-24[‡] (μM•hr)	20	28.0	(24.9, 31.6)	17	10.7	(9.00, 12.8)	0.38	(0.33, 0.45)	26.557
Cmax[‡] (nM)	20	2080	(1810, 2380)	17	1350	(1160, 1570)	0.65	(0.58, 0.73)	20.026
C24[‡] (nM)	20	625	(528, 740)	17	93.3	(56.5, 154)	0.15	(0.10, 0.23)	70.911
Tmax[§] (hr)	20	2.00	(1.00, 6.00)	17	1.50	(0.50, 3.04)			

SD MK-1439: A single dose of 100 mg MK-1439 (Day 1 of 100 mg MK-1439 QD for 5 days) without efavirenz pretreatment.
SD MK-1439 + Efavirenz: A single dose of 100 mg MK-1439 with efavirenz pretreatment (multiple doses of 600 mg efavirenz QD for 14 days in Period 2).
[†]Pseudo within-subject %CV = 100 x sqrt[(σ_A^2 + σ_B^2 -2 σ_{AB})/2], where σ_A^2 and σ_B^2 are the estimated variance on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for Tmax.
Note: Subject AN 0004 dropped on Day 11 of Period 2, Subject AN 0006 dropped on Day 4 of Period 1, and Subject AN 0014 dropped on Day 6 of Period 2.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

SUMMARY:	**Pharmacokinetics:** Results of the analyses of the multiple-dose plasma pharmacokinetics of MK-1439 following multiple-dose administration of 100 mg MK-1439 with or without pretreatment with 600 mg efavirenz QD in healthy adult subjects are summarized in the following table. The administration of multiple-dose MK-1439 following efavirenz pretreatment (Day 14 of Period 3) resulted in a 32% (GMR [90% CI] of 0.68 [0.58, 0.80]), 14% (GMR [90% CI] of 0.86 [0.77, 0.97]), and 50% (GMR [90% CI] of 0.50 [0.39, 0.64]) reduction in AUC0-24, Cmax, and C24, respectively, compared to that following multiple-dose MK-1439 without efavirenz pretreatment (Day 5 of Period 1). The median Tmax of MK-1439 following multiple-dose MK-1439 post efavirenz pretreatment was 1.50 hours versus 2.00 hours following multiple-dose MK-1439 without efavirenz pretreatment.

Statistical Comparison and Summary Statistics of MK-1439 Plasma Pharmacokinetics Following Multiple-Dose Administration of 100 mg MK-1439 QD to Steady State With or Without Pretreatment of 600 mg Efavirenz QD for 14 Days in Healthy Adult Subjects

MK-1439 Pharmacokinetic Parameter	MD MK-1439			MD MK-1439 + Efavirenz			MD MK-1439 + Efavirenz/MD MK-1439		Pseudo Within Subject %CV[†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC0-24[‡] (µM•hr)	19	41.1	(35.3, 47.9)	17	28.0	(23.9, 33.0)	0.68	(0.58, 0.80)	26.640
Cmax[‡] (nM)	19	2880	(2470, 3360)	17	2490	(2230, 2780)	0.86	(0.77, 0.97)	19.805
C24[‡] (nM)	19	902	(730, 1120)	17	449	(331, 610)	0.50	(0.39, 0.64)	41.040
Tmax[§] (hr)	19	2.00	(0.50, 3.00)	17	1.50	(1.00, 6.00)			

MD MK-1439: Multiple doses of 100 mg MK-1439 QD for 5 days without efavirenz pretreatment.
MD MK-1439 + Efavirenz: Multiple doses of 100 mg MK-1439 QD for 14 days with efavirenz pretreatment (multiple doses of 600 mg efavirenz QD for 14 days in Period 2).
[†]Pseudo within-subject %CV = 100 x sqrt[(σ_A^2 + σ_B^2 -2 σ_{AB})/2], where σ_A^2 and σ_B^2 are the estimated variance on the log scale for the 2 treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for Tmax.
Note: Subject AN 0004 dropped on Day 11 of Period 2, Subject AN 0006 dropped on Day 4 of Period 1, and Subject AN 0014 dropped on Day 6 of Period 2
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

SUMMARY:	**Pharmacokinetics:** Results of the analyses of the plasma C24 of MK-1439 on Days 1 - 14 of Period 3 and of Cefv, the plasma concentration of efavirenz, at predose of MK-1439 administration on Days 1 - 15 of Period 3 (excluding slow metabolizers [CYP2B6*6/*6]) during the multiple-dose administration of 100 mg MK-1439 QD with pretreatment with multiple doses of 600 mg efavirenz QD in healthy adult subjects are summarized in the following table.

Summary Statistics of MK-1439 Plasma C24 and Efavirenz Plasma Cefv During Multiple-Dose Administration of 100 mg MK-1439 QD for 14 Days With Pretreatment of 600 mg Efavirenz QD for 14 Days in Healthy Adult Subjects Excluding Subject AN 0008 Days 1 - 15 Cefv and Subjects AN 0015 and AN 0017 on Day 15

MK-1439 C24† (nM)				Cefv† (ng/mL)			
Day‡	N	GM	90% CI	Day‡	N	GM	90% CI
.				Day 1	16	3180	(1960, 5150)
Predose day 2	17	93.5	(67.4, 130)	Day 2	16	1690	(1050, 2740)
Predose day 3	17	112	(80.4, 155)	Day 3	16	1210	(744, 1950)
Predose day 4	17	119	(85.9, 165)	Day 4	16	919	(568, 1490)
Predose day 5	17	146	(105, 202)	Day 5	16	689	(425, 1120)
Predose day 6	17	170	(122, 236)	Day 6	16	542	(334, 877)
Predose day 7	17	197	(142, 274)	Day 7	16	423	(261, 685)
Predose day 8	17	243	(175, 337)	Day 8	16	352	(218, 571)
Predose day 9	17	267	(192, 370)	Day 9	16	280	(173, 453)
Predose day 10	17	328	(236, 456)	Day 10	16	223	(138, 362)
Predose day 11	17	367	(264, 509)	Day 11	16	189	(117, 307)
Predose day 12	17	424	(306, 589)	Day 12	16	161	(99.4, 261)
Predose day 13	17	485	(350, 674)	Day 13	16	144	(88.7, 233)
Predose day 14	17	475	(343, 660)	Day 14	16	113	(69.9, 183)
Predose day 15	17	449	(323, 623)	Day 15§	14	95.7	(58.8, 156)

MD MK-1439 + Efavirenz: Multiple doses of 100 mg MK-1439 QD for 14 days with efavirenz pretreatment (multiple doses of 600 mg efavirenz QD for 14 days in Period 2).
†Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.
‡Samples were taken prior to MK-1439 dosing on the day scheduled for the sample.
§Concentrations for Subjects AN 0015 (Day 15) and AN 0017 (Day 15) were not included in the Cefv analysis since the concentrations are questionable.
Efavirenz concentrations for Subject AN 0008 were not included in the Cefv analysis since this subject is a slow metabolizer (CYP2B6*6/*6).
Cefv BLQ values were set to ½ LLOQ (LLOQ = 20 ng/mL) for Subjects AN 0002 (Days 10 to 15), AN 0011 (Day 15), AN 0013 (Days 14 to 15), and AN 0020 (Days 12 to 15).
Note: Subject AN 0004 dropped on Day 11 of Period 2, Subject AN 0006 dropped on Day 4 of Period 1 and Subject N 0014 dropped on Day 6 of Period 2.
GM = Geometric least-squares mean; CI = Confidence interval.

ANALYSIS DECSRIPTION:	**Secondary Analysis - Safety** Incidence of the number of subjects with adverse experiences was descriptively summarized and listed by population. A summary of the incidence of the number of subjects with drug related adverse experiences was descriptively summarized by population. Since no meaningful changes in individual values for laboratory safety tests, ECGs, and vital signs were observed, summary statistics were not provided. Responses obtained from the Columbia-suicide severity rating scale (C-SSRS) were used to derive a category for suicidality according to the Columbia Classification Algorithm of Suicide Assessment (C-CASA). Responses to the C-SSRS were tabulated.

ANALYSIS POPULATION AND TIME POINT DESCRIPTION:	*All Subjects as Treated*: This population included all subjects who received at least one dose of the investigational drug. This population was used for assessments of safety and tolerability. All 20 subjects were included in the evaluation of safety.

SUMMARY:	The administration of MK-1439 and efavirenz was generally well tolerated in the healthy males and females in this study. No serious clinical or laboratory adverse events, pregnancies, events of clinical interest (ECIs), or deaths occurred in this study. Two (2) subjects were discontinued by the Sponsor due to adverse experiences (papular rash and maculo-papular rash) following efavirenz pretreatment in Period 2 For 1 subject, rash (papular) adverse experiences were considered related to efavirenz only and the other subject's rashes (maculo papular) were not related to the study drugs. A total of 15 subjects (75%) reported adverse experiences; 6 subjects (30.0%) following administration of MK-1439 alone, 9 subjects (47.4%) following efavirenz pretreatment, and 7 subjects (41.2%) following MK-1439 with efavirenz pretreatment. A total of 67 postdose and 2 predose adverse experiences were reported, of which 36 were considered related to study drug; 1 related to MK-1439 only, 31 related to efavirenz only, and 4 related to both MK-1439 and efavirenz. The most common drug-related adverse experiences reported in the study were headache and postural dizziness each reported by 4 (20.0%) subjects overall in the study. Drug-related headache was reported by 1 subject (5.0%) following administration of MK-1439 alone in Period 1, 3 subjects (15.8%) following efavirenz pretreatment in Period 2, and 1 subject (5.9%) following MK-1439 with efavirenz pretreatment in Period 3. Drug-related postural dizziness was reported by 4 subjects (21.1%) following efavirenz pretreatment in Period 2. All adverse experiences resolved by study completion, with the exception of weight decreased for 1 subject following administration of MK-1439 with efavirenz pretreatment. The adverse event of weight decreased was considered by the Investigator to be not related to study drugs. The Investigator deemed the adverse event of weight decreased medically stable and no further follow up was required. All adverse experiences were mild in intensity with the exception of 1 moderate headache considered related to efavirenz only. No clinically meaningful relationships were observed for changes in clinical laboratory values, vital signs, or ECG safety parameter values as a function of treatment. No suicidal ideations/behaviors were reported following treatment exposure in this study.

CONCLUSIONS:	1. Following multiple-dose efavirenz pretreatment relative to no pretreatment, single-dose MK-1439 AUC and Cmax were reduced by approximately 60% and 35%, respectively. 2. Following multiple-dose efavirenz pretreatment relative to no pretreatment, multiple-dose Day 14 AUC and Cmax were reduced by approximately 32% and 14%, respectively. 3. Following multiple-dose efavirenz pretreatment relative to no pretreatment, MK-1439 C24 was initially reduced by ~85% after a single dose, and gradually recovered, but was still reduced by ~50% after 14 days of MK-1439 dosing. 4. Efavirenz concentrations decreased steadily following cessation of dosing but remained detectable in all subjects for 9 days following cessation of therapy. 5. The administration of MK-1439 and efavirenz is generally well tolerated in healthy males and females.
REPORT DATE:	Final: [redacted]-20[redacted]

[redacted] – Version 3 Study Report
MK-1439 and Rifabutin Pharmacokinetic Drug Interaction Study
[redacted] Study Number: 20[redacted]-3732
Protocol Number: MK-1439-035-02
IND 112, 796

Title of Study:
A Study to Evaluate the Effect of Multiple Doses of Rifabutin on the Single-Dose Pharmacokinetics of Doravirine (MK-1439) in Healthy Subjects

Investigators:
[redacted] MD
[redacted] NP
[redacted] MD
[redacted] FNP
[redacted] MD
[redacted] ANP
[redacted] ACNP

Study Centre(s):

Clinical Facility:
[redacted] USA,

Clinical Laboratory Facility:
[redacted] USA,

[redacted] USA,

Bioanalytical Facility:
[redacted]
The Netherlands

Pharmacokinetic and Statistical Facility:
[redacted] Canada,

Report Issuing Facility:
[redacted] Canada,

[redacted] – Version 3 Study Report
MK-1439 and Rifabutin Pharmacokinetic Drug Interaction Study
[redacted] Study Number: 20[redacted]-3732
Protocol Number: MK-1439-035-02
IND 112, 796

Phase of Development: Phase 1

Study Periods:

Group 1 (Subjects 0001-0014)
- Period 1: [redacted], 20[redacted]
- Period 2: [redacted] 20[redacted]

Group 2 (Subjects 0015-0018)
- Period 1: [redacted], 20[redacted]
- Period 2: [redacted], 20[redacted]

Objective:

Primary Objective:

To evaluate the effect of multiple doses of rifabutin on the single-dose doravirine PK (C_{max}, $AUC_{0\text{-}inf}$, C_{24}) in healthy subjects.

Secondary Objective:

The secondary objective of this study was to evaluate the safety and tolerability of doravirine with and without rifabutin in healthy subjects.

Hypothesis:

Primary Objective Hypothesis:

The effect of multiple doses of rifabutin on the single-dose doravirine PK (C_{max}, $AUC_{0\text{-}inf}$, and C_{24}) will be estimated.

Methodology:

- This was an open-label, single- and multiple-dose, two-period, two-treatment, fixed-sequence, PK drug interaction study.
- This study was designed to evaluate the effect of multiple doses of rifabutin on the single-dose PK of doravirine in healthy male and female subjects.
- Concentrations of doravirine were measured from plasma samples collected over a 72-hour interval after dosing in each period.
- The values of the following PK parameters for doravirine were estimated using a non-compartmental approach:
    - C_{max}, C_{24}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, T_{max}, K_{el}, $t_{1/2}$, CL/F, and V_d/F

Number of subjects:

- Planned for inclusion: 18 subjects enrolled
- Total number of subjects that completed the study: 12 subjects (9 in Group 1 and 3 in Group 2)
- Included in the safety data analyses: 18 subjects
- Included in the PK data analyses: 18 subjects
- Included in the statistical data analyses: 18 subjects
- 18 subjects completed Period 1 and 12 subjects completed Period 2.

[redacted] – Version 3 Study Report
MK-1439 and Rifabutin Pharmacokinetic Drug Interaction Study
[redacted] Study Number: 20[redacted]-3732
Protocol Number: MK-1439-035-02
IND 112, 796

Main criteria for inclusion:
The study population included 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.

Drug Product 1 (Treatment A and Part of Treatment B):
Doravirine (MK-1439) 100 mg Tablets (Merck Sharp & Dohme Corp., USA)
Lot No.: [redacted]
Potency: 98.9% of label claim
Dose: 100 mg
Mode of Administration: Oral

Drug Product 2 (Part of Treatment B):
Mycobutin® (rifabutin) 150 mg Capsules, USP (Pharmacia & Upjohn Co., Division of Pfizer Inc., USA)
Lot No.: [redacted]
Expiry Date: [redacted]/20[redacted]
Dose: 150 mg
Mode of Administration: Oral

Treatments:

Treatment A (Period 1)
- Drug Product 1: 100 mg doravirine (one tablet)

Treatment B (Period 2)
- Drug Product 2: 300 mg rifabutin (2 capsules) once daily for 16 days
- Drug Product 1: 100 mg doravirine (one tablet) administered once on Day 14

Duration of treatment:
Doravirine: 100 mg (one tablet) on Day 1 of Period 1 and Day 14 of Period 2
Rifabutin : 300 mg (2 capsules) once daily from Days 1 to 16 in Period 2

[redacted] – Version 3 Study Report
MK-1439 and Rifabutin Pharmacokinetic Drug Interaction Study
[redacted] Study Number: 20[redacted]-3732
Protocol Number: MK-1439-035-02
IND 112, 796

Safety Results:

Doravirine administered alone and in combination with rifabutin was generally well tolerated. There were no deaths or serious adverse events (SAEs) reported. Overall, there were 70 adverse events (AEs) involving 17 subjects in this study; 3 (16.7%) subjects experienced an AE in Period 1 (doravirine alone) and 16 (94.1%) subjects experienced an AE in Period 2 (doravirine + rifabutin). The majority of AEs were mild. On the morning of his post-study procedures, Subject 0004 experienced presyncope which was severe in intensity and considered not related to treatment. The AE resolved by the end of the study. In Period 1, none of the AEs were considered treatment related. In Period 2, 14 subjects experienced AEs that were considered related to treatment; the majority (41 of 65 AEs reported) of which occurred prior to administration of doravirine (Day 14) and were considered related to rifabutin only. Sixteen (16) AEs occurred after doravirine dosing. Twelve (12) (75%) were judged related to both doravirine and rifabutin administration, while 4 (25%) of these AEs were judged as not related to either doravirine or rifabutin administration. All AEs resolved by the end of the study.
No more than one subject experienced any specific AE in Period 1, while the most common AEs experienced in Period 2 were back pain (3 subjects), chills (3 subjects), chromaturia (6 subjects), headache (8 subjects), lymphopenia (3 subjects), pyrexia (7 subjects), and tachycardia (2 subjects).

Five (5) subjects were discontinued from the study due to AEs:

- Subject 0002 was discontinued from the study in Period 2 due to AEs of fever and lymphopenia (last dosed on Day 10 – both AEs judged as related to rifabutin);
- Subject 0003 was discontinued from the study in Period 2 due to AEs of fever and lymphopenia (last dosed on Day 10 – both AEs judged as related to rifabutin);
- Subject 0007 was discontinued from the study in Period 2 due to a fever (last dosed on Day 6 – AE judged as related to rifabutin);
- Subject 0010 was discontinued from the study in Period 2 due to AEs of chills, lower back pain, and fever (last dosed on Day 3 – chills and fever judged as related and back pain judged as not related to rifabutin);
- Subject 0017 was discontinued from the study during Period 2 due to a fever and lymphopenia (last dosed on Day 3 – AE judged as related to rifabutin).

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

There were no clinically meaningful trends for abnormalities in clinical safety laboratories, ECGs, and vital signs.

[redacted] – Version 3 Study Report
MK-1439 and Rifabutin Pharmacokinetic Drug Interaction Study
[redacted] Study Number: 20[redacted]-3732
Protocol Number: MK-1439-035-02
IND 112, 796

Statistical Methods:
The PK values of C_{max}, $AUC_{0\text{-}inf}$, and C_{24} for doravirine were natural log-transformed prior to analysis and evaluated separately using a linear mixed effects model with fixed effects term for treatment. An unstructured covariance matrix was used to allow for unequal treatment variances and to model correlation between the treatments measured 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).

A two-sided 90% confidence interval (CI) for the true mean difference (rifabutin + doravirine minus doravirine alone) for doravirine $AUC_{0\text{-}inf}$, C_{max}, and C_{24} on the log scale was computed from the above linear-mixed effect model. The 90% CIs were then exponentiated to obtain the 90% CIs for the true GMRs (rifabutin + doravirine / doravirine alone) for doravirine $AUC_{0\text{-}inf}$, C_{max}, and C_{24}. Ninety-five percent (95%) CIs were generated from the above mixed-effect model for the geometric means (GMs) by treatment for doravirine $AUC_{0\text{-}inf}$, C_{max}, and C_{24}. Plots with the individual ratios, GMRs and 90% CIs were provided for doravirine $AUC_{0\text{-}inf}$, C_{max}, and C_{24}. $AUC_{0\text{-}last}$ was analyzed in a similar fashion as above.

[redacted] – Version 3 Study Report
MK-1439 and Rifabutin Pharmacokinetic Drug Interaction Study
[redacted] Study Number: 20[redacted]-3732
Protocol Number: MK-1439-035-02
IND 112, 796

Results:

Pharmacokinetic Results:

Summary Statistics for Plasma MK-1439 Pharmacokinetics Following Single Oral Dose Administration of 100 mg MK-1439 Alone or Co-administered with 300 mg rifabutin administered QD for 14 days in Healthy Male and Female Subjects

	MK-1439 100 mg + rifabutin 300 mg QD			*MK-1439 100 mg*			*MK-1439 100 mg + rifabutin 300 mg QD / MK-1439 100 mg*		
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	19.7	(17.7 , 21.8)	18	39.5	(34.3 , 45.5)	0.50	(0.45 , 0.55)	16.0
$AUC_{0\text{-}last}$ (hr·µM)†	12	19.5	(17.5 , 21.7)	18	37.5	(32.8 , 42.8)	0.52	(0.47 , 0.58)	15.6
C_{max} (nM)†	12	1730	(1470 , 2030)	18	1740	(1560 , 1950)	0.99	(0.85 , 1.15)	21.8
C_{24} (nM)†	12	197	(169 , 230)	18	625	(530 , 737)	0.32	(0.28 , 0.35)	14.6
T_{max} (hr)*	12	2.50	(0.50 , 4.00)	18	3.00	(1.00 , 6.00)			
$t_{½}$ (hr)**	12	9.39	(17.0)	18	15.7	(18.0)			
CL/F (L/hr)**	12	12.2	(18.8)	18	5.94	(29.0)			
V_d/F (L)**	12	166	(27.7)	18	134	(26.6)			

† 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 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.*

[redacted] – Version 3 Study Report
MK-1439 and Rifabutin Pharmacokinetic Drug Interaction Study
[redacted] Study Number: 20[redacted]-3732
Protocol Number: MK-1439-035-02
IND 112, 796

Conclusions:

1. Doravirine $AUC_{0\text{-}inf}$ was decreased by 50% and C_{24} was decreased by 68% when doravirine was co-administered with multiple doses of rifabutin compared to doravirine administered alone. Doravirine C_{max} was similar when either administered alone or with multiple doses of rifabutin.
2. Administration of doravirine alone and after multiple doses of rifabutin was generally well-tolerated.

Date of Version 3 Report: Final Report: [redacted] 20[redacted]

[redacted] – Study Report
MK-1439 and Atorvastatin Pharmacokinetic Drug Interaction Study
[redacted] Study Number: 20[redacted]-3733
Protocol Number: MK-1439-036-00
IND 112, 796

Title of Study:
A Study to Evaluate the Effect of MK-1439 at Steady-State on the Pharmacokinetics of Atorvastatin in Healthy Subjects

Investigators:
[redacted] MD
[redacted] NP
[redacted] MD
[redacted] FNP
[redacted] MD
[redacted] ANP
[redacted] ACNP

Study Centre(s):

Clinical Facility: [redacted] USA, [redacted]

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

[redacted] USA, [redacted]

Bioanalytical Facility: [redacted] Canada, [redacted]

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

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

Phase of Development: Phase 1

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

[redacted] – Study Report
MK-1439 and Atorvastatin Pharmacokinetic Drug Interaction Study
[redacted] Study Number: 20[redacted]-3733
Protocol Number: MK-1439-036-00
IND 112, 796

Objective:
Primary Objective:
To evaluate the effect of MK-1439 100 mg Tablets at steady-state on the PK of atorvastatin after a single-dose [C_{max}, $AUC_{0\text{-}inf}$ ($AUC_{0\text{-}\infty}$)] in healthy subjects.

Primary Objective Hypothesis:
The plasma $AUC_{0\text{-}inf}$ and C_{max} of single-dose atorvastatin co-administered with MK-1439 at steady-state are similar to those after single-dose atorvastatin alone. That is, the true geometric mean ratios (GMRs) (atorvastatin+MK-1439/atorvastatin) for $AUC_{0\text{-}inf}$ and C_{max} of atorvastatin are contained within [0.50, 2.00].

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.

Methodology:
- This was an open-label, single-dose and multiple-dose, two-period, two-treatment, fixed-sequence, PK drug interaction study.
- This study was designed to evaluate the effect of MK-1439 100 mg tablets at steady-state on the PK of atorvastatin in healthy male and female subjects.
- Concentrations of atorvastatin were measured from the samples collected over a 60-hour interval after dosing in each period.
- The values of the following PK parameters were estimated using a non-compartmental approach:
    - C_{max}, $AUC_{0\text{-}last}$ ($AUC_{0\text{-}t}$), $AUC_{0\text{-}inf}$, T_{max}, K_{el} (λ_z), $t_{1/2}$, CL/F and V_d/F

Number of subjects:
- Planned for inclusion: 16 subjects
- Total number of subjects that completed the study: 14 subjects
    - Subjects 0002 and 0007 completed Period 1 of the study receiving Treatment A.
    - Both subjects have data from at least one treatment, and in accordance with the protocol, were included in the PK analysis.
- Included in the safety data analyses: 16 subjects
- Included in the PK and statistical data analyses: 16 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.

[redacted] – Study Report
MK-1439 and Atorvastatin Pharmacokinetic Drug Interaction Study
[redacted] Study Number: 20[redacted]-3733
Protocol Number: MK-1439-036-00
IND 112, 796

Study Drug Product 1:

MK-1439 100 mg Tablets (Merck Sharp & Dohme Corp., USA)
Lot No.: [redacted]
Potency: 98.9% of label claim
Dose: 100 mg
Mode of Administration: Oral

Study Drug Product 2:

Atorvastatin - Lipitor® 20 mg Tablets (Pfizer Inc., USA)
Lot No.: [redacted]
Potency: N/A
Expiry Date: [redacted] 20[redacted]
Dose: 20 mg
Mode of Administration: Oral

Treatments:

Treatment A (Period 1)

- Drug Product 2: 20 mg of atorvastatin (1 tablet)

Treatment B (Period 2)

- Day 1 to Day 8: Drug Product 1 [100 mg of MK-1439 (1 tablet)] once daily for 8 days
- Day 5: Drug Product 2 [20 mg of atorvastatin (1 tablet)]

Duration of treatment:

MK-1439 100 mg Tablets: Once daily from Days 1 to 8 in Period 2
Atorvastatin 20 mg Tablets: Once on Day 1 in Period 1 and once on Day 5 in Period 2

[redacted] – Study Report
MK-1439 and Atorvastatin Pharmacokinetic Drug Interaction Study
[redacted] Study Number: 20[redacted]-3733
Protocol Number: MK-1439-036-00
IND 112, 796

Safety Results:

No serious adverse events (SAEs) were reported during the conduct of this study. There were 19 adverse events (AEs) involving 8 subjects in the study. Of these AEs, 79% (15/19) were deemed to be un-related to the study drug. Four (4) subjects experienced an AE in Period 1, Treatment A (atorvastatin) and 5 subjects experienced an AE in Period 2, Treatment B (MK-1439 + atorvastatin). The most commonly reported AEs were abdominal pain, back pain, and headache. All AEs were judged to be mild in severity and resolved prior to the end of the study. The most common adverse events were abdominal cramps (Treatment B), back pain including lower back pain (Treatment A and Treatment B), and headache (Treatment A) reported by 2 (12.5%) subjects each. No other AE was reported by more than one subject in any treatment.

Two (2) subjects were discontinued from the study due to AEs.

Subject 0002 discontinued from the study in Period 1 due to AEs of back pain, headache, and feeling feverish. The AEs were not considered related to the study drug.

Subject 0007 discontinued from the study during Period 2 check-in due to a fever. The AE was not considered related to the study drug.

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

There were no clinically significant abnormal laboratory values or ECG interpretations. Vital sign measurements were mostly within normal range with all abnormal readings resolving on repeat measurements. Two abnormal vital signs readings were considered clinically significant. Subject 0012 experienced tachycardia and hypertension during Period 1 of the study. Both AEs were considered not related to the study drug.

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

[redacted] – Study Report
MK-1439 and Atorvastatin Pharmacokinetic Drug Interaction Study
[redacted] Study Number: 20[redacted]-3733
Protocol Number: MK-1439-036-00
IND 112, 796

Statistical Methods:
The PK values (C_{max} and $AUC_{0\text{-}inf}$) for atorvastatin were natural log-transformed prior to analysis and evaluated separately using a linear mixed effects model with fixed effects terms for treatment in Periods 1 and 2. An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlation between the treatment measurements within each subject via the REPEATED statement in SAS PROC MIXED. Kenward and Roger's method was used to calculate the denominator degrees of freedom for the fixed effects (DDFM=KR).
The hypothesis was addressed by comparing atorvastatin $AUC_{0\text{-}inf}$ and C_{max} from administration of atorvastatin+MK-1439 to those obtained from administration of atorvastatin alone. A two-sided 90% confidence interval (CI) for the true mean difference (atorvastatin+MK-1439 – atorvastatin) for atorvastatin $AUC_{0\text{-}inf}$ 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 (atorvastatin+MK-1439/atorvastatin) for atorvastatin $AUC_{0\text{-}inf}$ 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 atorvastatin $AUC_{0\text{-}inf}$ and C_{max}. The primary hypothesis is supported if the 90% CIs for the true GMRs (atorvastatin+MK-1439/atorvastatin) for atorvastatin $AUC_{0\text{-}inf}$ and C_{max} are both within [0.50, 2.00].

Atorvastatin $AUC_{0\text{-}last}$ was analyzed in a similar fashion as above. Plots with the individual ratios, GMRs and 90% CIs were provided for atorvastatin C_{max}, $AUC_{0\text{-}inf}$ 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).

[redacted] – Study Report
MK-1439 and Atorvastatin Pharmacokinetic Drug Interaction Study
[redacted] Study Number: 20[redacted]-3733
Protocol Number: MK-1439-036-00
IND 112, 796

Results:

Pharmacokinetic Results:

Summary of Statistical Analysis Based on Plasma Atorvastatin Levels Following the Administration of a Single Dose of 20 mg Atorvastatin Alone or Co-administered with the 5th Dose of 100 mg MK-1439 QD to Healthy Volunteers

	Atorvastatin 20 mg Tablet + MK-1439 100 mg Tablet QD x 8 days			*Atorvastatin 20 mg Tablet*			*Atorvastatin 20 mg Tablet + MK-1439 100 mg Tablet QD x 8 days / Atorvastatin 20 mg Tablet*		
PK Parameter	***N***	***GM***	***95% CI***	***N***	***GM***	***95% CI***	***GMR***	***90% CI for GMR***	***Intra-Sbj % CV‡***
$AUC_{0-\infty}$ (hr·ng/mL)†	14	39.0	(31.2 , 48.8)	16	39.9	(32.0 , 49.8)	0.98	(0.90 , 1.06)	12.1
AUC_{0-t} (hr·ng/mL)†	14	38.2	(30.4 , 48.0)	16	39.2	(31.4 , 49.0)	0.97	(0.90 , 1.06)	12.6
C_{max} (ng/mL)†	14	5.25	(3.54 , 7.78)	16	7.87	(5.93 , 10.4)	0.67	(0.52 , 0.85)	36.0
T_{max} (hr)	14	1.00	(0.50 , 6.00)	16	0.50	(0.50 , 1.00)			
$t_{½}$ (hr)	14	10.80	(38.3)	16	11.06	(28.2)			
CL/F (L/hr)	14	508	(44.9)	16	501	(43.5)			
V_d/F (L)	14	7910	(69.6)	16	7990	(58.2)			

† 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: $CV(\%) = 100*sqrt[(\sigma_A^2 + \sigma_B^2 - 2*\sigma_{AB})/2]$
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.
All available data from the 16 subjects were included in the PP dataset.
T_{max}: Time of the maximum measured analyte concentration over the sampling period
$t_{½}$: The apparent elimination half-life
CL/F: Apparent total plasma clearance of drug after oral administration ($CL/F = Dose/AUC_{0-inf}$)
V_d/F: Apparent volume of distribution during the terminal phase after oral drug administration ($V_d/F = Dose/[AUC_{0-inf}*\lambda_z]$)

[redacted] – Study Report
MK-1439 and Atorvastatin Pharmacokinetic Drug Interaction Study
[redacted] Study Number: 20[redacted]-3733
Protocol Number: MK-1439-036-00
IND 112, 796

Conclusions:

1. The $AUC_{0\text{-}inf}$ and C_{max} of a single dose atorvastatin co-administered with MK-1439 at steady state are similar to those after single-dose atorvastatin administered alone.
2. Administration of atorvastatin 20 mg tablets alone and co-administration of atorvastatin 20 mg tablets with MK-1439 100 mg Tablets were generally well- tolerated by the subjects in this study.

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

[redacted] – Study Report
MK-1439/Lamivudine/Tenofovir 100 mg/300 mg/245 mg Tablets, Fasted Study
[redacted] Study Number: 20[redacted]-3708
Protocol Number: MK-1439-038-01

Title of Study:
A Component Interaction Study of MK-1439A in Healthy Subjects under Fasting Conditions

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

Study Centre(s):

Clinical Facility: [redacted] Canada, [redacted]

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

Bioanalytical Facility: Lamivudine and Tenofovir (Aliquots 2 and 3)
[redacted] Canada, [redacted]
and
MK-1439 (Aliquot 1)
[redacted]
The Netherlands

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

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

Phase of Development: DDI

Study Periods:
Period 1: [redacted], 20[redacted]
Period 2: [redacted], 20[redacted]
Period 3: [redacted], 20[redacted]

[redacted] – Study Report
MK-1439/Lamivudine/Tenofovir 100 mg/300 mg/245 mg Tablets, Fasted Study
[redacted] Study Number: 20[redacted]-3708
Protocol Number: MK-1439-038-01

Objective:
To evaluate the comparative bioavailability among:

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

after a single-dose in healthy subjects under fasted conditions

Hypotheses (estimation):

- The $AUC_{0\text{-}inf}$ and C_{max} geometric mean ratio (GMR) of MK-1439 when taken alone and concomitantly with lamivudine/tenofovir disoproxil fumarate (300/300 mg) will be estimated.
- The $AUC_{0\text{-}inf}$ and C_{max} GMR of lamivudine and tenofovir when administered together as lamivudine/tenofovir disoproxil fumarate (300/300 mg) with and without MK-1439 (100 mg) will be estimated.

Methodology:

- This was an open-label, single-dose, randomized, three-period, three-treatment, six-sequence, crossover, component interaction study.
- This study was designed to evaluate the comparative bioavailability 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 MK-1439 alone (Treatment A) and co-administered with Epivir® and Viread® (Treatment C).
- Concentrations of lamivudine and tenofovir were measured from the samples collected over a 72-hour interval after co-administration of Epivir® and Viread® with MK-1439 (Treatment C) and without MK-1439 (Treatment B).
- 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} (λ_z), 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} (λ_z), CL/F, V_d/F and $t_{1/2}$

Number of subjects:

- Planned for inclusion: 15 subjects
- Total number of subjects that completed the study: 15 subjects
- Included in the safety data analyses: 15 subjects
- Included in the PK data analyses: 15 subjects
- Included in the statistical data analyses: 15 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.

[redacted] – Study Report
MK-1439/Lamivudine/Tenofovir 100 mg/300 mg/245 mg Tablets, Fasted Study
[redacted] Study Number: 20[redacted]-3708
Protocol Number: MK-1439-038-01

Drug Product 1:
MK-1439 100 mg 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

Drug Product 2:
Epivir® 300 mg 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

Drug Product 3:
Viread® 245 mg Tablets (Gilead Sciences Intl Ltd., United Kingdom)
Lot No .: [redacted]
Expiry Date: [redacted] 20[redacted]
Dose: 245 mg
Mode of Administration: Oral under fasted conditions.
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. Refer to section *9.4.2 Treatments Administered* for more information

Duration of treatment:
Single-Dose treatment

Safety Results:

		Pre-dose	Trt A	Trt B	Trt C	Total
Severity	Mild	2	2	1	2	7
	Moderate	0	0	0	0	0
	Severe	0	0	0	0	0
Relationship to Study Drug	Related	0	1	0	1	2
	Not Related	2	1	1	1	5

There were 2 non-treatment emergent adverse events (NTEAEs) involving 2 subjects that occurred prior to administration of any drug product. Both of these events were judged mild in severity.

There were 5 adverse events (AEs) involving 4 subjects in the study. All 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.

[redacted] – Study Report
MK-1439/Lamivudine/Tenofovir 100 mg/300 mg/245 mg Tablets, Fasted Study
[redacted] Study Number: 20[redacted]-3708
Protocol Number: MK-1439-038-01

Statistical Methods:
The PK parameters of MK-1439 ($AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, C_{max} and C_{24}) after administration of MK-1439 100 mg Tablets alone, and co-administration of MK-1439 100 mg Tablets, lamivudine (Epivir® 300 mg Tablets), and tenofovir disoproxil (Viread® 245 mg Tablets) were estimated using a linear mixed-effect model appropriate for a three-period, two-treatment, crossover design.

The endpoints of MK-1439 $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, C_{max} and C_{24} were natural log-transformed prior to 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 (MK-1439 + lamivudine + tenofovir versus MK-1439 alone) for MK-1439 $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, C_{max} and C_{24} 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 (MK-1439 + lamivudine + tenofovir/MK-1439 alone) for MK-1439 $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, C_{max} and C_{24}. Ninety-five percent (95%) CIs were also generated from the above mixed-effect model for the geometric means (GMs) by treatment for MK-1439 $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, C_{max} and C_{24}. Plots with the individual ratios, GMRs and 90% CIs are provided for MK1439 $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, C_{max} and C_{24}.

The PK parameters of lamivudine and tenofovir $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} after co-administration of Epivir® 300 mg Tablets and Viread® 245 mg Tablets versus co-administration of MK-1439 100 mg Tablets, Epivir® 300 mg Tablets and Viread® 245 mg Tablets were analyzed in a similar fashion as the PK parameters of MK-1439. A two-sided 90% confidence interval of lamivudine and tenofovir $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} GMR (MK-1439 + lamivudine + tenofovir/lamivudine + tenofovir) were provided. Ninety-five percent (95%) CIs were also generated from the above mixed-effect model for the GMs by treatment for lamivudine and tenofovir $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max}. Plots with the individual ratios, GMRs and 90% CIs are provided for lamivudine and tenofovir $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max}.

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).

[redacted] – Study Report
MK-1439/Lamivudine/Tenofovir 100 mg/300 mg/245 mg Tablets, Fasted Study
[redacted] Study Number: 20[redacted]-3708
Protocol Number: MK-1439-038-01

Pharmacokinetic Results:

MK-1439

	MK-1439 100 mg + Epivir® 300 mg + Viread® 245 mg			*MK-1439 100 mg*			*MK-1439 100 mg + Epivir® 300 mg + Viread® 245 mg / MK-1439 100 mg*		
PK Parameter	***N***	***GM***	***95% CI***	***N***	***GM***	***95% CI***	***GMR***	***90% CI for GMR***	***Intra-Sbj % CV‡***
$AUC_{0\text{-}inf}$ (hr·µM)†	15	37.7	(28.7 , 49.4)	15	39.1	(31.5 , 48.6)	0.96	(0.87 , 1.06)	15.2
$AUC_{0\text{-}last}$ (hr·µM)†	15	36.2	(27.9 , 47.0)	15	37.7	(30.6 , 46.4)	0.96	(0.87 , 1.06)	15.1
C_{max} (nM)†	15	2030	(1720 , 2400)	15	2090	(1810 , 2420)	0.97	(0.88 , 1.07)	15.1
C_{24} (nM)†	15	507	(332 , 774)	15	541	(390 , 750)	0.94	(0.83 , 1.06)	19.6
T_{max} (hr)	15	2.00	(1.00 , 6.00)	15	3.00	(1.00 , 4.00)			
$t_{½}$ (hr)	15	13.48	(40.6)	15	13.77	(31.9)			
CL/F (L/hr)	15	6.24	(52.2)	15	6.00	(40.3)			
V_d/F (L)	15	121	(28.9)	15	119	(31.0)			

† 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.*

[redacted] – Study Report
MK-1439/Lamivudine/Tenofovir 100 mg/300 mg/245 mg Tablets, Fasted Study
[redacted] Study Number: 20[redacted]-3708
Protocol Number: MK-1439-038-01

Lamivudine

	MK-1439 100 mg + Epivir® 300 mg + Viread® 245 mg			*Epivir® 300 mg + Viread® 245 mg Tablets*			*MK-1439 100 mg + Epivir® 300 mg + Viread® 245 mg / Epivir® 300 mg + 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)†	15	14200	(12400,16200)	15	15000	(13800, 16500)	0.94	(0.88 , 1.00)	9.7
$AUC_{0\text{-last}}$ (hr·ng/mL)†	15	14000	(12200, 16000)	15	14900	(13600, 16300)	0.94	(0.88 , 1.00)	9.8
C_{max} (ng/mL)†	15	2910	(2460 , 3450)	15	3150	(2760, 3600)	0.92	(0.81 , 1.05)	19.4
T_{max} (hr)	15	1.00	(1.00 , 2.02)	15	1.00	(0.50, 2.00)			
$t_{½}$ (hr)	15	15.93	(57.6)	15	15.73	(32.2)			
CL/F (L/hr)	15	21.2	(25.0)	15	19.9	(16.9)			
V_d/F (L)	15	488	(39.6)	15	451	(31.1)			

† 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.*

[redacted] – Study Report
MK-1439/Lamivudine/Tenofovir 100 mg/300 mg/245 mg Tablets, Fasted Study
[redacted] Study Number: 20[redacted]-3708
Protocol Number: MK-1439-038-01

Tenofovir

PK Parameter	*MK-1439 100 mg + Epivir® 300 mg + Viread® 245 mg*			*Epivir® 300 mg + Viread® 245 mg Tablets*			*MK-1439 100 mg + Epivir® 300 mg + Viread® 245 mg / Epivir® 300 mg + 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)†	15	2790	(2470, 3150)	15	2500	(2090, 2990)	1.11	(0.97, 1.28)	20.5
$AUC_{0\text{-last}}$ (hr·ng/mL)†	15	2570	(2300, 2880)	15	2340	(1960, 2810)	1.10	(0.96, 1.26)	20.5
C_{max} (ng/mL)†	15	338	(286, 400)	15	289	(237, 352)	1.17	(0.96, 1.42)	29.7
T_{max} (hr)	15	1.00	(0.50, 2.02)	15	1.00	(0.50, 1.00)			
$t_{½}$ (hr)	15	20.87	(18.5)	15	19.68	(12.6)			
CL/F (L/hr)	15	48.5	(22.7)	15	54.7	(30.1)			
V_d/F (L)	15	1460	(21.3)	15	1550	(35.1)			

† 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(s²)-1), where s² is the observed between-subjects variance on the natural log-scale.*

[redacted] – Study Report
MK-1439/Lamivudine/Tenofovir 100 mg/300 mg/245 mg Tablets, Fasted Study
[redacted] Study Number: 20[redacted]-3708
Protocol Number: MK-1439-038-01

Conclusions:

1. The plasma AUC and C_{max} of MK-1439 are generally similar when administered alone or co-administered with lamivudine 300 mg tablets and tenofovir disoproxil 245 mg tablets.

2. The plasma AUC and C_{max} of lamivudine, administered with tenofovir disoproxil, are generally similar when administered with or without MK-1439.

3. The plasma AUC and C_{max} of tenofovir, administered as tenofovir disoproxil with lamivudine, are generally similar when administered with or without MK-1439.

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

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 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	
TRIAL IDENTIFIERS:	Protocol Number:	MK-1439-042-01
	Clinical Phase:	1
TRIAL CENTER:	[redacted], MD: [redacted], USA	
DESIGN:	This was an open-label, single-dose and multiple-dose, three-period, three-treatment, fixed-sequence PK drug interaction study to evaluate the effect of multiple doses of pantoprazole on the single-dose PK of doravirine and the effect of concomitant administration of a single 20 mL dose of an antacid oral suspension containing aluminum hydroxide (1600 mg), magnesium hydroxide (1600 mg), and simethicone (160 mg) on the single-dose PK of doravirine, administered to healthy male and female subjects. Subjects received Treatment A in Period 1, Treatment B in Period 2, and Treatment C in Period 3. Treatment A consisted of a single 100 mg oral dose of doravirine (one tablet). Treatment B consisted of a single 100 mg oral dose of doravirine (one tablet) co-administered with a single 20 mL dose of an antacid oral suspension containing 1600 mg aluminum hydroxide, 1600 mg magnesium hydroxide, and 160 mg simethicone. Treatment C consisted of a 40 mg daily oral dose of pantoprazole sodium (one delayed-release tablet per day) for 5 days and a single 100 mg oral dose of doravirine (one tablet) on Day 5. A washout of 10 days between drug administrations in each treatment period was observed. Safety parameters were closely monitored throughout the study. Plasma was collected pre-dose and at specified time points up to 72 hours post-dose for measurement of doravirine concentrations. Fourteen (14) healthy, male and female subjects between the ages of 31 and 60 (inclusive) with a body mass index (BMI) $\geq$ 20.3 to $\leq$ 31.7 kg/m^2, participated in the study.	
	Planned duration of main phase:	Approximately 38 days

Objectives	**Primary Objectives:** **Objective 1:** To evaluate the effect of multiple doses of pantoprazole on the single-dose PK of doravirine. **Objective 2:** To evaluate the effect of concomitant administration of a single dose of an antacid oral suspension containing aluminum hydroxide, magnesium hydroxide, and simethicone on the single-dose PK of doravirine. **Secondary Objective:** To evaluate the safety and tolerability of doravirine when administered with and without pantoprazole and with or without an antacid oral suspension containing aluminum hydroxide, magnesium hydroxide, and simethicone.	
Hypotheses	**Objective 1 Estimation Hypothesis:** The effect of multiple doses of pantoprazole on the single-dose doravirine Cmax, AUC0-∞, AUC0-last, and C24 were estimated. **Objective 2 Estimation Hypothesis:** The effect of concomitant administration of a single dose of an antacid oral suspension containing aluminum hydroxide, magnesium hydroxide, and simethicone on the single-dose doravirine Cmax, AUC0-∞, AUC0-last, and C24 were estimated.	
Treatment groups	Treatment A	One (1) MK-1439 100 mg Tablet. [14 Subjects]
	Treatment B	One (1) MK-1439 100 mg Tablet co-administered with 20 mL antacid oral suspension containing 400 mg/5 mL aluminium hydroxide, 400 mg/5 mL magnesium hydroxide, and 40 mg/5 mL simethicone. [14 Subjects]
	Treatment C	One (1) MK-1439 100 mg Tablet on Day 5 co-administered with one daily 40 mg Pantoprazole Sodium Delayed-Release Tablet on Days 1 to 5. [13 Subjects, one subject discontinued]

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 tablets	[redacted]
Protonix® (pantoprazole sodium) 40 mg delayed-release tablets	[redacted]
Equate® Maximum Strength Original Antacid/AntiGas Liquid (400 mg/5 mL aluminum hydroxide, 400 mg/5 mL magnesium hydroxide, and 40 mg/5 mL simethicone)	[redacted]

ENDPOINTS AND DEFINITIONS	**Primary Endpoints:**	PK	Cmax, C24, AUC0-last, AUC0-∞, Tmax, t1/2, CL/F, and Vz/F for doravirine in plasma.
	Secondary Endpoints:	Safety	An assessment of safety was based primarily on the frequency and severity of adverse events (AEs) laboratory safety tests, ECGs, and summary statistics for vital signs.
DATABASE LOCK	[redacted]-20[redacted]	**TRIAL STATUS:**	[redacted]-20[redacted] to [redacted]-20[redacted]

<table>
<tr><td>RESULTS AND ANALYSIS:</td><td colspan="2">All analyses for safety and PK were performed according to the protocol.
The plasma PK (Cmax, AUC0-∞, AUC0-last, and C24) for doravirine were natural log-transformed prior to analysis and evaluated separately using a linear mixed effects model with fixed effects term for treatment appropriate for a 3-period fixed sequence design. An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlation between the treatment measurements within each subject via the REPEATED statement in SAS PROC MIXED. Kenward and Roger's method was used to calculate the denominator degrees of freedom for the fixed effects (DDFM=KR).
A 2-sided 90% confidence interval (CI) for the true mean difference ([antacid + doravirine] minus [doravirine alone] and [pantoprazole + doravirine] minus [doravirine alone]) for doravirine Cmax, AUC0-∞, AUC0-last, and C24 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 ([pantoprazole + doravirine]/[doravirine alone] or [antacid + doravirine]/[doravirine alone]) for doravirine Cmax, AUC0-∞, AUC0-last, and C24. Ninety-five percent (95%) CIs were also generated from the above mixed-effect model for the geometric means (GMs) by treatment for doravirine Cmax, AUC0-∞, AUC0-last, and C24. Plots with the individual ratios, GMRs and 90% CIs were provided for doravirine Cmax, AUC0-∞, AUC0-last, and C24.</td></tr>
<tr><td rowspan="2">SUBJECT DISPOSITION:</td><td>RANDOMIZED:
Male (age range)
Female (age range)
COMPLETED:
DISCONTINUED:
Other</td><td>14
8 (31 to 58)
6 (40 to 60)
13
1
0</td></tr>
<tr><td colspan="2">Fourteen (14) subjects were initially enrolled as per the protocol.

Subject 0004 was discontinued from the study as the subject was unavailable for Period 3. This subject was not replaced.</td></tr>
<tr><td>ANALYSIS DESCRIPTION:</td><td colspan="2">Analysis
Doravirine Pharmacokinetics</td></tr>
</table>

ANALYSIS POPULATION AND TIME POINT DESCRIPTION:	PK analysis was performed on available data from subjects in the PP dataset, as defined in the protocol. All subjects in this dataset were compliant with the inclusion and exclusion criteria. Descriptive statistics were provided as follows: 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).
SUMMARY:	The GMRs and 90% CIs [doravirine + antacid/doravirine] of doravirine AUC0-∞, AUC0-last, Cmax, and C24 are 1.01 (0.92, 1.11), 1.00 (0.92, 1.09), 0.86 (0.74, 1.01), and 1.03 (0.94, 1.12), respectively. The GMRs and 90% CIs [doravirine + pantoprazole/doravirine] of doravirine AUC0-∞, AUC0-last, Cmax, and C24 are 0.83 (0.76, 0.91), 0.84 (0.77, 0.91), 0.88 (0.76, 1.01), and 0.84 (0.77, 0.92), respectively.

Summary Statistics for MK-1439 Plasma PK Following Single Oral Dose Administration of 100 mg MK-1439 Alone or Co-administered with Single Dose 20 mL Antacid Oral Suspension in Healthy Male and Female Subjects

	MK-1439 100 mg Tablet + 20 mL Antacid Oral Suspension§			*MK-1439 100 mg Tablet*			*MK-1439 100 mg Tablet + 20 mL Antacid Oral Suspension§/ MK-1439 100 mg Tablet*		
PK Parameter	***N***	***GM***	***95% CI***	***N***	***GM***	***95% CI***	***GMR***	***90% CI for GMR***	***Pseudo Within-subject % CV‡***
AUC0-∞ (hr·µM)†	14	43.9	(36.6 , 52.7)	14	43.5	(37.4 , 50.6)	1.01	(0.92 , 1.11)	13.5
AUC0-last (hr·µM)†	14	41.9	(35.4 , 49.7)	14	42.0	(36.3 , 48.5)	1.00	(0.92 , 1.09)	12.5
Cmax (nM)†	14	1840	(1480 , 2290)	14	2130	(1860 , 2440)	0.86	(0.74 , 1.01)	23.1
C24 (nM)†	14	698	(573 , 849)	14	680	(548 , 844)	1.03	(0.94 , 1.12)	12.4
Tmax (hr)#	14	2.50	(1.00 , 4.00)	14	3.00	(1.00 , 4.00)			
t½ (hr)	14	14.87	(26.5)	14	14.08	(19.5)			
CL/F (L/hr)	14	5.34	(32.3)	14	5.40	(26.6)			
Vz/F (L)	14	115	(27.8)	14	110	(25.3)			

§20 mL Antacid contains 1600 mg magnesium hydroxide, 1600 mg aluminum hydroxide, and 160 mg simethicone

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

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

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

t½ = Apparent terminal elimination half-life

#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 PK Following Single Oral Dose Administration of 100 mg MK-1439 Alone or Co-administered with Multiple Oral Doses of 40 mg Pantoprazole Tablet QD (Day 5) in Healthy Male and Female Subjects

	MK-1439 100 mg Tablet + Pantoprazole 40 mg Tablet QD (Day 5)			*MK-1439 100 mg Tablet*			*MK-1439 100 mg Tablet + Pantoprazole 40 mg Tablet QD (Day 5) / MK-1439 100 mg Tablet*		
PK Parameter	***N***	***GM***	***95% CI***	***N***	***GM***	***95% CI***	***GMR***	***90% CI for GMR***	***Pseudo Within-subject % CV‡***
AUC0-∞ (hr·µM)†	13	36.1	(30.3 , 43.1)	14	43.5	(37.4 , 50.6)	0.83	(0.76 , 0.91)	12.5
AUC0-last (hr·µM)†	13	35.2	(29.7 , 41.8)	14	42.0	(36.3 , 48.5)	0.84	(0.77 , 0.91)	12.3
Cmax (nM)†	13	1870	(1550 , 2260)	14	2130	(1860 , 2440)	0.88	(0.76 , 1.01)	20.3
C24 (nM)†	13	572	(465 , 703)	14	680	(548 , 844)	0.84	(0.77 , 0.92)	13.0
Tmax (hr)#	13	2.00	(1.00 , 6.00)	14	3.00	(1.00 , 4.00)			
t½ (hr)	13	12.94	(17.1)	14	14.08	(19.5)			
CL/F (L/hr)	13	6.48	(31.7)	14	5.40	(26.6)			
Vz/F (L)	13	121	(27.6)	14	110	(25.3)			

† Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values
GM = Geometric mean; CI = Confidence interval; GMR = Least-squares Geometric Mean Ratio between treatments
*‡ 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 corresponding treatment groups,
and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed effects model
t½ = Apparent terminal elimination half-life
#Statistics for Tmax: Median and Range (Minimum , Maximum)
*Statistics for t½, CL/F and Vz/F: GM and CV% = 100*sqrt(exp(s²)-1), where s² is the observed between-subjects variance on the natural log-scale.*

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 subjects who received at least one dose of the investigational drug 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 AEs throughout the study. Clinical and laboratory AEs were tabulated by treatment.

SUMMARY:	Based on the AE profile, laboratory safety tests, ECGs, and vital signs results, MK-1439 100 mg tablet was generally well-tolerated when administered alone or when co-administered with a 20 mL antacid oral suspension containing 1600 mg aluminum hydroxide, 1600 mg magnesium hydroxide, and 160 mg simethicone, or 40 mg pantoprazole sodium. No SAEs or deaths were reported during the conduct of this study and no subjects discontinued due to an AE. Overall, 3 subjects (21.4% of subjects dosed) reported at least one adverse event during the study. One (1) subject reported at least one AE in Period 1 (Treatment A; doravirine alone), 2 subjects reported at least one AE in Period 2 (Treatment B; doravirine co-administered with an antacid oral suspension containing aluminum hydroxide, magnesium hydroxide, and simethicone) and 3 subjects reported at least one AE in Period 3 (Treatment C; doravirine co-administered with pantoprazole). The most common AE was headache, reported by 3 subjects (21.4 % of subjects dosed). The only other AE reported was vertigo, reported by one subject following administration of treatment B. All the AEs were mild in severity and resolved by study completion. There were no trends for clinically meaningful changes in laboratory values, vital signs, or ECGs.
CONCLUSIONS:	1. Administration of doravirine with an antacid oral suspension does not have a clinically meaningful effect on the pharmacokinetics of doravirine. 2. Administration of doravirine following multiple doses of pantoprazole does not have a clinically meaningful effect on the pharmacokinetics of doravirine. 3. Administration of MK-1439 100 mg alone or co-administration of MK-1439 100 mg with an antacid oral suspension, or co-administration with pantoprazole, was generally well-tolerated by the subjects in this study.
FINAL REPORT DATE (VERSION 2):	[redacted]-20[redacted]

SPONSOR:	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.	
COMPOUND NAME:	Doravirine (MK-1439)	
INDICATION:	Treatment of HIV-1 Infection	
PROTOCOL TITLE:	A Multiple-Dose Clinical Trial to Study the Effect of MK-1439 (doravirine) on Methadone Pharmacokinetics	
TRIAL IDENTIFIERS:	Protocol Number:	045
	Clinical Phase:	1
	IND Number:	112,796
TRIAL CENTERS:	[redacted], MD, CPI: [redacted], USA [redacted], MD: [redacted], USA	
DESIGN:	This was an open-label, fixed-sequence, multiple-dose study to evaluate the pharmacokinetics (PK) of methadone administered alone and with MK-1439 (hereafter referred to as doravirine). Fourteen (14) male and female subjects 18 to 65 years of age who remained on stable oral methadone maintenance therapy 20 - 200 mg (20-180 mg actual) once daily (QD) were enrolled. Subjects received their usual oral maintenance dose of methadone on Days 1 through 7. On Days 2 through 6, subjects received a 100 mg oral dose QD of doravirine immediately after methadone administration. Blood samples for methadone and doravirine PK analysis were collected throughout Days 1 through 7. Safety and tolerability were evaluated throughout the study.	
	Planned duration of main phase:	Approximately 7 weeks per subject.

Objectives	Primary: To determine the effect of doravirine on the respective pharmacokinetics (e.g., AUC0-24, Cmax, C24, Tmax) of co-administered methadone (total, S- and R-enantiomers). Secondary: To evaluate the safety and tolerability of doravirine co-administered with methadone. Exploratory: To determine the effect of methadone on the pharmacokinetics (e.g., AUC0-24, C24, Cmax, Tmax) of co-administered doravirine.
Hypotheses	1. The methadone (R-enantiomer) plasma AUC0-24 obtained after multiple dose coadministration of methadone with doravirine is similar to the methadone (R-enantiomer) plasma AUC0-24 obtained after multiple dose administration of methadone alone. That is, the true geometric mean ratio (methadone and doravirine /methadone alone) for the dose-normalized AUC0-24 (AUC0-24/D) of methadone (R-enantiomer) is contained within [0.70, 1.43]. 2. The geometric mean ratio (methadone and doravirine / methadone alone) for the dose-normalized Cmax (Cmax/D) and C24 (C24/D) of methadone (R-enantiomer) will be estimated. 3. The geometric mean ratio (methadone and doravirine / methadone alone) for the dose-normalized AUC0-24 (AUC0-24/D), Cmax (Cmax/D) and C24 (C24/D) of methadone (total and S-enantiomer) will be estimated.
Treatment groups	Methadone QD on Day 1-7 + 100 mg doravirine QD on Day 2-6 14 subjects

Clinical Supplies Dispensed to Subjects

Bulk Product Description	Manufacturing Lot Number
FCT MK-1439 (005F) 100 mg	[redacted]
Methadone Oral Concentrate, 10 mg/mL (Mallinckrodt, Lot Number [redacted], Expiry date 28-Feb-2019; Mallinckrodt, Lot Number [redacted], Expiry date 31-Oct-2019) was supplied by the investigator. FCT = Film Coated Tablets	

Endpoints and definitions	**Primary endpoint**	**Pharmacokinetics** Methadone (total, S-, and R-enantiomers) AUC0-24, Cmax, C24, and Tmax	
	Secondary endpoint	**Safety and Tolerability** Adverse experiences (AEs), laboratory safery tests (hematology, chemistry, and urinalysis), 12-lead electrocardiograms (ECGs), vital signs (VS), and Clinical Opiate Withdrawal Scale (COWS)	
	Exploratory endpoint	**Pharmacokinetics** Doravirine AUC0-24, Cmax, C24, and Tmax	
Database lock	31-Aug-2016	Trial status	05-Oct-2015 to 15-Aug-2016
RESULTS AND ANALYSIS:	All analyses for PK and safety were performed according to the protocol.		

Subject Characteristics

	All Subjects n	(%)
Subjects in population	14	
Gender		
Male	7	(50.0)
Female	7	(50.0)
Age (Years)		
0 to 17	0	(0.0)
18 to 65	14	(100.0)
>65	0	(0.0)
Mean	36.7	
SD	10.7	
Median	35.0	
Range	20 to 59	
Race		
White	14	(100.0)
Ethnicity		
Hispanic Or Latino	2	(14.3)
Not Hispanic Or Latino	11	(78.6)
Unknown	1	(7.1)

Disposition of Subjects

	All Subjects	
	n	(%)
Subjects in population	14	
Trial Disposition		
Completed	14	(100.0)
Each subject is counted once for Trial Disposition based on the latest corresponding disposition record.		

Analysis description	**Primary Analysis**: Pharmacokinetics of methadone (R-, S-, and total enantiomers) AUC0-24, Cmax and C24 for methadone (R-, S-, and total enantiomers) were dose-normalized by each subject's methadone dose before the statistical analyses. A linear mixed-effects model was used to evaluate the primary hypothesis of the effect of doravirine on methadone. The model included a fixed effect term for treatment. An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlation between the two 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). A natural log transformation was applied to the R-methadone AUC0-24/D prior to the analysis. A ninety percent (90%) confidence interval (CI) was constructed for the difference in least-squares (LS) means on the log scale R-methadone AUC0-24/D. Exponentiating the log-scale 90% CI was provided for the AUC0-24/D geometric mean ratio (GMR) (methadone + doravirine/methadone alone). The hypothesis that the methadone (R-enantiomer) AUC0-24 obtained after multiple dose co-administration of methadone with doravirine is similar to the methadone (R-enantiomer) AUC0-24 obtained after multiple dose administration of methadone alone was supported if the 90% CI for the AUC0-24/D GMR of R-methadone was contained within the interval [0.70, 1.43]. Dose-normalized Cmax and C24 of R-methadone and dose-normalized AUC0-24, Cmax and C24 of total and S-methadone was analyzed based on the same above model. The GMR (methadone + doravirine/methadone alone) and 90% CI for every aforementioned parameter were estimated. Geometric means (GMs) and corresponding 95% CIs were also provided for AUC0-24/D, Cmax/D and C24/D of methadone (R-, S-, and total enantiomers) by treatment. Plots with the individual ratios, GMR and 90% confidence interval were provided for AUC0-24/D, Cmax/D and C24/D of methadone (R-, S-, and total enantiomers).

Analysis population and time point description	All subjects who complied 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 dose of the investigational drug, were included in the primary analysis dataset. All 14 subjects were included in the assessment of methadone PK.
Summary	**Primary pharmacokinetics (Effect of Doravirine on Methadone)** The GMR (90% CI) of dose-normalized R-methadone AUC0-24 for the methadone + doravirine / methadone alone comparison was 0.95 (0.90, 1.01), which was contained within the pre-specified interval [0.70, 1.43], thus the primary hypothesis that the methadone (R-enantiomer) AUC0-24 obtained after multiple dose co-administration of methadone with doravirine is similar to the methadone (R-enantiomer) AUC0-24 obtained after multiple dose administration of methadone alone was supported. The GMRs (90% CI) of dose-normalized R-methadone C24 and Cmax for the methadone + doravirine / methadone alone comparison were 0.95 (0.88, 1.03) and 0.98 (0.93, 1.03), respectively. The GMRs (90% CI) of dose-normalized S-methadone for the methadone + doravirine / methadone alone comparison were 0.98 (0.90, 1.06) for AUC0-24, 0.97 (0.86, 1.10) for C24 and 0.97 (0.91, 1.04) for Cmax. The GMRs (90% CI) of dose-normalized total-methadone for the methadone + doravirine / methadone alone comparison were 0.96 (0.90, 1.03) for AUC0-24, 0.96 (0.87, 1.05) for C24 and 0.98 (0.92, 1.03) for Cmax.

Statistical Comparison of Dose-Normalized Plasma Pharmacokinetics of R-Methadone Following the Administration of Maintenance Doses of 20-200 mg Methadone Once Daily (QD) With and Without Doses of 100 mg MK-1439 QD for 5 Days in Adult Methadone Maintenance Subjects

R-Methadone Pharmacokinetic Parameters	Methadone Alone			Methadone + MK-1439			Methadone + MK-1439/ Methadone Alone		Pseudo Within Subject % CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC0-24/D [‡] (ng*hr/mL/mg)	14	55.8	(46.4, 67.1)	14	53.2	(44.6, 63.5)	0.95	(0.90, 1.01)	8.8
C24/D [‡] (ng/mL/mg)	14	1.91	(1.56, 2.34)	14	1.82	(1.45, 2.27)	0.95	(0.88, 1.03)	11.9
Cmax/D [‡] (ng/mL/mg)	14	3.41	(2.89, 4.01)	14	3.33	(2.83, 3.91)	0.98	(0.93, 1.03)	7.6
Tmax [§] (hr)	14	2.00	(1.00, 6.00)	14	2.01	(1.02, 4.00)			

Methadone Alone: Maintenance dose of 20-200 mg methadone QD on Day 1 (subjects were to be administered the same dose and regimen of methadone for at least 2 weeks prior to the Day 1 dose).

Methadone + MK-1439: Co-administration of 100 mg MK-1439 QD with maintenance doses of 20-200 mg methadone QD for 5 days (Days 2-6).

[†] Pseudo Within-Subject % CV = 100*sqrt[(σ_A^2 + σ_B^2 - 2σ_{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.

[‡] Back-transformed least squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values.

[§] Median (Min, Max) reported for Tmax.

AUC0-24/D, C24/D and Cmax/D = Dose normalized AUC0-24, C24 and Cmax, respectively; GM = Geometric least-square mean; GMR = Geometric least-square mean ratio; CI = Confidence interval

Statistical Comparison of Dose-Normalized Plasma Pharmacokinetics of S-Methadone Following the Administration of Maintenance Doses of 20-200 mg Methadone Once Daily (QD) With and Without Doses of 100 mg MK-1439 QD for 5 Days in Adult Methadone Maintenance Subjects

S-Methadone Pharmacokinetic Parameters	Methadone Alone			Methadone + MK-1439			Methadone + MK-1439/ Methadone Alone		Pseudo Within Subject % CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC0-24/D [‡] (ng*hr/mL/mg)	14	52.0	(38.3, 70.4)	14	50.8	(37.5, 68.8)	0.98	(0.90, 1.06)	11.6
C24/D [‡] (ng/mL/mg)	14	1.51	(1.03, 2.22)	14	1.47	(0.974, 2.21)	0.97	(0.86, 1.10)	18.3
Cmax/D [‡] (ng/mL/mg)	14	3.77	(2.95, 4.82)	14	3.67	(2.87, 4.68)	0.97	(0.91, 1.04)	10.6
Tmax [§] (hr)	14	1.99	(1.00, 3.00)	14	2.00	(1.02, 4.00)			

Methadone Alone: Maintenance dose of 20-200 mg methadone QD on Day 1 (subjects were to be administered the same dose and regimen of methadone for at least 2 weeks prior to the Day 1 dose).

Methadone + MK-1439: Co-administration of 100 mg MK-1439 QD with maintenance doses of 20-200 mg methadone QD for 5 days (Days 2-6).

[†] Pseudo Within-Subject %CV = 100*sqrt[(σ_A^2 + σ_B^2 - 2σ_{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.

[‡] Back-transformed least squares mean and confidence interval from linear mixed-effects model performed on natural log transformed values.

[§] Median (Min, Max) reported for Tmax.

AUC0-24/D, C24/D and Cmax/D = Dose normalized AUC0-24, C24 and Cmax, respectively; GM = Geometric least-square mean; GMR = Geometric least-square mean ratio; CI = Confidence interval

Statistical Comparison of Dose-Normalized Plasma Pharmacokinetics of Total Methadone Following the Administration of Maintenance Doses of 20-200 mg Methadone Once Daily (QD) With and Without Doses of 100 mg MK-1439 QD for 5 Days in Adult Methadone Maintenance Subjects

Total Methadone Pharmacokinetic Parameters	Methadone Alone			Methadone + MK-1439			Methadone + MK-1439/ Methadone Alone		Pseudo Within Subject % CV [†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC0-24/D [‡] (ng*hr/mL/mg)	14	109	(86.0, 137)	14	105	(82.9, 132)	0.96	(0.90, 1.03)	9.5
C24/D [‡] (ng/mL/mg)	14	3.48	(2.65, 4.57)	14	3.34	(2.48, 4.51)	0.96	(0.87, 1.05)	14.0
Cmax/D [‡] (ng/mL/mg)	14	7.19	(5.86, 8.82)	14	7.01	(5.72, 8.60)	0.98	(0.92, 1.03)	8.7
Tmax [§] (hr)	14	2.00	(1.00, 6.00)	14	2.01	(1.02, 4.00)			

Methadone Alone: Maintenance dose of 20-200 mg methadone QD on Day 1 (subjects were to be administered the same dose and regimen of methadone for at least 2 weeks prior to the Day 1 dose).

Methadone + MK-1439: Co-administration of 100 mg MK-1439 QD with maintenance doses of 20-200 mg methadone QD for 5 days (Days 2-6).

[†] 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 two treatment groups, and σ_{AB} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.

[‡] Back-transformed least squares mean and confidence interval from linear mixed-effects model performed on natural log transformed values.

[§] Median (Min, Max) reported for Tmax.

AUC0-24/D, C24/D and Cmax/D = Dose normalized AUC0-24, C24 and Cmax, respectively; GM = Geometric least-square mean; GMR = Geometric least-square mean ratio; CI = Confidence interval

Analysis description	**Secondary Analysis**: Safety Incidence of the number of subjects with AEs was descriptively summarized and listed by treatment. The summary description for COWS based on the sum of score over 11 questions was provided by time points and treatments. The frequency table for the COWS ([0, 5), ≥5) were provided by time point and treatment.
Analysis population and time point description	All subjects who received at least one dose of investigational drug were included in the assessment of safety and tolerability. All 14 subjects were included in the evaluation of safety and tolerability.

Summary	Co-administration of methadone with doravirine was generally well tolerated. There were no SAEs, ECIs, deaths, or discontinuations due to a reported AE. One subject experienced an SAE of eardrum trauma during screening and was not enrolled in the study. Seven (7) of 14 subjects (50%) reported a total of 10 treatment-emergent AEs. Five (5) of the AEs were considered by the investigator to be drug related. The majority of AEs were mild to moderate in intensity, transient in nature, and all resolved by the end of the study. The most common AEs reported were drug withdrawal syndrome and headache, reported by 3 subjects (21%) and 2 subjects (14%), respectively. The most common drug-related AE was drug withdrawal syndrome, reported by 3 (21%) subjects. Abdominal discomfort and euphoric mood were drug-related AEs that were reported by 1 (7%) subject each. Two of the subjects who experienced drug withdrawal syndrome had unscheduled COWS assessments performed, scoring 6 and 11, which are categorized as mild symptoms based on the COWS, at the time withdrawal symptoms were reported. All scheduled COWS assessments were <5, which corresponds to no withdrawal symptoms on the COWS. One subject reported drug withdrawal syndrome on Day 17 relative to the initial study drug administration (11 days since their last dose of doravirine). No other AE was reported by more than 1 subject. No clinically meaningful trends were observed for changes in the clinical laboratory values, VSs, ECGs, or COWS assessment as a function of treatment.

Analysis description	**Exploratory Analysis:** Pharmacokinetics of doravirine AUC0-24, Cmax, C24, and Tmax To assess the effect of methadone on doravirine, the cross study comparison is conducted. Natural log transformed AUC0-24, Cmax and C24 for doravirine generated during co-administration with methadone from this study on Day 6 (co-administration on Days 2-6 for 5 days) was compared with pre-specified historical data from doravirine protocol number (PN) 020 Period 1 Day 5 (doravirine 100 mg dose at steady state). The data were analyzed using an ANOVA model for doravirine AUC0-24 and Cmax with fixed effect as treatment; since age and BMI were not statistically significant factors, these were removed from the model. For doravirine C24, ANCOVA model with a fixed effect as treatment (co-administration with methadone vs. doravirine alone) and BMI as covariate was used. The GMR (doravirine + methadone / doravirine alone) and 90% CI were provided for doravirine AUC0-24, Cmax and C24.
Analysis population and time point description	All subjects who complied 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 dose of the investigational drug, were included in the exploratory analysis dataset. All 14 subjects from this study and all 19 subjects from pre-specified historical study (PN020) were included in the assessment of doravirine PK.
Summary	**Exploratory pharmacokinetics (Effect of Methadone on Doravirine)** Based on a cross-study comparison, the GMRs (90% CI) of doravirine plasma PK for the methadone + doravirine/ doravirine alone comparison were 0.74 (0.61, 0.90) for AUC0-24, 0.80 (0.63, 1.03) for C24, and 0.76 (0.63, 0.91) for Cmax.

Statistical Comparison of Plasma Pharmacokinetics of MK-1439 Following the Administration of 100 mg MK-1439 Once Daily (QD) for 5 Days in Healthy Subjects and Co-administration of Maintenance Doses of 20-200 mg Methadone QD and 100 mg MK-1439 QD for 5 Days in Adult Methadone Maintenance Subjects

MK-1439 Pharmacokinetic Parameters	MK-1439 Alone			Methadone + MK-1439			Methadone + MK-1439/ MK-1439 Alone		
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	rMSE †
AUC0-24 ‡ (uM*hr)	19	41.1	(35.4, 47.9)	14	30.4	(25.5, 36.2)	0.74	(0.61, 0.90)	0.323
C24 ‡ (nM)	19	884	(733, 1070)	14	710	(570, 886)	0.80	(0.63, 1.03)	0.381
Cmax ‡ (nM)	19	2880	(2490, 3330)	14	2180	(1840, 2580)	0.76	(0.63, 0.91)	0.308
Tmax § (hr)	19	2.00	(0.50, 3.00)	14	3.00	(0.50, 6.00)			

MK-1439 Alone: 100 mg MK-1439 QD for 5 days (Historical data from MK-1439-PN020 Period 1 Day 5).

Methadone + MK-1439: Co-administration of 100 mg MK-1439 QD with maintenance doses of 20-200 mg methadone QD for 5 days (Days 2-6).

† rMSE: Square root of conditional mean squared error (residual error) from the linear fixed-effects model. rMSE*100% approximates the between-subject %CV on the raw scale.

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

§ Median (Min, Max) reported for Tmax.

GM = Geometric least-square mean; GMR = Geometric least-square mean ratio; CI = Confidence interval

CONCLUSIONS:	1. Multiple-dose administration of 100 mg of doravirine QD to subjects on stable methadone regimens does not have a clinically meaningful effect on the PK of methadone. 2. Multiple dose administration of methadone does not have a clinically meaningful effect on the PK of doravirine. 3. The co-administration of doravirine and methadone is generally well tolerated.
REPORT DATE:	16-MAR-2017

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 to Evaluate the Effect of Multiple Doses of MK-1439 (Doravirine) on Metformin Pharmacokinetics in Healthy Subjects	
TRIAL IDENTIFIERS:	Protocol Number:	MK-1439-048-00
	Clinical Phase:	1
TRIAL CENTERS:	[redacted], MD: [redacted], USA	
DESIGN:	This was an open-label, two-period, two-treatment, fixed-sequence PK drug interaction study to evaluate the effect of multiple doses of doravirine (MK-1439) on the single-dose PK of metformin in healthy male and female subjects. Subjects received Treatment A in Period 1 and Treatment B in Period 2. Treatment A consisted of a single oral dose of a 1000 mg tablet of metformin [immediate release (IR)]. Treatment B consisted of a once daily oral dose of a 100 mg tablet of doravirine on Day 1 to Day 7 and single oral dose of a 1000 mg metformin on Day 5. There was a washout period of at least 3 days between metformin drug administration in Period 1 and the first doravirine drug administration in Period 2. Safety and tolerability data were closely monitored throughout the study. In each period, plasma samples were collected prior to metformin dose and at specified time points up to 72 hours after metformin dose for measurement of metformin. Fourteen (14) healthy, male and female subjects between the ages (years) of 18 and 55 (inclusive) with a body mass index (BMI) $\geq$ 18.0 to $\leq$ 33.0 kg/m^2, participated in the study.	
	Planned duration of main phase:	Approximately 16 days

Objectives	**Primary Objective:** To evaluate the effect of 100 mg of doravirine administered once daily after multiple doses on metformin single-dose pharmacokinetics (Cmax and AUC0-inf). **Secondary Objective:** To evaluate the safety and tolerability of the co-administration of doravirine and metformin.	
Hypothesis	**Primary Objective Hypothesis:** The plasma metformin AUC0-inf and Cmax of single-dose metformin co-administered with multiple-dose doravirine are similar to those after single-dose metformin alone. That is, the true geometric mean ratio (GMR) (metformin+ doravirine /metformin) for AUC0-inf and Cmax of metformin is contained within [0.50, 2.00].	
Treatment groups	Treatment A	One (1) metformin 1000 mg Tablet (IR), administered under fed conditions. [14 Subjects]
	Treatment B	One (1) MK-1439 100 mg Tablet, administered under fed conditions from Day 1 to Day 7. One (1) metformin 1000 mg Tablet, administered under fed conditions on Day 5. [14 Subjects]

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

Clinical Supplies Dispensed to Subjects

Bulk Product Description	Manufacturing Lot Number
MK-1439 100 mg Tablets	[redacted]
*Glucophage® (metformin hydrochloride, IR) 1000 mg Tablets**	

*Provided by investigator site.

ENDPOINTS AND DEFINITIONS	**Primary Endpoint:**		Cmax and AUC0-inf
	Secondary Endpoints:		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 PK were performed according to the protocol. The Statistical Analysis Plan (SAP) is provided in [16.1.1.1]. The PK of metformin (Cmax, AUC0-inf and AUC0-last) were natural log-transformed and then estimated using a linear mixed-effect model with a fixed-effect terms 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. Kenward and Roger's method was used to calculate the denominator degrees of freedom for the fixed effects (DDFM=KR). The 90% confidence intervals (CIs) were generated from the above mixed-effect model for the geometric mean ratios (GMRs, metformin + doravirine /metformin alone) for metformin Cmax, AUC0-inf and AUC0-last. The hypothesis that the plasma AUC0-inf and Cmax of single-dose metformin co-administered with multiple dose MK1439 are similar to those after single-dose metformin alone would be supported if the 90% CIs for both metformin Cmax and AUC0-inf are contained within the interval [0.50, 2.00]. Plots with the individual ratios, GMR and 90% confidence interval were provided for metformin Cmax, AUC0-inf and AUC0-last. Ninety five percent (95%) CIs were also generated from the above mixed-effect model for the geometric means (GMs) by treatment for metformin Cmax, AUC0-inf, and AUC0-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).		

SUBJECT DISPOSITION:	ENROLLED: Male (age range) Female (age range) COMPLETED: DISCONTINUED: Other	14 9 (19 to 45) 5 (22 to 55) 14 0 0
	Fourteen (14) subjects were initially enrolled as per the protocol and all subjects completed the study.	
ANALYSIS DESCRIPTION:	**Analysis** **Metformin Pharmacokinetics**	
ANALYSIS POPULATION AND TIME POINT DESCRIPTION:	PK analysis was performed on available data from all subjects in the PP dataset. All subjects were compliant with the inclusion and exclusion criteria.	
SUMMARY:	The GMR (90% CI) of metformin AUC0-inf and Cmax were 0.94 (0.88, 1.00) and 0.94 (0.86, 1.03), respectively. The 90% CIs of GMRs [metformin + doravirine/metformin] were contained within the pre-specified bound of [0.50, 2.00] for both metformin $AUC_{0\text{-inf}}$ and Cmax.	

Summary Statistics for Metformin Plasma PK Following Single Oral Dose Administration of 1000 mg Metformin Alone or Co-administered on Day 5 of Once-Daily Administration of 100 mg MK-1439 QD for 7 Days in Healthy Male and Female Subjects

	Metformin 1000 mg + MK-1439 100 mg QD			*Metformin 1000 mg*			*Metformin 1000 mg + MK-1439 100 mg QD / Metformin 1000 mg*		
PK Parameter	***N***	***GM***	***95% CI***	***N***	***GM***	***95% CI***	***GMR***	***90% CI for GMR***	***Intra-Sbj % CV‡***
AUC0-inf (hr·ng/mL)†	14	9660	(8290 , 11300)	14	10300	(8740 , 12200)	0.94	(0.88 , 1.00)	10.1
AUC0-last (hr·ng/mL)†	14	9540	(8220 , 11100)	14	10200	(8650 , 12000)	0.93	(0.87 , 1.00)	10.2
Cmax (ng/mL)†	14	1270	(1130 , 1420)	14	1350	(1150 , 1570)	0.94	(0.86 , 1.03)	13.6
Tmax (hr)#	14	2.50	(1.50 , 4.02)	14	3.00	(1.00 , 4.00)			
$t_{½}$ (hr)*	14	12.53	(48.8)	14	13.82	(45.6)			
CL/F (L/hr)*	14	103	(27.0)	14	96.9	(29.3)			
V_z/F (L)*	14	1870	(39.9)	14	1930	(55.8)			

† Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log-transformed values
GM = Geometric mean; CI = Confidence interval; GMR = Least-squares Geometric Mean Ratio between treatments
*‡ 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.*

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 14 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 (including lactic acid). All subjects were assessed for AEs throughout the study. Lactic acid was evaluated prior to metformin administration and at the end of each period. A fingerstick for analysis of blood glucose was taken within 60 minutes prior to and at 3 hours (±20 minutes) after metformin dose in each period, and at the Inverstigator's discretion. Clinical and laboratory AEs were tabulated by treatment.

SUMMARY:	Single dose metformin co-administered with multiple dose MK 1439 (doravirine) was generally well tolerated. No SAE or deaths were reported. No subjects discontinued 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. Overall, a total of 31 AEs were reported by 10 subjects. All AEs were mild in severity, transient, and resolved by the end of the study. Overall, 10 (71.4%) subjects reported at least one AE; 8 (57.1%) subjects reported an AE in Treatment A (metformin alone) and 8 (57.1%) subjects reported an AE in Treatment B. The most common AE reported in Treatment A was hypoglycemia (8 [57.1%]). The most common AE reported in Treatment B were hypoglycemia (5 [35.7%]), dizziness (including lightheaded) (4 [28.6%]), diarrhea (4 [28.6%]), headache (including intermittent sharp left temple pain) (3 [21.4%]), and abdominal cramps (2 [14.3%]). The number of subjects experiencing AEs of hypoglycemia was similar when metformin was administered alone or co-administered with doravirine. Only 2 events of hypoglycemia were associated with symptoms (dizziness and headache), both occurring in Treatment B. There were no clinically meaningful trends in clinical safety laboratory values, vital signs or ECGs.
CONCLUSIONS:	*1.* Administration of MK-1439 100 mg tablets (doravirine) once daily does not have a clinically meaningful effect on the pharmacokinetics of metformin. 2. Administration of single dose metformin 1000 mg tablets alone or co-administered with multiple doses of MK-1439 100 mg tablets (doravirine) was generally well-tolerated.
FINAL REPORT DATE:	[redacted]-20[redacted]

SPONSOR:	**Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.**	
COMPOUND NAME:	Doravirine (MK-1439)	
INDICATION:	Treatment of Human immunodeficiency virus (HIV)-1 infection	
PROTOCOL TITLE:	Drug-Drug Interaction Study of MK-1439 (Doravirine) with MK-8742 + MK-5172 (Elbasvir + Grazoprevir)	
TRIAL IDENTIFIERS:	Protocol Number:	050
	Clinical Phase:	1
	IND Number:	112,796
TRIAL CENTERS:	[redacted], M.D., M.P.H., [redacted] USA	
DESIGN:	This was a nonrandomized, fixed-sequence, single-site, open-label trial of doravirine (also referred to as MK-1439), elbasvir (also referred to as MK-8742) and grazoprevir (also referred to as MK-5172) in 12 healthy male and female adult subjects 19 to 55 years of age. A dose of 100 mg doravirine was administered once daily (QD) on Days 1 to 5 of Period 1. Plasma samples for the assessment of doravirine pharmacokinetics (PK) were collected for 24 hours beginning on Day 5 of Period 1. Period 2 commenced after a washout period of at least 5 days (120 hours) from the last dose in 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. Plasma samples for the assessment of elbasvir and grazoprevir PK were collected for 24 hours beginning on Day 10 of Period 2. There was no washout following Period 2; rather Day 1 of Period 3 immediately followed Day 10 of Period 2. Starting immediately after the last PK sample 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. Plasma samples for assessment of doravirine, elbasvir and grazoprevir PK were collected for 24 hours beginning on Day 5 of Period 3. All study drug dosing was administered under fed conditions.	
	Duration of Study:	The duration of the study was approximately 7 weeks.

Objectives	Primary 1) Objective: To assess the effect of multiple oral doses of elbasvir and grazoprevir on the multiple dose plasma pharmacokinetics (eg, AUC0-24, Cmax, C24, and Tmax) of doravirine. 2) Objective: To assess the effect of multiple oral doses of doravirine on the multiple dose plasma pharmacokinetics (AUC0-24, Cmax, C24, and Tmax) of elbasvir and grazoprevir. Secondary 1) To evaluate the safety and tolerability of multiple doses of elbasvir + grazoprevir co-administered with multiple doses of doravirine.	
Hypotheses	Primary Hypothesis (Estimation): The effect of multiple oral doses of elbasvir and grazoprevir on the multiple dose plasma pharmacokinetics of doravirine will be estimated. That is, the true geometric mean ratio (GMR) (doravirine + elbasvir + grazoprevir)/doravirine alone for AUC0-24, Cmax and C24 of doravirine will be estimated. 1) The AUC0-24 of elbasvir is not meaningfully altered by concomitant administration of multiple doses of doravirine and elbasvir + grazoprevir as compared to that after multiple-dose administration of elbasvir + grazoprevir alone. That is, the true elbasvir AUC0-24 GMR (doravirine + elbasvir + grazoprevir)/(elbasvir + grazoprevir alone) is contained within the interval [0.50, 2.00]. 2) The AUC0-24 of grazoprevir is not meaningfully altered by concomitant administration of multiple doses of doravirine and elbasvir + grazoprevir as compared to that after multiple-dose administration of elbasvir + grazoprevir alone. That is, the true grazoprevir AUC0-24 GMR (doravirine + elbasvir + grazoprevir)/(elbasvir + grazoprevir alone) is contained within the interval [0.40, 5.00].	
Treatment groups	Period 1: Doravirine alone	100 mg doravirine (1 x 100 mg) administered QD on Days 1 to 5, N=12 Subjects

	Period 2: Elbasvir + grazoprevir co-administered	50 mg elbasvir (1 x 50 mg) and 200 mg grazoprevir (2 x 100 mg) co-administered QD on Days 1 to 10, N=12 Subjects
	Period 3: Doravirine + elbasvir + grazoprevir co-administered	100 mg doravirine (1 x 100 mg), 50 mg elbasvir (1 x 50 mg), and 200 mg grazoprevir (2 x 100 mg) co-administered, QD on Days 1 to 5, N=12 Subjects
Endpoints and definitions	Primary endpoint	Pharmacokinetics: Doravirine: AUC0-24, Cmax, C24, and Tmax Elbasvir and grazoprevir: AUC0-24, Cmax, C24, and Tmax
	Secondary endpoint	Safety and tolerability: Adverse experiences (AEs), laboratory safety tests, electrocardiograms (ECG), and vital signs.
Trial status	[redacted]-20[redacted] to [redacted]-20[redacted]	
Database lock	[redacted]-20[redacted]	
RESULTS AND ANALYSIS:	All analyses for PK and safety were performed according to the protocol.	

Subject Characteristics

	All Subjects	
	n	(%)
Subjects in population	12	
Gender		
Male	5	(41.7)
Female	7	(58.3)
Age (Years)		
0 to 18	0	(0.0)
19 to 55	12	(100.0)
>55	0	(0.0)
Mean	34.7	
SD	11.0	
Median	29.0	
Range	25 to 55	
Race		
American Indian Or Alaska Native	1	(8.3)
Black Or African American	2	(16.7)
White	9	(75.0)
Ethnicity		
Hispanic Or Latino	3	(25.0)
Not Hispanic Or Latino	9	(75.0)

Disposition of Subjects

	All Subjects	
	n	(%)
Subjects in population	12	
Trial Disposition		
Completed	12	(100.0)
Each subject is counted once for Trial Disposition based on the latest corresponding disposition record.		

Analysis population and time point description	The PK analysis population included the subset of 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. Compliance covered such considerations as exposure to treatment, availability of measurements and absence of major protocol deviations.
Summary	**Pharmacokinetics** The GMRs (90% CI) of doravirine AUC0-24, Cmax, and C24 (doravirine + elbasvir + grazoprevir / doravirine alone) were 1.56 (1.45, 1.68), 1.41 (1.25, 1.58), and 1.61 (1.45, 1.79), respectively. The GMRs (90% CI) of elbasvir AUC0-24, Cmax, and C24 (doravirine + elbasvir + grazoprevir / elbasvir + grazoprevir) were 0.96 (0.90, 1.02), 0.96 (0.91, 1.01), and 0.96 (0.89, 1.04), respectively. As the 90% CI of elbasvir AUC0-24 fell within the interval [0.50, 2.00], the primary hypothesis that the multiple-dose administration of doravirine together with elbasvir and grazoprevir does not meaningfully alter elbasvir PK was supported. The GMRs (90% CI) of grazoprevir AUC0-24, Cmax and C24 (doravirine + elbasvir + grazoprevir / (elbasvir + grazoprevir)) were 1.07 (0.94, 1.23), 1.22 (1.01, 1.47), and 0.90 (0.83, 0.96), respectively. As the 90% CI of grazoprevir AUC0-24 fell within the interval [0.40, 5.00], the primary hypothesis that the multiple-dose administration of doravirine together with elbasvir and grazoprevir does not meaningfully alter grazoprevir PK was supported.

Statistical Comparison of Plasma Pharmacokinetics of MK-1439 Following the Administration of 100 mg MK-1439 Once Daily for 5 Days and Co-administered with 50 mg MK-8742 and 200 mg MK-5172 Once Daily for 5 Days in Healthy Adult Subjects

MK-1439 Pharmacokinetic Parameter	MK-1439 Alone			MK-1439 + MK-8742 + MK-5172			MK-1439 + MK-8742 + MK-5172/ MK-1439 Alone		Pseudo Within-Subject %CV ‡
	N	GM†	95% CI	N	GM†	95% CI	GMR	90% CI	
AUC0-24 (µM*hr)	12	41.3	(35.5, 48.1)	12	64.6	(54.1, 77.3)	1.56	(1.45, 1.68)	9.9
Cmax (nM)	12	3400	(2950, 3910)	12	4770	(4080, 5590)	1.41	(1.25, 1.58)	16.1
C24 (nM)	12	814	(657, 1010)	12	1310	(1020, 1690)	1.61	(1.45, 1.79)	14.4
Tmax (hr)	12	3.98	(3.00, 4.00)	12	3.99	(2.98, 6.00)	.		.

MK-1439 Alone: QD oral dose of 100 mg MK-1439 Once Daily for 5 Days.

MK-1439 + MK-8742 + MK-5172: Oral dose of 50 mg MK-8742 and 200 mg MK-5172 administered QD for a total of 15 consecutive days (Days 1-10 in Period 2 and Days 1-5 in Period 3) and 100 mg MK-1439 QD (oral) on Days 1-5 of Period 3.

† Back-transformed least squares mean and confidence interval from mixed effects model performed on natural log-transformed values of AUC0-24, Cmax, and C24.

‡ Pseudo Within-Subject %CV=100×sqrt((σ_a^2 + σ_b^2 -2σ_{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.

* Median (min, max) reported for Tmax.

GM: Geometric least-squares mean, GMR: Geometric least-squares mean ratio, CI: Confidence interval.

Statistical Comparison of Plasma Pharmacokinetics of MK-8742 Following the Administration of 50 mg MK-8742 and 200 mg MK-5172 Once Daily for 10 Days and Co-administered with 100 mg MK-1439 Once Daily for 5 Days in Healthy Adult Subjects

MK-8742 Pharmacokinetic Parameter	MK-8742 + MK-5172			MK-1439 + MK-8742 + MK-5172			MK-1439 + MK-8742 + MK-5172/ MK-8742 + MK-5172		Pseudo Within-Subject %CV [‡]
	N	GM[†]	95% CI	N	GM[†]	95% CI	GMR	90% CI	
AUC0-24 (µM*hr)	12	3.89	(3.24, 4.67)	12	3.73	(3, 4.63)	0.96	(0.90, 1.02)	8.5
Cmax (nM)	12	298	(238, 373)	12	287	(222, 370)	0.96	(0.91, 1.01)	7.2
C24 (nM)	12	110	(88.8, 136)	12	106	(81.2, 138)	0.96	(0.89, 1.04)	10.1
Tmax (hr)	12	4.00	(2.98, 5.00)	12	4.00	(3.00, 5.00)	.		.

MK-8742 + MK-5172: QD oral dose of 50 mg MK-8742 and 200 mg MK-5172 Once Daily for 10 Days.

MK-1439 + MK-8742 + MK-5172: Oral dose of 50 mg MK-8742 and 200 mg MK-5172 administered QD for a total of 15 consecutive days (Days 1-10 in Period 2 and Days 1-5 in Period 3) and 100 mg MK-1439 QD (oral) on Days 1-5 of Period 3.

[†] Back-transformed least squares mean and confidence interval from mixed effects model performed on natural log-transformed values of AUC0-24, Cmax, and C24.

[‡] Pseudo Within-Subject %CV=100×sqrt((σ_a^2 + σ_b^2 -2σ_{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.

[*] Median (min, max) reported for Tmax.

GM: Geometric least-squares mean, GMR: Geometric least-squares mean ratio, CI: Confidence interval.

Statistical Comparison of Plasma Pharmacokinetics of MK-5172 Following the Administration of 50 mg MK-8742 and 200 mg MK-5172 Once Daily for 10 Days and Co-administered with 100 mg MK-1439 Once Daily for 5 Days in Healthy Adult Subjects

MK-5172 Pharmacokinetic Parameter	MK-8742 + MK-5172			MK-1439 + MK-8742 + MK-5172			MK-1439 + MK-8742 + MK-5172/ MK-8742 + MK-5172		Pseudo Within-Subject %CV ‡
	N	GM†	95% CI	N	GM†	95% CI	GMR	90% CI	
AUC0-24 (µM*hr)	12	5.64	(3.68, 8.66)	12	6.05	(4.12, 8.87)	1.07	(0.94, 1.23)	18.5
Cmax (nM)	12	1800	(1090, 2950)	12	2190	(1400, 3410)	1.22	(1.01, 1.47)	25.7
C24 (nM)	12	19.5	(14.2, 26.8)	12	17.5	(12.9, 23.8)	0.90	(0.83, 0.96)	9.9
Tmax (hr)	12	3.00	(2.00, 4.00)	12	3.00	(1.98, 4.00)	.		.

MK-8742 + MK-5172: QD oral dose of 50 mg MK-8742 and 200 mg MK-5172 Once Daily for 10 Days.

MK-1439 + MK-8742 + MK-5172: Oral dose of 50 mg MK-8742 and 200 mg MK-5172 administered QD for a total of 15 consecutive days (Days 1-10 in Period 2 and Days 1-5 in Period 3) and 100 mg MK-1439 QD (oral) on Days 1-5 of Period 3.

† Back-transformed least squares mean and confidence interval from mixed effects model performed on natural log-transformed values of AUC0-24, Cmax, and C24.

‡ Pseudo Within-Subject %CV=100×sqrt((σ_a^2 + σ_b^2 -2σ_{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.

* Median (min, max) reported for Tmax.

GM: Geometric least-squares mean, GMR: Geometric least-squares mean ratio, CI: Confidence interval.

Analysis description	**Primary Analysis:** Safety 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	The population included all subjects who received at least one dose of the investigational drug. This population was used for assessments of safety and tolerability. All 12 subjects were included in the assessment of safety and tolerability.

Summary	Doravirine was generally well tolerated in healthy adult subjects when administered alone or in combination with elbasvir and grazoprevir. Elbasvir and grazoprevir were also generally well tolerated when co-administered with or without doravirine. Across all three treatment periods, 6 of 12 subjects (50%) reported a total 9 treatment-emergent AEs and 3 Post Study AEs, including 1 SAE. The most common AEs were discolored feces, headache, and abnormal dreams which were reported by 2 (16.7%) subjects each. No other AE was reported by more than one subject. Four (4) subjects reported AEs which were considered drug-related by the Investigator and included headache in 1 (8.3%) subject after receiving 50 mg elbasvir and 200 mg grazoprevir, abnormal dreams in 2 (16.7%) subjects one after receiving 100 mg doravirine and one after receiving 50 mg elbasvir and 200 mg grazoprevir, and spontaneous abortion in 1 (8.3%) subject after receiving 100 mg doravirine, 50 mg elbasvir and 200 mg grazoprevir. One subject became pregnant during the study; the outcome of the pregnancy was spontaneous abortion. Since the cause of the spontaneous abortion could not be identified, and because the subject was pregnant throughout dosing with all three study medications, a causative relationship to study medication could not be ruled out. The spontaneous abortion was classified as an SAE and listed by the Investigator as related to all three study medications. With the exception of this SAE which was severe in intensity, all of the AEs were mild in intensity, of limited duration, and all resolved by the end of the study. There were no ECIs or deaths reported during the study, no discontinuations due to an AE, and no consistent treatment-related changes in routine clinical safety parameters, including blood chemistry, hematology, urinalysis, ECGs, or vital signs.

CONCLUSIONS:	1) Co-administration of multiple once daily 100 mg doses of doravirine with multiple once daily doses of 50 mg elbasvir + 200 mg grazoprevir resulted in modest increases in doravirine AUC, Cmax and C24 values of 56%, 41% and 61%, respectively. However, these increases are not considered clinically relevant. 2) Co-administration of multiple once daily doses of 50 mg elbasvir + 200 mg grazoprevir with multiple once daily doses of 100 mg doravirine results in similar elbasvir and grazoprevir exposure (AUC0-24) compared to that after a single oral dose of 50 mg elbasvir + 200 mg grazoprevir alone. 3) Co-administration of multiple oral daily doses of 100 mg doravirine with 50 mg elbasvir and 200 mg grazoprevir was generally well tolerated in healthy male and female subjects.
REPORT DATE:	[redacted]-20[redacted]

SPONSOR:	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.	
COMPOUND NAME:	MK-1439 (Doravirine)	
INDICATION:	Antiviral treatment for human immunodeficiency virus type 1 (HIV-1) infection	
PROTOCOL TITLE:	A Randomized, Open-Label, 3-Period Crossover Study to Evaluate the Pharmacokinetic Interaction of MK-1439 (Doravirine) and Ledipasvir/Sofosbuvir in Healthy Adult Subjects	
TRIAL IDENTIFIERS:	Protocol Number:	MK-1439-053
	Clinical Phase:	1
	EudraCT Number:	Not Applicable
	US IND Number:	112,796
TRIAL CENTER:	[redacted], MD [redacted] USA	
DESIGN:	**STUDY DESIGN:** This was an open-label, randomized, 3-period, crossover study to evaluate the PK interaction of doravirine and ledipasvir/sofosbuvir in 14 healthy adult subjects. On Day 1 of each period, subjects received a single oral dose of either doravirine alone, ledipasvir/sofosbuvir alone, or doravirine coadministered with ledipasvir/sofosbuvir in a randomized manner. Subjects received each treatment on 1 occasion. Serial blood samples were collected to characterize PK of ledipasvir (168 hours postdose), sofosbuvir and its metabolite, GS-331007 (120 hours postdose), and doravirine (72 hours postdose). There was a washout of 14 days between each dose. **DIAGNOSIS/INCLUSION CRITERIA:** Healthy adult male or female subjects ≥ 19 and ≤ 64 years of age, with a body mass index (BMI) ≥ 18.5 and ≤ 32.0 kg/m^2 at the prestudy (screening) visit were eligible to enter the study.	
	Planned duration of main phase:	8 weeks from screening to Day 7 of Period 3 9 weeks from screening to follow-up

OBJECTIVES:	**Primary:** 1: To assess the effect of a single oral dose of doravirine on the single oral dose plasma PK (e.g., AUC0-∞, AUC0-last, Cmax, Tmax, apparent terminal t½, CL/F [for parent only], and Vz/F [for parent only]) of ledipasvir/sofosbuvir, as reflected in the concentrations of ledipasvir and sofosbuvir and its metabolite, GS-331007. 2: To assess the effect of a single oral dose of ledipasvir/sofosbuvir on the single oral dose plasma PK (e.g., AUC0-∞, AUC0-last, Cmax, C24, Tmax, apparent terminal t½, CL/F, and Vz/F) of doravirine. **Secondary:** To evaluate the safety and tolerability of 100 mg doravirine and 90/400 mg ledipasvir/sofosbuvir when coadministered.
HYPOTHESES/ ESTIMATIONS:	**Primary:** Hypothesis 1a: The AUC0-∞ of ledipasvir after single oral dose administration of 90/400 mg ledipasvir/sofosbuvir coadministered with a single oral dose of 100 mg doravirine is similar to that after single oral dose administration of ledipasvir/sofosbuvir alone. That is, the true geometric mean ratio (GMR) (Ledipasvir/Sofosbuvir + Doravirine / Ledipasvir/Sofosbuvir Alone) for the AUC0-∞ of ledipasvir is contained within [0.7, 2.0]. Hypothesis 1b: The AUC0-∞ of sofosbuvir after single oral dose administration of 90/400 mg ledipasvir/sofosbuvir coadministered with a single oral dose of 100 mg doravirine is similar to that after single oral dose administration of ledipasvir/sofosbuvir alone. That is, the true GMR (Ledipasvir/Sofosbuvir + Doravirine / Ledipasvir/Sofosbuvir Alone) for the AUC0-∞ of sofosbuvir is contained within [0.7, 2.5]. Hypothesis 1c: The AUC0-∞ of GS-331007 after single oral dose administration of 90/400 mg ledipasvir/sofosbuvir coadministered with a single oral dose of 100 mg doravirine is similar to that after single oral dose administration of ledipasvir/sofosbuvir alone. That is, the true GMR (Ledipasvir/Sofosbuvir + Doravirine / Ledipasvir/Sofosbuvir Alone) for the AUC0-∞ of GS-331007 is contained within [0.8, 2.0]. Estimation 1: The Cmax of ledipasvir, sofosbuvir, and GS-331007 after single oral dose administration of 90/400 mg ledipasvir/sofosbuvir coadministered with a single oral dose of 100 mg doravirine will be estimated and compared with those after single oral dose administration of ledipasvir/sofosbuvir alone.

HYPOTHESES/ ESTIMATIONS (CONTINUED):	**Primary (Continued):** Estimation 2: The AUC0-∞, Cmax, and C24 of doravirine after single oral dose administration of 100 mg doravirine coadministered with a single oral dose of 90/400 mg ledipasvir/sofosbuvir will be estimated and compared with those after single oral dose administration of doravirine alone.	
TREATMENT GROUPS:	Ledipasvir/Sofosbuvir Alone	A single oral dose of 90 mg ledipasvir/400 mg sofosbuvir 14 subjects
	Ledipasvir/Sofosbuvir + Doravirine	Coadministration of a single oral dose of 90 mg ledipasvir/400 mg sofosbuvir and a single oral dose of 100 mg doravirine 14 subjects
	Doravirine Alone	A single oral dose of 100 mg doravirine 14 subjects

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 (005F) 100 mg (PhIII)	[redacted]
Harvoni® (ledipasvir, sofosbuvir) Tablets 90 mg/400 mg (Lot No. [redacted], Expiration date [redacted] 20[redacted]) were supplied by the Investigator.	

ENDPOINTS AND DEFINITIONS:	**Primary Endpoints**	**Pharmacokinetics** Ledipasvir and sofosbuvir AUC0-∞, AUC0-last, Cmax, Tmax, apparent terminal t½, CL/F, and Vz/F; GS-331007 AUC0-∞, AUC0-last, Cmax, Tmax, and apparent terminal t½; Doravirine AUC0-∞, AUC0-last, Cmax, C24, Tmax, apparent terminal t½, CL/F, and Vz/F.
	Secondary Endpoints	**Safety** Adverse events (AEs), physical examinations (PEs), vital signs (VS) (heart rate and blood pressure), 12-lead electrocardiograms (ECGs), and clinical laboratory tests (hematology, serum chemistry, and urinalysis).

DATABASE LOCK:	[redacted]-20[redacted]	**TRIAL STATUS:**	[redacted]-20[redacted] to [redacted]-20[redacted]

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

Fourteen (14) subjects were enrolled and completed the trial (no discontinuations, withdrawals, or replacements).

Disposition of Subjects

	MK-1439 Alone N (%)	Ledipasvir/ Sofosbuvir Alone N (%)	Ledipasvir/ Sofosbuvir+ MK-1439 N (%)	Overall N (%)
Subjects in population	14	14	14	14
Trial Disposition				
Completed	14 (100.0)	14 (100.0)	14 (100.0)	14 (100.0)
Discontinued	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

MK-1439 Alone: A single oral dose of 100 mg MK-1439
Ledipasvir/Sofosbuvir Alone: A single oral dose of 90 mg ledipasvir/400 mg sofosbuvir
Ledipasvir/Sofosbuvir + MK-1439: Coadministration of a single oral dose of 90 mg ledipasvir/400 mg sofosbuvir and a single oral dose of 100 mg MK-1439
Each subject is counted only once on each row within each treatment column based on the latest corresponding disposition record.

Summary of Subject Characteristics

	All Subjects	
	N	(%)
Subjects in population	14	
Gender		
Female	2	(14.3)
Male	12	(85.7)
Age (yrs)		
<19	0	(0.0)
19 to 29	3	(21.4)
30 to 39	7	(50.0)
40 to 49	2	(14.3)
50 to 59	1	(7.1)
60 to 64	1	(7.1)
>64	0	(0.0)
Mean	38.1	
SD	10.3	
Median	36.0	
Range	25 to 60	
Race		
American Indian/Alaska Native	1	(7.1)
Black or African American	3	(21.4)
White	10	(71.4)
Ethnicity		
Hispanic or Latino	1	(7.1)
Not Hispanic or Latino	13	(92.9)

Summary of Subject Characteristics (Continued)

Height (cm)		
Mean	176.4	
Range	162 to 191	
Weight (kg)		
Mean	78.0	
Range	56 to 93	
BMI (kg/m^2)		
Mean	25.2	
Range	20 to 31	

Age is calculated from the date of first dosing.
BMI = Body mass index
SD = Standard deviation

ANALYSIS DESCRIPTION:	**Primary Analysis – Pharmacokinetics** Individual values of AUC0-∞, AUC0-last, Cmax, and C24 (doravirine only) for ledipasvir, sofosbuvir, GS-331007, and doravirine were natural log (ln)-transformed prior to analysis and evaluated separately using 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 the treatment measurements within each subject via the REPEATED statement in SAS PROC MIXED. The Kenward-Roger adjustment was used to calculate the denominator degrees of freedom for the fixed-effects (DDFM=KR). The above statistical model by design had one missing observation for one of the treatments depending on the analyte comparison of interest. To address the primary hypotheses, two-sided 90% confidence intervals (CIs) for the GMRs (Ledipasvir/Sofosbuvir + Doravirine)/(Ledipasvir/Sofosbuvir Alone) for AUC0-∞ of ledipasvir, sofosbuvir, and GS-331007 were computed from the above model. If the 90% CI for AUC0-∞ of ledipasvir was within [0.7, 2.0], the 90% CI for AUC0-∞ of sofosbuvir was within [0.7, 2.5], and the 90% CI for AUC0-∞ of GS-331007 was within [0.8, 2.0], then the primary hypotheses were supported. The 95% CIs were constructed for the geometric means (GMs) for AUC0-∞ of ledipasvir, sofosbuvir, and GS-331007 by treatment. To address estimation 1, two-sided 90% CIs of GMRs [(Ledipasvir/Sofosbuvir + Doravirine)/(Ledipasvir/Sofosbuvir Alone)] for the Cmax of ledipasvir, sofosbuvir, and GS-331007 were computed from the same model.

ANALYSIS DESCRIPTION (CONTINUED)	**Primary Analysis – Pharmacokinetics (Continued):** The 95% CIs were constructed for the GMs of the Cmax of ledipasvir, sofosbuvir, and GS-331007 by treatment. To address estimation 2, two-sided 90% CIs of GMRs [(Ledipasvir/Sofosbuvir + Doravirine)/(Doravirine Alone)] for the AUC0-∞, AUC0-last, Cmax, and C24 of doravirine were computed from the same model. The 95% CIs were constructed for the GMs of the AUC0-∞, AUC0-last, Cmax, and C24 of doravirine by treatment.
ANALYSIS POPULATION AND TIME POINT DESCRIPTION:	*Per-Protocol* – This population consisted of the subset of 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. Compliance covered such considerations as exposure to treatment, availability of measurements, and absence of major protocol deviations. This population was used for the PK analyses. All 14 subjects completed the study and were included in the PK analyses.
SUMMARY:	**Pharmacokinetics:** **Ledipasvir** The statistical comparison and summary statistics of plasma ledipasvir PK following the administration of a single oral dose of 90 mg ledipasvir/400 mg sofosbuvir with and without the coadministration of a single oral dose of 100 mg doravirine in healthy adult subjects are presented in the following table. Ledipasvir AUC0-∞ and Cmax GMRs (90% CIs) for (Ledipasvir/Sofosbuvir + Doravirine)/(Ledipasvir/Sofosbuvir Alone) were 0.92 (0.80, 1.06) and 0.91 (0.80, 1.02), respectively. AUC0-∞ of ledipasvir after single oral dose administration of ledipasvir/sofosbuvir coadministered with a single oral dose of doravirine was similar to that after single oral dose administration of ledipasvir/sofosbuvir alone since the hypothesis that the true GMR is contained within [0.7, 2.0] was supported. Tmax and apparent terminal t½ of ledipasvir were similar for both treatments.

Statistical Comparison and Summary Statistics of Ledipasvir Plasma Pharmacokinetics Following the Administration of a Single Oral Dose of 90 mg Ledipasvir/400 mg Sofosbuvir With and Without the Coadministration of a Single Oral Dose of 100 mg MK-1439 in Healthy Adult Subjects

Ledipasvir Pharmacokinetic Parameters	Ledipasvir/ Sofosbuvir Alone			Ledipasvir/Sofosbuvir + MK-1439			(Ledipasvir/Sofosbuvir + MK-1439)/ (Ledipasvir/ Sofosbuvir Alone)		Pseudo Within Subject %CV[†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC0-∞[‡] (ng•hr/mL)	14	8080	(6060, 10800)	14	7450	(5470, 10100)	0.92	(0.80, 1.06)	20.2
AUC0-last[‡] (ng•hr/mL)	14	7610	(5680, 10200)	14	7050	(5160, 9630)	0.93	(0.80, 1.07)	20.8
Cmax[‡] (ng/mL)	14	248	(182, 339)	14	225	(165, 308)	0.91	(0.80, 1.02)	17.8
Tmax[§] (hr)	14	5.00	(5.00, 8.00)	14	5.00	(5.00, 6.01)			
Apparent terminal t½[‖] (hr)	14	41.96	31.9	14	41.59	24.9			
CL/F[‖] (L/hr)	14	11.1	52.4	14	12.1	56.9			
Vz/F[‖] (L)	14	674	72.2	14	725	70.7			

Ledipasvir/Sofosbuvir Alone: A single oral dose of 90 mg ledipasvir/400 mg sofosbuvir
Ledipasvir/Sofosbuvir + MK-1439: Coadministration of a single oral dose of 90 mg ledipasvir/400 mg sofosbuvir and a single oral dose of 100 mg MK-1439
[†]Pseudo within-subject %CV = 100 x Sqrt[(σ^2_B + σ^2_C - 2*σ_{BC})/2], where σ^2_B and σ^2_C are the estimated variance on the log scale for the 2 treatment groups, and σ_{BC} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for Tmax.
[‖]Geometric mean and geometric percent coefficient of variation reported for apparent terminal t½, CL/F and Vz/F.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio

SUMMARY (CONTINUED):	**Pharmacokinetics (Continued):** **Sofosbuvir** The statistical comparison and summary statistics of plasma sofosbuvir PK following the administration of a single oral dose of 90 mg ledipasvir/400 mg sofosbuvir with and without the coadministration of a single oral dose of 100 mg doravirine in healthy adult subjects are presented in the following table. Sofosbuvir AUC0-∞ and Cmax GMRs (90% CIs) for (Ledipasvir/Sofosbuvir + Doravirine)/(Ledipasvir/Sofosbuvir Alone) were 1.04 (0.91, 1.18) and 0.89 (0.79, 1.00), respectively. AUC0-∞ of sofosbuvir after a single oral dose administration of ledipasvir/sofosbuvir coadministered with a single oral dose of doravirine was similar to that after a single oral dose administration of ledipasvir/sofosbuvir alone since the hypothesis that the true GMR is contained within [0.7, 2.5] was supported. Tmax and apparent terminal t1/2 of sofosbuvir were similar for both treatments.

Statistical Comparison and Summary Statistics of Sofosbuvir Plasma Pharmacokinetics Following the Administration of a Single Oral Dose of 90 mg Ledipasvir/400 mg Sofosbuvir With and Without the Coadministration of a Single Oral Dose of 100 mg MK-1439 in Healthy Adult Subjects

Sofosbuvir Pharmacokinetic Parameters	Ledipasvir/ Sofosbuvir Alone			Ledipasvir/Sofosbuvir + MK-1439			(Ledipasvir/Sofosbuvir + MK-1439)/ (Ledipasvir/ Sofosbuvir Alone)		Pseudo Within Subject %CV[†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC0-∞[‡] (ng•hr/mL)	14	1130	(886, 1440)	14	1170	(949, 1440)	1.04	(0.91, 1.18)	19.1
AUC0-last[‡] (ng•hr/mL)	14	1110	(866, 1420)	14	1150	(934, 1420)	1.04	(0.91, 1.18)	19.0
Cmax[‡] (ng/mL)	14	1190	(949, 1500)	14	1060	(829, 1350)	0.89	(0.79, 1.00)	17.9
Tmax[§] (hr)	14	0.50	(0.50, 2.50)	14	0.67	(0.51, 2.50)			
Apparent terminal t½[‖] (hr)	14	0.49	51.1	14	0.49	35.9			
CL/F[‖] (L/hr)	14	354	42.8	14	342	37.1			
Vz/F[‖] (L)	14	251	80.0	14	242	46.8			

Ledipasvir/Sofosbuvir Alone: A single oral dose of 90 mg ledipasvir/400 mg sofosbuvir
Ledipasvir/Sofosbuvir + MK-1439: Coadministration of a single oral dose of 90 mg ledipasvir/400 mg sofosbuvir and a single oral dose of 100 mg MK-1439
[†]Pseudo within-subject %CV = 100 x Sqrt[(σ^2_B + σ^2_C - 2*σ_{BC})/2], where σ^2_B and σ^2_C are the estimated variance on the log scale for the 2 treatment groups, and σ_{BC} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for Tmax.
[‖]Geometric mean and geometric percent coefficient of variation reported for apparent terminal t½, CL/F and Vz/F.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio

SUMMARY (CONTINUED):	**Pharmacokinetics (Continued):** **GS-331007** The statistical comparison and summary statistics of plasma GS-331007 PK following the administration of a single oral dose of 90 mg ledipasvir/400 mg sofosbuvir with and without the coadministration of a single oral dose of 100 mg doravirine in healthy adult subjects are presented in the following table. GS-331007 AUC0-∞ and Cmax GMRs (90% CIs) for (Ledipasvir/Sofosbuvir + Doravirine)/(Ledipasvir/Sofosbuvir Alone) were 1.03 (0.98, 1.09) and 1.03 (0.97, 1.09), respectively. AUC0-∞ of GS-331007 after a single oral dose administration of ledipasvir/sofosbuvir coadministered with a single oral dose of doravirine was similar to that after a single oral dose administration of ledipasvir/sofosbuvir alone since the hypothesis that the true GMR is contained within [0.8, 2.0] was supported. Tmax and apparent terminal t1/2 of GS-331007 were similar for both treatments.

Statistical Comparison and Summary Statistics of GS-331007 Plasma Pharmacokinetics Following the Administration of a Single Oral Dose of 90 mg Ledipasvir/400 mg Sofosbuvir With and Without the Coadministration of a Single Oral Dose of 100 mg MK-1439 in Healthy Adult Subjects

GS-331007 Pharmacokinetic Parameters	Ledipasvir/ Sofosbuvir Alone			Ledipasvir/Sofosbuvir + MK-1439			(Ledipasvir/Sofosbuvir + MK-1439)/ (Ledipasvir/ Sofosbuvir Alone)		Pseudo Within Subject %CV[†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC0-∞[‡] (ng•hr/mL)	14	15800	(13900, 18000)	14	16400	(14400, 18600)	1.03	(0.98, 1.09)	7.4
AUC0-last[‡] (ng•hr/mL)	14	15100	(13200, 17300)	14	15700	(13800, 18000)	1.04	(0.99, 1.10)	7.9
Cmax[‡] (ng/mL)	14	981	(866, 1110)	14	1010	(877, 1160)	1.03	(0.97, 1.09)	8.8
Tmax[§] (hr)	14	2.76	(1.00, 4.03)	14	2.75	(1.01, 5.00)			
Apparent terminal t½[‖] (hr)	14	27.67	18.8	14	27.40	15.6			

Ledipasvir/Sofosbuvir Alone: A single oral dose of 90 mg ledipasvir/400 mg sofosbuvir
Ledipasvir/Sofosbuvir + MK-1439: Coadministration of a single oral dose of 90 mg ledipasvir/400 mg sofosbuvir and a single oral dose of 100 mg MK-1439
[†]Pseudo within-subject %CV = 100 x Sqrt[(σ^2_B + σ^2_C - 2*σ_{BC})/2], where σ^2_B and σ^2_C are the estimated variance on the log scale for the 2 treatment groups, and σ_{BC} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for Tmax.
[‖]Geometric mean and geometric percent coefficient of variation reported for apparent terminal t½.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio

SUMMARY (CONTINUED):	**Pharmacokinetics (Continued):** **Doravirine** The statistical comparison and summary statistics of plasma doravirine PK following the administration of a single oral dose of 100 mg doravirine with and without the coadministration of a single oral dose of 90 mg ledipasvir/400 mg sofosbuvir in healthy adult subjects are presented in the following table. Doravirine PK increased slightly following coadministration with ledipasvir and sofosbuvir. Doravirine AUC0-∞, Cmax, and C24 GMRs (90% CIs) for (Ledipasvir/Sofosbuvir + Doravirine)/(Doravirine Alone) were 1.15 (1.07, 1.24), 1.11 (0.97, 1.27), and 1.24 (1.13, 1.36), respectively. The median Tmax of doravirine occurred 1 hour earlier (3.00 hours postdose) following coadministration of doravirine with ledipasvir/sofosbuvir compared to following administration of doravirine alone (4.00 hours postdose). The GM apparent terminal t½ of doravirine was similar (approximately 14 hours) for both treatments.

Statistical Comparison and Summary Statistics of MK-1439 Plasma Pharmacokinetics Following the Administration of a Single Oral Dose of 100 mg MK-1439 With and Without the Coadministration of a Single Oral Dose of 90 mg Ledipasvir/400 mg Sofosbuvir in Healthy Adult Subjects

MK-1439 Pharmacokinetic Parameters	MK-1439 Alone			Ledipasvir/Sofosbuvir + MK-1439			(Ledipasvir/Sofosbuvir + MK-1439)/ (MK-1439 Alone)		Pseudo Within Subject %CV[†]
	N	GM	95% CI	N	GM	95% CI	GMR	90% CI	
AUC0-∞[‡] (µM•hr)	14	36.3	(30.2, 43.7)	14	41.8	(36.2, 48.3)	1.15	(1.07, 1.24)	11.0
AUC0-last[‡] (µM•hr)	14	34.8	(29.3, 41.4)	14	40.4	(35.2, 46.3)	1.16	(1.08, 1.25)	10.7
Cmax[‡] (nM)	14	1670	(1400, 1990)	14	1850	(1550, 2210)	1.11	(0.97, 1.27)	20.1
C24[‡] (nM)	14	550	(438, 690)	14	682	(568, 818)	1.24	(1.13, 1.36)	13.9
Tmax[§] (hr)	14	4.00	(1.00, 6.00)	14	3.00	(0.50, 6.00)			
Apparent terminal t½[‖] (hr)	14	14.25	25.6	14	13.63	26.8			
CL/F[‖] (L/hr)	14	6.52	30.8	14	5.60	26.4			
Vz/F[‖] (L)	14	134	25.0	14	110	24.8			

MK-1439 Alone: A single oral dose of 100 mg MK-1439
Ledipasvir/Sofosbuvir + MK-1439: Coadministration of a single oral dose of 90 mg ledipasvir/400 mg sofosbuvir and a single oral dose of 100 mg MK-1439
[†]Pseudo within-subject %CV = 100 x Sqrt[(σ^2_A + σ^2_C - 2*σ_{AC})/2], where σ^2_A and σ^2_C are the estimated variance on the log scale for the 2 treatment groups, and σ_{AC} is the corresponding estimated covariance, each obtained from the linear mixed-effects model.
[‡]Back-transformed least-squares mean and confidence interval from the linear mixed-effects model performed on natural log-transformed values.
[§]Median (Minimum, Maximum) reported for Tmax.
[‖]Geometric mean and geometric percent coefficient of variation reported for apparent terminal t½, CL/F and Vz/F.
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio

ANALYSIS DESCRIPTION:	**Secondary Analysis – Safety** Incidence of the number of subjects with AEs was descriptively summarized and listed by treatment. Incidence of the number of subjects with drug-related AEs was also descriptively summarized by treatment. Since no clinically meaningful changes in individual values for laboratory safety tests, ECGs, and VS were observed, summary statistics were not provided.
ANALYSIS POPULATION AND TIME POINT DESCRIPTION:	*All Subjects as Treated Population* - All subjects who received at least 1 dose of the investigational drugs were included in the analysis population. This population was used for assessments of safety and tolerability. All 14 subjects were included in the evaluation of safety.

SUMMARY:	Administration of a single oral dose of 100 mg doravirine, a single oral dose of 90 mg ledipasvir/400 mg sofosbuvir, or coadministration of 100 mg doravirine with 90 mg ledipasvir/ 400 mg sofosbuvir was generally well tolerated in healthy adult male and female subjects. Six (6) subjects (43%) reported at least 1 treatment-emergent adverse event (TEAE). No TEAE was reported by more than one subject. Two (2) subjects (14%) reported a drug-related TEAE with 1 subject reporting the drug-related TEAE of headache following coadministration of doravirine and ledipasvir/sofosbuvir and 1 subject reporting the drug-related TEAE of somnolence following administration of both doravirine alone and when coadministered with ledipasvir/sofosbuvir. All TEAEs were of mild intensity and resolved by study conclusion. There were no serious adverse events (SAEs), events of clinical interest (ECI), discontinuations due to TEAEs, or deaths during the study. One (1) subject signed the informed consent form (ICF), but was not randomized to treatment due to a positive pregnancy test at Period 1 check-in. There were no clinically meaningful treatment-related changes in laboratory, VS, or ECG measures.
CONCLUSIONS:	1. Coadministration of a single oral dose of 90 mg ledipasvir/400 mg sofosbuvir and a single oral dose of 100 mg doravirine results in similar ledipasvir, sofosbuvir, and GS-331007 exposure (AUC0-∞) compared to that after a single oral dose of 90 mg ledipasvir/400 mg sofosbuvir alone. 2. Coadministration of a single oral dose of 90 mg ledipasvir/400 mg sofosbuvir with a single oral dose of 100 mg doravirine has a small but not clinically meaningful effect on doravirine PK. Doravirine AUC0-∞, Cmax, and C24 increased by 15%, 11%, and 24% following coadministration compared to doravirine alone. 3. Coadministration of a single oral dose of 100 mg doravirine and a single oral dose of 90 mg ledipasvir/400 mg sofosbuvir was generally well tolerated in healthy adult male and female subjects.
REPORT DATE:	Final: [redacted]-20[redacted]

SPONSOR:	**Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.**	
COMPOUND NAME:	Doravirine (MK-1439), 25 mg or 200 mg, tablet formulation	
INDICATION:	Treatment of human immunodeficiency virus type 1 (HIV-1) infection	
PROTOCOL TITLE:	A Multiple Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antiretroviral Activity of MK-1439 in HIV-1-Infected Patients	
TRIAL IDENTIFIERS:	Protocol Number:	005
	Clinical Phase:	1b
	EudraCT Number:	2011-003508-19
	IND Number:	112,796
ETHICS:	This trial was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.	
TRIAL CENTERS:	This trial was conducted at 1 trial center in [redacted], Germany.	
DESIGN:	This was a double-blind, randomized, placebo-controlled, multiple-panel study to evaluate the safety, tolerability, pharmacokinetics (PK), and antiretroviral (ARV) activity of doravirine as short term monotherapy in ARV therapy (ART)-naïve, HIV-1-infected subjects. Two panels (Panels A and B) of 9 subjects each were randomized to receive doravirine or matching placebo (in a 6:3 ratio, respectively). Subjects in Panel A received doravirine 25 mg or matching placebo and subjects in Panel B received doravirine 200 mg or matching placebo once daily for 7 days.	
	Duration of main phase:	Approximately 25 weeks

Objectives	**Primary Objectives:** 1. To evaluate the ARV activity of doravirine at the studied doses for 7 consecutive days in HIV-1-infected male subjects. 2. To evaluate the safety and tolerability of doravirine at the studied doses for 7 consecutive days in HIV-1-infected male subjects. **Secondary Objectives:** 1. To evaluate the plasma PK profile (eg, plasma concentration at 24 hours [C24], area under the concentration-time curve from 0-24 hours [AUC0-24], maximum concentration [Cmax], time to Cmax [Tmax], and apparent terminal elimination half-life [t1/2]) of doravirine at the studied doses after administration for 7 consecutive days in HIV-1-infected subjects. 2. To evaluate the PK-pharmacodynamic (PD) association of doravirine with viral load reduction to refine the clinical dose range.	
Hypotheses	**Primary Hypotheses:** 1. At a dose that is sufficiently safe and generally well tolerated in HIV-1-infected male subjects, doravirine administered for 7 consecutive days has superior ARV activity compared with placebo, as measured by change from baseline in plasma HIV-1 RNA (log10 copies/mL) at the Day 7, 24-hour postdose time point (that is, the difference between doravirine versus placebo in plasma HIV-1 RNA change from baseline is less than -1 log10 copies/mL). 2. Administration of doravirine at the studied doses for 7 days is sufficiently safe and well tolerated in HIV-1-infected male subjects, based on assessment of clinical and laboratory adverse experiences (AEs), to permit continued clinical investigation. **Secondary Hypothesis:** 1. At a once daily dose that is sufficiently safe and generally well tolerated, the geometric mean (GM) of doravirine C24 exceeds 54 nM on Day 7 of dosing.	
Treatment groups	Panel A	Doravirine 25 mg once daily × 7 days; n=6 Doravirine placebo once daily × 7 days; n=3
	Panel B	Doravirine 200 mg once daily × 7 days; n=6 Doravirine placebo once daily × 7 days; n=3

Endpoints and definitions	Primary Endpoints	HIV-1 RNA	The change from baseline in plasma HIV-1 RNA (log10 copies/mL) from doravirine dose groups (Panels A and B), and placebo when administered for 7 consecutive days as a monotherapy.
		Safety	Adverse events, vital signs (VS), 12-lead electrocardiograms (ECGs), and laboratory safety evaluations (hematology, blood chemistry, and urinalysis) at prespecified time points.
	Secondary Endpoint	Pharmacokinetics	Doravirine C24, AUC0-24, Cmax, Tmax), and apparent t1/2.
Trial Status	31-OCT-2011 first subject first visit to 10-APR-2012 last subject last visit.		
Database lock	15-OCT-2012		
RESULTS AND ANALYSIS:	All analyses for PD, safety, PK (except apparent t1/2), and PK/PD were performed according to the protocol. For PK analyses, the protocol stated that harmonic mean and jackknife SD would be provided for apparent t1/2. Instead, GM and percent geometric coefficient of variation (GCV%) were provided, in order to be consistent with reporting done in other studies. In addition, for estimation purposes, the accumulation ratio of doravirine was assessed through the construction of a 90% confidence interval (CI) for the geometric means ratio (Day 7/Day 1) of AUC0-24, C24, and Cmax based on a linear-mixed model with fixed effects of treatment, day, and treatment by day interaction; and subject within treatment as a random effect. For the PD time profile across days assessment, due to an inconsistency in the slope of change in log10 plasma HIV-1 RNA versus day over the different groups, the model added the term of group by day interaction, which permitted point estimates and 95% CIs of the population mean slope by group. No subjects were discontinued from the study. All available data from 18 subjects dosed during the study were included in the PD, safety and tolerability, and PK/PD analysis.		

Subject Characteristics

	MK-1439 25 mg QD for 7 days		MK-1439 200 mg QD for 7 days		Placebo QD for 7 days		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	6		6		6		18	
Gender								
Male	6	(100.0)	6	(100.0)	6	(100.0)	18	(100.0)
Age (Years)								
0 to 17	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
18 to 55	6	(100.0)	6	(100.0)	6	(100.0)	18	(100.0)
>55	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Mean	36.7		34.8		26.8		32.8	
SD	5.8		8.4		1.0		7.1	
Median	36.5		35.0		27.0		30.5	
Range	28 to 43		24 to 45		25 to 28		24 to 45	
Race								
White	6	(100.0)	6	(100.0)	6	(100.0)	18	(100.0)
Ethnicity								
Not Hispanic Or Latino	6	(100.0)	6	(100.0)	6	(100.0)	18	(100.0)
Viral Load (copies/mL)								
Subjects with data	6		6		6		18	
Mean	76350.0		48716.7		162550.0		95872.2	
SD	43351.4		46000.2		175292.7		112699.2	
Median	92250.0		30400.0		116250.0		56600.0	
Range	18400.0 to 123000.0		10800.0 to 136000.0		15700.0 to 483000.0		10800.0 to 483000.0	
CD4 (/microL)								

Subject Characteristics

	MK-1439 25 mg QD for 7 days		MK-1439 200 mg QD for 7 days		Placebo QD for 7 days		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
CD4 (/microL)								
Subjects with data	6		6		6		18	
Mean	387.8		374.8		351.0		371.2	
SD	77.7		78.4		85.0		77.2	
Median	403.5		346.0		329.0		351.0	
Range	277.0 to 470.0		296.0 to 474.0		250.0 to 490.0		250.0 to 490.0	

QD=Once Daily

Disposition of Subjects

	MK-1439 25 mg QD for 7 days		MK-1439 200 mg QD for 7 days		Placebo QD for 7 days		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	6		6		6		18	
Trial Disposition								
Completed	6	(100.0)	6	(100.0)	6	(100.0)	18	(100.0)

Each subject is counted once for Trial Disposition based on the latest corresponding disposition record.
QD=Once Daily

Analysis description	**Primary Analysis - Pharmacodynamics** A formal statistical testing on the primary hypothesis, that the 7-day treatment of doravirine has superior ARV activity compared with placebo, was performed using data from Panels A and B. The change from baseline in log10 plasma HIV-1 RNA on Day 7 was analyzed using an analysis of covariance model including the Panel A and Panel B data. The analysis of covariance model contained factors of the group (the studied doses of doravirine and placebo), baseline CD4 cell count, and baseline log10 plasma HIV-1 RNA as covariates. Placebo data were pooled across Panels A and B for the comparison of change in plasma HIV-1 RNA from baseline. At the 200-mg dose, a 2-sided 90% CI for the difference between doravirine and placebo in log10 plasma HIV-1 RNA change from baseline was constructed. Since the upper bound of this 90% CI was smaller than -1, the primary hypothesis was supported. Similarly, at the 25-mg dose, a 2-sided 90% CI for the difference between doravirine and placebo in log10 plasma HIV-1 RNA change from baseline was also constructed. The primary hypothesis was also supported at 25 mg on Day 7.
Analysis population and time point description	The population for PD analysis was the Per Protocol (PP) population. The PP population was a subset of the All Subjects as Treated (ASaT) population and consisted of subjects who received at least 1 dose of the investigational drug and 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. All 18 subjects were included in the evaluation of PD.
Summary	**Pharmacodynamics** At the 200-mg dose, the least-squares (LS) mean difference between doravirine and placebo in log10 plasma HIV-1 RNA change from baseline and corresponding 90% CI was -1.26 (-1.51, -1.02), where the upper bound of this 90% CI was smaller than -1. The primary hypothesis that at least 1 dose level of doravirine administered for 7 consecutive days has superior ARV activity compared with placebo was supported. Similarly, at the 25-mg dose, the LS mean difference between doravirine and placebo in log10 plasma HIV-1 RNA change from baseline and corresponding 90% CI was -1.37 (-1.60, -1.14). There was no difference in the viral load reduction following 25 mg compared with 200 mg.

Summary of Change From Baseline in log10 Plasma HIV RNA (log10 copies/mL) on Day 7 Following the Administration of Once Daily Multiple Doses of MK-1439 25 mg, 200 mg and Placebo for 7 Days in HIV-1 Infected Subjects

Treatment	N	LS mean (95% CI)	Treatment difference	LS mean difference (90% CI)	P-value	rMSE †
MK-1439 25 mg	6	-1.52 (-1.71, -1.32)	MK-1439 25 mg - Placebo	-1.37 (-1.60, -1.14)	<0.001	0.221
MK-1439 200 mg	6	-1.41 (-1.61, -1.21)	MK-1439 200 mg - Placebo	-1.26 (-1.51, -1.02)	<0.001	
Placebo	6	-0.15 (-0.35, 0.06)	MK-1439 200 mg - 25 mg	0.11 (-0.13, 0.34)	0.4371	

† rMSE: Square root of conditional mean square error (residual error) from an analysis of covariance (ANCOVA) model for log10 plasma HIV RNA. When multiplied by 100, provides estimate of the pooled between-subject coefficient of variation.
LS = Least-squares; CI = Confidence interval.

Analysis description	**Primary Analysis - Safety and Tolerability** Safety and tolerability of doravirine at the studied doses for 7 consecutive days in HIV-1-infected male subjects were evaluated by clinical assessment of AEs and other safety measurements (eg, VS, ECGs, and safety laboratory assessments). Depending on the safety parameter, the change from baseline was computed on the original scale (raw change from baseline) or on the log scale and back-transformed for reporting (percent change from baseline). No summary statistics were computed as no clinically relevant change in safety laboratory tests, ECGs, or VS were observed.
Analysis population and time point description	The population for safety and tolerability analysis was the ASaT population, which consisted of those subjects who received at least 1 dose of the investigational drug. All 18 subjects were included in the evaluation of safety and tolerability.
Summary	**Safety** Doravirine (25 and 200 mg) once daily for 7 days was generally well tolerated by the HIV-1-infected male subjects in this study. There were no ECIs or deaths reported, and no subject was discontinued due to an AE during this study. A total of 12 subjects (66.7%) reported AEs after doravirine or placebo and 3 subjects (16.7%) reported AEs that were considered study drug-related by the investigator. One (1) subject experienced a serious AE (SAE) of elevated hepatic enzymes due to increased alanine aminotransferase (ALT; approximately 20 × ULN) and aspartate aminotransferase (AST; approximately 15 × ULN) poststudy, beginning approximately 24 days after the first daily dose of doravirine 25 mg that was considered not related to the study drug by the investigator. This was classified as an SAE as the elevations in hepatic enzymes met the criteria prespecified in the protocol for

	Other Medical Event. The SAE was preceded by steadily increasing ALT and AST values beginning the day following the last dose of doravirine. Through additional evaluations, it was determined that the subject had a new concomitant Hepatitis C virus infection that was present prior to enrollment into the study. This subject recovered from the SAE of elevated hepatic enzymes 36 days following the first dose of study medication. The most frequently reported clinical AEs during the study were headache (4 subjects [22.2%], 2 after receiving 200-mg doravirine and 2 after receiving placebo), diarrhea (3 subjects [16.7%], 1 after receiving 25-mg doravirine, and 2 after receiving 200-mg doravirine), nausea (2 subjects [11.1%], 1 after receiving 25-mg doravirine and 1 after receiving 200-mg doravirine), and night sweats (2 subjects [11.1%], 1 after receiving 200-mg doravirine and 1 after receiving placebo). No clinically meaningful trends were observed for changes in VS, physical examinations, and ECGs as a function of treatment.

Analysis description	**Secondary Analysis - Pharmacokinetics** The C24 of doravirine was analyzed using a 1-way analysis of variance (ANOVA) model containing a single factor of treatment (the studied doses of doravirine) including only Day 7 data from Panels A and B. At the 200-mg dose, a 90% CI for the GM of C24 on Day 7 was constructed. If the lower bound of this 90% CI was greater than 54 nM, the secondary hypothesis that at 1 dose level of doravirine that is sufficiently safe and generally well tolerated, the GM of doravirine C24 exceeds 54 nM on Day 7 of dosing was supported. Similarly, at the 25-mg dose, a 90% CI for the GM of doravirine C24 on Day 7, was also constructed. The secondary hypothesis was also tested at 25 mg on Day 7. Point estimates and 90% CIs for the GM of AUC0-24 and Cmax on Day 7 were constructed for each dose group based on the same model used for C24.
Analysis population and time point description	The population for PK analysis was the PP population. The PP population was a subset of the ASaT population and consisted of those subjects who received at least 1 dose of the investigational drug and 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. Twelve (12) subjects who received doravirine were included in the evaluation of PK.

Summary	**Pharmacokinetics** The GM (90% CI) of doravirine C24 was 1540 (1150, 2060) and 251 (188, 335) nM on Day 7 following the administration of 200 and 25 mg once daily for 7 days, respectively. As the lower bound of the 90% CI of doravirine C24 was greater than 54 nM, the secondary hypothesis, that at 1 dose level of doravirine that is sufficiently safe and generally well tolerated, the GM of doravirine C24 exceeds 54 nM on Day 7 of dosing was supported.

Summary of Plasma Pharmacokinetics of MK-1439 on Day 7 Following the Administration of Once Daily Multiple Doses of 25 mg and 200 mg for 7 Days in HIV-1 Infected Subjects

Pharmacokinetic Parameter	MK1439-25 mg			MK1439-200 mg			rMSE †
	N	GM ‡	90 % CI	N	GM ‡	90% CI	
AUC0-24 (µM*hr) ‡	6	11.2	(9.35, 13.4)	6	62.2	(52.0, 74.4)	0.242
Cmax (nM) ‡	6	826	(727, 938)	6	4300	(3790, 4890)	0.172
C24 (nM) ‡	6	251	(188, 335)	6	1540	(1150, 2060)	0.392
Tmax (hr) §	6	1.00	(1.00, 2.00)	6	2.00	(1.00, 4.00)	
Apparent t1/2 (hr) ‖	6	32.4	33.9	6	41.3	16.5	

† rMSE: Square root of conditional mean square error (residual error) on log-scale from a one-way analysis of variance (ANOVA) model. When multiplied by 100, provides estimate of the pooled between-subject percent coefficient of variation on the raw scale.

‡ Back-transformed least squares mean and confidence interval from a one-way analysis of variance (ANOVA) model performed on natural log-transformed values.

§ Median (min, max) reported for Tmax.

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

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

CONCLUSIONS:	• Once daily doses of 25 and 200 mg of doravirine for 7 days showed similarly robust antiviral activity against HIV-1 without evidence for the emergence of viral resistance. • At the 25-mg and 200-mg doses, the geometric mean of doravirine C24 exceeds 54 nM on Day 7 of dosing. • Doravirine (25 and 200 mg) once daily for 7 days was generally well tolerated in HIV-1-infected subjects.
PUBLICATION(S):	Schurmann D, Sobotha C, Gilmartin J, Robberechts M, De Lepeleire I, Yee KL, et. al. A randomized, double-blind, placebo-controlled, short-term monotherapy study of doravirine in treatment-naive HIV-infected individuals. *AIDS* 2016;30:57-63
REPORT DATE:	06-JUN-2017

SPONSOR:	Merck Sharp & Dohme Corp., a Subsidiary of Merck & Co., Inc.	
COMPOUND NAME:	MK-1439	
INDICATION:	Human immunodeficiency virus (HIV)	
PROTOCOL TITLE:	A Single Dose Trial to Assess the Effect of MK-1439 on QTc Interval in Healthy Adult Volunteers	
TRIAL IDENTIFIERS:	Protocol Number:	017
	Clinical Phase:	1
	IND Number:	112,796
TRIAL CENTERS:	[redacted], United States of America	
DESIGN:	This was a single center, randomized, 3-period, 6-sequence, crossover trial designed to evaluate the effect of a single oral MK-1439 administration on the QT interval corrected with Fridericia's formula (QTcF) in healthy male and female subjects of 18 to 55 years of age (inclusive). The trial was placebo-controlled and double-blinded with respect to MK-1439. Moxifloxacin was administered as positive control in an open-label manner. The electrocardiograms (ECGs) were read by cardiovascular physicians, who were blinded to the trial treatments. Subjects participated in 3 treatment periods and each received the following treatments in a randomized sequence: - Treatment A: 1200 mg oral MK-1439 (supra-therapeutic dose) - Treatment B: 400 mg oral moxifloxacin - Treatment C: Matching oral placebo for MK-1439	
	Planned duration of main phase:	Approximately 3 months
	Planned duration of run-in phase:	Not applicable
	Planned duration of extension phase:	Not applicable

Objectives	Primary Objective: 1. To evaluate effects of a supra-therapeutic dose of MK-1439 on QTcF interval. Secondary Objectives: 1. To demonstrate sensitivity of this QTcF assay using moxifloxacin as a positive control. 2. The pharmacokinetic parameter values (area under the concentration time curve until 24 hours post-dose [AUC_{0-24hr}], maximum plasma concentration [C_{max}], time to reach maximum plasma concentration [T_{max}] and plasma concentration at 24 hours post-dose [C_{24hr}]) of MK-1439 will be calculated. 3. To evaluate the safety and tolerability of MK-1439 after administration of single supra-therapeutic oral dose to healthy young adult subjects. Exploratory Objective: 1. To describe changes in other ECG parameter values including PR and RR intervals, heart rate, QRS duration, T-wave morphology, presence of U-waves and outlier assessment.	
Hypotheses	Primary Hypothesis: 1. Administration of a single supra-therapeutic dose of MK-1439 does not prolong the QTcF interval to a clinically significant degree. Specifically, the true mean difference (1200 mg MK-1439 - placebo) in QTcF change from baseline is less than 10 msec. Secondary Hypothesis: 1. Administration of moxifloxacin is associated with an increase in QTcF interval. Specifically, the true mean difference (moxifloxacin - placebo) in QTcF change from baseline is larger than 5 msec at least at 1 relevant time point.	
Treatments groups	Treatment A	Single administration of 1200 mg (supra-therapeutic dose) MK-1439.
	Treatment B	Single administration of 400 mg moxifloxacin.
	Treatment C	Single administration matching oral placebo for MK-1439.

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

Product Description	Product Potency	Lot-No.
MK-1439 (100 mg tablet)	12 x 100 mg	[redacted]
Matching Placebo for MK-1439 (0 mg tablet)	0 mg	
Moxifloxacin* (400 mg tablet)	400 mg	[redacted]

Endpoints and definitions	Primary endpoint	Pharmacody-namic Endpoint	QTcFs were determined. After QT correction method evaluation there was enough evidence to suggest that the correction factor was not adequate and the analyses described for hypotheses 1 and 2 were re-run using population specific rate correction (QTcP). QTcF and QTcP observed values and changes from baseline were determined.
	Secondary endpoints	Pharmacoki-netic Endpoint	Pharmacokinetic endpoints derived included $AUC_{0\text{-}24hr}$, C_{max}, T_{max}, and C_{24hr}.
		Safety Endpoint	Safety was monitored throughout the trial by repeated clinical and laboratory evaluations. In addition, safety was assessed by the collection of adverse events (AEs), vital signs, and ECGs (including 24-hour Holter ECG assessments).
	Exploratory endpoints	Exploratory endpoint	Changes in ECG parameter values (PR and RR intervals, heart rate, QRS duration, T-wave morphology, presence of U-waves and outlier assessment) were described
Database lock	[redacted]-20[redacted]	Trial status	[redacted]-20[redacted] to [redacted]-20[redacted]
RESULTS AND ANALYSIS:	All analyses for safety and pharmacokinetics were performed according to the trial protocol.		

Table 1:Subject Disposition (Randomized Subjects)	
	Overall N = 45
Enrolled	45(100.0%)
Completed the Study	39(86.7%)
Discontinued from the Study	6(13.3%)
Reason for Discontinuation	
Adverse Event	0(00.0%)
Protocol Deviation	0(00.0%)
Consent Withdrawn	1(2.2%)
Loss to Follow-up	1(2.2%)
Death	0(00.0%)
Other*	4(8.9%)

N = number of subjects
Refer to Section 10.4 for more details of missing data.
* Three (3) subjects were permanently withdrawn due to non-compliance, 1 subject was excluded due to poor venous access after randomization, but prior to trial drug administration.

Analysis description	**Primary Analysis** Pharmacodynamics: QT Correction Method: The QTcF was used in order to correct for heart rate. The appropriateness of the correction factor was assessed graphically and *via* a simple linear regression of QTcF versus RR interval using placebo and pre-dose data. If the methods provided evidence that Fridericia's correction was inadequate, then additional correction methods were explored. Since Fridericia's correction did not appear to be adequate, a population correction factor was applied to obtain QTcP for each subject. A pairwise analysis of covariance (ANCOVA) model was used to analyze the difference of change from baseline in QTc for MK-1439 versus placebo, conducted separately at each time point. The model included a fixed effect to account for the order in which the treatments were administered (variable 'seqstar') and the corresponding difference in QTc at baseline as a covariate. To address the primary hypothesis that administration of a single supra-therapeutic dose of MK-1439 does not prolong the QTcP interval to a clinically significant degree, means and 2-sided 90% confidence interval (CI) (equivalent to 1-sided upper 95% CI) for the true mean difference (MK-1439 – placebo) in QTcP change from baseline were provided at each pre-specified time point. If all of the upper limits of the 90% CIs fell below 10 msec, the primary hypothesis that administration of a single supra-therapeutic dose of MK-1439 does not prolong the QTc interval to a clinically significant degree was supported. However, if any of the upper limits exceeded 10 msec, then there was insufficient evidence to accept the primary hypothesis. To address the secondary hypothesis, the 1-tailed p-value of the mean difference between moxifloxacin and placebo in QTcP change from baseline compared to 5 msec at each of the following time points (1, 2, 3, and 4 hours post-dose) was computed. The Hochberg's step-up method was applied to preserve the overall alpha level at 0.05 for the hypothesis testing. **Secondary Analysis** Pharmacokinetics: Plasma concentrations for MK-1439 were listed by treatment, subject, period, day, nominal time and actual time. This listing displays for each subject actual sample times, protocol scheduled sample times (nominal time), and the difference between the actual

and nominal sample time. The plasma concentrations obtained at each nominal time point were summarized using descriptive statistics.

Individual plasma concentrations versus actual sample times, were plotted by treatment for each analyte in linear and semi-logarithmic scale. Mean plasma concentrations versus nominal times were presented in linear and semi-logarithmic scale. All treatments were overlaid on the same plot.

All derived plasma MK-1439 pharmacokinetic parameter values were listed by treatment and subject and summarized descriptively by treatment. Individual values were listed for each MK-1439 pharmacokinetic parameter by treatment and (non-model-based) descriptive statistics were provided.

Safety:

Adverse events and concomitant medication were captured throughout the trial. All AEs reported were coded and classified using the Sponsor, in-house dictionary. Unless specified otherwise, AE summary counts of AEs were the number of subjects reporting AEs and not the number of events reported. The observed and percent change from baseline values of all safety laboratory assessments for clinical chemistry and hematology were summarized using descriptive statistics. Laboratory parameter values (clinical chemistry, hematology, and urinalysis), vital signs (blood pressure, heart rate etc.) and ECGs (including 24-hour Holter assessments) were assessed at designated time points during the trial. The abnormal laboratory values are flagged with 'L' (low) for values below the lower limit of the laboratory's normal range or 'H' (high) for values above the upper limit of the laboratory's normal range. Abnormal values were graded as not clinically significant (NCS) or clinically significant (CS). Clinically significant laboratory results are included in the AE listings.

Exploratory Analysis

Categorical Analysis:

Categorical analysis was performed for QTcF, QTcP, heart rate, PR and QRS values by treatment and time point as well as QTcF and QTcP change from baseline.

Other Analysis:

Means and 95% CIs for the QTcF, QTcP and QTcF and QTcP change-from-baseline were descriptively summarized for each treatment by time point. The values of ECG parameters of interest including PR, RR, heart rate, and QRS interval or duration were summarized using a similar model as applied to QTcF and QTcP.

	T-wave morphology and the presence of U-waves were summarized. Pharmacokinetic/Pharmacodynamic Relationship: An analysis of pharmacokinetic/pharmacodynamic relationship was performed.
Analysis population and time point description	The pharmacokinetic, pharmacodynamic, and exploratory analyses were performed on the Per-Protocol population defined as the subset of subjects whose data were included in the stated analyses and 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.

Summary	Pharmacodynamic Summary: The appropriateness of Fridericia's correction method was assessed and there was evidence to suggest that this correction factor was inadequate: QTcF versus RR estimated slope coefficient was 0.033 with the 95% CI of (0.026, 0.041) for the slope. Therefore, the analyses described for the primary and secondary hypotheses were re-run using the QTcP values. All results described below were obtained using a QTcP method, which was found to be an adequate adjustment for heart rate in this trial. Table 2 shows that for the primary comparison of the mean change from baseline of QTcP of 1200 mg MK-1439 (supra-therapeutic dose), MK-1439 versus placebo, the upper limit of the 90% CI did not exceed 10 msec at any time point post-dose, supporting the primary hypothesis that 1200 mg MK-1439 does not prolong the QTc to a clinically significant degree. The largest mean difference (90% CI) was 3.12 (0.824, 5.42), occurring at 5 hours post-dose. As indicated by the p-values in Table 3, the mean difference between moxifloxacin change from baseline and placebo was significantly greater than 5 msec at all time points from 1 through 4 hours post-dose, supporting the hypothesis that moxifloxacin increases the QTc interval (i.e., that the placebo-adjusted increase is greater than 5 msec), and thus demonstrating assay sensitivity for this trial. The largest effect (moxifloxacin – placebo) occurred at 2 hours post-dose, with mean (90% CI) of 13.1 (11.4, 14.8) msec, as shown in Table 2 and Table 3. None of the subjects had average QTcF or QTcP readings of >450 msec and all subjects had a QTcF and QTcP change from baseline of ≤30 msec at all treatments at all time points. Pharmacokinetic Summary Following a single oral MK-1439 dose at 1200 mg, concentrations increased rapidly with peak concentrations occurring at approximately 3.1 hours. Concentrations declined in a single exponential phase over the 24-hour sampling period. After a single 1200 mg dose, MK-1439 $AUC_{0\text{-}24hr}$ and C_{max} were 119 µM.hr and 9240 nM, respectively, and were generally comparable to the $AUC_{0\text{-}24hr}$ of 157 µM.hr and C_{max} of 11.200 nM observed in a previous trial in healthy adult male subjects. Safety Summary: Forty-four (44) of the 45 enrolled subjects received trial drug administration and 39 subjects successfully completed the trial as per protocol. In total, 6 subjects were permanently withdrawn from the trial: 2 subjects tested positive for alcohol on admission to the

	Clinical Research Unit (CRU) for Period 2 and Period 3, respectively; 1 subject tested positive for cotinine on admission to the CRU for Period 2; 1 subject was lost to follow-up; 1 subject was randomized, but discontinued due to poor venous access; and 1 subject withdrew consent. Single dose administrations of 1200 mg MK-1439 and 400 mg moxifloxacin doses were generally well tolerated. No deaths, serious adverse events (SAEs), events of clinical interest, pregnancies or AEs leading to discontinuation were reported. In total, 9 treatment-emergent adverse events (TEAEs) were reported for 5 (12.2%) subjects after placebo administration, 7 TEAEs were reported for 5 subjects (12.2%) following MK-1439 administration, and 4 TEAEs were reported for 4 (9.8%) subjects following moxifloxacin administration. All of these reported TEAEs were mild in intensity. Seven (7) TEAEs after placebo administration reported by 3 subjects (abdominal pain, diarrhea, nausea, dizziness and 3 events of headache) and 5 TEAEs after MK-1439 administration reported by 3 subjects (flatulence, arthralgia, dry skin, and 2 events of headache), were considered related to the trial drug. One (1) TEAE (nausea) reported by 1 subject after moxifloxacin treatment was considered related to the trial drug. Within any treatment group no TEAEs were reported by more than 1 subject. All AEs were limited in duration. There were no clinically significant abnormal clinical laboratory test results, vital signs, ECG findings, or physical examination findings.

Table 2:Statistical Analysis Primary Hypothesis: Placebo-adjusted Mean Change from Baseline in QTcP (ΔΔQTcP) Following a Single Dose of Placebo/1200 mg MK-1439/400 mg Moxifloxacin to Healthy Fasted Adult Subjects

		QTcP Value (msec)			Change from Baseline (msec)		Difference in change from baseline from Placebo (msec)	
Treatment	**Time (h)**	**N**	**Mean**	**95% CI**	**Mean**	**95% CI**	**LSMean Difference**	**90% CI**
Placebo	0	40	402	(397, 408)				
	1	39	400	(395, 405)	-3.11	(-4.93, -1.30)		
	2	40	400	(395, 404)	-2.79	(-4.93, -0.653)		
	3	40	400	(395, 405)	-2.01	(-4.20, 0.178)		
	4	40	402	(397, 406)	-0.769	(-2.70, 1.16)		
	5	40	400	(396, 405)	-2.20	(-5.39, 0.995)		
	6	40	396	(391, 401)	-6.23	(-9.02, -3.44)		
	12	39	400	(396, 404)	-3.29	(-5.78, -0.814)		
	24	39	400	(395, 405)	-2.92	(-5.14, -0.712)		
1200 mg oral MK-1439	0	41	400	(396, 405)				
	1	41	399	(394, 404)	-1.49	(-3.22, 0.240)	1.15	(-0.902, 3.21)
	2	41	399	(394, 404)	-1.38	(-3.06, 0.305)	1.11	(-0.748, 2.97)
	3	41	402	(397, 407)	1.23	(-0.698, 3.16)	2.34	(0.406, 4.28)
	4	41	402	(396, 407)	1.28	(-0.791, 3.35)	1.02	(-1.10, 3.15)
	5	41	402	(398, 407)	1.79	(-1.15, 4.74)	3.12	(0.824, 5.42)
	6	41	398	(393, 402)	-2.75	(-5.10, -0.400)	2.53	(0.434, 4.62)
	12	41	400	(396, 405)	-0.226	(-3.13, 2.68)	2.13	(-0.021, 4.29)
	24	41	398	(394, 403)	-1.94	(-4.36, 0.491)	0.530	(-1.45, 2.51)
400 mg oral Moxifloxacin	0	41	403	(398, 407)				
	1	40	411	(406, 416)	8.01	(5.86, 10.2)	12.8	(10.9, 14.6)
	2	40	412	(407, 417)	9.10	(7.39, 10.8)	13.1	(11.4, 14.8)
	3	41	412	(407, 417)	9.01	(7.19, 10.8)	12.1	(10.2, 14.0)
	4	40	413	(408, 418)	9.85	(7.42, 12.3)	11.4	(9.36, 13.4)
	5	41	408	(403, 412)	4.81	(1.98, 7.65)	8.25	(6.12, 10.4)
	6	41	404	(400, 409)	1.49	(-0.830, 3.81)	8.58	(6.38, 10.8)
	12	39	406	(401, 411)	3.28	(0.504, 6.06)	7.50	(5.15, 9.86)

Table 2:Statistical Analysis Primary Hypothesis: Placebo-adjusted Mean Change from Baseline in QTcP (ΔΔQTcP) Following a Single Dose of Placebo/1200 mg MK-1439/400 mg Moxifloxacin to Healthy Fasted Adult Subjects

		QTcP Value (msec)			Change from Baseline (msec)		Difference in change from baseline from Placebo (msec)	
Treatment	**Time (h)**	**N**	**Mean**	**95% CI**	**Mean**	**95% CI**	**LSMean Difference**	**90% CI**
	24	39	404	(399, 409)	1.86	(-0.154, 3.87)	5.69	(3.76, 7.62)

CI = confidence interval; LS mean = least squares mean; N = number of subjects; QTcP = population specific rate correction method
The two-sided 90% CIs is equivalent to one-sided upper 95% CIs.
An analysis of covariance (ANCOVA) linear model was used to analyze the difference of change from baseline in QTcP by time point for MK-1439 at treatment versus placebo.
Means and 95% CI for the QTcP and QTcP change-from-baseline are descriptively summarized for each treatment by time point. Time 0 represents the baseline time point derived as the average of the 3 pre-dose assessments within each period.

Table 3:Statistical Analysis Secondary Hypothesis: Statistical Comparison of Change from Baseline in QTcP for Moxifloxacin Compared with Placebo over 1 to 4 Hours to Test Assay Sensitivity in Healthy Fasted Adult Subjects

	400 mg Moxifloxacin Change From Baseline QTcP (msec)			Placebo Change From Baseline QTcP (msec)			Difference in change from baseline from placebo QTcP (msec)		
Time (h)	N	Mean	95% CI	N	Mean	95% CI	LSMean Difference	90% CI [1]	p-value [2]
1	40	8.01	(5.86, 10.2)	39	-3.11	(-4.93, -1.30)	12.8	(10.9, 14.6)	0.0001
2	40	9.10	(7.39, 10.8)	40	-2.79	(-4.93, -0.653)	13.1	(11.4, 14.8)	0.0001
3	41	9.01	(7.19, 10.8)	40	-2.01	(-4.20, 0.178)	12.1	(10.2, 14.0)	0.0001
4	40	9.85	(7.42, 12.3)	40	-0.769	(-2.70, 1.16)	11.4	(9.36, 13.4)	0.0001

CI = confidence interval; LS mean = least squares mean; N = number of subjects; QTcP = population specific rate correction method
[1] The two-sided 90% CIs are equivalent to one-sided lower 95% CIs.
[2] The one-sided p-values, that the mean treatment difference is greater than 5 msec, are evaluated at 1, 2, 3, and 4 hours post-dose and are ranked in ascending order $p(4) \leq p(3) \leq p(2) \leq (1)$. The p-values are compared to alpha 0.05 sequentially using Hochberg's step-up method: p(1) versus 0.05, p(2) versus 0.05/2, p(3) versus 0.05/3, p(4) versus 0.05/4.
All one-sided p-values were significant using Hochberg's step-up method.

CONCLUSIONS:	1. Following a single supra-therapeutic 1200 mg dose, MK-1439 does not prolong the QTc interval to a clinically relevant degree. The true mean difference (MK-1439 – placebo) in change from baseline is less than 10 msec. 2. A single 400 mg dose of moxifloxacin is associated with an increase in the QTc interval. The true mean difference (moxifloxacin-placebo) in QTc change from baseline is greater than 5 msec over the first 4 hours post-dose, demonstrating assay sensitivity. 3. MK-1439 pharmacokinetic parameter values after a single 1200 mg dose were generally comparable to those observed in a previous study in healthy adult male subjects. 4. A single supra-therapeutic dose of 1200 mg MK-1439 and a single dose of 400 mg moxifloxacin were generally well tolerated during the trial.
REPORT DATE:	[redacted]-20[redacted]
REVISED REPORT DATE	[redacted]-20[redacted]

SPONSOR:	**Merck Sharp & Dohme Corp., a Subsidiary of Merck & Co., Inc.**	
COMPOUND NAME:	MK-1439 (doravirine)	
INDICATION:	HIV-1	
PROTOCOL TITLE:	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	
TRIAL IDENTIFIERS:	Protocol Number:	PN007
	Clinical Phase:	2b
	EudraCT Number:	2012-001573-93
	US IND Number	112,796
	ClinicalTrials.gov Identifier:	NCT01632345
TRIAL CENTERS:	This trial was conducted at seventy-three (73) approved centers that were shipped study medication: 6 in Australia, 2 in Belgium, 3 in Canada, 6 in France, 9 in Germany, 4 in the Netherlands, 2 in Poland, 3 in Puerto Rico, 4 in Romania, 4 in Russia, 5 in Spain, and 25 in the United States.	
DESIGN:	This was a multicenter, double-blind (with in-house blinding), randomized, 2-part dose ranging Phase 2b trial in approximately 320 antiretroviral -naïve human immunodeficiency virus type 1 (HIV-1) infected subjects (210 subjects were enrolled in Part I and 132 subjects were enrolled in Part II). All subjects were stratified by their initial (Screening) HIV-1 ribonucleic acid (RNA) (≤ or >100,000 copies/mL). Part I examined the safety, tolerability, pharmacokinetics (PK), and efficacy of 4 once daily doses of doravirine (25 mg, 50 mg, 100 mg, and 200 mg) versus once daily efavirenz (600 mg), each in combination with TRUVADA™ (emtricitabine 200 mg (+) tenofovir disoproxil fumarate 300 mg) for at least 24 weeks in approximately 200 subjects. Subjects were randomized to 1 of the 5 treatment arms in a 1:1:1:1:1 ratio (approximately 40 subjects per treatment arm). A single dose of doravirine was selected for further study after all subjects completed the Week 24 visit in Part I. Each site received an administrative letter that communicated the selected dose (100 mg), and all subjects on other doses of doravirine were switched to the selected dose at their next planned trial visit while maintaining the study blind.	

<table>
<tr><td></td><td colspan="2">Part II was initiated after the doravirine 100 mg dose was selected. Approximately 120 additional subjects (132 actual subjects) were randomized in a 1:1 ratio (approximately 60 additional subjects per treatment arm) to the selected dose of doravirine (100 mg once daily) or efavirenz (600 mg once daily at bedtime), each in combination with TRUVADA™ for a total of 96 weeks of blinded treatment. These additional subjects were enrolled in Part II to provide sufficient data at the selected dose of doravirine, for a comparative analysis of selected central nervous system (CNS) adverse events. In addition, this cohort of 215 subjects (107 on doravirine 100 mg; 108 on efavirenz) from Part I and Part II combined provided data to confirm the overall safety and efficacy of doravirine 100 mg versus efavirenz at Week 24. Longer-term safety and efficacy data were evaluated at Week 48 and Week 96.

A post therapy follow-up visit was performed 14 days after the last dose of study medication. All subjects were to return to the clinic in the event of early discontinuation or possible virological failure.

Efficacy/PK parameters: Clinical efficacy and PK measures included HIV-1 RNA, CD4 cell counts, viral resistance, and plasma concentration of doravirine.

Safety parameters: Safety assessments included physical examinations, vital signs, hematology, chemistry, clinical serology, virology, hemostatic function, urinalysis, serum β-human chorionic gonadotropin for female subjects of childbearing potential, and adverse event reporting (up to 14 days after the last dose of study medication).</td></tr>
<tr><td></td><td>Planned duration of main phase:</td><td>Part I: 96 weeks of treatment and 14 days of follow-up
Part II: 96 weeks of treatment and 14 days of follow-up</td></tr>
<tr><td></td><td>Planned duration of run-in phase:</td><td>Not applicable</td></tr>
<tr><td></td><td>Planned duration of extension phase:</td><td>Not applicable</td></tr>
</table>

Objectives	**Primary** **Part I** 1. Evaluate the safety and tolerability of doravirine, at the studied doses, compared to efavirenz, each in combination with TRUVADA™ for 24 weeks. 2. Evaluate the antiretroviral activity of doravirine, at the studied doses, compared to efavirenz, each in combination with TRUVADA™ for 24 weeks, as measured by the proportion of subjects with HIV-1 RNA <40 copies/mL at Week 24. **Part I and Part II Combined** 1. Evaluate the safety and tolerability of doravirine, at the final selected dose, compared to efavirenz, each in combination with TRUVADA™ for 24 weeks. 2. Evaluate the CNS adverse events associated with the use of the final selected dose of doravirine compared with efavirenz, each in combination with TRUVADA™ as measured by the proportion of subjects with CNS events by Week 8 and by Week 24. 3. Evaluate the antiretroviral activity of doravirine, at the final selected dose, compared to efavirenz, each in combination with TRUVADA™ for 24 weeks, as measured by the proportion of subjects with HIV-1 RNA <40 copies/mL at Week 24. **Secondary** **Part I** Evaluate the antiretroviral activity and immunological effect of doravirine, at the studied doses, compared to efavirenz, each in combination with TRUVADA™ for 24 weeks, as measured by a) proportion of subjects with HIV-1 RNA <200 copies/mL at Week 24, and b) change from baseline in CD4 cell count at Week 24. **Part I and Part II Combined** 1. Evaluate the antiretroviral activity and immunological effect of doravirine, at the final selected dose, compared to efavirenz, each in combination with TRUVADA™ at 24 weeks, as measured by a) proportion of subjects with HIV-1 RNA <200 copies/mL at Week 24, and b) change from baseline in CD4 cell count at Week 24. 2. Evaluate the safety and antiretroviral activity and immunological effect of doravirine, at the final selected dose, compared to efavirenz, each in combination with TRUVADA™ for 48 and 96 weeks.

Hypotheses	**Primary** **Part I and Part II Combined** Doravirine at the final selected dose is superior to efavirenz, each in combination therapy with TRUVADA™, as measured by proportion of subjects with CNS events by Week 8. If superiority is established at Week 8, the same hypothesis will be tested at Week 24.	
Treatment groups	Part I – Doravirine 25 mg	Doravirine 25 mg once daily + TRUVADA™ once daily. 41 Subjects Randomized 40 Subjects Treated
	Part I – Doravirine 50 mg	Doravirine 50 mg once daily + TRUVADA™ once daily. 43 Subjects Randomized and Treated
	Part I – Doravirine 100 mg	Doravirine 100 mg once daily + TRUVADA™ once daily. 42 Subjects Randomized and Treated
	Part I – Doravirine 200 mg	Doravirine 200 mg once daily + TRUVADA™ once daily. 41 Subjects Randomized and Treated
	Part I – Efavirenz 600 mg	Efavirenz 600 mg once daily + TRUVADA™ once daily. 43 Subjects Randomized 42 Subjects Treated
	Note: After dose selection, all Part I doravirine-treated subjects were switched to doravirine 100 mg for the remainder of their 96 weeks of total study medication.	
	Part II – Doravirine 100 mg	Doravirine 100 mg once daily + TRUVADA™ once daily. 66 Subjects Randomized and Treated
	Part II – Efavirenz 600 mg	Efavirenz 600 mg once daily + TRUVADA™ once daily. 66 Subjects Randomized and Treated

Clinical Supplies Dispensed to Subjects

Bulk Product Description	Manufacturing Lot Number
Doravirine 100 mg Doravirine 100 mg Placebo Doravirine 25 mg Doravirine 25 mg Placebo Efavirenz 600 mg Efavirenz 600 mg Placebo TRUVADA™.	[redacted]

Endpoints and definitions	Primary efficacy endpoint	HIV-1 RNA <40 copies/ mL	Proportion of subjects with HIV-1 RNA <40 copies/mL at Week 24 in Part I and in Part I/II combined.
	Secondary efficacy endpoints	HIV-1 RNA <40 copies/ mL	Proportion of subjects with HIV-1 RNA <40 copies/mL at Week 48 or Week 96 in Part I and in Part I/II combined.
		HIV-1 RNA <200 copies /mL	Proportion of subjects with HIV-1 RNA <200 copies/mL at Weeks 24, 48, and 96 in Part I and in Part I/II combined.
		CD4 cell count	Change from baseline in CD4 cell counts at Weeks 24, 48, and 96 in Part I and in Part I/II combined.
	Safety endpoints	Tier 1	• Proportion of subjects with CNS events by Week 8 and by Week 24 in Part I/II combined.
		Tier 2	• Proportion of subjects (incidence ≥4 subjects in 1 or more treatment groups): o With at least 1 adverse event o With a drug-related adverse event o With a serious adverse event o With a serious and drug-related adverse event o Discontinued study medication due to an adverse event. • Specific adverse events, system organ class (SOC), or predefined limits of change (PDLCs) (incidence of ≥4 subjects in 1 or more treatment groups)

		Tier 3	• Specific adverse events, SOC, or PDLCs (incidence of <4 subjects in all of the treatment groups) • Change from baseline in laboratory measurements and vital signs
Database lock	[redacted]-20[redacted]	Trial status	15-OCT-2012 (first subject first visit) to 22-MAR-2016 (last subject last visit)
RESULTS AND ANALYSIS:	Part I was an estimation trial intended to provide preliminary data on antiviral activity and general tolerability. Part I randomized approximately 200 subjects to the 4 dose groups of doravirine and the efavirenz group. There were approximately 100 subjects per group who received the final selected dose of doravirine or efavirenz after pooling data from Parts I and II. CNS events were evaluated using Part I and Part II combined data. With 100 subjects per arm for Part I and Part II combined, assuming the proportions of subjects with CNS events by Week 8 were 20% and 52% in the final selected doravirine dose group and the efavirenz group, respectively, the trial had >99% power and 95% confidence to declare that this dose of doravirine had a significantly lower rate of CNS events than efavirenz.		

Baseline Subject Characteristics
Part I/II Combined (Doravirine All Doses vs. Efavirenz)
All Subjects as Treated

	Doravirine 25 mg (N=40)	Doravirine 50 mg (N=43)	Doravirine 100 mg (N=108)	Doravirine 200 mg (N=41)	Doravirine Combined (N=232)	Efavirenz 600 mg (N=108)	Total (N=340)
Gender n (%)							
Male	38 (95.0)	37 (86.0)	99 (91.7)	40 (97.6)	214 (92.2)	101 (93.5)	315 (92.6)
Female	2 (5.0)	6 (14.0)	9 (8.3)	1 (2.4)	18 (7.8)	7 (6.5)	25 (7.4)
Age (Years)							
18-64 n (%)	38 (95.0)	42 (97.7)	107 (99.1)	41 (100.0)	228 (98.3)	108 (100.0)	336 (98.8)
≥65 n (%)	2 (5.0)	1 (2.3)	1 (0.9)	0 (0.0)	4 (1.7)	0 (0.0)	4 (1.2)
N	40	43	108	41	232	108	340
Mean (SD)	38.9 (13.42)	38.3 (10.71)	36.8 (11.31)	34.4 (8.85)	37.0 (11.23)	35.2 (9.08)	36.4 (10.62)
Median	36.5	36	35	32	35	34	35
Range	21 to 69	25 to 66	19 to 67	21 to 50	19 to 69	20 to 57	19 to 69

Baseline Subject Characteristics (Cont.)
Part I/II Combined (Doravirine All Doses vs. Efavirenz)
All Subjects as Treated

	Doravirine 25 mg (N=40)	Doravirine 50 mg (N=43)	Doravirine 100 mg (N=108)	Doravirine 200 mg (N=41)	Doravirine Combined (N=232)	Efavirenz 600 mg (N=108)	Total (N=340)
Race n (%)							
American Indian or Alaska Native	1 (2.5)	1 (2.3)	0 (0.0)	1 (2.4)	3 (1.3)	0 (0.0)	3 (0.9)
Asian	3 (7.5)	3 (7.0)	5 (4.6)	2 (4.9)	13 (5.6)	2 (1.9)	15 (4.4)
Black or African American	13 (32.5)	8 (18.6)	16 (14.8)	6 (14.6)	43 (18.5)	17 (15.7)	60 (17.6)
Multi-Racial	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	1 (0.4)	2 (1.9)	3 (0.9)
White	23 (57.5)	31 (72.1)	86 (79.6)	31 (75.6)	171 (73.7)	87 (80.6)	258 (75.9)
Missing	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
Ethnicity n (%)							
Hispanic or Latino	5 (12.5)	8 (18.6)	15 (13.9)	10 (24.4)	38 (16.4)	17 (15.7)	55 (16.2)
Not Hispanic or Latino	33 (82.5)	35 (81.4)	90 (83.3)	30 (73.2)	188 (81.0)	90 (83.3)	278 (81.8)
Unknown	2 (5.0)	0 (0.0)	3 (2.8)	1 (2.4)	6 (2.6)	1 (0.9)	7 (2.1)
Japanese Ancestry n (%)							
Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	40 (100.0)	43 (100.0)	108 (100.0)	41 (100.0)	232 (100.0)	108 (100.0)	340 (100.0)

Baseline Subject Characteristics (Cont.)
Part I/II Combined (Doravirine All Doses vs. Efavirenz)
All Subjects as Treated

	Doravirine 25 mg (N=40)	Doravirine 50 mg (N=43)	Doravirine 100 mg (N=108)	Doravirine 200 mg (N=41)	Doravirine Combined (N=232)	Efavirenz 600 mg (N=108)	Total (N=340)
Region n (%)							
Asia-Pacific	4 (10.0)	5 (11.6)	15 (13.9)	8 (19.5)	32 (13.8)	15 (13.9)	47 (13.8)
Europe	11 (27.5)	17 (39.5)	59 (54.6)	16 (39.0)	103 (44.4)	49 (45.4)	152 (44.7)
North America	25 (62.5)	21 (48.8)	34 (31.5)	17 (41.5)	97 (41.8)	44 (40.7)	141 (41.5)
History of AIDS n (%)							
Yes	6 (15.0)	5 (11.6)	4 (3.7)	6 (14.6)	21 (9.1)	7 (6.5)	28 (8.2)
No	34 (85.0)	38 (88.4)	104 (96.3)	35 (85.4)	211 (90.9)	101 (93.5)	312 (91.8)
Baseline HIV-1 RNA (log_{10} copies/mL)							
N	40	43	108	41	232	108	340
Mean (SD)	4.4 (0.75)	4.7 (0.68)	4.6 (0.78)	4.6 (0.65)	4.6 (0.74)	4.6 (0.72)	4.6 (0.73)
Median	4.5	4.8	4.6	4.5	4.6	4.6	4.6
Range	2.8 to 5.6	3.0 to 6.1	2.6 to 6.5	2.9 to 5.8	2.6 to 6.5	3.0 to 6.7	2.6 to 6.7
Baseline HIV-1 RNA (copies/mL)							
N	40	43	108	41	232	108	340
Geometric Mean	27944.7	46793.5	40680.8	43198.5	39550.1	39961.7	39680.4
Median	32973.0	57152.0	39025.5	33835.0	40037.5	42419.0	41095.0
Range	568 to 377069	1049 to 1401107	432 to 3106564	784 to 606555	432 to 3106564	1085 to 4631008	432 to 4631008

Baseline Subject Characteristics (Cont.)
Part I/II Combined (Doravirine All Doses vs. Efavirenz)
All Subjects as Treated

	Doravirine 25 mg (N=40)	Doravirine 50 mg (N=43)	Doravirine 100 mg (N=108)	Doravirine 200 mg (N=41)	Doravirine Combined (N=232)	Efavirenz 600 mg (N=108)	Total (N=340)
Stratum (Screening HIV-1 RNA level) n (%)							
≤100,000 copies/mL	29 (72.5)	30 (69.8)	70 (64.8)	29 (70.7)	158 (68.1)	68 (63.0)	226 (66.5)
>100,000 copies/mL	11 (27.5)	13 (30.2)	38 (35.2)	12 (29.3)	74 (31.9)	40 (37.0)	114 (33.5)
Baseline HIV-1 RNA Level n (%)							
≤100,000 copies/mL	28 (70.0)	30 (69.8)	73 (67.6)	29 (70.7)	160 (69.0)	76 (70.4)	236 (69.4)
>100,000 copies/mL	12 (30.0)	13 (30.2)	35 (32.4)	12 (29.3)	72 (31.0)	32 (29.6)	104 (30.6)
CD4 Cell Count (cells/mm^3)							
N	40	43	108	41	232	108	340
Mean (SD)	411.2 (210.07)	463.5 (239.01)	431.9 (187.06)	418.5 (214.74)	431.8 (205.72)	448.0 (188.66)	436.9 (200.32)
Median	385.0	431.0	401.5	403.0	402.5	430.0	404.0
Range	110 to 930	83 to 1140	92 to 1110	86 to 976	83 to 1140	118 to 1121	83 to 1140

Baseline Subject Characteristics (Cont.)
Part I/II Combined (Doravirine All Doses vs. Efavirenz)
All Subjects as Treated

	Doravirine 25 mg (N=40)	Doravirine 50 mg (N=43)	Doravirine 100 mg (N=108)	Doravirine 200 mg (N=41)	Doravirine Combined (N=232)	Efavirenz 600 mg (N=108)	Total (N=340)
Baseline CD4 Cell Counts n (%)							
≤200 cells/mm^3	7 (17.5)	3 (7.0)	7 (6.5)	5 (12.2)	22 (9.5)	10 (9.3)	32 (9.4)
>200 cells/mm^3 and ≤350 cells/mm^3	11 (27.5)	13 (30.2)	35 (32.4)	12 (29.3)	71 (30.6)	25 (23.1)	96 (28.2)
>350 cells/mm^3	22 (55.0)	27 (62.8)	66 (61.1)	24 (58.5)	139 (59.9)	73 (67.6)	212 (62.4)
Viral Subtype n (%)							
Clade B	35 (87.5)	34 (79.1)	75 (69.4)	36 (87.8)	180 (77.6)	86 (79.6)	266 (78.2)
Non-Clade B	5 (12.5)	8 (18.6)	33 (30.6)	5 (12.2)	51 (22.0)	22 (20.4)	73 (21.5)
Missing	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)

Treated is defined as subjects who took any non-zero dose of any study medication, blinded doravirine/placebo, blinded efavirenz/placebo or open label TRUVADA™.
Count (percent) and other summary statistics are calculated based on number of subjects in each sub-category for each group.
N = Number of subjects randomized in each treatment group.
SD = Standard Deviation.
Note: Both doravirine and efavirenz were administered with TRUVADA™.

Disposition of Subjects
Part I/II Combined (Doravirine All Doses vs. Efavirenz)
All Subjects Randomized

	Doravirine 25 mg		Doravirine 50 mg		Doravirine 100 mg		Doravirine 200 mg		Doravirine Combined		Efavirenz 600 mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total Randomized	41		43		108		41		233		109		342	
Never Treated	1	(2.4)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.9)	2	(0.6)
Treated	40	(97.6)	43	(100.0)	108	(100.0)	41	(100.0)	232	(99.6)	108	(99.1)	340	(99.4)
Discontinued the study	12	(29.3)	15	(34.9)	21	(19.4)	8	(19.5)	56	(24.0)	24	(22.0)	80	(23.4)
Adverse Event	1	(2.4)	4	(9.3)	5	(4.6)	1	(2.4)	11	(4.7)	11	(10.1)	22	(6.4)
Lack of Efficacy	0	(0.0)	1	(2.3)	0	(0.0)	1	(2.4)	2	(0.9)	1	(0.9)	3	(0.9)
Lost to Follow-up	3	(7.3)	2	(4.7)	4	(3.7)	3	(7.3)	12	(5.2)	5	(4.6)	17	(5.0)
Non-Compliance with Study Drug	3	(7.3)	2	(4.7)	5	(4.6)	1	(2.4)	11	(4.7)	0	(0.0)	11	(3.2)
Physician Decision	2	(4.9)	1	(2.3)	0	(0.0)	0	(0.0)	3	(1.3)	1	(0.9)	4	(1.2)
Pregnancy	0	(0.0)	1	(2.3)	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.3)
Protocol Deviation	0	(0.0)	0	(0.0)	1	(0.9)	1	(2.4)	2	(0.9)	0	(0.0)	2	(0.6)
Withdrawal by Subject	3	(7.3)	4	(9.3)	6	(5.6)	1	(2.4)	14	(6.0)	6	(5.5)	20	(5.8)

Note: Both doravirine and efavirenz were administered with TRUVADA™.

Analysis description	**Primary Efficacy Analysis** Statistical methodology: For the analysis of the primary endpoint (the proportion of subjects with virologic response HIV-1 RNA <40 copies/mL at Week 24 in Part I and Part I/II combined) the difference in proportion of subjects with virologic responses between treatment groups and the associated 95% CI were calculated using Miettinen and Nurminen's method with stratification by screening HIV-1 RNA ≤100,000 or >100,000 copies/mL. The Non-Completer=Failure (NC=F) approach was used as the primary approach to handle missing data. All missing values were considered as failures unless intermittent missing flanked by 2 successes (Note, at the primary timepoint of Week 24 in Parts I/II combined, the number of subjects in the doravirine 100 mg arm is 107 subjects as 1 subject satisfied this criterion).
Analysis population and time point description	The primary population for analysis of the primary analysis of efficacy data was the Full Analysis Set (FAS) population. The FAS population consisted of all randomized subjects who received at least 1 dose of blinded study medication and had baseline data for those analyses that required baseline data. The primary timepoint is Week 24. For Part I, the FAS population included a total of 208 subjects (166 for all doravirine groups; and 42 for efavirenz). For Part I/II, the FAS population included a total of 340 subjects (232 for all doravirine groups, 108 for efavirenz). The key cohort of 215 subjects (107 on doravirine 100 mg; 108 on efavirenz) from Part I/II combined provided data to confirm the overall safety and efficacy of doravirine 100 mg versus efavirenz at Week 24.
Summary	For Part I: -All doravirine treatment groups demonstrated potent and similar antiviral efficacy compared to efavirenz, with 71.4%-80.5% versus 64.3% achieving HIV-1 RNA <40 copies/mL, respectively, at Week 24 -There was no dose differentiation among doravirine treatment groups. For Part I/II: -Doravirine at selected dose of 100 mg demonstrated potent and similar antiviral efficacy compared to efavirenz, with 72.9% versus 73.1% achieving HIV-1 RNA <40, respectively, at Week 24.

Proportion of Subjects with HIV-1 RNA <40 copies/mL at Week 24
Part I (Doravirine All Doses vs. Efavirenz)
Full Analysis Set

Missing Data Approach	Treatment	Proportion of Subjects With HIV-1 RNA <40 copies/mL		Difference in Percent Response [Doravirine minus Efavirenz][†]
		n/N	% (95% CI)	(95% CI)[††]
Non-Complete=Failure (NC=F)	Doravirine 25 mg	32/40	80.0 (64.4, 90.9)	15.7 (-4.1, 34.4)
	Doravirine 50 mg	32/43	74.4 (58.8, 86.5)	10.0 (-9.6, 29.1)
	Doravirine 100 mg	30/42	71.4 (55.4, 84.3)	6.6 (-13.2, 26.0)
	Doravirine 200 mg	33/41	80.5 (65.1, 91.2)	15.9 (-3.4, 34.4)
	Doravirine Combined	127/166	76.5 (69.3, 82.7)	11.9 (-2.5, 28.2)
	Efavirenz 600 mg	27/42	64.3 (48.0, 78.4)	
Treatment-Related Disc.=Failure (TRD=F)	Doravirine 25 mg	32/38	84.2 (68.7, 94.0)	19.9 (0.3, 38.0)
	Doravirine 50 mg	32/43	74.4 (58.8, 86.5)	10.0 (-9.6, 29.1)
	Doravirine 100 mg	30/42	71.4 (55.4, 84.3)	6.6 (-13.2, 26.0)
	Doravirine 200 mg	33/40	82.5 (67.2, 92.7)	18.0 (-1.1, 36.2)
	Doravirine Combined	127/163	77.9 (70.8, 84.0)	13.4 (-1.0, 29.6)
	Efavirenz 600 mg	27/42	64.3 (48.0, 78.4)	
Observed Failure (OF)	Doravirine 25 mg	32/37	86.5 (71.2, 95.5)	18.8 (-0.3, 37.0)
	Doravirine 50 mg	32/41	78.0 (62.4, 89.4)	10.4 (-8.9, 29.3)
	Doravirine 100 mg	30/41	73.2 (57.1, 85.8)	4.8 (-14.7, 24.2)
	Doravirine 200 mg	33/40	82.5 (67.2, 92.7)	14.5 (-4.4, 32.9)
	Doravirine Combined	127/159	79.9 (72.8, 85.8)	11.9 (-2.0, 28.3)
	Efavirenz 600 mg	27/40	67.5 (50.9, 81.4)	

Proportion of Subjects With HIV-1 RNA <40 copies/mL at Week 24 (Cont.)
Part I (Doravirine All Doses vs. Efavirenz)
Full Analysis Set

Missing Data Approach	Treatment	Proportion of Subjects With HIV-1 RNA <40 copies/mL		Difference in Percent Response [Doravirine minus Efavirenz][†]
		n/N	% (95% CI)	(95% CI)[††]
FDA Snapshot Approach	Doravirine 25 mg	32/40	80.0 (64.4, 90.9)	15.7 (-4.1, 34.4)
	Doravirine 50 mg	32/43	74.4 (58.8, 86.5)	10.0 (-9.6, 29.1)
	Doravirine 100 mg	30/42	71.4 (55.4, 84.3)	6.6 (-13.2, 26.0)
	Doravirine 200 mg	33/41	80.5 (65.1, 91.2)	15.9 (-3.4, 34.4)
	Doravirine Combined	127/166	76.5 (69.3, 82.7)	11.9 (-2.5, 28.2)
	Efavirenz 600 mg	27/42	64.3 (48.0, 78.4)	

[†] A positive value favors doravirine over efavirenz.
[††] The 95% CIs were calculated using Miettinen and Nurminen's method with weights proportional to the size of each stratum (screening HIV-1 RNA >100,000 copies/mL or ≤100,000 copies/mL).
For each treatment group, n/N = (number of responders) / (number of subjects).
Note: Both doravirine and efavirenz were administered with TRUVADA™.

Proportion of Subjects with HIV-1 RNA <40 copies/mL at Week 24
Part I/II Combined (Doravirine 100 mg vs. Efavirenz)
Full Analysis Set

Missing Data Approach	Treatment	Proportion of Subjects With HIV-1 RNA <40 copies/mL		Difference in Percent Response [Doravirine minus Efavirenz][†]
		n/N	% (95% CI)	(95% CI)[††]
Non-Complete=Failure (NC=F)	Doravirine 100 mg	78/107	72.9 (63.4, 81.0)	-0.5 (-12.3, 11.2)
	Efavirenz 600 mg	79/108	73.1 (63.8, 81.2)	
Treatment-Related Disc.=Failure (TRD=F)	Doravirine 100 mg	78/105	74.3 (64.8, 82.3)	0.2 (-11.4, 11.8)
	Efavirenz 600 mg	79/107	73.8 (64.4, 81.9)	
Observed Failure (OF)	Doravirine 100 mg	78/104	75.0 (65.6, 83.0)	-3.4 (-14.8, 8.0)
	Efavirenz 600 mg	79/101	78.2 (68.9, 85.8)	
FDA Snapshot Approach	Doravirine 100 mg	78/108	72.2 (62.8, 80.4)	-1.2 (-13.0, 10.5)
	Efavirenz 600 mg	79/108	73.1 (63.8, 81.2)	

[†] A positive value favors doravirine over efavirenz.
[††] The 95% CIs were calculated using Miettinen and Nurminen's method with weights proportional to the size of each stratum (screening HIV-1 RNA >100,000 copies/mL or ≤100,000 copies/mL).
For each treatment group, n/N = (number of responders) / (number of subjects).
Note: Both doravirine and efavirenz were administered with TRUVADA™.

Analysis description	**Secondary Efficacy Analysis** Statistical methodology: For the analysis of the secondary endpoints of the proportion of subjects with HIV-1 RNA <40 copies/mL at Week 48 or Week 96 in Part I and Part I/II combined and the proportion of subjects with virologic response HIV-1 RNA <200 copies/mL at Weeks 24, 48, or 96 in Part I and Part I/II combined, the same methodology as described for the primary efficacy analyses was used. Missing data was handled using the NC=F approach. For the analysis of the secondary endpoint of change from baseline in CD4 cell counts at Weeks 24, 48, or 96 in Part I (Week 24 only) or Part I/II combined, descriptive statistics including 95% CIs were provided. Missing data were handled using the OF approach. Under this approach, baseline values were carried forward for subjects who discontinued due to lack of efficacy.
Analysis population and time point description	The primary population for the secondary efficacy analyses was the FAS population.
Summary	The proportion of subjects with virologic response HIV-1 RNA <40 copies/mL at Weeks 48 or 96 in Part I/II combined showed potent, durable, and similar antiretroviral efficacy between doravirine 100 mg compared with efavirenz 600 mg. In Part I/II combined, at 48 weeks, the proportions of subjects with HIV-1 RNA <40 copies/mL were 77.8% of subjects randomized to doravirine 100 mg and 79.4% of subjects randomized to efavirenz (difference (95% CI): -1.9% (-12.9, 9.2)). In Part I/II combined, at 96 weeks, the proportions of subjects with HIV-1 RNA <40 copies/mL were 75.0% of subjects randomized to doravirine 100 mg and 75.9% of subjects randomized to efavirenz (difference (95% CI): -0.8% (-12.4, 10.7)). The proportion of subjects with virologic response HIV-1 RNA <200 copies/mL at Weeks 24, 48, or 96 in Part I and Part I/II combined showed potent and similar efficacy across treatment groups. All secondary efficacy analyses showed similar results when comparing doravirine treatment groups (individually and combined) versus the efavirenz group.
Analysis description	**Safety Analysis** Statistical methodology: Tier 1 adverse events (CNS events by Week 8 and Week 24 in Part I/II combined) were subjected to inferential testing for statistical significance with p-values and 95% CIs provided for between-group comparisons. Tier 2 parameters were assessed via point estimates with 95% CIs provided for between-group comparisons; only point estimates by treatment group were provided for Tier 3 safety parameters.

Analysis population and time point description	The All Subjects as Treated (ASaT) population was used for the analysis of safety data in this trial, for both Part I and Part I/II combined analyses. The ASaT population is based on the actual treatment a subject received. Since no subject received the wrong treatment for the entire trial period the ASaT population treatment assignment is identical to the randomized treatment assignment.
Summary	In Part I, the overall safety profile of each of the doravirine groups at Week 24 was similar, and did not support selection of one particular dose (Table 12–6). There was no evidence of dose related toxicity. Each of the doravirine dose groups showed fewer drug-related adverse experiences (range: 16.7% – 46.5% and 36.7% combined) compared with efavirenz (57.1%). The rates of discontinuations due to drug-related adverse experiences was low overall (range: 0 – 4.7% and 2.4% for doravirine combined versus 4.8% for efavirenz). Similar trends were observed regarding the overall safety profile of Part I/II combined out to the conclusion of the trial at Week 96, during which time the majority of exposure to doravirine was at the 100 mg dose (Table 12–8). These observations included a lower rate of drug-related adverse experiences in the doravirine groups combined compared with efavirenz. Additionally there was a trend to fewer overall adverse experiences, fewer serious adverse experiences, and fewer discontinuations due to any adverse experiences including drug-related adverse experiences for the combined doravirine groups versus efavirenz. In Part I/II, the results confirmed the superiority of doravirine 100 mg over efavirenz in regard to the proportions of subjects with CNS adverse events by Weeks 8 and 24 (Table 12–10): 1) At Week 8, there were fewer subjects with CNS adverse events (24.1% versus 44.4% for doravirine 100 mg versus efavirenz, respectively; difference [95% CI] of -20.4 [-32.4, -7.8] and p=0.002). 2) At Week 24, there continued to be fewer subjects with CNS adverse events (26.9% versus 47.2% for doravirine 100 mg versus efavirenz, respectively; difference [95% CI] of -20.4 [-32.6, -7.5] and p=0.002). The following tables summarize the overall adverse events and CNS adverse events, respectively.

Adverse Event Summary
Part I (Doravirine All Doses vs. Efavirenz; Weeks 0-24)
All Subjects as Treated

	Doravirine 25 mg		Doravirine 50 mg		Doravirine 100 mg		Doravirine 200 mg		Doravirine Combined		Efavirenz 600 mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	40		43		42		41		166		42		208	
With one or more adverse events	36	(90.0)	40	(93.0)	30	(71.4)	35	(85.4)	141	(84.9)	35	(83.3)	176	(84.6)
With no adverse event	4	(10.0)	3	(7.0)	12	(28.6)	6	(14.6)	25	(15.1)	7	(16.7)	32	(15.4)
With drug-related[†] adverse events	16	(40.0)	20	(46.5)	7	(16.7)	18	(43.9)	61	(36.7)	24	(57.1)	85	(40.9)
With serious adverse events	3	(7.5)	1	(2.3)	0	(0.0)	2	(4.9)	6	(3.6)	3	(7.1)	9	(4.3)
With serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to adverse events	1	(2.5)	3	(7.0)	1	(2.4)	0	(0.0)	5	(3.0)	2	(4.8)	7	(3.4)
Discontinued due to drug-related adverse events	1	(2.5)	2	(4.7)	1	(2.4)	0	(0.0)	4	(2.4)	2	(4.8)	6	(2.9)
Discontinued due to serious adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

[†]Determined by the investigator to be drug related.

Note: Both doravirine and efavirenz were administered with TRUVADA™.

Adverse Event Summary
Part I/II Combined (Doravirine All Doses vs. Efavirenz; Weeks 0-96)
All Subjects as Treated

	Doravirine 25 mg		Doravirine 50 mg		Doravirine 100 mg		Doravirine 200 mg		Doravirine Combined		Efavirenz 600 mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	40		43		108		41		232		108		340	
With one or more adverse events	38	(95.0)	41	(95.3)	97	(89.8)	36	(87.8)	212	(91.4)	104	(96.3)	316	(92.9)
With no adverse event	2	(5.0)	2	(4.7)	11	(10.2)	5	(12.2)	20	(8.6)	4	(3.7)	24	(7.1)
With drug-related[†] adverse events	18	(45.0)	21	(48.8)	38	(35.2)	19	(46.3)	96	(41.4)	63	(58.3)	159	(46.8)
With serious adverse events	4	(10.0)	1	(2.3)	11	(10.2)	3	(7.3)	19	(8.2)	13	(12.0)	32	(9.4)
With serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(2.8)	3	(0.9)
Who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to adverse events	1	(2.5)	4	(9.3)	5	(4.6)	1	(2.4)	11	(4.7)	11	(10.2)	22	(6.5)
Discontinued due to drug-related adverse events	1	(2.5)	2	(4.7)	2	(1.9)	0	(0.0)	5	(2.2)	10	(9.3)	15	(4.4)
Discontinued due to serious adverse events	0	(0.0)	0	(0.0)	3	(2.8)	1	(2.4)	4	(1.7)	1	(0.9)	5	(1.5)
Discontinued due to serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.9)	1	(0.3)

[†]Determined by the investigator to be drug related.

Note: Both doravirine and efavirenz were administered with TRUVADA™.

Analysis of Subjects With Central Nervous System Adverse Events (CNS Events) by Week 8 and by Week 24
Part I/II Combined (Doravirine 100 mg vs. Efavirenz)
All Subjects as Treated

Treatment	Percent of Subjects With One or More Selected		Doravirine minus Efavirenz‡	
	n/N	%(95% CI)	Difference (95% CI)	p-Value
CNS Events† by Week 8				
Doravirine 100 mg	26/108	24.1 (16.4, 33.3)	-20.4 (-32.4, -7.8)	0.002
Efavirenz 600 mg	48/108	44.4 (34.9, 54.3)		
CNS Events† by Week 24				
Doravirine 100 mg	29/108	26.9 (18.8, 36.2)	-20.4 (-32.6, -7.5)	0.002
Efavirenz 600 mg	51/108	47.2 (37.5, 57.1)		

† Selected adverse events are from MedDRA terms of depression, nightmare, confusional state, suicidal ideation, nervous system disorder, psychotic disorder, abnormal dreams, suicide attempt, acute psychosis, delirium, depressed level of consciousness, hallucination, hallucination auditory, hallucination visual, completed suicide, suicidal behavior, major depression, depressed mood, depressive symptom, insomnia, disturbance in attention, somnolence, dizziness, concentration impaired.

‡ A negative value favors doravirine over efavirenz. The 95% CIs were calculated using Miettinen and Nurminen's method.

Subjects are counted once for each unique adverse event and may have had more than one unique adverse event.

n/N=Number of subjects included in a given category / number of subjects in each treatment group.

Note: Both doravirine and efavirenz were administered with TRUVADA™.

CONCLUSIONS:	**Efficacy** **Part I** In treatment naïve HIV-1 infected subjects, doravirine at doses of 25 mg, 50 mg, 100 mg, and 200 mg compared with efavirenz, each in combination with TRUVADA™ demonstrated potent and similar antiretroviral activity, as measured by the proportion of subjects with HIV-1 RNA <40 copies/mL or <200 copies/mL, and immunological effect, as measured by change from baseline in CD4 cell count, for 24 weeks for all doses of doravirine. **Parts I and II Combined** In treatment naïve HIV-1 infected subjects: 1. Doravirine 100 mg compared with efavirenz, each in combination with TRUVADA™ demonstrated potent and similar antiretroviral activity, as measured by the proportion of subjects with HIV-1 RNA <40 copies/mL, for 24 weeks. 2. Doravirine 100 mg compared with efavirenz, each in combination with TRUVADA™ demonstrated potent and similar antiretroviral activity, as measured by the proportion of subjects with HIV-1 RNA <200 copies/mL, and immunological effect, as measured by change from baseline in CD4 cell count for 24 weeks. 3. Doravirine 100 mg compared with efavirenz, each in combination with TRUVADA™ demonstrated potent and similar antiretroviral activity and immunological effect that are durable for 48 and 96 weeks. **Safety** **Part I** In treatment naïve HIV-1 infected subjects, doravirine at doses of 25 mg, 50 mg, 100 mg, and 200 mg were generally safe and well tolerated for 24 weeks compared with efavirenz, each in combination with TRUVADA™, with no dose-related toxicities. **Parts I and II Combined** In treatment naïve HIV-1 infected subjects: 1. Doravirine 100 mg was generally safe and well tolerated for 24 weeks compared with efavirenz, each in combination with TRUVADA™. 2. Doravirine 100 mg demonstrated superior CNS safety with a significantly lower proportion of subjects experiencing CNS adverse events by Week 8 and by Week 24 compared with efavirenz, each in combination with TRUVADA™. 3. Doravirine 100 mg was generally safe and well tolerated for

	48 weeks compared with efavirenz, each in combination with TRUVADA™. 4. Doravirine 100 mg was generally safe and well tolerated for 96 weeks compared with efavirenz, each in combination with TRUVADA™.

PUBLICATION(S):	Gatell JM, Raffi F, Plettenberg A, Smith D, Portiall J, Hoffmann C, et al. Efficacy and safety of doravirine 100 mg QD vs efavirenz 600 mg QD with TDF/FTC in ART-Naive HIV-infected patients: week 24 results. 8th International AIDS Society Conference on HIV Pathogenesis, Treatment & Prevention; July 19-22, 2015; Vancouver, Canada. Levin: Conference Reports for National AIDS Treatment Advocacy Project (NATAP); 2015. http://www.natap.org/2015/IAS/IAS_22.htm. Accessed October 26, 2016. Gatell JM, Raffi F, Plettenberg A, Smith D, Portiall J, Hoffmann C, Arasteh K, et al. Doravirine 100 mg QD vs efavirenz +TDF/FTC in ART-Naive HIV+ patients: week 48 results. Poster presented at: 23rd Conference on Retroviruses and Opportunistic Infections (CROI); February 22-25, 2016; Boston, MA. Poster 470. http://www.croiconference.org/sites/default/files/posters-2016/470.pdf. Accessed October 26, 2016. Morales-Ramirez JO, Gatell JM, Hagins DP, Thompson M, Arastéh K, Hoffmann C, et al. Safety and antiviral effect of MK-1439, a novel NNRTI (+FTC/TDF) in ART-Naive HIV-infected patients. Abstract presented at: 21st Conference on Retroviruses and Opportunistic Infections (CROI); March 3-6, 2014; Boston, MA. Abstract 92LB. http://www.croiconference.org/sites/default/files/abstracts/92LB.pdf. Accessed October 26, 2016. Gatell JM, Morales-Ramirez JO, Hagins DP, Thompson M, Arastéh K, Hoffmann C, et al. 48-week efficacy and safety and early CNS tolerability of doravirine, a novel NNRTI, with TDF/FTC in ART-Naïve HIV-infected patients. Poster presented at: 12th International Congress on Drug Therapy in HIV Infection; November 2-6, 2014; Glasgow, Scotland. Poster O434. https://s3-eu-west-1.amazonaws.com/hivglasgow/wp- content/uploads/2014/12/ORAL-PAPERS.pdf. Accessed October 26, 2016. Gatell JM, Morales-Ramirez JO, Hagins DP, Thompson M, Arastéh K, Hoffmann C, et al. Forty-eight-week efficacy and safety and early CNS tolerability of doravirine (MK-1439), a novel NNRTI, with TDF/FTC in ART-naive HIV-positive patients. J Int AIDS Soc 2014;17(4 Suppl 3):19532.
Report date:	[redacted]-20[redacted]
Revised report date:	[redacted]-20[redacted] (Final Draft word version [redacted]-201[redacted])

SPONSOR:	**Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.**	
COMPOUND NAME:	MK-1439, doravirine 100-mg oral compressed tablet	
INDICATION:	Treatment of HIV-1 infection	
PROTOCOL TITLE:	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	
TRIAL IDENTIFIERS:	Protocol Number:	018
	Clinical Phase:	3
	EudraCT Number:	2014-001127-69
	Other Codes: IND Number: ClinicalTrials.gov identifier:	 112,796 NCT02275780
ETHICS:	This trial was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.	
TRIAL CENTERS:	This trial was conducted at 133 sites: 40 sites in the United States, 12 in Germany, 11 in the Russian Federation, 11 in the United Kingdom, 10 in Spain, 8 in France, 6 each in Australia and Romania, 5 each in Canada and Chile, 4 each in Argentina and Austria, 4 in Puerto Rico, 3 each in Denmark and South Africa, and 1 in Italy. (An additional site was opened in Mexico; however, no subjects were screened or randomized at that site.)	

DESIGN:	Multicenter, double-blind (with in-house blinding), 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™), in human immunodeficiency virus type 1 (HIV-1)-infected, treatment-naïve adults ≥18 years of age, with plasma HIV-1 RNA ≥1000 copies/mL at screening (within 45 days of randomization [first day of treatment]) and no known resistance to DOR or any other study drug. An external Data Monitoring Committee provides ongoing monitoring of safety data. In addition, an interim safety analysis was performed at Week 8, and an interim efficacy analysis was performed when complete Week 24 data were available for approximately 340 subjects for the purpose of stopping the study if there was a lack of efficacy as prespecified (futility).	
	Planned duration of main phase (base study): Planned duration of extension phase:	96 weeks; Week 48 is primary timepoint. (Data from Week 96 will be presented in a future report.) 96 weeks
Objectives in Base Study	<u>Primary Objective</u>: To evaluate the antiretroviral activity of MK-1439 (DOR) 100 mg once daily (q.d.), compared with DRV+r (800 mg/100 mg) q.d., each in combination with TRUVADA™ or EPZICOM™/KIVEXA™, as measured by the proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 48 <u>Secondary Objectives</u>: To evaluate MK-1439 (DOR) 100 mg q.d., compared with DRV+r (800 mg/100 mg) q.d., each in combination with TRUVADA™ or EPZICOM™/KIVEXA™, with respect to: 1. safety and tolerability, as assessed by review of the accumulated safety data at Week 48 and Week 96. 2. effect on fasting serum lipids, as measured by mean change from baseline in fasting serum lipids at Week 48. 3. safety and tolerability, as measured by the time to discontinuation from study due to an adverse experience (AE). 4. immunologic effect, as measured by the change from baseline in $CD4^+$ T-cell count at Week 48 and Week 96. 5. antiretroviral activity, as measured by the proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 96. 6. antiretroviral activity, as measured by the proportion of subjects achieving HIV-1 RNA <40 copies/mL at Week 48 and Week 96.	

Hypotheses	MK-1439 100 mg q.d. is non-inferior to darunavir/ritonavir (800 mg/100 mg) q.d., each in combination with TRUVADA™ or EPZICOM™/KIVEXA™, as assessed by the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48. Superiority of MK-1439 100 mg q.d. to darunavir/ritonavir (800 mg/100 mg) q.d. will be assessed if non-inferiority is established. MK-1439 100 mg q.d. is superior to darunavir/ritonavir (800 mg/100 mg) q.d., each in combination with TRUVADA™ or EPZICOM™/KIVEXA™, as assessed by the mean change from baseline in fasting low-density lipoprotein cholesterol (LDL-C) at Week 48. If superiority is established with respect to LDL-C, the following subsequent hypothesis will be tested: MK-1439 100 mg q.d. is superior to darunavir/ritonavir (800 mg/100 mg) q.d., each in combination with TRUVADA™ or EPZICOM™/KIVEXA™, as assessed by the mean change from baseline in fasting non-high-density lipoprotein cholesterol (HDL-C) at Week 48. MK-1439 100 mg q.d. is non-inferior to darunavir/ritonavir (800 mg/100 mg) q.d., each in combination with TRUVADA™ or EPZICOM™/KIVEXA™, as assessed by the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 96. Superiority of MK-1439 100 mg q.d. to darunavir/ritonavir (800 mg/100 mg) q.d. will be assessed if non-inferiority is established.	
Treatment groups	DOR (doravirine; MK-1439)	Doravirine 100-mg oral compressed tablet, in combination with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF; supplied as TRUVADA™) or abacavir/lamivudine (ABC/3TC; supplied as EPZICOM™ or KIVEXA™), administered q.d. for 96 weeks 385 subjects randomized, 383 treated
	DRV+r (darunavir + ritonavir) [Note: appears in results tables as 'Darunavir/ritonavir']	Darunavir 800-mg tablet, in combination with ritonavir 100-mg tablet and with either FTC/TDF (supplied as TRUVADA™) or ABC/3TC (supplied as EPZICOM™ or KIVEXA™), administered q.d. for 96 weeks 384 subjects randomized, 383 treated

Endpoints and definitions	Primary efficacy endpoint	Proportion of subjects achieving plasma HIV-1 RNA level <50 copies/mL at Week 48
	Secondary efficacy endpoints	Proportion of subjects achieving plasma HIV-1 RNA level <50 copies/mL at Week 96 Change from baseline in $CD4^+$ T-cell count at Week 48 and Week 96 Proportion of subjects achieving plasma HIV-1 RNA level <40 copies/mL at Week 48 and Week 96
	Exploratory efficacy endpoints	Time to loss of virologic response (TLOVR) Protocol-defined virologic failure (PDVF) Viral drug resistance
	Tier 1 safety endpoint	Change from baseline in fasting LDL-C and non-HDL-C at Week 48
	Tier 2 safety endpoints	Change from baseline in total cholesterol, triglycerides, and HDL-C at Week 48 Broad categories of AEs through Week 48 (any AE, serious AE [SAE], drug-related AE, drug-related SAE, discontinuation due to AE) Time to discontinuation from study due to AE AEs (preferred term and system organ class) with incidence ≥4 subjects in any treatment group Predefined limits of change in laboratory parameters with incidence ≥4 subjects in any treatment group
	Tier 3 safety endpoints	AEs (preferred term and system organ class) and predefined limits of change in laboratory parameters with incidence <4 subjects in both treatment groups Change from baseline in laboratory parameters and vital signs
	Pharmacokinetics endpoint	Descriptive statistics for doravirine plasma concentrations collected over 48 weeks.

Trial status	The trial is ongoing; the current report contains complete data through Week 48 for the primary endpoint analysis.
Database lock	[redacted]-20[redacted]

RESULTS AND ANALYSIS:	With 340 subjects planned for each treatment arm, the trial has 90% power to demonstrate the primary hypothesis that DOR (MK-1439) 100 mg q.d. is non-inferior to DRV+r (800 mg/100 mg) q.d., each in combination with FTC/TDF or ABC/3TC, at an overall one-sided 2.5% alpha level, as measured by the proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 48. This assumes a true response rate of 80% at Week 48 for both arms, using the Food and Drug Administration (FDA) "Snapshot" approach.

Subject Baseline Characteristics by Treatment Group

	Doravirine 100 mg QD (N = 383)	Darunavir/ritonavir 800/100 mg QD (N = 383)	Total (N = 766)
Gender n (%)			
Male	319 (83.3)	326 (85.1)	645 (84.2)
Female	64 (16.7)	57 (14.9)	121 (15.8)
Race n (%)			
American Indian or Alaska Native	3 (0.8)	3 (0.8)	6 (0.8)
Asian	7 (1.8)	7 (1.8)	14 (1.8)
Black or African American	86 (22.5)	88 (23.0)	174 (22.7)
Multiple	6 (1.6)	2 (0.5)	8 (1.0)
Native Hawaiian or Other Pacific Islander	1 (0.3)	2 (0.5)	3 (0.4)
White	280 (73.1)	280 (73.1)	560 (73.1)
Missing	0 (0.0)	1 (0.3)	1 (0.1)
Ethnicity n (%)			
Hispanic or Latino	93 (24.3)	86 (22.5)	179 (23.4)
Not Hispanic or Latino	284 (74.2)	290 (75.7)	574 (74.9)
Unknown	6 (1.6)	7 (1.8)	13 (1.7)
Region n (%)			
Africa	23 (6.0)	22 (5.7)	45 (5.9)
Asia/Pacific	12 (3.1)	3 (0.8)	15 (2.0)
Europe	170 (44.4)	179 (46.7)	349 (45.6)
Latin America	38 (9.9)	33 (8.6)	71 (9.3)
North America	140 (36.6)	146 (38.1)	286 (37.3)
Age (years)			
18 to 64	381 (99.5)	379 (99.0)	760 (99.2)
>=65	2 (0.5)	4 (1.0)	6 (0.8)
Mean (SD)	34.8 (10.5)	35.7 (10.7)	35.2 (10.6)
Median (min, max)	33.0 (18, 68)	34.0 (18, 69)	33.0 (18, 69)
Baseline CD4 Cell Count (cells/mm^3)			
N[†]	383	383	766
Mean (SD)	432.6 (208.4)	411.9 (229.6)	422.2 (219.4)
Median (min, max)	410.0 (19, 1822)	393.0 (19, 1303)	403.0 (19, 1822)
Baseline CD4 Cell Counts n (%)			
<=50 cells/mm^3	6 (1.6)	19 (5.0)	25 (3.3)
>50 cells/mm^3 and <=200 cells/mm^3	36 (9.4)	48 (12.5)	84 (11.0)
>200 cells/mm^3	341 (89.0)	316 (82.5)	657 (85.8)
Baseline Plasma HIV-1 RNA (log_{10} copies/mL)			
N[†]	383	382	765
Mean (SD)	4.4 (0.7)	4.4 (0.7)	4.4 (0.7)
Median (min, max)	4.4 (2.0, 6.4)	4.4 (2.4, 6.5)	4.4 (2.0, 6.5)

Subject Baseline Characteristics by Treatment Group

	Doravirine 100 mg QD (N = 383)	Darunavir/ritonavir 800/100 mg QD (N = 383)	Total (N = 766)
Baseline Plasma HIV-1 RNA (copies/mL)			
N[†]	383	382	765
Geometric Mean	26917.6	26630.5	26773.8
Median (min, max)	27073.0 (105, 2776658)	27357.0 (235, 3272236)	27073.0 (105, 3272236)
Baseline Plasma HIV-1 RNA n (%)			
<=100,000 copies/mL	300 (78.3)	308 (80.4)	608 (79.4)
>100,000 copies/mL	83 (21.7)	74 (19.3)	157 (20.5)
Missing	0 (0.0)	1 (0.3)	1 (0.1)
Baseline Plasma HIV-1 RNA n (%)			
<=500,000 copies/mL	366 (95.6)	370 (96.6)	736 (96.1)
>500,000 copies/mL	17 (4.4)	12 (3.1)	29 (3.8)
Missing	0 (0.0)	1 (0.3)	1 (0.1)
History of AIDS n (%)			
Yes	36 (9.4)	37 (9.7)	73 (9.5)
No	347 (90.6)	346 (90.3)	693 (90.5)
Stratum n (%)			
Screening HIV RNA<= 100,000	290 (75.7)	289 (75.5)	579 (75.6)
Screening HIV RNA> 100,000	93 (24.3)	94 (24.5)	187 (24.4)
TRUVADA™	333 (86.9)	335 (87.5)	668 (87.2)
EPZICOM™/KIVEXA™	50 (13.1)	48 (12.5)	98 (12.8)
Baseline Hepatitis Status[††]			
Hep B and/or C Positive	11 (2.9)	18 (4.7)	29 (3.8)
Hep B Positive Only	4 (1.0)	12 (3.1)	16 (2.1)
Hep C Positive Only	7 (1.8)	6 (1.6)	13 (1.7)
Hep B and C Negative	372 (97.1)	365 (95.3)	737 (96.2)
Viral Subtype n (%)			
Subtype B	266 (69.5)	272 (71.0)	538 (70.2)
Non-Subtype B	117 (30.5)	111 (29.0)	228 (29.8)

[†] Subjects with missing results excluded.

[††] Evidence of hepatitis B surface antigen or evidence of HCV RNA by polymerase chain reaction (PCR) quantitative test for hepatitis C virus.

Note: Doravirine 100 mg QD and darunavir/ritonavir 800/100 mg QD were administered with TRUVADA™ or EPZICOM™/KIVEXA™.

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

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

Source: [P018V01MK1439: analysis-adsl]

Subject Disposition by Treatment Group
Weeks 0-48

	Doravirine 100 mg QD		Darunavir/ritonavir 800/100 mg QD		Total	
	n	(%)	n	(%)	n	(%)
Total Randomized	385		384		769	
Not Treated	2	(0.5)	1	(0.3)	3	(0.4)
Treated	383	(99.5)	383	(99.7)	766	(99.6)
Discontinued Study	56	(14.5)	71	(18.5)	127	(16.5)
Adverse Event	4	(1.0)	12	(3.1)	16	(2.1)
Death	1	(0.3)	0	(0.0)	1	(0.1)
Lack Of Efficacy	12	(3.1)	14	(3.6)	26	(3.4)
Lost To Follow-Up	17	(4.4)	19	(4.9)	36	(4.7)
Non-Compliance With Study Drug	7	(1.8)	4	(1.0)	11	(1.4)
Physician Decision	3	(0.8)	3	(0.8)	6	(0.8)
Pregnancy	1	(0.3)	0	(0.0)	1	(0.1)
Protocol Deviation	1	(0.3)	6	(1.6)	7	(0.9)
Withdrawal By Subject	10	(2.6)	13	(3.4)	23	(3.0)

Note: Doravirine 100 mg QD and darunavir/ritonavir 800/100 mg QD were administered with TRUVADA™ or EPZICOM™/KIVEXA™.
n (%) = Number (percent) of subjects in each sub-category.

Source: [P018V01MK1439: analysis-adsl] [P018V01MK1439: tabulations-dsplus]

Analysis description	**Primary Efficacy Analysis:** Proportion of Subjects With HIV-1 RNA <50 copies/mL at Week 48 *Statistical Methodology*: The primary hypothesis on antiretroviral activity was assessed by the percentage of subjects achieving plasma HIV-1 RNA <50 copies/mL at Week 48 using the Abbott RealTime HIV-1 Assay. A margin of 10 percentage points was used to define non-inferiority: DOR (100 mg q.d.) was concluded to be non-inferior to DRV+r (800 mg/100 mg q.d.) if the lower bound of the two-sided 95% CI for the difference in the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48 (DOR – DRV+r) was greater than −10 percentage points. The FDA Snapshot approach was used as the primary approach to analysis with respect to the proportion of subjects with virologic response (HIV-1 RNA <50 copies/mL): all missing data were treated as failures regardless of the reason. **Secondary Efficacy Analysis**: Proportion of Subjects With HIV-1 RNA <40 copies/mL at Week 48 *Statistical Methodology*: The same methodology used for the primary endpoint was used for this endpoint. **Secondary Efficacy Analysis**: Change from baseline in $CD4^+$ T-cell count at Week 48 *Statistical Methodology*: The difference between the treatment groups in change from baseline in $CD4^+$ T-cell count was estimated at each timepoint. However, these estimates were not subject to an absolute criterion for similarity. The clinical interpretation of the treatment difference is dependent upon the absolute value at baseline, and the magnitude and direction of the $CD4^+$ T-cell changes seen in each treatment arm. The observed failure (OF) approach was used for calculations of change from baseline in $CD4^+$ T-cell count. Under this approach, baseline values were carried forward for subjects who discontinued due to lack of efficacy.
Analysis population and timepoint description	The primary population for efficacy analyses was the Full Analysis Set (FAS) population. The FAS population consisted of all randomized subjects who received at least one dose of study drug and had baseline data for those analyses that require baseline data.
Summary	With respect to the primary efficacy endpoint, the proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 48 by the FDA Snapshot approach was 83.8% (321/383) in the DOR group and 79.9% (306/383) in the DRV+r group. The treatment difference (DOR − DRV+r) was 3.9% with an associated 95% CI of (-1.6, 9.4), demonstrating non-inferiority of DOR 100 mg q.d. versus DRV+r (800 mg/100 mg q.d.), each in combination with FTC/TDF or ABC/3TC. In addition, the proportion of subjects achieving HIV-1 RNA <40 copies/mL at Week 48 (FDA Snapshot approach) was 83.3% in the DOR group and 79.1% in the DRV+r group, with a treatment difference (95% CI) of 4.2% (-1.4, 9.7). With respect to the secondary efficacy analysis, the DOR group had a similar mean change from baseline in $CD4^+$ T-cell count (193 cells/mm^3) compared with that in the DRV+r group (186 cells/mm^3), with a treatment difference (95% CI) of 7.1 (-20.8, 35.0).

Efficacy Analysis at Week 48

Parameter	Missing Data Approach[†]	Unadjusted Data Summary by Treatment Group		Treatment Difference (Doravirine - Darunavir)[‡]		Conclusion[§]
		Doravirine 100 mg QD n/N (%)	Darunavir/ritonavir 800/100 mg QD n/N (%)	Estimated Difference	95% CI	
Primary						
Proportion of Subjects with HIV-1 RNA <50 copies/mL	Snapshot	321/383 (83.8)	306/383 (79.9)	3.913	(-1.590, 9.415)	Non-inferior
Secondary and Exploratory						
Proportion of Subjects with HIV-1 RNA <50 copies/mL	OF	321/364 (88.2)	306/355 (86.2)	1.880	(-3.072, 6.833)	
Proportion of Subjects with HIV-1 RNA <40 copies/mL	Snapshot	319/383 (83.3)	303/383 (79.1)	4.169	(-1.404, 9.743)	
Proportion of Subjects with HIV-1 RNA <40 copies/mL	OF	319/364 (87.6)	303/355 (85.4)	2.160	(-2.898, 7.218)	
Proportion of Subjects with HIV-1 RNA <200 copies/mL	Snapshot	328/383 (85.6)	316/383 (82.5)	3.141	(-2.095, 8.378)	
Proportion of Subjects with HIV-1 RNA <200 copies/mL	OF	328/364 (90.1)	316/355 (89.0)	1.068	(-3.504, 5.641)	
		Mean (95% CI)	Mean (95% CI)	Mean Difference	95% CI	
Change from Baseline in CD4 Cell Count (cells/mm^3)	OF	192.7 (171.5, 213.9)	185.6 (167.5, 203.6)	7.1	(-20.8, 35.0)	

[†] Snapshot: Defined by FDA Snapshot approach; OF: Observed Failure approach.

[‡] The 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum. The 95% CI for mean difference in CD4 change was based on t-distribution.

[§] Doravirine 100 mg QD is concluded non-inferior to darunavir/ritonavir 800/100 mg QD if the lower bound of the 95% CI for the difference in percent response is above -10 percentage points.

Analysis of post-baseline data only includes laboratory records collected after the first dose of study medication through 14 days after the last dose of study medication.

Note: Doravirine 100 mg QD and darunavir/ritonavir 800/100 mg QD were administered with TRUVADA™ or EPZICOM™/KIVEXA™.

n = Number of subjects in each subcategory.

N = Number of subjects in each treatment group.

Source: [P018V01MK1439: analysis-adsl; adcd4; adrna]

Analysis description	**Supportive Analysis**: Virologic Outcome *Statistical methodology*: To provide a full picture of virologic outcome at a timepoint, besides the primary analysis of proportion of subjects achieving virologic success (HIV-1 RNA <50 copies/mL) at Week 48, subjects who were not classified as virologic success were further categorized as HIV-1 RNA ≥50 copies/mL or no virologic data in the time window with reasons of 1) discontinued study due to AE or death, 2) discontinued study for other reasons (including loss to follow-up, noncompliance with study drug, etc), or 3) on study but missing data in window.
Summary	The virologic outcomes of the DOR group were similar to those of the DRV+r group. In addition to the similarity between treatment groups with respect to the proportion of subjects with HIV-1 RNA <50 copies/mL described above, similar proportions of subjects in the DOR and DRV+r groups were categorized as having HIV-1 RNA ≥50 copies/mL (11.2% and 13.1%, respectively), and similar proportions of subjects were categorized as having no virologic data at Week 48 window (5% and 7% of subjects, respectively).

Virologic Outcome at Week 48
FDA Snapshot Approach

Outcome	Doravirine 100 mg QD (N=383) n	(%)	Darunavir/ritonavir 800/100 mg QD (N=383) n	(%)
HIV-1 RNA <50 copies/mL	321	(83.8)	306	(79.9)
HIV-1 RNA ≥ 50 copies/mL[†]	43	(11.2)	50	(13.1)
No Virologic Data at Week 48 Window	19	(5.0)	27	(7.0)
Reasons				
Discontinued study due to AE or Death[‡]	5	(1.3)	11	(2.9)
Discontinued study for Other Reasons[§]	11	(2.9)	15	(3.9)
On study but missing data in window	3	(0.8)	1	(0.3)

[†] Includes subjects who changed any component of background therapy to a new drug class or changed background components that were not permitted per protocol or changed any background drug in the regimen because of lack of efficacy (perceived or documented) before Week 48, subjects who discontinued study drug or study before Week 48 for lack or loss of efficacy and subjects with HIV-1 RNA equal to or above 50 copies/mL in the Week 48 window (relative day 295-378).

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

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

Analysis of post-baseline data only includes laboratory records collected after the first dose of study medication through 14 days after the last dose of study medication.

Note:Doravirine 100 mg QD and darunavir/ritonavir 800/100 mg QD were administered with TRUVADA™ or EPZICOM™/KIVEXA™.

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

Source: [P018V01MK1439: analysis-adsl; adrna]

Analysis description	**Supportive Analysis**: Subgroup Efficacy *Statistical methodology*: To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the efficacy endpoint was calculated within each category of the subgroup factors.
Summary	Across all subgroups defined by baseline prognostic and demographic factors, the DOR group showed antiretroviral efficacy comparable to that of the DRV+r group (based on 95% CIs that included 0), consistent with the findings seen for the DOR and DRV+r treatment groups overall. Of note, among subjects with a high baseline HIV-1 RNA level (>100,000 copies/mL), similarly high proportions of subjects achieved HIV-1 RNA <50 copies/mL at Week 48 in the DOR and DRV+r treatment groups (81.0% and 76.4%, respectively). Similarly, among subjects with baseline $CD4^+$ T-cell counts ≤50 cells/mm^3 or >50 and ≤200 cells/mm^3, the proportion of subjects who achieved HIV-1 RNA <50 copies/mL at Week 48 was at least as high in the DOR group (83.3% and 82.9%) as in the DRV+r group (66.7% and 74.4%). Within both treatment groups, trends of lower efficacy were seen with high baseline HIV-1 RNA (>100,000 and >500,000 copies/mL) and low pre-treatment $CD4^+$ T-cell counts; these trends were less pronounced for the DOR group than for the DRV+r group.

Analysis description	**Supportive Analysis**: Time to Loss of Virologic Response *Statistical methodology*: TLOVR was estimated using Kaplan-Meier product-limit estimates and graphically displayed. Log-rank tests and Cox Proportional Hazards models could also be applied to this time-to-event data.
Summary	Kaplan-Meier analysis and analyses using the log-rank test and the Cox model demonstrate that the DOR and DRV+r groups were similar with respect to the risk of loss-of-virologic-response events; such events were infrequently noted among subjects in either treatment group through Week 48.

Analysis description	**Exploratory Analysis**: Protocol-Defined Virologic Failure (PDVF) and Viral Drug Resistance *Statistical methodology*: The proportion of subjects with protocol-defined virologic failure was summarized by treatment group. The protocol definition of virologic failure is (1) rebounder: subject with confirmed HIV-1 RNA ≥50 copies/mL after initial response of HIV-1 RNA <50 copies/mL at any time during the study; or (2) non-responder: subject with confirmed (2 consecutive measures at least 1 week apart) HIV-1 RNA ≥200 copies/mL at Week 24 or Week 36 OR confirmed HIV-1 RNA ≥50 copies/mL at Week 48.
Summary	Rates of PDVF by Week 48 were low and comparable among subjects in the DOR (4.9%) and DRV+r (6.3%) treatment groups. Development of viral drug resistance was rare: no primary genotypic resistance was seen among subjects who met PDVF criteria in either the DOR or DRV+r group, while virus from 1 DOR-treated subject who discontinued due to noncompliance was found to have genotypic and phenotypic resistance to both DOR and FTC.

Analysis description	**Safety Analyses:** Change From Baseline at Week 48 in Fasting Lipids *Statistical Methodology*: Changes from baseline in fasting LDL-C and non-HDL-C were Tier 1 events. Changes from baseline in other fasting lipids (total cholesterol, triglycerides, HDL-C) were Tier 2 events. Change from baseline in fasting lipids was analyzed using ANCOVA models adjusted by baseline fasting lipids level and treatment group. The treatment differences and 95% CIs were provided for all lipids parameters and p-value for the between-treatment comparison was provided for LDL-C and non-HDL-C. The significance of the treatment difference for LDL-C was tested first; sequential testing for non-HDL-C was to be done only if superiority was established for LDL-C.
Analysis population and timepoint description	Safety analyses were based on the All Subjects as Treated (ASaT) population, which consisted of all randomized subjects who received at least one dose of study medication.

Summary	The differences between the DOR and DRV+r groups for the mean change from baseline to Week 48 in fasting LDL-C and fasting non-HDL-C were statistically significant (p <0.0001 in each case): for LDL-C, DOR was associated with a mean decrease from baseline of 4.5 mg/dL and DRV+r with a mean increase of 9.9 mg/dL; for non-HDL-C, DOR was associated with a mean decrease of 5.3 mg/dL and DRV+r with a mean increase of 13.8 mg/dL. A similar result was observed with respect to changes from baseline to Week 48 for fasting total cholesterol and fasting triglycerides; for fasting HDL-C, the between-treatment-group differences were not clinically meaningful.

Change From Baseline in Fasting Lipids at Week 48

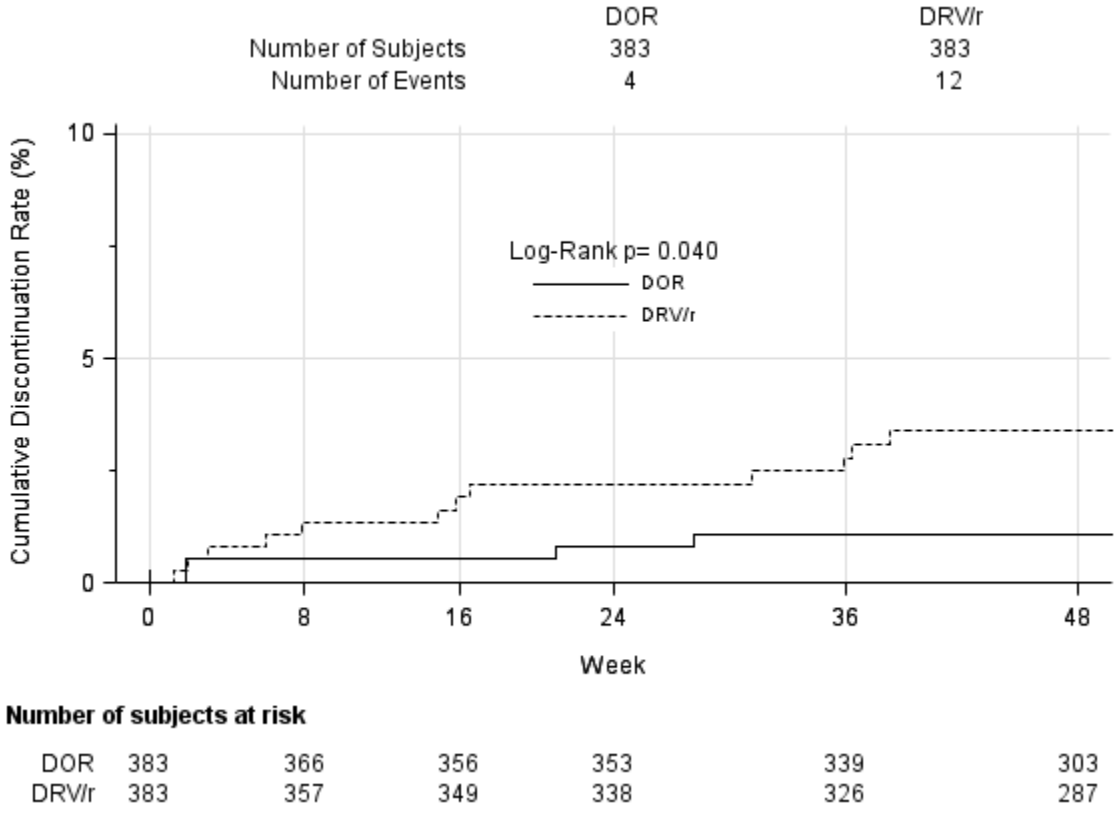
Treatment	N	Baseline Mean	Change from Baseline at Week 48		Difference Estimates (Doravirine - Darunavir)	
			Mean Change (SD)	95% CI[†]	Difference[‡] 95% CI	2-sided p-Value
Fasting LDL Cholesterol (mg/dL)						
Doravirine 100 mg QD	326	91.10	-4.51 (20.64)	(-6.76, -2.26)	-14.61 (-18.15, -11.06)	<0.0001
Darunavir/ritonavir 800/100 mg QD	318	91.76	9.92 (27.31)	(6.91, 12.94)		
Fasting Non-HDL Cholesterol (mg/dL)						
Doravirine 100 mg QD	329	113.34	-5.30 (23.28)	(-7.83, -2.78)	-19.34 (-23.33, -15.35)	<0.0001
Darunavir/ritonavir 800/100 mg QD	325	114.44	13.75 (31.08)	(10.36, 17.14)		
Fasting Cholesterol (mg/dL)						
Doravirine 100 mg QD	329	156.92	-1.37 (25.47)	(-4.13, 1.39)	-19.50 (-23.82, -15.17)	nps*
Darunavir/ritonavir 800/100 mg QD	325	157.71	17.90 (33.95)	(14.20, 21.61)		
Fasting Triglyceride (mg/dL)						
Doravirine 100 mg QD	329	111.16	-3.14 (68.81)	(-10.61, 4.32)	-27.87 (-38.71, -17.02)	nps*
Darunavir/ritonavir 800/100 mg QD	325	117.02	21.97 (92.59)	(11.86, 32.07)		
Fasting HDL Cholesterol (mg/dL)						
Doravirine 100 mg QD	329	43.58	3.94 (10.66)	(2.78, 5.09)	-0.15 (-1.75, 1.45)	nps*
Darunavir/ritonavir 800/100 mg QD	325	43.27	4.15 (11.01)	(2.95, 5.36)		

The Last Observation Carry Forward (LOCF) approach is applied for the missing data or data collected after modifying lipid-lowering therapy.
[†] Within group 95% CIs were based on t-distribution.
[‡] The 95% CIs and 2-sided p-value for treatment difference were calculated from an ANOCOVA model with terms for baseline lipid level and treatment.
[*] Not pre-specified for statistical testing
Analysis of post-baseline data only includes laboratory records collected after the first dose of study medication through 14 days after the last dose of study medication.
Note: Doravirine 100 mg QD and darunavir/ritonavir 800/100 mg QD were administered with TRUVADA™ or EPZICOM™/KIVEXA™.
N = Number of subjects with baseline and at least one postbaseline test result.

Source: [P018V01MK1439: analysis-adsl; adlpd]

Analysis description	**Safety Analysis:** Time to Discontinuation Due to Adverse Event *Statistical Methodology*: The time to discontinuation from the trial due to an adverse event was estimated using Kaplan-Meier product-limit estimates and graphically displayed. The log-rank test was also performed for this time to event endpoint.
Summary	There were fewer discontinuations due to AEs in the DOR group (4 subjects) compared with the DRV+r group (12 subjects), though such events occurred at a low frequency in both groups. The log-rank test indicated that the DRV+r group is associated with a higher risk of discontinuation due to AE than the DOR group (nominal p=0.040). As expected, the higher number of discontinuations in the DRV+r group was primarily due to gastrointestinal AEs.

Kaplan-Meier Plot for Time to Discontinuation Due to Adverse Event, Weeks 0–48



Number of subjects at risk

DOR	383	366	356	353	339	303
DRV/r	383	357	349	338	326	287

Analysis description	**Safety Analysis:** Overall Adverse Events and Predefined Limits of Change (PDLC) in Laboratory Parameters *Statistical Methodology*: The treatment differences, and associated 95% confidence intervals, in percentage of subjects for the Tier 2 events were calculated using the Miettinen and Nurminen method. Tier 2 events include the following AE categories: any AE, drug-related AE, SAE, drug-related SAE, discontinuation due to AE. In addition, AEs (specific terms as well as system organ class terms) and predefined limits of change in laboratory parameters with incidence ≥4 subjects in any treatment groups were classified as Tier-2 events. All other AEs and predefined limits of change are classified as Tier 3, for which only a descriptive summary by treatment group was provided.
Summary	The overall safety profile was similar between the DOR and the DRV+r groups. Both treatments were associated with a low incidence of drug-related SAEs and a low number of AEs that resulted in discontinuation of study drug (lower in the DOR group than in the DRV+r group). Of those laboratory parameters with any worsened toxicity grade (ie, meeting PDLC), the serum chemistry parameters fasting LDL-C, fasting cholesterol, fasting triglycerides and fasting glucose were among those seen in the largest numbers of subjects; few laboratory parameters reached Division of Acquired Immunodeficiency Syndrome (DAIDS) Grade 3 levels. Between-group differences were noted in the proportions of subjects with Grade 2 LDL-C (0.3%, 7.2% in the DOR and DRV+r groups, respectively) and Grade 3 LDL-C (0.3%, 2.8%), Grade 2 cholesterol (1.2%, 9.8%), Grade 1 triglycerides (12.2%, 21.7%), and Grade 1 bilirubin (5.0%, 1.1%). A higher proportion of subjects in the DOR group (6.6%) than in the DRV+r group (1.4%) had Grade 1 and/or Grade 2 elevations in total bilirubin, however, the majority of these elevations were transient and no subject met the criteria for DILI through Week 48. None of the bilirubin elevations resulted in a subject being discontinued from the trial, and none was associated with a clinically significant AE.

Analysis of Adverse Event Summary
Weeks 0-48

	Doravirine 100 mg QD		Darunavir/ritonavir 800/100 mg QD		Difference in % vs Darunavir/ritonavir 800/100 mg QD
	n	(%)	n	(%)	Estimate (95% CI)[†]
Subjects in population	383		383		
with one or more adverse events	307	(80.2)	300	(78.3)	1.8 (-3.9, 7.6)
with no adverse events	76	(19.8)	83	(21.7)	-1.8 (-7.6, 3.9)
with drug-related[‡] adverse events	117	(30.5)	123	(32.1)	-1.6 (-8.1, 5.0)
with serious adverse events	19	(5.0)	23	(6.0)	-1.0 (-4.4, 2.3)
with serious drug-related adverse events	1	(0.3)	1	(0.3)	0.0 (-1.2, 1.2)
who died	1	(0.3)	0	(0.0)	0.3 (-0.7, 1.5)
discontinued[§] due to an adverse event	6	(1.6)	12	(3.1)	-1.6 (-4.0, 0.6)
discontinued due to a drug-related adverse event	4	(1.0)	8	(2.1)	-1.0 (-3.1, 0.8)
discontinued due to a serious adverse event	1	(0.3)	2	(0.5)	-0.3 (-1.6, 1.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	1	(0.3)	-0.3 (-1.5, 0.7)

[†] Based on Miettinen & Nurminen method.

[‡] Determined by the investigator to be related to the drug.

[§] Study medication withdrawn.

Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.

Only includes AEs occurring or worsening after the first dose of study medication through 14 days after the last dose of study medication.

Note: Doravirine 100 mg QD and darunavir/ritonavir 800/100 mg QD were administered with TRUVADA™ or EPZICOM™/KIVEXA™.

Source: [P018V01MK1439: analysis-adsl] [P018V01MK1439: tabulations-aeplus]

CONCLUSIONS:	The following conclusions can be drawn from the data presented above with respect to the efficacy of DOR 100 mg once daily in comparison with DRV+r, each in combination with FTC/TDF or ABC/3TC, in HIV-1-infected, treatment-naïve patients: • DOR was shown to have antiretroviral efficacy that was robust and non-inferior to that of DRV+r, as assessed by the primary efficacy endpoint: proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 48. • DOR was shown to have immunologic efficacy that was similar to that of DRV+r. • Antiretroviral and immunologic responses were similar in the DOR and DRV+r treatment groups across all prespecified demographic and prognostic factors. Notably, antiretroviral efficacy among subjects with baseline HIV-1 RNA >100,000 copies/mL or with baseline $CD4^+$ T-cells $\leq 200/mm^3$ was also similar in the DOR and DRV+r groups. • There was a low rate of development of viral drug resistance in both groups. Only 1 of 383 subjects in the DOR group demonstrated significant resistance to any study drug through 48 weeks of treatment. • DOR was generally well tolerated and safe over 48 weeks of treatment when compared with DRV+r. • DOR had a superior lipid profile to DRV+r with respect to change from baseline in fasting LDL-C and non-HDL-C. • A lower risk of discontinuation due to any AE was seen for DOR compared with DRV+r (nominal p=0.040, log-rank test).
PUBLICATION(S):	Molina J-M, Squires K, Sax P, Cahn P, Lombaard J, DeJesus E et al (2017). Doravirine is non-inferior to darunavir/r in Phase 3 treatment-naive trial at week 48. *Top Antivir Med.* 2017; 25(suppl 1):983: Abstract no. 45LB
REPORT DATE:	[redacted]-20[redacted]
REVISED REPORT DATE:	[redacted]-20[redacted]

SPONSOR:	**Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.**	
COMPOUND NAME:	MK-1439A, fixed-dose combination (FDC) oral tablet of doravirine (DOR) 100 mg/lamivudine (3TC) 300 mg/tenofovir disoproxil fumarate (TDF) 300 mg	
INDICATION:	Treatment of HIV-1 infection	
PROTOCOL TITLE:	A Phase III Multicenter, Double-Blind, Randomized, Active Comparator-Controlled Clinical Trial to Evaluate the Safety and Efficacy of MK-1439A Once-Daily Versus ATRIPLA™ Once-Daily in Treatment-Naïve HIV-1 Infected Subjects	
TRIAL IDENTIFIERS:	Protocol Number:	021
	Clinical Phase:	3
	EudraCT Number:	2014-003382-17
	Other Codes: IND Number: ClinicalTrials.gov identifier:	 124997 NCT02403674
ETHICS:	This trial was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.	
TRIAL CENTERS:	This trial was conducted at 126 sites: 33 in the United States; 9 in South Africa; 8 in Russia; 7 in the United Kingdom; 7 in Peru; 6 in Germany; 6 in Taiwan; 6 in Thailand; 5 in Portugal; 4 in Canada; 4 in Chile; 4 in Guatemala; 4 in Spain; 3 in Belgium; 3 in Colombia; 3 in Puerto Rico; 3 in Switzerland; 3 in Mexico; 2 in Australia; 2 in Denmark; 2 in Israel; 1 in Honduras; and 1 in New Zealand.	
DESIGN:	This is an ongoing, Phase 3, multicenter, multinational, randomized, double-blind, active-controlled trial designed to evaluate the safety and efficacy of DOR/3TC/TDF once daily (QD) (MK-1439A) compared with efavirenz (EFV)/emtricitabine (FTC)/TDF QD (ATRIPLA) in HIV-1-infected, treatment-naïve adults ≥18 years of age, with plasma HIV-1 RNA ≥1000 copies/mL at screening (within 45 days of randomization [first day of treatment]) and no known resistance to DOR or any other study drug. Safety data during the base study (through Week 96 of treatment plus the 14-day follow-up period) are monitored by an external Data Monitoring Committee, with reviews approximately every 6 months.	
	Planned duration of main phase (base study):	96 weeks; Week 48 is primary time point. (Data from Week 96 will be presented in a future report.)
	Planned duration of extension phase:	96 weeks

Objectives in Base Study	<u>Primary Objectives:</u> In HIV-1 positive, treatment-naïve subjects with pretreatment HIV-1 RNA ≥1000 copies/mL: 1. To evaluate the noninferior antiretroviral activity of MK-1439A QD compared to ATRIPLA QD as measured by the proportion of subjects achieving HIV-1 RNA <50 copies/mL (by the Abbott RealTime HIV-1 Assay) at Week 48. 2. To evaluate the safety and tolerability of MK-1439A QD compared with ATRIPLA QD as measured by the proportion of subjects with neuropsychiatric adverse events (AEs) in the following categories: dizziness, sleep disorders and disturbances, and altered sensorium. <u>Secondary Objectives:</u> In HIV-1 positive, treatment-naïve subjects with pretreatment HIV-1 RNA ≥1000 copies/mL: 1. To evaluate the safety and tolerability of MK-1439A QD compared to ATRIPLA QD as assessed by review of the accumulated safety data by Week 48 and Week 96. 2. To evaluate the effect of MK-1439A QD compared to ATRIPLA QD on fasting low-density lipoprotein cholesterol (LDL-C) as measured by the mean change from baseline at Week 48. 3. To evaluate the effect of MK-1439A QD compared to ATRIPLA QD on fasting non–high-density lipoprotein cholesterol (HDL-C) as measured by the mean change from baseline at Week 48. 4. To evaluate the safety and tolerability of MK-1439A QD compared with ATRIPLA QD as measured by the proportion of subjects with neuropsychiatric AEs in the following categories: depression and suicide/self-injury, and psychosis and psychotic disorders. 5. To evaluate the safety and tolerability of MK-1439A QD compared with ATRIPLA QD as measured by the proportion of subjects with at least one neuropsychiatric AE across the 5 categories of: dizziness, sleep disorders and disturbances, altered sensorium, depression and suicide/self-injury, and psychosis and psychotic disorders. 6. To evaluate the safety and tolerability of MK-1439A QD compared to ATRIPLA QD as measured by the time to discontinuation from study due to an AE.

	7. To evaluate the immunologic effect of MK-1439A QD compared to ATRIPLA QD as measured by the change from baseline in $CD4^+$ T-cell count at Week 48 and Week 96. 8. To evaluate the superior antiretroviral activity of MK-1439A QD compared to ATRIPLA QD as measured by the proportion of subjects achieving HIV-1 RNA <50 copies/mL (by the Abbott RealTime HIV-1 Assay) at Week 48. 9. To evaluate the noninferior antiretroviral activity of MK-1439A QD compared to ATRIPLA QD as measured by the proportion of subjects achieving HIV-1 RNA <50 copies/mL (by the Abbott RealTime HIV-1 Assay) at Week 96. 10. To evaluate the superior antiretroviral activity of MK-1439A QD compared to ATRIPLA QD as measured by the proportion of subjects achieving HIV-1 RNA <50 copies/mL (by the Abbott RealTime HIV-1 Assay) at Week 96. 11. To evaluate the antiretroviral activity of MK-1439A QD compared to ATRIPLA QD as measured by the proportion of subjects achieving HIV-1 RNA below the limit of quantification (BLoQ) of the Abbott RealTime HIV-1 Assay (<40 copies/mL) at Week 48 and Week 96. 12. To evaluate the pharmacokinetics of MK-1439, when administered as a component of MK-1439A, and the pharmacokinetic-pharmacodynamic association, if supported by the data. <u>Exploratory Objectives:</u> In HIV-1 positive, treatment-naïve subjects with pretreatment HIV-1 RNA ≥1000 copies/mL: 1. To evaluate the antiretroviral activity of MK-1439A QD compared to ATRIPLA QD as measured by the proportion of subjects achieving HIV-1 RNA <200 copies/mL at Week 48 and Week 96. 2. To evaluate the antiretroviral activity of MK-1439A QD compared to ATRIPLA QD as measured by the Time to Loss of Virologic Response (TLOVR). 3. To assess the development of resistance to MK-1439A in subjects who have virologic failure. 4. To describe the outcomes for work productivity and activity impairment related to general health during the study in MK-1439A relative to ATRIPLA QD. 5. 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 study.

Hypotheses	<u>Primary Objectives:</u> MK-1439A QD is noninferior to ATRIPLA QD as assessed by the proportion of subjects with HIV-1 RNA <50 copies/mL (by the Abbott RealTime HIV-1 Assay) at Week 48. A margin of 10 percentage points is used to define noninferiority. MK-1439A QD is superior to ATRIPLA QD as measured by the proportion of subjects with neuropsychiatric AEs in the following categories by Week 48 (superiority will be tested within category, sequentially, in the order indicated below): dizziness, sleep disorders and disturbances, and altered sensorium. <u>Secondary Objectives:</u> MK-1439A QD is superior to ATRIPLA QD as assessed by the mean change from baseline in LDL-C at Week 48. MK-1439A QD is superior to ATRIPLA QD as assessed by the mean change from baseline in non-HDL-C at Week 48. MK-1439A QD is superior to ATRIPLA QD as assessed by the proportion of subjects with HIV-1 RNA <50 copies/mL (by the Abbott RealTime HIV-1 Assay) at Week 48. MK-1439A QD is noninferior to ATRIPLA QD as assessed by the proportion of subjects with HIV-1 RNA <50 copies/mL (by the Abbott RealTime HIV-1 Assay) at Week 96. A margin of 10 percentage points is used to define noninferiority. MK-1439A QD is superior to ATRIPLA QD as assessed by the proportion of subjects with HIV-1 RNA <50 copies/mL (by the Abbott RealTime HIV-1 Assay) at Week 96.	
Treatment groups	DOR/3TC/TDF (MK-1439A)	DOR/3TC/TDF single oral tablet FDC containing DOR 100 mg, 3TC 300 mg, and TDF 300 mg, administered QD for 96 weeks. 368 subjects randomized, 364 treated
	EFV/FTC/TDF (ATRIPLA)	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. 366 subjects randomized, 364 treated
Endpoints and definitions	Primary efficacy endpoint	Proportion of subjects achieving plasma HIV-1 RNA level <50 copies/mL at Week 48
	Secondary efficacy endpoints	• Proportion of subjects achieving plasma HIV-1 RNA level <40 copies/mL at Week 48 and Week 96 • Change from baseline in $CD4^+$ T-cell count at Week 48 and Week 96

	Exploratory efficacy endpoints	• Proportion of subjects achieving plasma HIV-1 RNA level <200 copies/mL at Week 48 and Week 96 • Time to loss of virologic response (TLOVR) • Viral resistance for subjects who meet viral failure criteria and whose virus can be amplified.
	Tier 1 safety endpoint	• Proportion of subjects with neuropsychiatric AEs in the following categories: dizziness, sleep disorders and disturbances, and altered sensorium • Change from baseline in fasting LDL-C and non-HDL-C.
	Tier 2 safety endpoint	• Proportion of subjects with neuropsychiatric AEs in the following categories: depression and suicide / self-injury, and psychosis and psychotic disorders • Proportion of subjects with one or more neuropsychiatric AEs • Change from baseline in fasting lipids not classified as Tier 1 • Modified lipid-lowering therapy • Any AE • Any Serious AE (SAE) • Any Drug-Related AE • Any Serious and Drug-Related AE • Discontinuation due to AE • Specific AEs, system organ classes (SOCs), or Pre-Defined Limit of Changes (PDLCs) (incidence ≥4 subjects in at least one of the treatment groups).
	Tier 3 safety endpoint	• Specific AEs, SOCs, or PDLCs (incidence <4 subjects in all of the treatment groups) • Change from Baseline Results (Labs, Vital Signs).
	Pharmacokinetics endpoint	Descriptive statistics for DOR plasma concentrations collected over 48 weeks.
	Patient-reported outcome endpoints	Subjects to complete a Work Productivity and Activity Impairment Questionnaire (WPAI) at Day 1, Week 4, Week 8, Week 16, and Week 48 (or the discontinuation visit). This patient-reported outcome questionnaire is designed to assess the quantitative impact of health conditions on loss of time and impaired productivity for functional activities such as work-for-pay, school work, and work around the house.
Trial status	The trial is ongoing; the current report contains complete data through Week 48 for the primary endpoint analysis	
Database lock	[redacted]-20[redacted] (Last subject's last visit for 48-week analysis: 20-Mar-2017.)	

RESULTS AND ANALYSIS:	With 340 subjects planned for each treatment arm, the trial has 90% power to demonstrate the primary hypothesis that DOR/3TC/TDF (MK-1439A) QD is noninferior to ATRIPLA (EFV/FTC/TDF) QD at an overall one-sided 2.5% alpha level, as measured by the proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 48. This assumes a true response rate of 80% at Week 48 for both arms, using the United States Food and Drug Administration (FDA) "snapshot" approach.

Subject Baseline Characteristics by Treatment Group

	DOR/3TC/TDF QD (N = 364)	EFV/FTC/TDF QD (N = 364)	Total (N = 728)
Gender n (%)			
Male	305 (83.8)	311 (85.4)	616 (84.6)
Female	59 (16.2)	53 (14.6)	112 (15.4)
Race n (%)			
American Indian or Alaska Native	10 (2.7)	6 (1.6)	16 (2.2)
Asian	59 (16.2)	65 (17.9)	124 (17.0)
Black or African American	67 (18.4)	68 (18.7)	135 (18.5)
Multiple	51 (14.0)	55 (15.1)	106 (14.6)
White	177 (48.6)	170 (46.7)	347 (47.7)
Ethnicity n (%)			
Hispanic or Latino	126 (34.6)	120 (33.0)	246 (33.8)
Not Hispanic or Latino	236 (64.8)	238 (65.4)	474 (65.1)
Unknown	2 (0.5)	6 (1.6)	8 (1.1)
Region n (%)			
Africa	37 (10.2)	27 (7.4)	64 (8.8)
Asia/Pacific	59 (16.2)	62 (17.0)	121 (16.6)
Europe	88 (24.2)	94 (25.8)	182 (25.0)
Latin America	89 (24.5)	87 (23.9)	176 (24.2)
North America	91 (25.0)	94 (25.8)	185 (25.4)
Age (years)			
18 to 64	362 (99.5)	362 (99.5)	724 (99.5)
>=65	2 (0.5)	2 (0.5)	4 (0.5)
Mean (SD)	33.6 (10.5)	32.7 (9.9)	33.1 (10.2)
Median (min, max)	32.0 (18, 70)	30.0 (18, 69)	31.0 (18, 70)
Baseline CD4 Cell Count (cells/mm^3)			
N[†]	364	364	728
Mean (SD)	434.9 (217.9)	415.5 (210.6)	425.2 (214.3)
Median (min, max)	413.5 (19, 1399)	388.0 (19, 1452)	397.0 (19, 1452)
Baseline CD4 Cell Counts n (%)			
<=50 cells/mm^3	9 (2.5)	10 (2.7)	19 (2.6)
>50 cells/mm^3 and <=200 cells/mm^3	35 (9.6)	36 (9.9)	71 (9.8)
>200 cells/mm^3	320 (87.9)	318 (87.4)	638 (87.6)
Baseline Plasma HIV-1 RNA (log_{10} copies/mL)			
N[†]	364	364	728
Mean (SD)	4.4 (0.7)	4.5 (0.7)	4.4 (0.7)
Median (min, max)	4.4 (2.4, 6.1)	4.5 (2.6, 6.4)	4.4 (2.4, 6.4)

Subject Baseline Characteristics by Treatment Group

	DOR/3TC/TDF QD (N = 364)	EFV/FTC/TDF QD (N = 364)	Total (N = 728)
Baseline Plasma HIV-1 RNA (copies/mL)			
N[†]	364	364	728
Geometric Mean	23760.4	29087.1	26289.2
Median (min, max)	22438.5 (259, 1268560)	29732.5 (403, 2692740)	25467.5 (259, 2692740)
Baseline Plasma HIV-1 RNA n (%)			
<=100,000 copies/mL	291 (79.9)	282 (77.5)	573 (78.7)
>100,000 copies/mL	73 (20.1)	82 (22.5)	155 (21.3)
Baseline Plasma HIV-1 RNA n (%)			
<=500,000 copies/mL	354 (97.3)	346 (95.1)	700 (96.2)
>500,000 copies/mL	10 (2.7)	18 (4.9)	28 (3.8)
History of AIDS n (%)			
Yes	46 (12.6)	53 (14.6)	99 (13.6)
No	318 (87.4)	311 (85.4)	629 (86.4)
Stratum n (%)			
Screening HIV RNA<= 100,000	275 (75.5)	274 (75.3)	549 (75.4)
Screening HIV RNA> 100,000	89 (24.5)	90 (24.7)	179 (24.6)
Hep B and/or C Positive	19 (5.2)	18 (4.9)	37 (5.1)
Hep B and C Negative	345 (94.8)	346 (95.1)	691 (94.9)
Baseline Hepatitis Status[††]			
Hep B and/or C Positive	11 (3.0)	9 (2.5)	20 (2.7)
Hep B Positive Only	9 (2.5)	8 (2.2)	17 (2.3)
Hep C Positive Only	2 (0.5)	1 (0.3)	3 (0.4)
Hep B and C Negative	353 (97.0)	355 (97.5)	708 (97.3)
Viral Subtype n (%)			
Subtype B	232 (63.7)	253 (69.5)	485 (66.6)
Non-Subtype B	130 (35.7)	111 (30.5)	241 (33.1)
Missing	2 (0.5)	0 (0.0)	2 (0.3)

[†] Subjects with missing results excluded.

[††] Evidence of hepatitis B surface antigen or evidence of HCV RNA by polymerase chain reaction (PCR) quantitative test for hepatitis C virus.

21 subjects previously classified as hepatitis B and/or C positive were subsequently identified based on lab tests as being hepatitis B and C negative. 4 subjects previously classified as hepatitis B and C negative were subsequently identified based on lab tests as being hepatitis B and/or C positive.

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

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

Source: [P021V01MK1439A: analysis-adsl]

Subject Disposition by Treatment Group
Weeks 0-48

	DOR/3TC/TDF QD		EFV/FTC/TDF QD		Total	
	n	(%)	n	(%)	n	(%)
Total Randomized	368		366		734	
Not Treated	4	(1.1)	2	(0.5)	6	(0.8)
Treated	364	(98.9)	364	(99.5)	728	(99.2)
Discontinued Study	51	(13.9)	61	(16.7)	112	(15.3)
Adverse Event	10	(2.7)	23	(6.3)	33	(4.5)
Death	1	(0.3)	3	(0.8)	4	(0.5)
Lack Of Efficacy	18	(4.9)	10	(2.7)	28	(3.8)
Lost To Follow-Up	6	(1.6)	7	(1.9)	13	(1.8)
Non-Compliance With Study Drug	1	(0.3)	2	(0.5)	3	(0.4)
Physician Decision	2	(0.5)	2	(0.5)	4	(0.5)
Pregnancy	1	(0.3)	1	(0.3)	2	(0.3)
Protocol Deviation	4	(1.1)	2	(0.5)	6	(0.8)
Withdrawal By Subject	8	(2.2)	11	(3.0)	19	(2.6)

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

Source: [P021V01MK1439A: analysis-adsl] [P021V01MK1439A: tabulations-dsplus]

Analysis description	**Primary Efficacy Analysis: Proportion of Subjects With HIV-1 RNA <50 copies/mL at Week 48** *Statistical Methodology:* The primary hypothesis on antiretroviral activity was assessed by the proportion of subjects achieving plasma HIV-1 RNA <50 copies/mL at Week 48 using the Abbott RealTime HIV-1 Assay. A margin of 10 percentage points was used to specify the criterion for noninferiority: DOR/3TC/TDF was concluded to be noninferior to EFV/FTC/TDF if the lower bound of the two-sided 95% confidence interval (CI) for the difference in the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48 (DOR/3TD/TDF – EFV/FTC/TDF) was greater than −10 percentage points. The FDA Snapshot approach was used as the primary approach for this analysis: all missing data were treated as failures regardless of the reason. **Secondary Efficacy Analysis: Proportion of subjects achieving plasma HIV-1 RNA level <40 copies/mL at Week 48 and Week 96** *Statistical Methodology:* The proportion of subjects achieving HIV-1 RNA <40 copies/mL were analyzed using the same approach as described above for the proportion of subjects achieving HIV-1 RNA <50 copies/mL. **Secondary Efficacy Analysis: Change from baseline in $CD4^+$ T-cell count at Week 48 and Week 96** *Statistical Methodology:* The treatment difference in changes from baseline in $CD4^+$ T cell count at each time point was estimated with a key interest at Week 48; however, these estimates were not subject to an absolute criterion for similarity. The clinical interpretation of the treatment difference was dependent upon the absolute value at baseline, and the magnitude and direction of the $CD4^+$ T-cell changes seen in each treatment arm. The OF approach was used for the calculations of change from baseline in $CD4^+$ T-cell count. Under this approach, baseline values were carried forward for subjects who discontinued due to lack of efficacy.

	Exploratory Efficacy Analysis: Proportion of subjects achieving plasma HIV-1 RNA level <200 copies/mL at Week 48 and Week 96 *Statistical Methodology:* The proportion of subjects achieving HIV-1 RNA <200 copies/mL were analyzed using the same approach as described above for the proportion of subjects achieving HIV-1 RNA <50 copies/mL. **Exploratory Efficacy Analysis: Time to Loss of Virologic Response** *Statistical Methodology:* TLOVR was estimated using Kaplan-Meier product-limit estimates and graphically displayed. Log-rank tests and Cox Proportional Hazards models were also applied to these time-to-event data. **Exploratory Efficacy Analysis: Protocol-Defined Virologic Failure (PDVF) and Viral Drug Resistance** *Statistical Methodology:* The number of subjects with PDVF was summarized for each treatment group. Genotypic and phenotypic resistance data from subjects with protocol-defined virologic failure were summarized.
Analysis population and time point description	The primary population for efficacy analyses was the Full Analysis Set (FAS) population. The FAS population consisted of all randomized subjects who received at least one dose of study drug and had baseline data for those analyses that require baseline data.

Summary	The proportion of subjects achieving the primary endpoint of HIV-1 RNA <50 copies/mL at Week 48 (FDA snapshot approach) was 84.3% (307/364) in the DOR/3TC/TDF group and 80.8% (294/364) in the EFV/FTC/TDF group with a treatment difference (95% CI) of 3.5% (-2.0, 9.0). Therefore, DOR/3TC/TDF was noninferior to EFV/FTC/TDF in achieving the primary endpoint because the lower bound of the 95% CI for treatment difference was above the predefined noninferiority bound of -10 percentage points. Analysis results for this endpoint using the OF approach were consistent with those of the FDA snapshot approach. Note that the lower bound of the 95% CI for the treatment difference was not greater than zero, indicating that the proportion of subjects achieving HIV-1 RNA <50 copies/mL in the DOR/3TC/TDF group was not superior to that of the EFV/FTC/TDF group. The proportion of subjects achieving the secondary endpoint of HIV-1 RNA <40 copies/mL (FDA snapshot approach) was 83.8% and 79.7% in the DOR/3TC/TDF and EFV/FTC/TDF groups, respectively, with a treatment difference (95% CI) of 4.1% (-1.5, 9.7). Similar results for this endpoint were also observed using the OF approach. The proportion of subjects achieving HIV-1 RNA <200 copies/mL at Week 48 (using both missing data approaches) were supportive of the results for the primary and key secondary endpoints. Analysis of the change from baseline in $CD4^+$ T-cell count indicated similar results for both treatment groups, with a mean increase from baseline at Week 48 of 198 cells/mm^3 in the DOR/3TC/TDF group and 188 cells/mm^3 in the EFV/FTC/TDF group. The key efficacy endpoints (proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 48 [DOR/3TC/TDF: 89.3%; EFV/FTC/TDF: 85.8%] and proportion of subjects achieving HIV-1 RNA <40 copies/mL at Week 48 [DOR/3TC/TDF: 88.8%; EFV/FTC/TDF: 84.7%]) were also analyzed for the per-protocol population, and these results are consistent with the results of the FAS analysis.

	Rates of PDVF were low in both the DOR/3TC/TDF and EFV/FTC/TDF treatment groups: a total of 22 subjects (6.0%) in the DOR/3TC/TDF group and 14 subjects (3.8%) in the EFV/FTC/TDF group were identified as meeting PDVF criteria by Week 48. Subjects with PDVF generally had low-level viremia at the time of failure. Ten of the 16 subjects in the DOR/3TC/TDF group who met the rebound definition of PDVF had HIV-1 RNA between 50 and 200 copies/mL at the viral failure confirmation visit (as did 4 of 10 in the EFV/FTC/TDF group). Seven subjects who met PDVF criteria in the DOR/3TC/TDF group had genotypic and/or phenotypic resistance to DOR (as did 9 subjects in the EFV/FTC/TDF group with genotypic and phenotypic resistance to EFV) and 7 subjects had genotypic and/or phenotypic resistance to NRTIs (as did 5 subjects in the EFV/FTC/TDF group). Three subjects in the EFV/FTC/TDF group who discontinued for reasons other than PDVF had both genotypic and phenotypic resistance to EFV; in comparsion, none of the subjects in the DOR/3TC/TDF group who discontinued for reasons other than PDVF had both genotypic and phenotypic resistance to EFV. The risk of loss of virologic response was observed at similar rates for both treatment groups. Based on the Kaplan-Meier plot for TLOVR and analyses using the log-rank test and the Cox model, the DOR/3TC/TDF and EFV/FTC/TDF groups were similar with respect to risk of loss of virologic response.

Efficacy Analysis at Week 48

Parameter	Missing Data Approach[†]	Unadjusted Data Summary by Treatment Group		Treatment Difference (DOR/3TC/TDF - EFV/FTC/TDF)[‡]		Conclusion[§]
		DOR/3TC/TDF QD n/N (%)	EFV/FTC/TDF QD n/N (%)	Estimated Difference	95% CI	
Primary						
Proportion of Subjects with HIV-1 RNA <50 copies/mL	Snapshot	307/364 (84.3)	294/364 (80.8)	3.537	(-1.951, 9.026)	Non-inferior
Secondary and Exploratory						
Proportion of Subjects with HIV-1 RNA <50 copies/mL	OF	307/346 (88.7)	294/331 (88.8)	-0.179	(-4.936, 4.578)	
Proportion of Subjects with HIV-1 RNA <40 copies/mL	Snapshot	305/364 (83.8)	290/364 (79.7)	4.084	(-1.493, 9.661)	
Proportion of Subjects with HIV-1 RNA <40 copies/mL	OF	305/346 (88.2)	290/331 (87.6)	0.442	(-4.463, 5.346)	
Proportion of Subjects with HIV-1 RNA <200 copies/mL	Snapshot	313/364 (86.0)	301/364 (82.7)	3.274	(-2.012, 8.561)	
Proportion of Subjects with HIV-1 RNA <200 copies/mL	OF	313/346 (90.5)	301/331 (90.9)	-0.523	(-4.943, 3.897)	
		Mean (95% CI)	Mean (95% CI)	Mean Difference	95% CI	
Change from Baseline in CD4 Cell Count (cells/mm^3)	OF	198.4 (180.2, 216.7)	188.4 (169.5, 207.2)	10.1	(-16.1, 36.3)	

[†] Snapshot: Defined by FDA Snapshot approach; OF: Observed Failure approach.
[‡] The 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (screening HIV-1 RNA ≤100,000 or >100,000 copies/mL). The 95% CI for mean difference in CD4 change was based on t-distribution.
[§] DOR/3TC/TDF QD is concluded non-inferior to EFV/FTC/TDF QD if the lower bound of the 95% CI for the difference in percent response is above -10 percentage points.
Analysis of post-baseline data only includes laboratory records collected after the first dose of study medication through 14 days after the last dose of study medication.
n = Number of subjects in each subcategory.
N = Number of subjects in each treatment group.

Source: [P021V01MK1439A: analysis-adsl; adcd4; adrna]

Efficacy Analysis at Week 48
Per Protocol Analysis

Parameter	Missing Data Approach[†]	Unadjusted Data Summary by Treatment Group		Treatment Difference (DOR/3TC/TDF - EFV/FTC/TDF)[‡]		Conclusion[§]
		DOR/3TC/TDF QD n/N (%)	EFV/FTC/TDF QD n/N (%)	Estimated Difference	95% CI	
Primary						
Proportion of Subjects with HIV-1 RNA <50 copies/mL	Snapshot	302/338 (89.3)	291/339 (85.8)	3.561	(-1.355, 8.477)	Non-inferior
Secondary						
Proportion of Subjects with HIV-1 RNA <40 copies/mL	Snapshot	300/338 (88.8)	287/339 (84.7)	4.154	(-0.895, 9.202)	

[†] Snapshot: Defined by FDA Snapshot approach.
[‡] The 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (screening HIV-1 RNA ≤100,000 or >100,000 copies/mL).
[§] DOR/3TC/TDF QD is concluded non-inferior to EFV/FTC/TDF QD if the lower bound of the 95% CI for the difference in percent response is above -10 percentage points.
Analysis of post-baseline data only includes laboratory records collected after the first dose of study medication through 14 days after the last dose of study medication.
n = Number of subjects in each subcategory.
N = Number of subjects in each treatment group.

Source: [P021V01MK1439A: analysis-adsl; adrna]

Analysis description	**Supportive Analysis: Virologic Outcome** *Statistical Methodology:* Subjects who were not classified as virologic success were categorized as virologic failure (HIV-1 RNA ≥50 copies/mL) or as having no virologic data in the time window with reasons of: 1) discontinued study due to an AE; 2) discontinued study for other reasons (includes withdraw consent, loss to follow-up, moved); or 3) on study but missing data in window. The full categorization of virologic outcome at Week 48 was summarized by treatment group.
Summary	The virologic outcomes of DOR/3TC/TDF are comparable to those of EFV/FTC/TDF, in regard to proportion of participants with HIV-1 RNA <50 copies/mL (84.3% vs. 80.8%, respectively) and HIV-1 RNA ≥50 copies/mL (10.7% vs. 10.2%, respectively). A higher proportion of participants in the EFV/FTC/TDF group (9.1%) than in the DOR/3TC/TDF group (4.9%) had no virologic data at Week 48 window, driven by a higher proportion of subjects in the EFV/FTC/TDF group discontinuing from the trial due to an AE.

Virologic Outcome at Week 48
FDA Snapshot Approach

Outcome	DOR/3TC/TDF QD (N=364) n	(%)	EFV/FTC/TDF QD (N=364) n	(%)
HIV-1 RNA <50 copies/mL	307	(84.3)	294	(80.8)
HIV-1 RNA ≥ 50 copies/mL[†]	39	(10.7)	37	(10.2)
No Virologic Data at Week 48 Window	18	(4.9)	33	(9.1)
Reasons				
Discontinued study due to AE or Death[‡]	9	(2.5)	24	(6.6)
Discontinued study for Other Reasons[§]	9	(2.5)	8	(2.2)
On study but missing data in window	0	(0.0)	1	(0.3)

[†] Includes subjects who changed any component of background therapy to a new drug class or changed background components that were not permitted per protocol or changed any background drug in the regimen because of lack of efficacy (perceived or documented) before Week 48, subjects who discontinued study drug or study before Week 48 for lack or loss of efficacy and subjects with HIV-1 RNA equal to or above 50 copies/mL in the Week 48 window (relative day 295-378).

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

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

Analysis of post-baseline data only includes laboratory records collected after the first dose of study medication through 14 days after the last dose of study medication.

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

Source: [P021V01MK1439A: analysis-adsl; adrna]

Analysis description	**Supportive Analysis: Subgroup Efficacy** *Statistical Methodology*: To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI unadjusted for stratification factors) for the primary endpoint (as well as the HIV-1 RNA <40 copies/mL endpoint) was calculated within each category of the subgroup factors.
Summary	Similar results (based on 95% CI for treatment difference that includes 0) were found for the DOR/3TC/TDF and EFV/FTC/TDF groups across most of the subgroups defined by baseline prognostic and demographic factors. The overall trend of antiretroviral efficacy for subjects with HIV-1 RNA <40 copies/mL and <200 copies/mL was consistent with the results for the <50 copies/mL threshold and similar in the two treatment groups, regardless of baseline prognostic and demographic factors. Specifically, similar results for both treatment groups were seen for the proportions of subjects who achieved HIV-1 RNA <50 copies/mL at Week 48 among subjects with a high baseline HIV-1 RNA level (>100,000 copies/mL). Among subjects with baseline $CD4^+$ T-cell counts ≤50 cells/mm^3, the proportions of subjects who achieved HIV-1 RNA <50 copies/mL at Week 48 were similar in the DOR/3TC/TDF and EFV/FTC/TDF groups (62.5% and 66.7%, respectively), while among subjects with baseline $CD4^+$ T-cell counts >50 and ≤200 cells/mm^3, a larger proportion in the EFV/FTC/TDF group (although the 95% CI excluded 0) achieved HIV-1 RNA <50 copies/mL at Week 48 (70.6% and 88.2% [95% CI: -37.1, 1.9]), although the numbers of subjects in each of these baseline-$CD4^+$ subgroups were too small to be clinically meaningful. The overall trend of antiretroviral efficacy for subjects with HIV-1 RNA <40 copies/mL and <200 copies/mL, using the OF approach, was consistent with the results for the <50 copies/mL threshold and similar in the two treatment groups, regardless of baseline prognostic and demographic factors. The proportions of subjects with HIV-1 RNA <50 copies/mL, <40 copies/mL, and <200 copies/mL at Week 48 by prognostic and demographic factors for combined baseline $CD4^+$ subgroups, using the OF approach, show an overall trend of antiretroviral efficacy that was similar in the treatment groups for these analyses, with no meaningful differences at Week 48 identified.

Analysis description	**Safety Analyses: Neuropsychiatric Adverse Events at Week 48** *Statistical Methodology*: A selected list of neuropsychiatric adverse event categories was examined, including the following: ▪ **Prespecified Tier-1 categories/primary endpoints**: Dizziness, sleep disorders/disturbances, and altered sensorium (including disturbance in attention) ▪ **Prespecified Tier-2 categories/secondary endpoints**: Depression/suicide/self-injury, and psychosis/psychotic disorders. Testing of the hypotheses on neuropsychiatric AE categories sequentially followed after the efficacy noninferiority hypothesis and was in the order of dizziness, sleep disorders and disturbances, and altered sensorium.
Analysis population and time point description	Safety analyses were based on the All Subjects as Treated (ASaT) population, which consisted of all randomized subjects who received at least one dose of study medication.
Summary	The proportion of subjects with neuropsychiatric events by Week 48 was significantly lower in the DOR/3TC/TDF group compared with the EFV/FTC/TDF group for each of the 3 Tier 1 categories of dizziness (8.8% vs. 37.1%), sleep disorders/disturbances (12.1% vs. 25.2%), and altered sensorium (4.4% vs. 8.2%) (2-sided $p<0.001$, 2-sided $p<0.001$ and 2-sided $p=0.033$, respectively). As planned in the protocol, an alpha level of 0.00001 was to be allocated for each DMC safety review through Week 48 before testing the primary safety hypothesis and subsequent safety hypotheses. By the time of the Week 48 database lock, 3 interim DMC safety reviews had taken place. Therefore, all safety hypotheses were tested at a 1-sided significance level of 0.02497. Since the 1-sided p-values (2-sided p-values divided by 2) comparing between treatment differences were <0.02497 for all 3 AE categories, it was concluded that the DOR/3TC/TDF group was superior to the EFV/FTC/TDF group in terms of having a significantly lower proportion of subjects with neuropsychiatric AEs in all prespecified Tier 1 categories by Week 48. The proportion of subjects with the Tier 2 neuropsychiatric event categories of depression/suicide/self-injury and psychosis/psychotic disorders was also lower in the DOR/3TC/TDF group compared to the EFV/FTC/TDF group. Overall, the majority of subjects (74.1%) with neuropsychiatric AEs had AEs which were mild in intensity.

Analysis of Subjects with Neuropsychiatric Adverse Events by Week 48

	DOR/3TC/TDF QD (N=364)		EFV/FTC/TDF QD (N=364)		Treatment Difference (DOR/3TC/TDF - EFV/FTC/TDF)	2-Sided
	n	%	n	%	Estimate (95% CI)[†]	P-value[‡]
Subjects in population	364		364			
with one or more neuropsychiatric adverse events	86	(23.6)	207	(56.9)	-33.2 (-39.8, -26.4)	
with no neuropsychiatric adverse events	278	(76.4)	157	(43.1)	33.2 (26.4, 39.8)	
Dizziness	32	(8.8)	135	(37.1)	-28.3 (-34.0, -22.5)	<0.001
Sleep Disorders and Disturbances	44	(12.1)	93	(25.5)	-13.5 (-19.1, -7.9)	<0.001
Altered Sensorium	16	(4.4)	30	(8.2)	-3.8 (-7.6, -0.3)	0.033
Depression and Suicide/self-injury	15	(4.1)	24	(6.6)	-2.5 (-5.9, 0.8)	nps[*]
Psychosis and Psychotic Disorders	1	(0.3)	4	(1.1)	-0.8 (-2.5, 0.5)	nps[*]

The five categories of neuropsychiatric adverse event were predefined. Specific terms included for each category were based on MedDRA 19.1. Every subject is counted a single time for each applicable specific adverse event. A subject with multiple adverse events within a category is counted a single time for that category.

[†] The 95% CIs were calculated using Miettinen and Nurminen's method.

[‡] Superiority is tested sequentially for dizziness, sleep disorders and disturbances, and altered sensorium.

[*] Not pre-specified for statistical testing.

Only includes AEs occurring or worsening after the first dose of study medication through 14 days after the last dose of study medication.

Source: [P021V01MK1439A: analysis-adsl; adcns]

Analysis description	**Safety Analyses: Change From Baseline at Week 48 in Fasting Lipids** *Statistical Methodology*: Changes from baseline in fasting LDL-C and non-HDL-C were Tier 1 events. Changes from baseline in other fasting lipids (total cholesterol, triglycerides, and HDL-C) were Tier 2 events. Change from baseline in fasting lipids was analyzed using ANCOVA models to provide treatment comparisons adjusted for baseline fasting lipid level. The treatment differences and 95% CIs were provided for all lipids parameters and p-value for the between-treatment comparison was provided for LDL-C and non-HDL-C. The significance of the treatment difference for LDL-C was tested first; sequential testing for non-HDL-C was to be done only if superiority was established for LDL-C.
Analysis population and time point description	Safety analyses were based on the All Subjects as Treated (ASaT) population, which consisted of all randomized subjects who received at least one dose of study medication.
Summary	The difference between the DOR/3TC/TDF and EFV/FTC/TDF groups in mean change from baseline to Week 48 in fasting LDL-C was statistically significant (1-sided p-value <0.0001) at significance level of 0.02497, with a mean decrease of 1.58 mg/dL in the DOR/3TC/TDF group and a mean increase of 8.74 mg/dL in the EFV/FTC/TDF group. Similarly, the difference in mean change from baseline to Week 48 in fasting non-HDL-C was statistically significant (1-sided p-value <0.0001) at significance level of 0.02497 between the DOR/3TC/TDF and EFV/FTC/TDF groups, with a mean decrease of 3.83 mg/dL in the DOR/3TC/TDF group and a mean increase of 13.26 mg/dL in the EFV/FTC/TDF group from baseline. A similar result was observed with respect to changes from baseline to Week 48 for fasting total cholesterol and fasting triglycerides: while testing for statistical significance was not done for these parameters, the estimated differences between treatment groups indicate that, relative to EFV/FTC/TDF, which was associated with mean increases from baseline in fasting cholesterol and triglycerides, these parameters decreased among DOR/3TC/TDF-treated subjects. For fasting HDL-C, the between-treatment-group differences were not clinically meaningful.

Change From Baseline in Fasting Lipids at Week 48

Treatment	N	Baseline Mean	Change from Baseline at Week 48		Difference Estimates (DOR/3TC/TDF - EFV/FTC/TDF)	
			Mean Change (SD)	95% CI[†]	Difference[‡] 95% CI	2-sided p-Value
Fasting LDL Cholesterol (mg/dL)						
DOR/3TC/TDF QD	330	92.03	-1.58 (22.12)	(-3.98, 0.81)	-10.01 (-13.53, -6.49)	<0.0001
EFV/FTC/TDF QD	305	90.75	8.74 (25.54)	(5.86, 11.62)		
Fasting Non-HDL Cholesterol (mg/dL)						
DOR/3TC/TDF QD	333	115.23	-3.83 (22.59)	(-6.27, -1.40)	-17.02 (-20.89, -13.16)	<0.0001
EFV/FTC/TDF QD	314	114.84	13.26 (28.76)	(10.07, 16.45)		
Fasting Cholesterol (mg/dL)						
DOR/3TC/TDF QD	333	157.38	-1.97 (25.67)	(-4.74, 0.79)	-23.44 (-27.57, -19.32)	nps*
EFV/FTC/TDF QD	314	156.21	21.77 (30.74)	(18.35, 25.18)		
Fasting Triglyceride (mg/dL)						
DOR/3TC/TDF QD	333	119.45	-12.40 (67.30)	(-19.66, -5.15)	-35.96 (-47.10, -24.82)	nps*
EFV/FTC/TDF QD	314	122.97	22.01 (93.03)	(11.68, 32.34)		
Fasting HDL Cholesterol (mg/dL)						
DOR/3TC/TDF QD	333	42.15	1.86 (9.59)	(0.83, 2.89)	-6.47 (-7.97, -4.96)	nps*
EFV/FTC/TDF QD	314	41.37	8.51 (10.66)	(7.32, 9.69)		

The Last Observation Carry Forward (LOCF) approach is applied for the missing data or data collected after modifying lipid-lowering therapy.

[†] Within group 95% CIs were based on t-distribution.

[‡] The 95% CIs and 2-sided p-value for treatment difference were calculated from an ANOCOVA model with terms for baseline lipid level and treatment.

[*] Not pre-specified for statistical testing

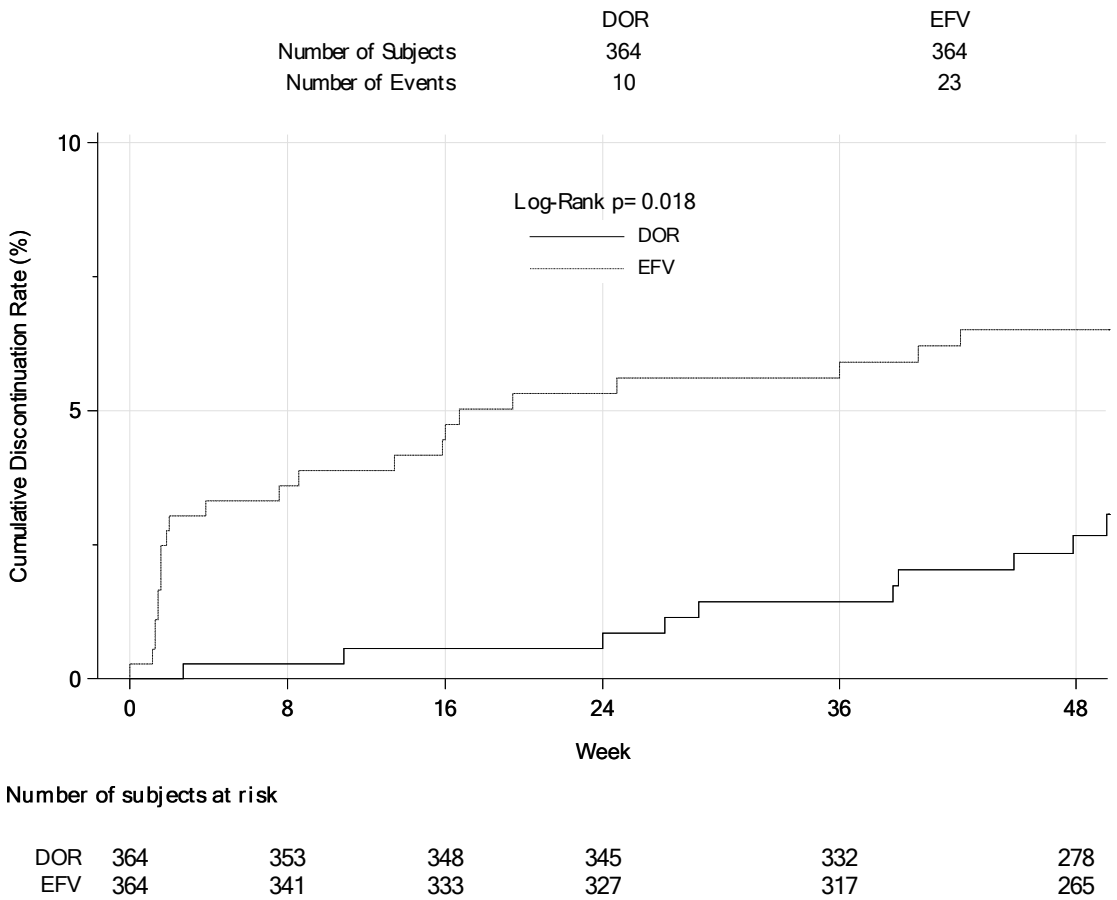
Analysis of post-baseline data only includes laboratory records collected after the first dose of study medication through 14 days after the last dose of study medication.

N = Number of subjects with baseline and at least one postbaseline test result.

Source: [P021V01MK1439A: analysis-adsl; adlpd]

Analysis description	**Safety Analysis: Time to Discontinuation Due to Adverse Event** *Statistical Methodology*: The time to discontinuation from the trial due to an AE was estimated using Kaplan-Meier product-limit estimates and graphically displayed. The log-rank test was also performed for this time-to-event endpoint.
Summary	There were fewer discontinuations due to AEs in the DOR/3TC/TDF group (10 subjects) compared with the EFV/FTC/TDF group (23 subjects). The log-rank test indicated that the EFV/FTC/TDF group is associated with a higher risk of discontinuation due to AE than the DOR/3TC/TDF group (nominal p=0.018). The higher number of discontinuations in the EFV/FTC/TDF group was primarily due to rash.

Kaplan-Meier Plot for Time to Discontinuation Due to Adverse Event
Weeks 0-48



DOR=DOR/3TC/TDF QD; EFV=EFV/FTC/TDF QD
Source: [P021V01MK1439A: analysis-adtte]

Analysis description	**Safety Analysis: Overall Adverse Events and Predefined Limits of Change (PDLC) in Laboratory Parameters** *Statistical Methodology*: The treatment differences, and associated 95% CIs, in percentage of subjects for the Tier 2 events were calculated using the Miettinen and Nurminen method. Tier 2 events include the following AE categories: any AE, drug-related AE, SAE, drug-related SAE, discontinuation due to AE. In addition, AEs (PT as well as SOC) and PDLC with incidence ≥4 subjects in at least one treatment group were classified as Tier 2 events. All other AEs and PDLC are classified as Tier 3, for which only a descriptive summary by treatment group was provided.
Summary	DOR/3TC/TDF was generally well tolerated as evidenced by fewer drug-related AEs (31.0% in DOR/3TC/TDF vs. 62.9% in EFV/FTC/TDF), fewer discontinuations due to AEs (3.0% in the DOR/3TC/TDF group vs. 6.6% in the EFV/FTC/TDF group), and fewer discontinuations due to drug-related AEs (2.2% in the DOR/3TC/TDF group compared with 5.8% in the EFV/FTC/TDF group). The frequency of rash AEs was lower in the DOR/3TC/TDF group compared to the EFV/FTC/TDF group (6.0% and 17.6%, respectively), and no subjects in the DOR/3TC/TDF group discontinued due to rash compared to 10 subjects in the EFV/FTC/TDF group. PDLC between-group differences (all lower for DOR/3TC/TDF) occurred in the proportions of subjects with Grade 2 LDL-C (0.9% and 4.9% in the DOR/3TC/TDF and EFV/FTC/TDF groups, respectively), Grade 1 cholesterol (6.3% and 13.8%), Grade 2 cholesterol (0.6% and 7.5%), and Grade 1 triglycerides (9.5% and 16.0%). DOR/3TC/TDF was associated with higher proportions of subjects with Grade 1 and Grade 2 elevations in total bilirubin (3.6% and 2.5%, respectively; none for either in the EFV/FTC/TDF group). The majority of these elevations were Grade 1 and, across all grades, single transient elevations with no pattern relative to dosing. None of these elevations resulted in a subject being discontinued from the trial. Five of 9 subjects with Grade 2 bilirubin elevations had Grade 1 bilirubin levels at screening and/or baseline. The absence of bilirubin elevations in the EFV/FTC/TDF group is likely due to the induction of UGT1A1and MRPs that reduces bilirubin levels. Similar findings of no elevations in total bilirubin with EFV have been observed in other clinical trials.

Analysis of Adverse Event Summary
Weeks 0-48

	DOR/3TC/TDF QD		EFV/FTC/TDF QD		Difference in % vs EFV/FTC/TDF QD
	n	(%)	n	(%)	Estimate (95% CI)[†]
Subjects in population	364		364		
with one or more adverse events	301	(82.7)	330	(90.7)	-8.0 (-13.0, -3.1)
with no adverse events	63	(17.3)	34	(9.3)	8.0 (3.1, 13.0)
with drug-related[‡] adverse events	113	(31.0)	229	(62.9)	-31.9 (-38.6, -24.8)
with serious adverse events	13	(3.6)	21	(5.8)	-2.2 (-5.5, 0.9)
with serious drug-related adverse events	1	(0.3)	4	(1.1)	-0.8 (-2.5, 0.5)
who died	0	(0.0)	2	(0.5)	-0.5 (-2.0, 0.5)
discontinued[§] due to an adverse event	11	(3.0)	24	(6.6)	-3.6 (-6.9, -0.5)
discontinued due to a drug-related adverse event	8	(2.2)	21	(5.8)	-3.6 (-6.7, -0.8)
discontinued due to a serious adverse event	2	(0.5)	4	(1.1)	-0.5 (-2.3, 1.0)
discontinued due to a serious drug-related adverse event	1	(0.3)	3	(0.8)	-0.5 (-2.2, 0.8)

[†] Based on Miettinen & Nurminen method.
[‡] Determined by the investigator to be related to the drug.
[§] Study medication withdrawn.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.
Only includes AEs occurring or worsening after the first dose of study medication through 14 days after the last dose of study medication.

Source: [P021V01MK1439A: analysis-adsl] [P021V01MK1439A: tabulations-aeplus]

CONCLUSIONS:	▪ DOR/3TC/TDF was shown to have robust antiretroviral efficacy that was statistically non-inferior to that of EFV/FTC/TDF, as assessed by the primary efficacy endpoint: proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 48 (84.3% in the DOR/3TC/TDF group and 80.8% in the EFV/FTC/TDF group with a treatment difference [95% CI] of 3.5% [-2.0, 9.0]). ▪ DOR/3TC/TDF was shown to have immunologic efficacy that was similar to that of EFV/FTC/TDF as assessed by the change from baseline in $CD4^+$ T-cell counts at Week 48. ▪ Antiretroviral and immunologic responses at Week 48 were similar in the DOR/3TC/TDF and EFV/FTC/TDF treatment groups across most prespecified demographic and prognostic factors. Notably, antiretroviral efficacy among subjects with baseline HIV-1 RNA >100,000 copies/mL or with baseline <200 $CD4^+$ T-cells/mm^3 was also similar in the DOR/3TC/TDF and EFV/FTC/TDF treatment groups. ▪ There was a low rate of development of viral drug resistance mutations in both treatment groups. ▪ DOR/3TC/TDF was generally well tolerated, with a favorable safety profile over 48 weeks of treatment when compared with EFV/FTC/TDF. ▪ DOR/3TC/TDF has a superior safety profile to that of EFV/FTC/TDF over 48 weeks of treatment for the neuropsychiatric categories of dizziness, sleep disorders/ disturbances, and altered sensorium. ▪ DOR/3TC/TDF has a superior lipid profile to that of EFV/FTC/TDF over 48 weeks of treatment with respect to change from baseline in fasting LDL-C and non-HDL-C. ▪ A lower rate of discontinuation due to any AE was seen for DOR/3TC/TDF compared with EFV/FTC/TDF over 48 weeks of treatment ($p < 0.05$, log-rank test).
PUBLICATION(S):	Squires KE, Molina JM, Sax PE, Wong WW, Orkin C, Sussmann O, et al. Fixed dose combination of doravirine/lamivudine/TDF is non-inferior to efavirenz/emtricitabine/TDF in treatment-naive adults with HIV-1 infection: week 48 results of the Phase 3 DRIVE-AHEAD study. Poster session presented at Ninth IAS Conference on HIV Science (IAS 2017); 2017 Jul 23-26; France, Paris.
REPORT DATE:	[redacted]-20[redacted]

TABLE OF CONTENTS

Table of All Clinical Studies

Trial ID	Phase	Country / Region	Study Title	Study design	Dosing regimen	Study population	Participant exposure
1439A-024 [Ref. 5.3.5.1: P024 MK1439A]	3	USA Canada Italy United Kingdom Germany Israel Spain Russia Belgium Argentina Australia Denmark France Austria Mexico Poland Switzerland South Korea Puerto Rico Columbia Guatemala New Zealand Peru	A Phase III Multicenter, Open-Label, Randomized Study to Evaluate a Switch to MK-1439A in HIV-1-Infected Subjects Virologically Suppressed on a Regimen of a Ritonavir-boosted Protease Inhibitor and Two Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	Double-blind, randomized, open-label, active-controlled	DOR/3TC/TDF single oral tablet FDC containing DOR 100 mg, 3TC 300 mg, and TDF 300 mg, administered QD for 48 weeks Ritonavir- or cobicistat-boosted PI (specifically, atazanavir, darunavir, or lopinavir) or cobicistat-boosted elvitegravir or an NNRTI (specifically, efavirenz, nevirapine, or rilpivirine) each administered with 2 NRTIs for 24 weeks	Males/females: 84.5%/15.5% Age: 21-71 HIV-1-Infected Subjects Who are Virologically Suppressed	Doravirine 100 mg/3TC 300 mg/TDF 300 mg Doravirine 200 mg/3TC 600 mg/TDF 600 mg

2 SYNOPSIS

SPONSOR: Merck Sharp & Dohme Corp., a Subsidiary of Merck & Co., Inc., NJ, USA (MSD)

COMPOUND NAME: Fixed-dose combination (FDC) oral tablet of doravirine (DOR) /lamivudine (3TC) /tenofovir disoproxil fumarate (TDF) (MK-1439A, DELSTRIGO™)

PROTOCOL TITLE: A Phase III Multicenter, Open-Label, Randomized Study to Evaluate a Switch to MK-1439A in HIV-1-Infected Subjects Virologically Suppressed on a Regimen of a Ritonavir-boosted Protease Inhibitor and Two Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

STUDY IDENTIFIERS:

IND: 124,997	EudraCT: 2014-005550-18	WHO: N/A	NCT: NCT02397096

STUDY PHASE: 3

INDICATION: Treatment of HIV-1 (Human immunodeficiency virus type 1) infection

STUDY CENTERS: This trial was conducted at 122 centers in 23 countries.

STUDY STATUS: This report is based on the analysis of data from the 48-week base study. Participants who complete the base study may continue treatment with DOR/3TC/TDF in study extensions.

First Patient, First Visit	Last Patient, Last Visit	Data Cut-off Date
17-JUN-2015	22-FEB-2018	22-FEB-2018

METHODOLOGY:

In a population of virologically-suppressed, HIV-1-infected participants, this ongoing trial was designed to evaluate a switch to oral DOR/3TC/TDF QD from a stable antiretroviral regimen of a ritonavir- or cobicistat-boosted protease inhibitor (PI), specifically, atazanavir (ATV), darunavir (DRV), or lopinavir (LPV), or cobicistat-boosted elvitegravir (EVG), or a non-nucleoside reverse transcriptase inhibitor (NNRTI), specifically, efavirenz (EFV), nevirapine (NVP), or rilpivirine (RPV), each administered with 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs). Participants were stratified in the base study by their regimen at screening (one of the PIs specified above boosted with ritonavir versus one of the PIs specified above boosted with cobicistat versus EVG boosted with cobicistat or one of the NNRTIs specified above); subjects in the ritonavir-boosted PI stratum were further stratified by use of lipid-lowering therapy at Study Day 1 (yes/no). Consenting, eligible participants were randomized (2:1) to the immediate switch group (ISG) to receive DOR/3TC/TDF on Study Day 1, or to the delayed switch group (DSG) to receive their baseline regimen until Study Week 24, at which time they were to switch to DOR/3TC/TDF. At Study Week 48 (end of base study), participants who remained eligible and provided consent were enrolled in open-label study extensions for up to 192 weeks total, wherein all participants receive DOR/3TC/TDF.

Treatment Group	Unit Dose and Frequency	Route
ISG		
DOR/3TC/TDF for 48 weeks (from Study Day 1 to Study Week 48)	FDC containing DOR (100 mg), 3TC (300 mg), and TDF (300 mg) administered QD	Oral
DSG		
Baseline regimen for 24 weeks (Study Day 1 to Study Week 24, also referred to as the Baseline Regimen DSG): Ritonavir- or cobicistat-boosted PI[A] or cobicistat-boosted EVG or an NNRTI[B] each administered with 2 NRTIs	Dose and frequency determined by baseline regimen	Oral
DOR/3TC/TDF for 24 weeks (Study Weeks 24 to 48)	FDC containing DOR (100 mg), 3TC (300 mg), and TDF (300 mg) administered QD	Oral

[A] Specifically, ATV, DRV, or LPV.
[B] Specifically, EFV, NVP, or RPV.
3TC = lamivudine; ATV= atazanavir; DOR = doravirine; DRV= darunavir; DSG= delayed switch group; EFV= efavirenz; EVG= elvitegravir; FDC= fixed-dose combination; ISG= immediate switch group; LPV= lopinavir; NVP= nevirapine; NRTI= nucleos(t)ide reverse transcriptase inhibitors; NNRTI= non-nucleoside reverse transcriptase inhibitor; PI= protease inhibitor; RPV= rilpivirine; TDF = tenofovir disoproxil fumarate.

ELIGIBILITY CRITERIA: Eligible participants were clinically stable, HIV-1-infected adults (≥18 years), who were virologically suppressed for ≥6 months, had HIV-1 RNA levels BLoQ (<40 copies/mL) at screening, were on a stable antiretroviral regimen (one of the ritonavir- or cobicistat-boosted PIs [specifically, ATV, DRV, or LPV]; or cobicistat-boosted EVG, or one of the NNRTIs [specifically, EFV, NVP, RPV];—each on a background of 2 NRTIs), and had no prior history of virologic failure on any regimen or resistance to study interventions.

OBJECTIVES AND ENDPOINTS: Base Study

Primary Objective: To evaluate the non-inferior antiretroviral activity of an immediate switch to DOR/3TC/TDF on Study Day 1 compared with continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted EVG-based or NNRTI-based regimen for 24 weeks, as measured by the proportion of subjects maintaining HIV-1 RNA <50 copies/mL by the Abbott RealTime HIV-1 Assay at Study Week 48 in the ISG and at Study Week 24 in the DSG.

Secondary Objectives:

1. To evaluate the effect on fasting LDL-C of an immediate switch to DOR/3TC/TDF on Study Day 1 compared with continuation of a ritonavir-boosted, PI-based regimen for 24 weeks, as measured by mean change from baseline at Study Week 24 in each treatment group.
2. To evaluate the effect on fasting non-HDL-C of an immediate switch to DOR/3TC/TDF on Study Day 1 compared with continuation of a ritonavir-boosted, PI-based regimen for 24 weeks, as measured by mean change from baseline at Study Week 24 in each treatment group.
3. To evaluate the non-inferior antiretroviral activity of an immediate switch to DOR/3TC/TDF on Study Day 1 compared with continuation of a ritonavir- or

cobicistat-boosted PI-based or cobicistat-boosted EVG-based or NNRTI-based regimen for 24 weeks, as measured by the proportion of subjects maintaining HIV-1 RNA <50 copies/mL by the Abbott RealTime HIV-1 Assay at Study Week 24 in each treatment group.

4. To evaluate the superior antiretroviral activity of an immediate switch to DOR/3TC/TDF on Study Day 1 compared with continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted EVG-based or NNRTI-based regimen for 24 weeks, as measured by the proportion of subjects maintaining HIV-1 RNA <50 copies/mL by the Abbott RealTime HIV-1 Assay at Study Week 48 in the ISG and at Study Week 24 in the DSG.

5. To evaluate the superior antiretroviral activity of an immediate switch to DOR/3TC/TDF on Study Day 1 compared with continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted EVG-based or NNRTI-based regimen for 24 weeks, as measured by the proportion of subjects maintaining HIV-1 RNA <50 copies/mL by the Abbott RealTime HIV-1 Assay at Study Week 24 in each treatment group.

6. To evaluate the antiretroviral activity of an immediate switch to DOR/3TC/TDF on Study Day 1 compared with continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted EVG-based or NNRTI-based regimen for 24 weeks, as measured by the proportion of subjects maintaining HIV-1 RNA BLoQ by the Abbott RealTime HIV-1 Assay (<40 copies/mL) at Study Week 48 in the ISG versus Study Week 24 in the DSG and at Study Week 24 in both treatment groups.

7. To evaluate the immunological effect of an immediate switch to DOR/3TC/TDF on Study Day 1 compared with continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted EVG-based or NNRTI-based regimen for 24 weeks, as measured by the change from baseline in CD4 cell count at Study Week 48 in the ISG and at Study Week 24 in the DSG.

8. To evaluate the immunological effect of an immediate switch to DOR/3TC/TDF on Study Day 1 compared with continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted EVG-based or NNRTI-based regimen for 24 weeks, as measured by the change from baseline in CD4 cell count at Study Week 24 in each treatment group.

9. To evaluate the safety and tolerability of an immediate switch to DOR/3TC/TDF on Study Day 1 compared with continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted EVG-based or NNRTI-based regimen for 24 weeks, as assessed by review of the accumulated safety data by Study Week 24 in each treatment group.

10. To evaluate the pharmacokinetics of DOR, when administered as a component of DOR/3TC/TDF, and the pharmacokinetic-pharmacodynamic association, if supported by the data.

11. To evaluate the antiretroviral activity of an immediate switch to DOR/3TC/TDF on Study Day 1 compared with continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted EVG-based or NNRTI-based regimen for 24 weeks, as measured by the proportion of subjects with HIV-1 RNA ≥50 copies/mL at Study Week 48 in the ISG and at Study Week 24 in the DSG based on the FDA snapshot approach.

NUMBER OF PARTICIPANTS (planned and analyzed):

A total of 660 participants was planned for 2:1 randomization to either the ISG (planned=440 participants) or DSG (planned=220 participants). A total of 673 participants were randomized (n=450 ISG; n=223 DSG), and 670 participants were treated (n=447 ISG; n=223 DSG).

STATISTICAL METHODS:

Antiretroviral activity was assessed by the proportion of participants maintaining plasma HIV-1 RNA <50 copies/mL or <40 copies/mL. Analyses used the FDA snapshot approach to missing data, such that participants with missing data were treated as failures regardless of reason. The OF approach was used as a supportive approach to missing data.

The difference and associated 95% CI between the ISG (at Week 48) and DSG (at Week 24) in the proportion of participants maintaining plasma HIV-1 RNA <50 copies/mL or <40 copies/mL was calculated using the stratum-adjusted Mantel-Haenszel method, with the difference weighted by the harmonic mean of the sample size per arm for each stratum (antiretroviral therapy [ART] class included in baseline regimen: ritonavir- or cobicistat-boosted PI versus cobicistat-boosted EVG or NNRTI). For the primary hypothesis, a margin of 8 percentage points was used to define non-inferiority. Superiority of an immediate switch to DOR/3TC/TDF over continuation of the baseline regimen was defined by a lower bound of the two-sided 95% CI for the difference in response rates being greater than zero (contingent upon satisfying the multiplicity criteria). A similar approach was used for the supportive secondary efficacy hypotheses for non-inferiority and superiority at Study Week 24 for both treatment groups. The proportion of subjects with suppressed HIV-RNA at baseline who lose virologic control after switching to a new drug or regimen is currently recommended as the primary endpoint for HIV switch trials in the FDA Guidance for Industry: Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment (November 2015), which was issued after the trial began. This endpoint was included on 03-NOV-2015 in amendment 3 of the protocol as a secondary endpoint for assessing non-inferiority and a margin of 4 percentage points was used to define non-inferiority.

The change from baseline in fasting lipids (total cholesterol, LDL-C, non-HDL-C, and triglycerides) at Study Week 24 was analyzed using ANCOVA models adjusted by baseline lipid level, use of lipid-lowering therapy at Study Day 1, and treatment group. The treatment difference (95% CIs) was provided for all lipid parameters, and p-values for between-treatment comparisons were provided for LDL-C and non-HDL-C.

Adverse events (both clinical and laboratory-related) were summarized with descriptive statistics. For most Tier-2 AE categories, 95% CIs were provided for between-treatment differences using the Miettinen and Nurminen method for the percentage of participants with events.

Efficacy and safety data were collected through Study Week 48 for both ISG and DSG groups. Efficacy and safety analyses at Study Week 48 were also conducted for participants who switched to DOR/3TC/TDF QD at Study Week 24 for the DSG group.

To assess the overall safety profile of DOR, safety data from ISG Study Weeks 0 to 48 and DSG Study Weeks 24 to 48 were pooled and summarized.

RESULTS:

Disposition, Demographics and Baseline Characteristics:

Number of participants randomized/treated/ongoing/discontinued:

- In the ISG, 450 participants were randomized, 447 (99.3%) were treated with DOR/3TC/TDF, 427 continued DOR/3TC/TDF at Study Week 24, 407 (90.4%) completed the base study, 399 (88.7%) entered the ongoing study extension, and 40 (8.9%) discontinued the base study.
- In the DSG, 223 participants were randomized, 223 (100%) were treated and continued the baseline regimen, 209 (93.7%) switched to DOR/3TC/TDF at Study Week 24, 202 (90.6%) completed the base study and entered the ongoing study extension, and 21 (9.4%) discontinued the base study.

Overall Median Age (range): 43.0 years (21 to 71 years)
Sex: 566 (84.5%) male, 104 (15.5%) female
Ethnicity: 144 (21.5%) Hispanic or Latino, 516 (77.0%) not Hispanic or Latino, 10 (1.5%) unknown)
Race: 7 (1.0%) American Indian or Alaska Native, 25 (3.7%) Asian, 90 (13.4%) black or African-American, 35 (5.2%) multiple, 1 (0.1%) native Hawaiian or other Pacific islander, 512 (76.4%) white

Efficacy Through Study Week 48 (Base Study):

The efficacy of DOR/3TC/TDF in the ISG is non-inferior or comparable to that observed in the DSG for all primary and secondary endpoints, using either the FDA Snapshot or OF approach or both.

- The efficacy of DOR/3TC/TDF, as assessed by the proportion of participants with HIV-1 RNA levels <50 copies/mL, in the DOR/3TC/TDF ISG at Study Week 48 is non-inferior (treatment difference [ISG – DSG]: -3.8%, 95% CI [-7.9%, 0.3%]) to that observed in the Baseline Regimen DSG at Study Week 24
- The efficacy of DOR/3TC/TDF, as assessed by the proportion of participants with HIV-1 RNA levels <50 copies/mL, in the DOR/3TC/TDF ISG at Study Week 24 met the criteria for non-inferiority (not adjusted for multiplicity) (treatment difference [ISG – DSG]: -0.9%, 95% CI [-4.7%, 2.9%] as compared to that observed in the Baseline Regimen DSG at Study Week 24.
- The efficacy of DOR/3TC/TDF, as assessed by the proportion of participants with HIV-1 RNA levels <50 copies/mL, in the DOR/3TC/TDF ISG at Study Weeks 48 was not demonstrated to be superior to that observed in the Baseline Regimen DSG at Study Week 24.
- The efficacy of DOR/3TC/TDF, as assessed by the proportion of participants with HIV-1 RNA levels <40 copies/mL, in the DOR/3TC/TDF ISG at both Study Weeks 48 and 24 was comparable to that observed in the Baseline Regimen DSG at Study Week 24.

- The efficacy of DOR/3TC/TDF, as assessed by the proportion of participants with HIV-1 RNA levels ≥50 copies/mL, in the DOR/3TC/TDF ISG at Study Weeks 48 met the criteria for non-inferiority (not adjusted for multiplicity) (treatment difference [ISG – DSG]: -0.2%, 95% CI [-2.5%, 2.1%]) as compared to that in the Baseline Regimen DSG at Study Week 24 and non-inferior (not adjusted for multiplicity) (treatment difference [ISG – DSG]: -0.003%, 95% CI [-2.3%, 2.3%]) at Study Week 24 for both groups.
- The efficacy of DOR/3TC/TDF, as assessed by the change from baseline in $CD4^+$ T-cell count, in the DOR/3TC/TDF ISG at both Study Weeks 48 and 24 was comparable to that in the Baseline Regimen DSG at Study Week 24.

Safety Through Study Week 48:

Adverse Events

ISG Study Weeks 0 to 24 (DOR/3TC/TDF), DSG Study Weeks 0 to 24 (Baseline Regimen)

- A higher proportion of participants in the ISG (DOR/3TC/TDF) compared with the Baseline Regimen DSG reported AEs (68.9% and 52.5%, respectively) and drug-related AEs (19.5% and 2.2%) in this open-label trial. Nasopharyngitis and headache were the only AEs reported by ≥5% of participants in either treatment group during Study Weeks 0 to 24.
- The incidences of SAEs, drug-related SAEs, and discontinuation due to AE were low (<4%) and occurred with similar frequency in both groups through Study Week 24.
- In both groups (DOR/3TC/TDF ISG and Baseline Regimen DSG), the majority of AEs were of mild to moderate intensity and were considered by the investigator to be unrelated to study medication.

ISG Study Weeks 0 to 24 (DOR/3TC/TDF), DSG Study Weeks 24 to 48 (DOR/3TC/TDF)

- Participants had a similar safety profile following their switch to DOR/3TC/TDF, regardless of whether the switch was immediate (ISG: Study Weeks 0 to 24) or delayed (DSG: Study Weeks 24 to 48).

Overall DOR/3TC/TDF: ISG Study Weeks 0 to 48 + DSG Study Weeks 24 to 48

- Participants who received DOR/3TC/TDF (pooled data from ISG: Study Weeks 0 to 48 and DSG: Study Weeks 24 to 48) experienced a low incidence of discontinuations due to AEs (2.9%), discontinuations due to drug-related AEs (2.0%), SAEs (4.0%), and drug-related SAEs (0.8%); the most frequently reported AEs for participants who received DOR/3TC/TDF during the base study were nasopharyngitis (8.2%), headache (8.1%), and diarrhea (6.1%).

- The most common drug-related AE reported during treatment with DOR/3TC/TDF (pooled data from ISG Study Weeks 0 to 48 and DSG Study Weeks 24 to 48) was increased ALT, occurring in 2.2% of participants in the ISG, and 1.9% of participants in the DSG following the switch. Drug-related AEs of increased ALT were generally mild or moderate in severity, rarely led to discontinuation (n=2 [0.3%]), and generally resolved despite continuation of DOR/3TC/TDF.
- No randomized participant died during the 48-week base study. One participant died during the screening period; 2 participants died after discontinuation of study drug (1 participant from unrelated unknown causes and 1 participant from drug-related myocardial infarction).

Clinical Laboratory Results

- In participants who were receiving a stable antiretroviral regimen of a ritonavir-boosted PI + 2 NRTIs at screening, DOR/3TC/TDF had a superior lipid profile in participants in the ISG compared to that observed in the Baseline Regimen DSG with respect to change from baseline to Study Week 24 in fasting LDL-C (-14.65 difference [95% CI: -18.92, -10.38]) and non-HDL-C (-23.03 difference [95% CI: -28.00, -18.05]). The differences between these two groups in mean changes from Study Weeks 0 to 24 in fasting LDL-C and non-HDL-C were statistically significant ($p<0.0001$).
- A comprehensive review of the imbalance noted for elevations of ALT/AST and lipase showed these elevations were generally transient, asymptomatic, and not associated with clinical AEs. Nearly all resolved with continued therapy, and rarely led to discontinuation. Most were not attributed to study drug and not considered clinically significant. The elevations in ALT/AST were not associated with elevations in bilirubin, and no participant met the criteria for DILI.

Adverse Event Summary
Study Weeks 0-48; Base Study

	DOR/3TC/TDF QD ISG Study Weeks 0-24		Baseline Regimen DSG Study Weeks 0-24		DOR/3TC/TDF QD DSG Study Weeks 24-48		DOR/3TC/TDF QD ISG Study Weeks 0-48		DOR/3TC/TDF QD ISG(Study Weeks 0-48) + DSG(Study Weeks 24-48)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	447		223		209		447		656	
with one or more adverse events	308	(68.9)	117	(52.5)	126	(60.3)	359	(80.3)	485	(73.9)
with no adverse event	139	(31.1)	106	(47.5)	83	(39.7)	88	(19.7)	171	(26.1)
with drug-related[†] adverse events	87	(19.5)	5	(2.2)	29	(13.9)	100	(22.4)	129	(19.7)
with serious adverse events	13	(2.9)	8	(3.6)	4	(1.9)	22	(4.9)	26	(4.0)
with serious drug-related adverse events	2	(0.4)	0	(0.0)	1	(0.5)	4	(0.9)	5	(0.8)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	11	(2.5)	1	(0.4)	4	(1.9)	15	(3.4)	19	(2.9)
discontinued drug due to a drug-related adverse event	7	(1.6)	0	(0.0)	4	(1.9)	9	(2.0)	13	(2.0)
discontinued drug due to a serious adverse event	4	(0.9)	1	(0.4)	1	(0.5)	6	(1.3)	7	(1.1)
discontinued drug due to a serious drug-related adverse event	2	(0.4)	0	(0.0)	1	(0.5)	3	(0.7)	4	(0.6)

[†] Determined by the investigator to be related to the drug.

Analysis includes AEs occurring or worsening after the first dose of study medication through last dose of base study medication (or 14 days after the last dose of base study medication if not continuing into the study extension).

Baseline Regimen = ritonavir or cobicistat-boosted PI, or cobicistat-boosted elvitegravir, or NNRTI, each administered with two NRTIs.

ISG = Immediate Switch Group; DSG = Delayed Switch Group.

Note: The DSG continues their baseline regimen until the time of the switch to DOR/3TC/TDF QD at Study Week 24.

Source: [P024MK1439A: adam-adsl; adae]

CONCLUSIONS:

Based on the results from this study, the following efficacy conclusions can be made:

- An immediate switch to DOR/3TC/TDF on Study Day 1 is non-inferior to continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted EVG-based or NNRTI-based regimen for 24 weeks, as assessed by the proportion of participants maintaining HIV-1 RNA <50 copies/mL at Study Week 48 in the DOR/3TC/TDF ISG and at Study Week 24 in the Baseline Regimen DSG, and met the criteria for non-inferiority (not adjusted for multiplicity) at Study Week 24 for both groups.

The following key efficacy results were also observed:

- An immediate switch to DOR/3TC/TDF on Study Day 1 met the criteria for non-inferiority (not adjusted for multiplicity) when compared to continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted EVG-based or NNRTI-based regimen for 24 weeks, as assessed by the proportion of subjects with HIV-1 RNA ≥50 copies/mL at both Study Weeks 48 and 24 in the DOR/3TC/TDF ISG and at Study Week 24 in the Baseline Regimen DSG.
- An immediate switch to DOR/3TC/TDF on Study Day 1 was comparable to continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted EVG-based or NNRTI-based regimen for 24 weeks, as assessed by the proportion of subjects maintaining HIV-1 RNA <40 copies/mL at both Study Weeks 48 and 24 in the DOR/3TC/TDF ISG and at Study Week 24 in the Baseline Regimen DSG.
- An immediate switch to DOR/3TC/TDF on Study Day 1 was comparable to continuation of a ritonavir- or cobicistat-boosted PI-based or cobicistat-boosted EVG-based or NNRTI-based regimen for 24 weeks, as measured by the change from baseline in $CD4^+$ T cell count at both Study Weeks 48 and 24 in the DOR/3TC/TDF ISG and at Study Week 24 in the Baseline Regimen DSG.
- No participant who received DOR/3TC/TDF in the ISG or DSG and met the criteria for resistance testing had genotypic or phenotypic resistance to any of the components.
- None of the 24 subjects (11 immediate switch group [Day 1], 13 delayed switch group [Week 24]) on PI and InSTI regimens who had virus with baseline NNRTI mutations (RT K103N, G190A, or Y181C) experienced virologic failure through Week 48 or at the time of discontinuation

Based on the results from this study, the following safety conclusions can be made:

- An immediate switch to DOR/3TC/TDF is generally well tolerated, with a favorable safety profile when compared with continuation of a ritonavir- or cobicistat boosted PI-based or cobicistat-boosted EVG-based or NNRTI-based regimen for 24 weeks, as assessed by review of the accumulated safety data by Study Week 24 in each treatment group.

- An immediate switch to DOR/3TC/TDF on Study Day 1 is superior to the continuation of a ritonavir-boosted PI regimen for 24 weeks, as assessed by the mean change from baseline in fasting LDL-C and non-HDL-C at Study Week 24 in each treatment group.

The following key safety results were also observed:

- Participants had a similar safety profile following their switch to DOR/3TC/TDF, regardless of whether the switch was immediate (ISG: Study Weeks 0 to 24) or delayed (DSG: Study Weeks 24 to 48).
- Participants who switched to DOR/3TC/TDF immediately had a higher incidence of AEs and drug-related AEs through Study Weeks 0 to 24 when compared with the incidence of these events among participants who remained on their baseline regimen through Study Weeks 0 to 24 in this open-label trial.

PUBLICATION(S):
Kumar P, Johnson M, Molina J-M, Rizzardini G, Cahn P, Bickel M, et al. Switch to Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate (DOR/3TC/TDF) maintains virologic suppression through 48 weeks: results of the DRIVE-SHIFT trial [abstract]. Oral Presentation at IDWeek 2018; 2018 Oct 3-7; San Francisco, CA. Abstract no. LB2.

REPORT DATE: [redacted]-20[redacted]

Table of all Clinical Trials

Trial ID	Phase	Country / Region	Study Title	Study design	Dosing regimen	Study population	Participant exposure
MK-1439 [Ref. 5.3.5.1: P018MK1439]	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 = 578 days) DRV+r (800 mg / 100 mg): 383 treated subjects (mean duration of exposure to both DRV and RTV = 555 days)

Trial ID	Phase	Country / Region	Study Title	Study design	Dosing regimen	Study population	Participant exposure
1439A-021 [Ref. 5.3.5.1: P021MK1439A]	3	United States; Puerto Rico; Mexico; Canada; Honduras; Guatemala; Chile; Colombia; Peru; Belgium; Denmark; Germany; Israel; Portugal; Russia; Spain; Switzerland; United Kingdom; South Africa; Taiwan; Thailand; Australia; 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, doubleblind, parallel-group, activecomparator-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 Treatment- naïve HIV-1-infected individuals	Doravirine 100 mg/ lamivudine 300 mg/ TDF 300 mg: 364 Doravirine 200 mg/ lamivudine 600 mg/ TDF 600 mg: 58 Efavirenz 600 mg/ emtricitabine 200 mg / TDF 300 mg: 363 Efavirenz 1200 mg/ emtricitabine 400 mg / TDF 600 mg: 64 Efavirenz 1800 mg/ emtricitabine 600 mg / TDF 900 mg: 4

2 SYNOPSIS

SPONSOR: Merck Sharp & Dohme Corp., a Subsidiary of Merck & Co., Inc., NJ, USA (MSD)

COMPOUND NAME: Doravirine (MK-1439)

PROTOCOL TITLE: 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

STUDY IDENTIFIERS:

IND:	EudraCT:	WHO:	NCT:
112,796	2014-001127-69	N/A	NCT02275780

STUDY PHASE: 3

INDICATION: Treatment of HIV-1 infection

STUDY CENTERS: This study was conducted at 124 centers in 15 countries.

STUDY STATUS: This report is based on the analysis of the double-blind base study Week 96 data; an open-label study extension, with participation for up to an additional 192 weeks, is ongoing (all participants in extension treated with DOR).

First Subject, First Visit	Last Subject, Last Visit (Data Cut-off Date)	Database Lock Date
01-DEC-2014	[redacted]-20[redacted]	[redacted]-20[redacted]

METHODOLOGY: This trial was designed to evaluate the safety, efficacy, and pharmacokinetics of oral doravirine (DOR; MK-1439) 100 mg QD compared with oral ritonavir-boosted darunavir (DRV+r [800 mg darunavir + 100 mg ritonavir]) when administered to HIV-1-infected, treatment-naïve adults in double-blind fashion for 96 weeks (base study). Both treatments (DOR and DRV+r) were given in combination with emtricitabine plus tenofovir disoproxil fumarate (FDC/TDF) or abacavir plus lamivudine (ABC/3TC). After completion of the 96-week base study, participants who remained eligible and provided consent were enrolled in an open-label study extension for up to 192 weeks total (2 consecutive 96-week extensions), wherein all participants received DOR 100 mg QD in combination with NRTI background therapy (ie, participants who received DRV+r in the base study were switched to DOR).

Intervention	Unit Dose and Frequency	Route of Administration
Doravirine	100-mg oral compressed tablet, QD	oral
DRV+r	darunavir 800-mg tablet in combination with ritonavir 100-mg tablet, QD	oral

ELIGIBILITY CRITERIA: Eligible participants were clinically stable, HIV-1-infected adults (≥18 years) who had screening HIV-1 RNA concentrations ≥1000 copies/mL, were naïve to antiretroviral therapy (ART), and had no documented or known resistance to study

medications (and respective mutations), and who agreed to avoid becoming pregnant or impregnating a partner, or were unlikely for other reasons to become pregnant or impregnate a partner.

OBJECTIVES AND ENDPOINTS:

Objectives of the Base Study

Primary Objective: To evaluate the antiretroviral activity of MK-1439 (DOR) 100 mg QD compared with DRV+r (800 mg/100 mg) QD, each in combination with TRUVADA™ or EPZICOM™/KIVEXA™, as measured by the proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 48.

Secondary Objectives: To evaluate MK-1439 (DOR) 100 mg QD, compared with DRV+r (800 mg/100 mg) QD, each in combination with TRUVADA™ or EPZICOM™/KIVEXA™, with respect to:

1. safety and tolerability, as assessed by review of the accumulated safety data at Week 48 and Week 96.
2. effect on fasting serum lipids, as measured by mean change from baseline in fasting serum lipids at Week 48.
3. safety and tolerability, as measured by the time to discontinuation from study due to an adverse experience (AE).
4. immunologic effect, as measured by the change from baseline in CD4+ T-cell count at Week 48 and Week 96.
5. antiretroviral activity, as measured by the proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 96.
6. antiretroviral activity, as measured by the proportion of subjects achieving HIV-1 RNA <40 copies/mL at Week 48 and Week 96.

Hypotheses (relevant to primary objective and Week 96 objectives)

MK-1439 100 mg QD is non-inferior to darunavir/ritonavir (800 mg/100 mg) QD, each in combination with TRUVADA™ or EPZICOM™/KIVEXA™, as assessed by the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48. Superiority of MK-1439 100 mg QD to darunavir/ritonavir (800 mg/100 mg) QD was to be assessed if non-inferiority was established.

MK-1439 100 mg QD is non-inferior to darunavir/ritonavir (800 mg/100 mg) QD, each in combination with TRUVADA™ or EPZICOM™/KIVEXA™, as assessed by the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 96. Superiority of MK-1439 100 mg QD to darunavir/ritonavir (800 mg/100 mg) QD will be assessed if non-inferiority is established.

Endpoints (relevant to primary objective and Week 96 objectives)

Primary efficacy endpoint	Proportion of subjects achieving plasma HIV-1 RNA level <50 copies/mL at Week 48
Secondary efficacy endpoints	Proportion of subjects achieving plasma HIV-1 RNA level <50 copies/mL at Week 96 Change from baseline in $CD4^+$ T-cell count at Week 48 and Week 96 Proportion of subjects achieving plasma HIV-1 RNA level <40 copies/mL at Week 48 and Week 96
Tier 1 safety endpoint	Change from baseline in fasting LDL-C and non-HDL-C at Week 48

Tier 2 safety endpoints	Broad categories of AEs (any AE, serious AE [SAE], drug-related AE, drug-related SAE, discontinuation due to AE) Time to discontinuation from study due to AE AEs (preferred term and system organ class) with incidence ≥4 subjects in any treatment group Predefined limits of change in laboratory parameters with incidence ≥4 subjects in any treatment group
Tier 3 safety endpoints	AEs (preferred term and system organ class) and predefined limits of change in laboratory parameters with incidence <4 subjects in both treatment groups Change from baseline in laboratory parameters and vital signs

NUMBER OF PARTICIPANTS (planned and analyzed): 340 participants were planned for each treatment arm. A total of 385 participants were randomized to DOR, and 384 were randomized to DRV+r; 383 participants were treated in each group.

STATISTICAL METHODS: Antiretroviral activity was assessed by the percentage of participants achieving plasma HIV-1 RNA <50 copies/mL or <40 copies/mL. Analyses used the FDA snapshot approach to missing data, such that participants with missing data were treated as failures regardless of reason, with the exception that participants missing HIV-1 RNA data due to assay recall (for samples from Week 72, 84, and/or 96)were excluded from the analyses at that time point. The Observed Failure (OF) approach was used as a supportive approach to missing data.

For each time point of interest, the difference between the DOR and DRV+r groups in proportion of responders and the associated 95% confidence interval (CI) were calculated using the stratum-adjusted Mantel-Haenszel method, with the difference weighted by the harmonic mean of the sample size per arm for each stratum. For the primary hypothesis, a margin of 10 percentage points was used to define non-inferiority. For immunologic efficacy, between-group differences in change from baseline in $CD4^+$ T-cell count were estimated using the observed failure (OF) approach.

AEs (both clinical and laboratory-related) and predefined limits of change (PDLC) in laboratory parameters were summarized with descriptive statistics; for most Tier 2 AE and PDLC categories, 95% CIs were provided for between-treatment differences in the percentage of participants with events using the Miettinen and Nurminen method. Time to discontinuation from the study due to an AE was estimated using Kaplan-Meier product-limit estimates; results were graphed.

RESULTS:

Disposition, Demographics and Baseline Characteristics:

Number of participants randomized/treated/ongoing/discontinued:

DOR: 385 participants randomized, 383 (99.5%) treated, 91 (23.6%) discontinued study medication (during base study), 292 (75.8%) completed the base study, and 260 (67.5%) entered the ongoing open-label extension study.

DRV+r: 384 participants randomized, 383 (99.7%) treated, 110 (28.6%) discontinued study medication (during base study), 273 (71.1%) completed the base study, and 233 (60.7%) entered the ongoing open-label extension study.

Baseline Characteristics:

The DOR and DRV+r treatment groups were well balanced with respect to baseline prognostic and demographic characteristics, with no clinically meaningful differences observed:

Median Age (range):
DOR**:** 33.0 years (18 to 68 years); DRV+r: 34.0 years (18 to 69 years);

Gender:
DOR**:** 83.3% male; DRV+r: 85.1% male.

Race:
DOR**:** 73.1% white; 22.5% black/African-American; 1.8% Asian; 1.6% multiple; 0.8% American Indian/Alaska Native;

DRV/r**:** 73.1% white; 23.0% black/African-American; 1.8% Asian; 0.8% American Indian/Alaska Native.

Mean (SD) Baseline $CD4^+$ T-Cell Count:
DOR: 432.6 (208.4) cells/mm^3; DRV+r**:** 411.9 (229.6) cells/mm^3.

Baseline $CD4^+$ T-Cell Count – Number (%) Participants in Categorized Levels:

≤50 cells/mm^3:	DOR: 6 (1.6); DRV+r**:** 19 (5.0)
>50, ≤200 cells/mm^3:	DOR: 36 (9.4); DRV+r**:** 48 (12.5)
>200 cells/mm^3:	DOR: 341 (89.0); DRV+r**:** 316 (82.5).

Mean (SD) Baseline Plasma HIV-1 RNA:
DOR and DRV+r: 4.4 (0.7) $\log_{10}$ copies/mL.

Baseline Plasma HIV-1 RNA ≤100,000 copies/mL:
DOR: 78.3%; DRV+r**:** 80.7%.

Screening HIV-1 RNA:
≤100,000 copies/mL: DOR: 290 (75.7); DRV+r: 289 (75.5);
>100,000 copies/mL: DOR: 93 (24.3); DRV+r: 94 (24.5).

% Participants Receiving FTC/TDF as NRTI Therapy (vs. ABC/3TC):
DOR: 86.9%; DRV+r: 87.5%.

Efficacy Through Week 96:

- At Week 96, efficacy in the DOR treatment group was higher than in the DRV+r treatment group, using the FDA snapshot approach: 73.1% and 66.0% of participants in the DOR and DRV+r treatment groups, respectively, achieved HIV-1 RNA <50 copies/mL, with an estimated treatment difference of 7.1% (95% CI: 0.5, 13.7), and 72.0% and 64.4% of participants, respectively, achieved HIV-1 RNA <40 copies/mL, with an estimated treatment difference of 7.6% (95% CI: 1.0, 14.2). These results support the non-inferiority of DOR to DRV+r previously established at Week 48.

- When analyzed using the OF approach, antiretroviral efficacy responses (measured as proportions of participants who achieved HIV-1 RNA <50 copies/mL) to DOR 100 mg were comparable to responses to DRV+r at Week 96. Specifically, 81.0% and 76.8% of participants achieved HIV-1 RNA <50 copies/mL respectively, with a treatment difference of 4.0% (95% CI: -2.2, 10.2), and 79.8% and 74.9% of participants achieved HIV-1 RNA <40 copies/mL, respectively, with an estimated treatment difference of 4.7% (95% CI -1.7, 11.0).
- Changes from baseline to Week 96 in CD4+ T-cell count were similar in the DOR and DRV+r treatment groups, with mean increases from baseline of 224 and 207 cells/mm^3, respectively.
- Rates of development of viral drug resistance were low among participants who met viral failure criteria as well as among participants who discontinued for any other reason. Of 383 DOR-treated participants, 34 met criteria for PDVF and 61 discontinued for a reason other than PDVF. Of these, 15 participants had results reported for genotypic and/or phenotypic drug resistance testing; viral isolates from 2 of the 383 participants (0.5%) were found to have primary genotypic and phenotypic resistance to DOR and to the NRTI FTC. Of 383 DRV+r-treated participants, 43 met criteria for PDVF and 71 discontinued for a reason other than PDVF. Of these, 19 had results reported for genotypic and phenotypic drug resistance testing; virus from 1 participant with PDVF remained susceptible to DRV but was phenotypically resistant to FTC (genotypic testing was not successful), and no primary resistance was seen among participants who discontinued for another reason.

Safety Through Week 96:

- While most participants in both the DOR and DRV+r groups reported AEs (84.6% and 82.8%, respectively), the majority of AEs were nonserious, mild to moderate in severity, and were not considered by the investigator to be related to study medication. Among DOR-treated participants, the most common AEs were diarrhea (17.0%), headache (14.9%), upper respiratory tract infections (13.3%), and viral upper respiratory tract infection (11.5%). Among DRV+r-treated participants, the most common AEs were diarrhea (23.8%), nausea (13.6%), viral upper respiratory tract infection (13.1%), and headache (12.0%).
- Drug-related AEs were reported for 32.1% of participants in each treatment group and were most frequently associated with the SOC of gastrointestinal disorders (17.8% and 23.0% in the DOR and DRV+r groups, respectively). The most commonly reported drug-related AEs among DOR- and DRV+r –treated participants were nausea (7.0% and 8.1%, respectively), headache (6.0%, 2.6%), and diarrhea (5.7%, 13.1%).
- Serious AEs were reported for 7.0% and 8.6% of participants in the DOR and DRV+r groups, respectively. No single SAE was experienced by more than 2 participants, and the incidence of SAEs considered by the investigator to be related to study treatment was low (1 participant each treatment group).
- Few participants discontinued through Week 96 due to an AE (DOR: 1.6%; DRV+r: 3.4%). Most discontinuations (6 of 6 participants in the DOR group; 12 of 13 in the DRV+r group) occurred during the first 48 weeks.

- Two participants died while on study medication through Week 96 (1 in each treatment group), and 2 additional participants' deaths (both in the DOR group) were presumed to have occurred while on study medication. While these deaths were recorded as occurring poststudy, it is presumed that these participants were taking study medication up to the time of death. Another participant (DRV+r group) died approximately 14 weeks after the last recorded dose and participant withdrawal from the study (ie, poststudy). None of the deaths was considered by the investigator to be related to study medication.
- DOR had a favorable lipid profile compared with DRV+r with respect to the change from baseline in fasting LDL-C and non-HDL-C at Week 96, consistent with findings at Week 48.
- More participants in the DOR than in the DRV+r treatment group had elevations in bilirubin values. The majority of bilirubin elevations in the DOR group were either single, transient elevations or 2 nonconsecutive Grade 1 elevations; no common etiology has been identified. None of the bilirubin elevations resulted in a participant being discontinued from the trial.

Efficacy Analysis at Week 96
Base Study (Double Blind)

Parameter	Missing Data Approach[†]	Unadjusted Data Summary by Treatment Group		Treatment Difference (Doravirine - Darunavir)[‡]		Conclusion[§]
		Doravirine 100 mg QD n/N (%)	Darunavir 800 mg + ritonavir 100 mg QD n/N (%)	Estimated Difference	95% CI	
Primary						
Proportion of Subjects with HIV-1 RNA <50 copies/mL	Snapshot	277/379 (73.1)	248/376 (66.0)	7.082	(0.508, 13.656)	Non-inferior
Secondary and Exploratory						
Proportion of Subjects with HIV-1 RNA <50 copies/mL	OF	277/342 (81.0)	248/323 (76.8)	4.007	(-2.201, 10.214)	
Proportion of Subjects with HIV-1 RNA <40 copies/mL	Snapshot	273/379 (72.0)	242/376 (64.4)	7.606	(0.980, 14.232)	
Proportion of Subjects with HIV-1 RNA <40 copies/mL	OF	273/342 (79.8)	242/323 (74.9)	4.662	(-1.663, 10.988)	
Proportion of Subjects with HIV-1 RNA <200 copies/mL	Snapshot	286/379 (75.5)	257/376 (68.4)	7.076	(0.642, 13.510)	
Proportion of Subjects with HIV-1 RNA <200 copies/mL	OF	286/342 (83.6)	257/323 (79.6)	3.899	(-2.028, 9.825)	
		Mean (95% CI)	Mean (95% CI)	Mean Difference	95% CI	
Change from Baseline in CD4 Cell Count (cells/mm^3)	OF	224.1 (200.8, 247.4)	206.7 (184.9, 228.5)	17.4	(-14.5, 49.3)	

[†] Snapshot: Defined by FDA Snapshot approach; OF: Observed Failure approach. Subjects with missing HIV-1 RNA due to Abbott manufacture agent recall were excluded from the analysis.

[‡] The 95% CIs for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum. The 95% CI for mean difference in CD4 change was based on t-distribution.

[§] Doravirine 100 mg QD is concluded non-inferior to Darunavir 800 mg + ritonavir 100 mg QD if the lower bound of the 95% CI for the difference in percent response is above -10 percentage points.

Analysis of post-baseline data includes laboratory records collected after the first dose of study medication through last dose of base study medication (or 14 days after the last dose of base study medication if not continuing into the study extension).

Note: Doravirine 100 mg QD and Darunavir 800 mg + ritonavir 100 mg QD were administered with FTC/TDF or ABC/3TC.

n = Number of subjects in each subcategory.

N = Number of subjects in each treatment group.

Analysis of Adverse Event Summary
Weeks 0-96; Base Study (Double Blind)

	Doravirine 100 mg QD		Darunavir 800 mg + ritonavir 100 mg QD		Difference in % vs Darunavir 800 mg + ritonavir 100 mg QD
	n	(%)	n	(%)	Estimate (95% CI)[†]
Subjects in population	383		383		
with one or more adverse events	324	(84.6)	317	(82.8)	1.8 (-3.4, 7.1)
with no adverse events	59	(15.4)	66	(17.2)	-1.8 (-7.1, 3.4)
with drug-related[‡] adverse events	123	(32.1)	123	(32.1)	0.0 (-6.6, 6.6)
with serious adverse events	27	(7.0)	33	(8.6)	-1.6 (-5.5, 2.3)
with serious drug-related adverse events	1	(0.3)	1	(0.3)	0.0 (-1.2, 1.2)
who died	1	(0.3)	1	(0.3)	0.0 (-1.2, 1.2)
discontinued[§] due to an adverse event	6	(1.6)	13	(3.4)	-1.8 (-4.3, 0.4)
discontinued due to a drug-related adverse event	5	(1.3)	8	(2.1)	-0.8 (-2.9, 1.2)
discontinued due to a serious adverse event	0	(0.0)	3	(0.8)	-0.8 (-2.3, 0.2)
discontinued due to a serious drug-related adverse event	0	(0.0)	1	(0.3)	-0.3 (-1.5, 0.7)

[†] Based on Miettinen & Nurminen method.
[‡] Determined by the investigator to be related to the drug.
[§] Study medication withdrawn.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.
Analysis includes AEs occurring or worsening after the first dose of study medication through last dose of base study medication (or 14 days after the last dose of base study medication if not continuing into the study extension).
Note: Doravirine 100 mg QD and Darunavir 800 mg + ritonavir 100 mg QD were administered with FTC/TDF or ABC/3TC.

Source: [P018MK1439: analysis-adsl] [P018MK1439: tabulations-aeplus]

CONCLUSIONS:

- DOR showed higher antiretroviral efficacy and similar immunologic efficacy versus DRV+r at Week 96, supporting the non-inferiority of DOR to DRV+r previously established at Week 48.
- Rates of development of viral drug resistance through Week 96 were low, with viral isolates from 2 of 383 (0.5%) DOR-treated participants shown to have primary genotypic and high-level phenotypic resistance to DOR via the RT V106 pathway. No primary genotypic or phenotypic resistance to DRV was observed among 383 DRV+r-treated participants.
- DOR was well tolerated throughout the 96-week trial as compared with DRV+r, evidenced in part by a low frequency of participant withdrawal due to AEs.
- DOR had a favorable lipid profile to DRV+r with respect to change from baseline in fasting LDL-C and non-HDL-C.

PUBLICATION(S): Molina J-M, Squires K, Sax PE, Cahn P, Lombaard J, DeJesus E, et al. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blind, phase 3, non-inferiority trial. *The Lancet HIV* 2018; 5(5):e211-220.

REPORT DATE: [redacted]-20[redacted]
REVISED REPORT DATE: [redacted]-20[redacted]

2 SYNOPSIS

SPONSOR: Merck Sharp & Dohme Corp., a Subsidiary of Merck & Co., Inc., NJ, USA (MSD)

COMPOUND NAME: MK-1439A, fixed-dose combination (FDC) oral tablet of doravirine (DOR) 100 mg/lamivudine (3TC) 300 mg/tenofovir disoproxil fumarate (TDF) 300 mg

PROTOCOL TITLE: A Phase III 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

STUDY IDENTIFIERS:

IND:	EudraCT:	WHO:	NCT:
124997	2014-003382-17	N/A	NCT02403674

STUDY PHASE: 3

INDICATION: Treatment of HIV-1 infection

STUDY CENTERS: This study was conducted at 126 centers in 23 countries.

STUDY STATUS: This study is ongoing; this report is based on the Week 96 analysis; an extension for up to 192 weeks of open-label treatment is ongoing.

First Participant, First Visit	Last Participant, Last Visit (Week 96)	Data Cut-off or Database Lock Date (Week 96)
10-JUN-2015	[redacted]-20[redacted]	[redacted]-20[redacted]

METHODOLOGY: This is an ongoing, Phase 3, multicenter, multinational, randomized, double-blind, active-controlled trial designed to evaluate the safety and efficacy of DOR/3TC/TDF (MK-1439A) once daily (QD) compared with efavirenz (EFV)/emtricitabine (FTC)/TDF QD (ATRIPLA™). Safety data during the base study (through Week 96 of treatment plus the 14-day follow-up period) were monitored by an external Data Monitoring Committee, with reviews approximately every 6 months. Week 48 was the primary analysis time point. Data from Week 96 are presented in this report. Study participants who remained eligible and consented were enrolled in an open-label study extension (up to 192 weeks of open-label treatment) and received DOR/3TC/TDF.

Group 1	n=340 (planned)	MK-1439A one tablet PO QD†+ placebo to match ATRIPLA™ one tablet PO QD#
Group 2	n=340 (planned)	ATRIPLA™ one tablet PO QD‡+ placebo to match MK-1439A one tablet PO QD#

Abbreviations: FDC = Fixed dose combination; PO = orally
† MK-1439A is a single tablet FDC containing MK-1439 100 mg, lamivudine 300 mg, and TDF 300 mg.
‡ ATRIPLA™ is a single tablet FDC containing efavirenz 600 mg, emtricitabine 200 mg, and TDF 300 mg (which is equivalent to 245 mg of tenofovir disoproxil).
# Placebo was used to maintain blinding

ELIGIBILITY CRITERIA: HIV-1-infected, treatment-naïve adults ≥18 years of age, with plasma HIV-1 RNA ≥1000 copies/mL at screening and no known resistance to DOR or any other study drug.

OBJECTIVES AND ENDPOINTS FOR WEEK 96:

Objectives of the Base Study	
Week 96 Secondary Objectives: To evaluate MK-1439A QD compared with ATRIPLA™ QD for: • Non-inferior antiretroviral activity • Superior antiretroviral activity • Immunologic effect • Safety and tolerability	
Hypotheses (relevant to Week 96 objectives)	
MK-1439A QD is non-inferior to ATRIPLA™ QD as assessed by the proportion of subjects with HIV-1 RNA <50 copies/mL (by the Abbott RealTime HIV-1 Assay) at Week 96. A margin of 10 percentage points is used to define non-inferiority. MK-1439A QD is superior to ATRIPLA™ QD as assessed by the proportion of subjects with HIV-1 RNA <50 copies/mL (by the Abbott RealTime HIV-1 Assay) at Week 96.	
Endpoints (relevant to Week 96 objectives)	
Secondary efficacy endpoints	Proportion of subjects achieving plasma HIV-1 RNA level <50 copies/mL at Week 96. Change from baseline in cluster of differentiation (CD)4+ T-cell count at Week 96. Proportion of subjects achieving plasma HIV-1 RNA level <40 copies/mL at Week 96.
Tier 2 safety endpoints	Change from baseline in fasting low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (HDL-C). Proportion of subjects with neuropsychiatric AEs of dizziness; altered sensorium; sleep disorders and disturbances; depression and suicide/self-injury; and psychosis and psychotic disorders. Time to discontinuation from study due to an AE. Categories of AEs (any AE, serious AE [SAE], drug-related AE, drug-related SAE, discontinuation due to AE). Adverse events (preferred term and system organ class) with incidence ≥4 subjects in any treatment group. Predefined limits of change in laboratory parameters with incidence ≥4 subjects in any treatment group.
Tier 3 safety endpoints	Adverse events (preferred term and system organ class) and predefined limits of change in laboratory parameters with incidence <4 subjects in both treatment groups. Change from baseline in laboratory parameters and vital signs.

NUMBER OF PARTICIPANTS: *Planned:* 680 randomized (340 per treatment group) participants; *Analyzed:* 728 participants randomized (364 in each treatment group).

STATISTICAL METHODS:

Secondary Efficacy Analysis: *Proportion of subjects achieving plasma HIV-1 RNA level <50 (or <40) copies/mL at Week 96:* The secondary hypothesis on antiretroviral activity was assessed by the proportion of subjects achieving plasma HIV-1 RNA <50 (or <40) copies/mL at Week 96. A margin of 10 percentage points was used to specify the criterion for

noninferiority: DOR/3TC/TDF was concluded to be noninferior to EFV/FTC/TDF if the lower bound of the two-sided 95% confidence interval (CI) for the difference in the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 96 (DOR/3TD/TDF – EFV/FTC/TDF) was greater than −10 percentage points. The Food and Drug Administration (FDA) Snapshot approach was used as the primary approach for this analysis: all missing data were treated as failures regardless of the reason. After successfully meeting the noninferiority criterion at Week 48, DOR/3TC/TDF was not shown to be statistically superior to EFV/FTC/TDF at Week 48 with respect to proportion of subjects achieving plasma HIV-1 RNA level <50 copies/mL.

Change from baseline in CD4+ T-cell count at Week 96: The treatment difference in changes from baseline in CD4+ T-cell count at each time point was estimated with a key interest at Week 96; however, these estimates were not subject to an absolute criterion for similarity. The clinical interpretation of the treatment difference was dependent upon the absolute value at baseline, and the magnitude and direction of the CD4+ T-cell changes seen in each treatment arm. The observed failure (OF) approach was used for the calculations of change from baseline in CD4+ T-cell count. Under this approach, baseline values were carried forward for subjects who discontinued due to lack of efficacy.

RESULTS:

Disposition: DOR/3TC/TDF: 368 participants were randomized, 364 (98.9%) were treated, 296 (80.4%) completed the base study (Week 96), 68 (18.5%) discontinued before Week 96, and 291 (79.1%) entered the study extension. EFV/FTC/TDF: 366 participants were randomized, 364 (99.5%) were treated, 276 (75.4%) completed the base study (Week 96), 88 (24.0%) discontinued before Week 96, and 269 (73.5%) entered the study extension.

Demographics: *Overall Median Age (range):* 31.0 years (18 to 70 years); *Gender:* 84.6% male, 15.4% female; *Race:* 47.7% white, 18.5% black or African-American, 17.0% Asian, 14.6% multiple, 2.2% American Indian or Alaska Native.

Efficacy:

- At Week 96, antiretroviral efficacy of DOR/3TC/TDF was similar to that of EFV/FTC/TDF when analyzed using the FDA snapshot approach: 77.5% and 73.6% of participants, respectively, achieved HIV-1 RNA <50 copies/mL, with an estimated treatment difference of 3.8% (95% CI: -2.4, 10.0); analyses using additional HIV-1 RNA thresholds (<40 and <200 copies/mL), as well as analyses using the OF approach, yielded similar results. These results support the non-inferiority of DOR/3TC/TDF to EFV/FTC/TDF as previously established at Week 48.
- Changes from baseline to Week 96 in CD4+ T-cell count were similar in the DOR/3TC/TDF and EFV/FTC/TDF treatment groups, with mean increases from baseline of 238 and 223 cells/mm^3, respectively.

- Rates of development of viral drug resistance were low among participants who met viral failure criteria or who discontinued for any other reason. No new DOR resistance was identified in DOR-treated participants between Week 48 and Week 96 compared with 2 EFV-treated participants identified with resistance to EFV between Week 48 and Week 96. Cumulatively through Week 96, viral isolates from 6 of the 364 DOR-treated participants (1.6%) were found to have primary genotypic and phenotypic resistance to DOR and 6 participants carried viruses that showed genotypic and/or phenotypic resistance to NRTIs. Virus from 12 of the 364 EFV- treated participants (3.3%) were found to have primary genotypic and/or phenotypic resistance to EFV, and 7 participants carried viruses that showed genotypic and/or phenotypic resistance to NRTIs.

Safety:

Safety findings were generally similar to those observed at Week 48, with differences in certain categories of AEs suggesting a more favorable profile of DOR/3TC/TDF versus EFV/FTC/TDF, based on a 95% CI excluding zero. Categories in which this trend was observed included: occurrence of any AE, drug-related AEs, discontinuation due to AE, and discontinuations due to drug-related AE and are similar to what was observed at Week 48.

- The most commonly reported AE, outside the predefined neuropsychiatric AEs of interest, through Week 96 was headache (15.7% for the DOR/3TC/TDF group, 15.4% for the EFV/FTC/TDF group).
- Neuropsychiatric AEs at Week 96 were markedly less common in the DOR/3TC/TDF (26.4%) compared with the EFV/FTC/TDF group (58.5%) (treatment difference: -32.1% [95% CI: -38.8, -25.2]). The 95% CI for the treatment difference excluded 0 for 2 of the 5 predefined categories: dizziness and sleep disorders.
- AEs associated with rash occurred less commonly for the DOR/3TC/TDF group (7.1%) compared with the EFV/FTC/TDF group (18.1%). No participants in the DOR/3TC/TDF group discontinued or interrupted study drug due to rash compared with 10 participants in the EFV/FTC/TDF group.
- DOR/3TC/TDF had a favorable lipid profile compared with EFV/FTC/TDF with respect to mean changes from baseline in fasting LDL-C and non-HDL-C at Week 96, consistent with findings at Week 48. With respect to individual values meeting pre-defined criteria, fewer participants in the DOR/3TC/TDF group compared with the EFV/FTC/TDF group had elevations in LDL-C, total cholesterol and triglycerides, with greater differences at higher grades and the CIs for the treatment differences excluding 0. Smaller increases in fasting HDL-C were observed in the DOR/3TC/TDF group than in the EFV/FTC/TDF group.
- Grade 1 and 2 bilirubin elevations were observed in 7.5% of participants in the DOR/3TC/TDF group compared with 0% in the EFV/FTC/TDF group. The majority of Grade 1 bilirubin elevations in the DOR group were either single, transient elevations or 2 nonconsecutive Grade 1 elevations. The majority of participants with Grade 2 values had predose values that were Grade 1, and values that fluctuated between Grade 1 and Grade 2 during the trial. No common etiology has been identified. None of the bilirubin elevations resulted in discontinuation from the study.

Analysis of Adverse Event Summary
Weeks 0-96; Base Study (Double Blind)

	DOR/3TC/TDF QD		EFV/FTC/TDF QD		Difference in % vs EFV/FTC/TDF QD
	n	(%)	n	(%)	Estimate (95% CI)[†]
Subjects in population	364		364		
with one or more adverse events	321	(88.2)	339	(93.1)	-4.9 (-9.3, -0.7)
with no adverse events	43	(11.8)	25	(6.9)	4.9 (0.7, 9.3)
with drug-related[‡] adverse events	116	(31.9)	236	(64.8)	-33.0 (-39.6, -26.0)
with serious adverse events	21	(5.8)	30	(8.2)	-2.5 (-6.3, 1.3)
with serious drug-related adverse events	1	(0.3)	4	(1.1)	-0.8 (-2.5, 0.5)
who died	0	(0.0)	2	(0.5)	-0.5 (-2.0, 0.5)
discontinued[§] due to an adverse event	11	(3.0)	27	(7.4)	-4.4 (-7.9, -1.2)
discontinued due to a drug-related adverse event	8	(2.2)	24	(6.6)	-4.4 (-7.7, -1.5)
discontinued due to a serious adverse event	2	(0.5)	4	(1.1)	-0.5 (-2.3, 1.0)
discontinued due to a serious drug-related adverse event	1	(0.3)	3	(0.8)	-0.5 (-2.2, 0.8)

[†] Based on Miettinen & Nurminen method.
[‡] Determined by the investigator to be related to the drug.
[§] Study medication withdrawn.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.
Analysis includes AEs occurring or worsening after the first dose of study medication through last dose of base study medication (or 14 days after the last dose of base study medication if not continuing into the study extension).

Source: [P021MK1439A: analysis-adsl] [P021MK1439A: tabulations-aeplus]

CONCLUSIONS:

In this 96-week trial in treatment-naïve participants infected with HIV-1:

Efficacy Conclusions

- DOR/3TC/TDF showed similar antiretroviral and immunologic efficacy versus EFV/FTC/TDF at Week 96, supporting the non-inferiority of DOR/3TC/TDF to EFV/FTC/TDF previously established at Week 48.
- Rates of development of viral drug resistance through Week 96 were low, with viral isolates from 6 of 364 (1.6%) DOR/3TC/TDF-treated participants shown to have primary genotypic and phenotypic resistance to DOR, and none occurring after Week 48. Primary genotypic or phenotypic resistance to EFV was observed among 12 of 364 (3.3%) EFV/FTC/TDF-treated participants.

Safety Conclusions

- DOR/3TC/TDF was well tolerated throughout the 96-week trial as compared with EFV/FTC/TDF, supported in part by a lower frequency of study drug discontinuation due to AEs.
- Neuropsychiatric AEs at Week 96 remained markedly less common for DOR/3TC/TDF compared with EFV/FTC/TDF.

- DOR/3TC/TDF had a favorable lipid profile compared to EFV/FTC/TDF with respect to changes from baseline in fasting LDL-C and non-HDL-C.

PUBLICATION(S): Orkin C, Squires K, Molina J-M, Sax P, Wong W-W, Sussmann O, et al. Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate is Non-inferior to Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate in Treatment-naive Adults With Human Immunodeficiency Virus–1 Infection: Week 48 Results of the DRIVE-AHEAD Trial. *Clin Infect Dis* 2018; https://doi.org/10.1093/cid/ciy540.

REPORT DATE: [redacted]-20[redacted]

REVISED REPORT DATE: [redacted]-20[redacted]