This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

2. Synopsis

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC. MK-0518 Raltegravir potassium, 400 mg Film-coated tablet HIV-1 Infection	**CLINICAL STUDY REPORT SYNOPSIS**

PROTOCOL TITLE/NO.: Early Access of MK-0518 in Combination With an Optimized Background Antiretroviral Therapy (OBT) in Highly Treatment Experienced HIV-1 Infected Patients With Limited to No Treatment Options	0518-023

PROTECTION OF HUMAN SUBJECTS: With the exception of the study sites noted below, this study was conducted in conformance with Good Clinical Practice (GCP) standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research. The following study sites participating in this study were identified as non-compliant with some/all requirements of GCP: Site [redacted] (Investigator: [redacted] and Site [redacted] For study audit information see [redacted]

INVESTIGATOR(S)/STUDY CENTER(S): The study was performed at 538 study centers in 26 countries in Africa, Asia, Europe, North America, and New Zealand. A list of investigators and study centers are provided in [redacted]

PUBLICATION(S): Cooper DA, Steigbigel R, Lennox J, Grinsztejn B, Markowitz M, Sklar P, et al. Review of cancer incidence in raltegravir clinical trials: Studies of cancer incidence [abstract]. 16th Conference on Retroviruses and Opportunistic Infections; 2009 Feb 8-11. Montreal, Canada, 2009:386 [redacted]

PRIMARY THERAPY PERIOD: First patient in (FPE): 07-Sep-2006 Last patient last visit (LPLV): 14-Jul-2010	**CLINICAL PHASE:** III

DURATION OF TREATMENT: Patients took MK-0518 400 mg orally by mouth (p.o.) twice daily (b.i.d.) beginning on Day 1 throughout study participation. The study continued until 14-Jul-2010.

OBJECTIVE(S): To provide expanded access to MK-0518 in highly treatment experienced human immunodeficiency virus - type 1 (HIV-1) infected patients with limited or no treatment options prior to the product's approval and availability on the market. The safety and tolerability of MK-0518 400 mg b.i.d. for the treatment of HIV-1 infection was monitored.

STUDY DESIGN: This was an expanded access, noncomparative, multicenter, open-label, treatment use study. The investigator followed patients according to the standard of care. The study was to continue until approximately 3 months after product launch. For further information see [redacted]

SUBJECT/PATIENT DISPOSITION†:

	MK-0518 400 mg (N=5792)
SCREENING FAILURES‡:	569
TREATED:	5792
Gender, n (%)	
Male	4856 (83.8)
Female	924 (16.0)
Unknown	12 (0.2)
Age (years)	
Mean (SD)	46.2 (8.76)
Median (Range)	46.0 (16-81)

Race, n (%)	
White	3965 (68.5)
Black	992 (17.1)
Hispanic American	574 (9.9)
Asian	188 (3.2)
Native American	7 (0.1)
Other	54 (0.9)
Unknown	12 (0.2)
COMPLETED:	5235
DISCONTINUED:	557
Clinical adverse experience	119
Laboratory adverse experience	12
Other	426

† Based on the number of patients who entered the study (received study drug) unless noted otherwise.
‡ Patients who never received study drug.
SD=standard deviation
Data Source: [redacted]

DOSAGE/FORMULATION NOS.: MK-0518 400 mg p.o. b.i.d. / Formulation Number (Control Number): [redacted]

DIAGNOSIS/INCLUSION CRITERIA: A patient with documented HIV-1 infection was eligible to participate in this study if all of the following criteria applied: 1) Patient was a male or female at least 16 years of age; 2) Patient had limited or no treatment options due to resistance or significant intolerance to antiretroviral regimens defined by (a) patient had documented resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) by genotype or phenotype testing OR according to Protocol Amendment 2 (dated 19-Dec-2007) was defined as clinical failure on an NNRTI containing regimen that in the opinion of the investigator suggested resistance, (b) patient had documented resistance to at least 1 drug in the nucleoside reverse transcriptase inhibitor (NRTI) class and at least 1 drug in the protease inhibitor (PI) class by genotype or phenotype testing, or (c) significant intolerance defined as having had a clinically significant adverse experience (AE; adverse event) which in the opinion of the investigator provided a contraindication to the use of any drug in that class; 3) Patient was not achieving adequate virologic suppression on his/her current regimen and at risk of clinical or immunologic progression. According to Protocol Amendment 2, a patient who was virologically suppressed but had a significant intolerance to a drug in their regimen may have been enrolled and switched to MK-0518; 4) Patient was to have been considered clinically stable, in the opinion of the investigator, at the time of entry into the study; 5) Patient who was of reproductive potential agreed to use an acceptable method of birth control throughout the study. Protocol Amendment 2 also allowed patients with chronic hepatitis to be eligible, but caution was recommended if patients with clinically significant chronic liver disease including but not limited to cirrhosis, ascites, encephalopathy, hypoalbuminemia, prolonged prothrombin time / partial thromboplastin time (PT/PTT) and/or esophageal varices were enrolled.

EVALUATION CRITERIA: Safety data of serious AEs (SAEs) and drug-related AEs that resulted in Grade 3 or above laboratory toxicity, led to treatment interruption, or discontinuation were documented on case report forms (CRFs). Guidelines for grading the severity of AEs were based on the DAIDS (Division of Acquired Immunodeficiency Syndrome [AIDS]) Table for Grading the Severity of Adult and Pediatric AE criteria.

STATISTICAL PLANNING AND ANALYSIS: Entered patients (i.e., received study drug) were identified based on having at least one of the following: first or last date of therapy; any AE; any SAE with a causality of probably not, possibly, probably, definitely, or of unknown relationship; or who completed the study and had missing values for any exclusion or discontinuation fields.

The primary safety analyses were based upon the All Patients as Treated (APaT) approach which included all patients who received one or more doses of test drug therapy. All patients who took study drug were included in the analysis of safety and tolerability. Only those AEs that occurred while the patient was on study therapy or within 14 days after discontinuation of study therapy were included in the analysis.

For assessment of safety and tolerability, counts and percentages of patients with clinical or laboratory AEs of the following type were tabulated: 1) SAE; 2) drug-related AEs that resulted in Grade 3 or above laboratory toxicity; 3) drug-related AEs that led to treatment interruption; and 4) drug-related AEs leading to discontinuation. A patient may have had two or more clinical or laboratory AEs but was counted only once within a category. Drug-related events are those determined by the investigator to be possibly, probably, or definitely drug-related. If relatedness was missing, possibly related was imputed.

Version 13.0 of the Medical Dictionary for Regulatory Activities (MedDRA) was used for reporting. No formal hypothesis testing was done.

RESULTS:

Safety: The primary AE tables presented in [redacted] include the number (%) of patients with: 1) SAEs by system organ class (SOC) and preferred term (PT); 2) drug-related AEs that resulted in Grade 3 or above laboratory toxicity by SOC and PT; 3) drug-related AEs that led to treatment interruption by SOC and PT; 4) drug-related AEs leading to discontinuation by SOC and PT; 5) all drug-related AEs; and 6) AEs leading to discontinuation by SOC and PT. For summary purposes, any patient who had more that one AE PT within the same SOC was summarized only once for that PT within the SOC.

Of the 5792 patients treated with raltegravir, 5657 patients had a start of therapy date. Based on data from these 5657 patients, the mean study duration per patient was 215.6 days (range 1-997 days).

Study Duration Per Patient and Total Study Time[†]

Duration Per Patient (days)				Total Days Each Site was Active
N	Mean (SD)	Median (IQR)	Min, Max	
5657	215.6 (119.98)	205.0 (141)	1, 997	1407

[†] Based on patients who entered the study (received study drug) and have a start of therapy date.
Data Source: [redacted]

Raltegravir was generally well tolerated in this study. Of the 5792 patients treated with raltegravir, 817 (14.1%) experienced at least one clinical AE. One hundred seventeen (2.0%) patients died due to a clinical AE and 630 (10.9%) patients experienced at least one clinical SAE. A total of 108 (1.9%) patients treated with raltegravir discontinued due to a clinical AE. The following table presents an overview of clinical AEs reported during the study.

Clinical Adverse Experience Summary (All Entered Patients)[†]

	MK-0518 400 mg (N=5792)
	n (%)
Number (%) of Patients	
With One or More Clinical Adverse Experiences	817 (14.1)
With No Clinical Adverse Experiences	4975 (85.9)
With Drug-related Clinical Adverse Experiences[‡]	288 (5.0)
With Clinical Serious Adverse Experiences	630 (10.9)
With Clinical Serious Drug-related Adverse Experiences[‡]	69 (1.2)
Who Died	117 (2.0)
Discontinued due to Clinical Adverse Experiences[§]	108 (1.9)
Discontinued due to Drug-related Clinical Adverse Experiences[‡,§]	45 (0.8)
Discontinued due to Clinical Serious Adverse Experiences[§]	85 (1.5)
Discontinued due to Clinical Serious Drug-related Adverse Experiences[‡,§]	21 (0.4)

[†] Based on the number of patients who entered the study (received study drug).
[‡] Determined by the investigator to be possibly, probably, or definitely drug-related.
[§] Discontinued = Patient discontinued from therapy.
Data Source: [redacted]

The most common clinical AEs were diarrhoea in 55 (0.9%) patients, pneumonia in 49 (0.8%) patients, rash in 42 (0.7%) patients, nausea in 30 (0.5%) patients, pyrexia in 28 (0.5%) patients, renal failure acute in 27 (0.5%) patients, and headache in 21 (0.4%) patients [redacted]

Clinical AEs were considered drug-related in 288 (5.0%) patients as displayed in the table below. The most common drug-related clinical AEs were diarrhoea in 41 (0.7%) patients, rash in 40 (0.7%) patients, nausea in 25 (0.4%) patients, and headache in 18 (0.3%) patients [redacted] Drug-related clinical AEs led to discontinuation in 45 (0.8%) patients [redacted] and to treatment interruption in 38 (0.7%) patients [redacted] Rash was the most common drug-related clinical AE leading to discontinuation (in 7 [0.1%] patients). It was also the most common drug-related clinical AE leading to treatment interruption (in 11 [0.2%] patients).

Drug-related Clinical Adverse Experiences Reported by 0.2% or More of Patients (All Entered Patients)[†]

System Organ Class Preferred Term	MK-0518 400 mg (N=5792) n (%)
Patients with One or More Drug-related Clinical Adverse Experiences[‡]	288 (5.0)
Patients with No Drug-related Clinical Adverse Experiences	5504 (95.0)
Gastrointestinal Disorders	
Diarrhoea	41 (0.7)
Nausea	25 (0.4)
Vomiting	10 (0.2)
General Disorders and Administration Site Conditions	
Fatigue	13 (0.2)
Pyrexia	12 (0.2)
Immune System Disorders	
Immune Reconstitution Syndrome	12 (0.2)
Injury, Poisoning and Procedural Complication	
Overdose	10 (0.2)
Nervous System Disorders	
Headache	18 (0.3)
Dizziness	10 (0.2)
Psychiatric Disorders	
Insomnia	14 (0.2)
Skin and Subcutaneous Tissue Disorders	
Rash	40 (0.7)

[†] Based on the number of patients who entered the study (received study drug).
[‡] Determined by the investigator to be possibly, probably, or definitely drug-related. If relatedness was missing, possibly related was imputed.
Data Source: [redacted]

The most common clinical SAEs were pneumonia in 49 (0.8%) patients, renal failure acute in 27 (0.5%) patients, pyrexia in 20 (0.3%) patients, immune reconstitution syndrome in 19 (0.3%) patients, pneumocystis jiroveci pneumonia in 19 (0.3%) patients, anemia in 17 (0.3%) patients, sepsis in 17 (0.3%) patients, cellulitis in 15 (0.3%) patients, diarrhoea in 15 (0.3%) patients, and mycobacterium avium complex infection in 15 (0.3%) patients [redacted]. Serious clinical AEs were considered drug-related in 69 (1.2%) patients as displayed in the table below. The most common drug-related clinical SAE was immune reconstitution syndrome in 12 (0.2%) patients and overdose in 10 (0.2%) patients.

Drug-related Serious Clinical Adverse Experiences Reported by 2 or More Patients (All Entered Patients)[†]

System Organ Class Preferred Term	MK-0518 400 mg (N=5792) n (%)
Patients with One or More Drug-related Serious Clinical Adverse Experiences[‡]	69 (1.2)
Patients with No Drug-related Serious Clinical Adverse Experiences	5723 (98.8)
Blood and Lymphatic System Disorders	
Anaemia	3 (0.1)
General Disorders and Administration Site Conditions	
Pyrexia	4 (0.1)
Death[§]	3 (0.1)
Hepatobiliary Disorders	
Hepatitis	2 (0.0)
Immune System Disorders	
Immune Reconstitution Syndrome	12 (0.2)
Drug Hypersensitivity	2 (0.0)
Infections and Infestations	
Herpes Zoster	2 (0.0)
Injury, Poisoning and Procedural Complication	
Overdose	10 (0.2)
Musculoskeletal and Connective Tissue Disorders	
Rhabdomyolysis	3 (0.1)
Myopathy	2 (0.0)
Nervous System Disorders	
Convulsion	2 (0.0)
Renal and Urinary Disorders	
Renal Failure Acute	4 (0.1)
Skin and Subcutaneous Tissue Disorders	
Rash	2 (0.0)

[†] Based on the number of patients who entered the study (received study drug).

[‡] Determined by the investigator to be possibly, probably, or definitely drug-related. If relatedness was missing, possibly related was imputed.

[§] Two patients with the event of death had relatedness missing from the CRF, therefore, "possibly" related was imputed. In the safety database, a causality of "unknown" was assigned for the same events due to lack of records. The event of death for a third patient was also considered possibly drug-related although the medical examiner noted the cause of death as arteriosclerotic cardiovascular disease.

Data Source: [redacted]

A total of 85 (1.5%) patients treated with raltegravir discontinued due to a clinical SAE [redacted] Drug-related clinical SAEs led to discontinuation in 21 (0.4%) patients [redacted] and to treatment interruption in 13 (0.2%) patients [redacted] The most common drug-related clinical SAEs leading to discontinuation were death in 2 (<0.1%) patients and rhabdomyolysis in 2 (<0.1%) patients. The most common drug-related clinical SAE leading to treatment interruption was immune reconstitution syndrome in 4 (0.1%) patients.

Patient information in the clinical database was reconciled to the safety database (Worldwide Adverse Event System [WAES]). Missing and mismatched SAEs that are considered permanently irreconcilable between the clinical and safety databases are summarized in [redacted] WAES narratives are provided in [redacted] for SAEs (including deaths).

Laboratory assessments were performed at screening and at Weeks 4 and 12 with additional laboratory testing performed according to the study center's standard of care and at the investigator's discretion. Laboratory test results were only reported in the CRF if they were a drug-related non-serious AE or an SAE with toxicity Grade 3 or above.

Of the 5792 patients entered into the study, 115 had a post baseline laboratory test reported. Of these 115 patients, 92 (80.0%) patients experienced at least one laboratory AE as displayed in the table below. Seventy-one (61.7%) patients experienced a drug-related AE that resulted in a Grade 3 or above laboratory toxicity [redacted]. One (0.9%) patient died due to a laboratory AE, and 23 (20.0%) patients experienced at least 1 serious laboratory AE. Eleven (9.6%) patients with post baseline laboratory tests discontinued due to a laboratory AE.

Laboratory Adverse Experience Summary
(All Entered Patients with Post Baseline Laboratory Test)[†]

	MK-0518 400 mg (N=115)
	n (%)
Number (%) of Patients	
With at Least One Post Baseline Laboratory Test	115 (100)
With One or More Laboratory Adverse Experience	92 (80.0)
With No Laboratory Adverse Experience	23 (20.0)
With Drug-related Laboratory Adverse Experience[‡]	71 (61.7)
With Serious Laboratory Adverse Experience	23 (20.0)
With Serious Laboratory Drug-related Adverse Experience[‡]	2 (1.7)
Who Died	1 (0.9)
Discontinued due to Laboratory Adverse Experience[‡,§]	11 (9.6)
Discontinued due to Drug-related Laboratory Adverse Experience[‡,§]	9 (7.8)
Discontinued due to Serious Laboratory Adverse Experience[§]	3 (2.6)
Discontinued due to Serious Drug-related Laboratory Adverse Experience[‡,§]	1 (0.9)

[†] Based on the number of patients who entered the study (received study drug) and had at least one post baseline laboratory test reported.
[‡] Determined by the investigator to be possibly, probably, or definitely drug-related. If relatedness was missing, possibly related was imputed.
[§] Discontinued = Patient discontinued from therapy.
Data Source: [redacted]

The most common laboratory AEs were blood creatinine increased in 12 (10.4%) patients and alanine aminotransferase (ALT) increased in 11 (9.6%) patients with post baseline laboratory tests [redacted] Laboratory AEs were considered drug-related in 71 (61.7%) patients. The most common drug-related laboratory AEs were blood creatinine increased in 12 (10.4%) patients, ALT increased in 10 (8.7%) patients, blood creatine phosphokinase increased in 6 (5.2%) patients, and blood triglycerides increased in 6 (5.2%) patients.

Drug-related Laboratory Adverse Experiences
(All Entered Patients with Post Baseline Laboratory Test)[†]

System Organ Class Preferred Term	MK-0518 400 mg (N=115) n (%)
Patients with One or More Drug-related Laboratory Adverse Experiences[‡]	71 (61.7)
Patients with No Drug-related Laboratory Adverse Experiences	44 (38.3)
General Disorders and Administration Site Conditions	
Drug Resistance	1 (0.9)
Immune System Disorders	
Immune Reconstitution Syndrome	1 (0.9)
Investigations	
Alanine Aminotransferase Increased	10 (8.7)
Aspartate Aminotransferase Increased	4 (3.5)
Blood Alkaline Phosphatase Increased	4 (3.5)
Blood Amylase Increased	3 (2.6)
Blood Bilirubin Increased	3 (2.6)
Blood Creatinine Phosphokinase Increased	6 (5.2)
Blood Creatinine Increased	12 (10.4)
Blood Glucose Increased	3 (2.6)
Blood Triglycerides Increased	6 (5.2)
Gamma-Glutamyltransferase Increased	1 (0.9)
Haemoglobin Decreased	3 (2.6)
Hepatic Enzyme Increased	3 (2.6)
Lipase Increased	1 (0.9)
Liver Function Test Abnormal	3 (2.6)
Neutrophil Count Decreased	3 (2.6)
Platelet Count Decreased	4 (3.5)
Transaminases Increased	3 (2.6)
Viral Load Increased	1 (0.9)
Metabolism and Nutrition Disorders	
Diabetes Mellitus	2 (1.7)
Dyslipidaemia	1 (0.9)
Hyperlipidaemia	3 (2.6)
Hypertriglyceridaemia	2 (1.7)
Hyponatraemia	1 (0.9)

[†] Based on the number of patients who entered the study (received study drug) and had at least one post baseline laboratory test reported.

[‡] Determined by the investigator to be possibly, probably, or definitely drug-related. If relatedness was missing, possibly related was imputed.

Data Source: [redacted]

Eleven (9.6%) of the 115 patients with post baseline laboratory tests discontinued due to a laboratory AE [redacted]. Drug-related laboratory AEs led to discontinuation in 9 (7.8%) patients [redacted] The most common drug-related laboratory AEs leading to discontinuation were ALT increased and hepatic enzyme increased, each reported in 2 (1.7%) patients. Six (5.2%) patients with post baseline laboratory tests had a drug-related laboratory AE that resulted in treatment interruption [redacted] Each event leading to treatment interruption occurred in 1 (0.9%) patient.

One (0.9%) of the 115 patients with post baseline laboratory tests died during the study due to a laboratory AE (anemia) [redacted]. This patient also had a clinical AE (brain hypoxia) with a fatal outcome[redacted] A total of 23 (20.0%) patients with post baseline laboratory tests experienced at least 1 laboratory SAE [redacted] The most common laboratory SAEs were anemia in 4 (3.5%) patients and blood alkaline phosphatase increased, hypokalaemia, liver function test (LFT) abnormal, and thrombocytopenia each in 2 (1.7%) patients. Serious laboratory AEs were considered drug-related in 2 (1.7%) patients with post baseline laboratory tests. Drug-related laboratory SAEs were hyponatraemia and LFT abnormal in 1 (0.9%) patient each.

Drug-related Serious Laboratory Adverse Experiences
(All Entered Patients with Post Baseline Laboratory Test)[†]

System Organ Class Preferred Term	MK-0518 400 mg (N=115)
	n (%)
Patients with One or More Drug-related Serious Laboratory Adverse Experiences[‡]	2 (1.7)
Patients with No Drug-related Serious Laboratory Adverse Experiences	113 (98.3)
Investigations	
Liver Function Test Abnormal	1 (0.9)
Metabolism and Nutrition Disorders	
Hyponatraemia	1 (0.9)

[†] Based on the number of patients who entered the study (received study drug) and had at least one post baseline laboratory test reported.
[‡] Determined by the investigator to be possibly, probably, or definitely drug-related. If relatedness was missing, possibly related was imputed.
Data Source: [redacted]

Three (2.6%) of the 115 patients with post baseline laboratory tests had serious laboratory AEs that led to discontinuation [redacted] The events were anaemia, hyperglycemia, and hyponatraemia (each in 1 [0.9%] patient). One (0.9%) of the 115 patients with post baseline laboratory tests had serious drug-related laboratory AEs that led to discontinuation [redacted] Six (5.2%) of the 115 patients with post baseline laboratory tests had laboratory AEs that led to treatment interruption [redacted]

WAES narratives are provided in [redacted] for laboratory SAEs (including deaths).

CONCLUSIONS: Raltegravir potassium, 400 mg (MK-0518) was generally well tolerated in this population of highly treatment experienced HIV-1 infected patients during this expanded access program of patients with HIV-1 infection.

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