CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

22-145/S004

Trade Name: Isentress

Generic Name: Raltegravir Potassium

Sponsor: Merck Sharp Dohme

Approval Date: July 8, 2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22 – 145/S004

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	✓
Other Action Letters	
Labeling	✓
REMS	
Summary Review	
Officer/Employee List	✓
Office Director Memo	
Cross Discipline Team Leader Review	✓
Medical Review(s)	✓
Chemistry Review(s)	✓
Environmental Assessment	
Pharmacology Review(s)	✓
Statistical Review(s)	✓
Microbiology Review(s)	✓
Clinical Pharmacology/Biopharmaceutics Review(s)	✓
Other Reviews	✓
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	✓

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22 – 145/S004

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993-0002

NDA 22-145/S-004

Merck & Co., Inc.
Attention: Robert A. Fromtling, Ph.D.
Director, Worldwide Regulatory Affairs
126 E. Lincoln Avenue
P.O. Box 2000, RY 33-212
Rahway, NJ 07065-0900

Dear Dr. Fromtling:

Please refer to your supplemental new drug application dated September 25, 2008, received September 26, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ISENTRESS® (raltegravir potassium) 400 mg tablets.

We also acknowledge receipt of your submissions dated January 12, 2009, January 21, 2009, January 29, 2009, January 30, 2009, February 9, 2009, February 24, 2009, March 4, 2009, April 10, 2009, May 7, 2009, May 8, 2009, May 15, 2009, June 12, 2009, June 19, 2009, and June 26, 2009.

This supplemental new drug application provides for the use of ISENTRESS® (raltegravir potassium) tablets in combination with other antiretrovirals for the treatment of HIV-1 infection in treatment-naive adult patients.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

Approval of this supplement fulfills the following postmarketing commitment acknowledged in our October 12, 2007, approval letter:

6. Submit Week 48 report and datasets for Protocol 021.

CONTENT OF LABELING
As soon as possible, but no later than 14 days from the date of this letter, submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling (text for the package insert and patient package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission **"SPL for approved supplement NDA 22-145/S-004."**

In addition, within 21 days of the date of this letter, amend any pending application for this NDA with content of labeling in structured product labeling (SPL) format to include the changes approved in this application.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and patient package insert).

PROMOTIONAL MATERIALS
In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division, the Division of Antiviral Products, and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

LETTERS TO HEALTH CARE PROFESSIONALS
If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS
We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Amalia Himaya, Regulatory Project Manager, at (301) 796-3391.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure (Package and Patient Package Inserts)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Debra Birnkrant
7/8/2009 04:33:28 PM
NDA 22-145

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22 – 145/S004

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ISENTRESS safely and effectively. See full prescribing information for ISENTRESS.

ISENTRESS (raltegravir) Tablets
Initial U.S. Approval: 2007

---------- RECENT MAJOR CHANGES ----------

Indications And Usage (1)	07/2009
Dosage And Administration (2)	01/2009
Warnings And Precautions (5.2) – removal	07/2009

---------- INDICATIONS AND USAGE ----------

ISENTRESS® is a human immunodeficiency virus integrase strand transfer inhibitor (HIV-1 INSTI) indicated:

- In combination with other antiretroviral agents for the treatment of HIV-1 infection in adult patients (1).

The safety and efficacy of ISENTRESS have not been established in pediatric patients (1).

---------- DOSAGE AND ADMINISTRATION----------

- 400 mg administered orally, twice daily with or without food (2).
- During coadministration with rifampin, 800 mg twice daily (2).

---------- DOSAGE FORMS AND STRENGTHS ----------

Tablets: 400 mg (3).

---------- CONTRAINDICATIONS ----------

None (4)

---------- WARNINGS AND PRECAUTIONS ----------

Monitor for Immune Reconstitution Syndrome (5.1).

---------- ADVERSE REACTIONS----------

- The most common adverse reactions of moderate to severe intensity (≥2%) which occurred at a higher rate than the comparator are insomnia, headache, nausea, asthenia and fatigue (6.1).
- Creatine kinase elevations were observed in subjects who received ISENTRESS. Myopathy and rhabdomyolysis have been reported; however, the relationship of ISENTRESS to these events is not known. Use with caution in patients at increased risk of myopathy or rhabdomyolysis, such as patients receiving concomitant medications known to cause these conditions (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Merck & Co., Inc. at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS----------

- Coadministration of ISENTRESS with drugs that are strong inducers of UGT1A1 may result in reduced plasma concentrations of raltegravir (7.2).

---------- USE IN SPECIFIC POPULATIONS ----------

Pregnancy:

- ISENTRESS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Physicians are encouraged to register pregnant women exposed to ISENTRESS by calling 1-800-258-4263 so that Merck can monitor maternal and fetal outcomes (8.1).

Nursing Mothers:

- Breast-feeding is not recommended while taking ISENTRESS (8.3).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 07/2009

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ISENTRESS[1] is indicated in combination with other anti-retroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection in adult patients.

This indication is based on analyses of plasma HIV-1 RNA levels up through 48 weeks in three double-blind controlled studies of ISENTRESS. Two of these studies were conducted in clinically advanced, 3-class antiretroviral (NNRTI, NRTI, PI) treatment-experienced adults and one was conducted in treatment-naïve adults.

The use of other active agents with ISENTRESS is associated with a greater likelihood of treatment response *[see Clinical Studies (14)]*.

The safety and efficacy of ISENTRESS have not been established in pediatric patients.

2 DOSAGE AND ADMINISTRATION

For the treatment of patients with HIV-1 infection, the dosage of ISENTRESS is 400 mg administered orally, twice daily with or without food. During coadministration with rifampin, the recommended dosage of ISENTRESS is 800 mg twice daily with or without food.

3 DOSAGE FORMS AND STRENGTHS

400 mg pink, oval-shaped, film-coated tablets with "227" on one side.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Immune Reconstitution Syndrome

During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* complex, cytomegalovirus, *Pneumocystis jiroveci* pneumonia, *Mycobacterium* tuberculosis, or reactivation of varicella zoster virus), which may necessitate further evaluation and treatment.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Treatment-Naïve Studies

The following safety assessment of ISENTRESS in treatment-naïve subjects is based on the randomized double-blind active controlled study of treatment-naïve subjects, STARTMRK (Protocol 021) with ISENTRESS 400 mg twice daily in combination with a fixed dose of emtricitabine 200 mg (+) tenofovir 300 mg, (N=281) versus efavirenz (EFV) 600 mg at bedtime in combination with emtricitabine (+) tenofovir, (N=282). During double-blind treatment, the total follow-up for subjects receiving ISENTRESS 400 mg twice daily + emtricitabine (+) tenofovir was 247 patient-years and 241 patient-years for subjects receiving efavirenz 600 mg at bedtime + emtricitabine (+) tenofovir.

In Protocol 021, the rate of discontinuation of therapy due to adverse reactions was 3% in subjects receiving ISENTRESS + emtricitabine (+) tenofovir and 6% in subjects receiving efavirenz + emtricitabine (+) tenofovir.

The clinical adverse drug reactions (ADRs) listed below were considered by investigators to be causally related to ISENTRESS + emtricitabine (+) tenofovir or efavirenz + emtricitabine (+) tenofovir. Clinical ADRs of moderate to severe intensity occurring in ≥2% of treatment-naïve subjects treated with ISENTRESS and occurring at a higher rate than efavirenz are presented in Table 1.

[1] Registered trademark of MERCK & CO., Inc.

Table 1: Adverse Reactions* of Moderate to Severe Intensity† Occurring in ≥2% of Treatment-Naïve Adult Subjects Receiving ISENTRESS and at a Higher Rate Compared to Efavirenz (48 Week Analysis)

System Organ Class, Preferred Term	Randomized Study Protocol 021	
	ISENTRESS 400 mg Twice Daily + Emtricitabine (+) Tenofovir (n = 281)‡ %	Efavirenz 600 mg At Bedtime + Emtricitabine (+) Tenofovir (n = 282)‡ %
Psychiatric Disorders		
Insomnia	4	3

*Includes adverse experiences considered by investigators to be at least possibly, probably, or definitely related to the drug
†Intensities are defined as follows: Moderate (discomfort enough to cause interference with usual activity); Severe (incapacitating with inability to work or do usual activity).
‡n = total number of subjects per treatment group

Less Common Adverse Reactions

The following ADRs occurred in <2% of subjects receiving ISENTRESS + emtricitabine (+) tenofovir. These events have been included because of their seriousness, increased frequency on ISENTRESS compared with efavirenz or investigator's assessment of potential causal relationship.
General Disorders and Administration Site Conditions: fatigue
Psychiatric Disorders: abnormal dreams

Laboratory Abnormalities

The percentages of adult subjects treated with ISENTRESS 400 mg twice daily or efavirenz in Protocol 021 with selected Grades 2 to 4 laboratory abnormalities that represent a worsening from baseline are presented in Table 2.

Table 2: Selected Grade 2 to 4 Laboratory Abnormalities Reported in Treatment-Naïve Subjects (48 Week Analysis)

Laboratory Parameter Preferred Term (Unit)	Limit	Randomized Study Protocol 021 ISENTRESS 400 mg Twice Daily + Emtricitabine (+) Tenofovir (N = 281)	Randomized Study Protocol 021 Efavirenz 600 mg At Bedtime + Emtricitabine (+) Tenofovir (N = 282)
Hematology			
Absolute neutrophil count ($10^3/\mu L$)			
Grade 2	0.75 - 0.999	3%	3%
Grade 3	0.50 - 0.749	1%	<1%
Grade 4	<0.50	<1%	0%
Hemoglobin (gm/dL)			
Grade 2	7.5 - 8.4	<1%	<1%
Grade 3	6.5 - 7.4	<1%	<1%
Grade 4	<6.5	0%	0%
Platelet count ($10^3/\mu L$)			
Grade 2	50 - 99.999	2%	0%
Grade 3	25 - 49.999	0%	<1%
Grade 4	<25	0%	.0%
Blood chemistry			
Fasting (non-random) serum glucose test (mg/dL)			
Grade 2	126 - 250	2%	3%
Grade 3	251 - 500	<1%	0%
Grade 4	>500	0%	0%
Total serum bilirubin			
Grade 2	1.6 - 2.5 x ULN	4%	0%

Grade 3	2.6 - 5.0 x ULN	<1%	0%
Grade 4	>5.0 x ULN	0%	0%
Serum aspartate aminotransferase			
Grade 2	2.6 - 5.0 x ULN	3%	4%
Grade 3	5.1 - 10.0 x ULN	1%	1%
Grade 4	>10.0 x ULN	<1%	<1%
Serum alanine aminotransferase			
Grade 2	2.6 - 5.0 x ULN	4%	6%
Grade 3	5.1 - 10.0 x ULN	<1%	2%
Grade 4	>10.0 x ULN	<1%	<1%
Serum alkaline phosphatase			
Grade 2	2.6 - 5.0 x ULN	<1%	2%
Grade 3	5.1 - 10.0 x ULN	0%	<1%
Grade 4	>10.0 x ULN	0%	0%

ULN = Upper limit of normal range-

Lipids, Change from Baseline

Changes from baseline in fasting lipids are shown in Table 3.

Table 3: Lipid Values, Mean Change from Baseline, Protocol 021

Laboratory Parameter Preferred Term	**ISENTRESS 400 mg Twice Daily + Emtricitabine (+) Tenofovir N = 281**			**Efavirenz 600 mg At Bedtime + Emtricitabine (+) Tenofovir N = 282**		
			Change from Baseline at Week 48			**Change from Baseline at Week 48**
	Baseline Mean (mg/dL)	**Week 48 Mean** (mg/dL)	**Mean Change** (mg/dL)	**Baseline Mean** (mg/dL)	**Week 48 Mean** (mg/dL)	**Mean Change** (mg/dL)
LDL-Cholesterol†	97	103	6	92	108	16
HDL-Cholesterol†	38	42	4	38	48	10
Total Cholesterol†	159	169	10	156	188	33
Triglyceride†	125	122	-3	136	174	37

†Fasting (non-random) laboratory tests.

Notes:

N = Number of subjects in the treatment group. The analysis is based on all available data.

If subjects initiated or increased serum lipid-reducing agents, the last available lipid values prior to the change in therapy were used in the analysis. If the missing data was due to other reasons, subjects were censored thereafter for the analysis.

At baseline, serum lipid-reducing agents were used in 5% of subjects in the group receiving ISENTRESS and 3% in the efavirenz group. Through Week 48, serum lipid-reducing agents were used in 6% of subjects in the group receiving ISENTRESS and 6% in the efavirenz group.

Treatment-Experienced Studies

The safety assessment of ISENTRESS in treatment-experienced subjects is based on the pooled safety data from the randomized, double-blind, placebo-controlled trials, BENCHMRK 1 and BENCHMRK 2 (Protocols 018 and 019) in antiretroviral treatment-experienced HIV-1 infected adult subjects. A total of 462 subjects received the recommended dose of ISENTRESS 400 mg twice daily in combination with optimized background therapy (OBT) compared to 237 subjects taking placebo in combination with OBT. The median duration of therapy in these trials was 48 weeks for subjects receiving ISENTRESS and 38 weeks for subjects receiving placebo. The total exposure to ISENTRESS was 387 patient-years versus 156 patient-years on placebo. The rates of discontinuation due to adverse events were 2% in subjects receiving ISENTRESS and 3% in subjects receiving placebo.

Clinical ADRs were considered by investigators to be causally related to ISENTRESS + OBT or placebo + OBT. Clinical ADRs of moderate to severe intensity occurring in ≥2% of subjects treated with

ISENTRESS and occurring at a higher exposure adjusted rate compared to placebo are presented in Table 4.

Table 4: Adverse Drug Reactions* of Moderate to Severe Intensity† Occurring in ≥2% of Treatment-Experienced Adult Subjects Receiving ISENTRESS and at a Higher Exposure Adjusted Rate Compared to Placebo (48 Week Analysis, Exposure Adjusted Incidence Rates)

System Organ Class, Adverse Reactions	Randomized Studies Protocol 018 and 019	
	ISENTRESS 400 mg Twice Daily + OBT (n = 462)‡	Placebo + OBT (n = 237)‡
	Rate per 100 Patient-Years	Rate per 100 Patient-Years
Nervous System Disorders		
Headache	3	1
Gastrointestinal Disorders		
Nausea	2	1
General Disorders and Administration Site Conditions		
Asthenia	2	1
Fatigue	2	1

*Includes adverse reactions at least possibly, probably, or definitely related to the drug.
†Intensities are defined as follows: Moderate (discomfort enough to cause interference with usual activity); Severe (incapacitating with inability to work or do usual activity).
‡n=total number of subjects per treatment group.

Less Common Adverse Reactions

The following ADRs occurred in <2% of subjects receiving ISENTRESS + OBT. These events have been included because of either their seriousness, increased frequency on ISENTRESS compared with placebo or investigator's assessment of potential causal relationship.
Gastrointestinal Disorders: abdominal pain, gastritis
Hepatobiliary Disorders: hepatitis
Immune System Disorders: hypersensitivity
Infections and Infestations: genital herpes, herpes zoster
Nervous System Disorders: dizziness
Renal and Urinary Disorders: renal failure

Laboratory Abnormalities

The percentages of adult subjects treated with ISENTRESS 400 mg twice daily or placebo in Protocols 018 and 019 with selected Grade 2 to 4 laboratory abnormalities representing a worsening from baseline are presented in Table 5.

Table 5: Selected Grade 2 to 4 Laboratory Abnormalities Reported in Treatment-Experienced Subjects (48 Week Analysis)

Laboratory Parameter Preferred Term (Unit)	Limit	Randomized Studies Protocol 018 and 019	
		ISENTRESS 400 mg Twice Daily + OBT (N = 462)	Placebo + OBT (N = 237)
Hematology			
Absolute neutrophil count ($10^3/\mu L$)			
Grade 2	0.75 - 0.999	3%	5%
Grade 3	0.50 - 0.749	3%	3%
Grade 4	<0.50	1%	<1%
Hemoglobin (gm/dL)			
Grade 2	7.5 - 8.4	1%	3%
Grade 3	6.5 - 7.4	1%	<1%
Grade 4	<6.5	<1%	0%
Platelet count ($10^3/\mu L$)			

Grade 2	50 - 99.999	3%	5%
Grade 3	25 - 49.999	1%	<1%
Grade 4	<25	1%	<1%
Blood chemistry			
Fasting (non-random) serum glucose test (mg/dL)			
Grade 2	126 - 250	8%	5%
Grade 3	251 - 500	2%	1%
Grade 4	>500	0%	0%
Total serum bilirubin			
Grade 2	1.6 - 2.5 x ULN	5%	3%
Grade 3	2.6 - 5.0 x ULN	2%	2%
Grade 4	>5.0 x ULN	1%	0%
Serum aspartate aminotransferase			
Grade 2	2.6 - 5.0 x ULN	8%	6%
Grade 3	5.1 - 10.0 x ULN	3%	3%
Grade 4	>10.0 x ULN	<1%	1%
Serum alanine aminotransferase			
Grade 2	2.6 - 5.0 x ULN	7%	8%
Grade 3	5.1 - 10.0 x ULN	3%	2%
Grade 4	>10.0 x ULN	1%	2%
Serum alkaline phosphatase			
Grade 2	2.6 - 5.0 x ULN	2%	<1%
Grade 3	5.1 - 10.0 x ULN	<1%	1%
Grade 4	>10.0 x ULN	1%	<1%
Serum pancreatic amylase test			
Grade 2	1.6 - 2.0 x ULN	2%	1%
Grade 3	2.1 - 5.0 x ULN	3%	3%
Grade 4	>5.0 x ULN	<1%	0%
Serum lipase test			
Grade 2	1.6 - 3.0 x ULN	4%	3%
Grade 3	3.1 - 5.0 x ULN	1%	<1%
Grade 4	>5.0 x ULN	0%	0%
Serum creatine kinase			
Grade 2	6.0 - 9.9 x ULN	2%	2%
Grade 3	10.0 - 19.9 x ULN	3%	3%
Grade 4	≥20.0 x ULN	2%	1%

ULN = Upper limit of normal range-

Selected Adverse Events

Regardless of Drug Relationship

Cancers were reported in treatment-experienced subjects who initiated ISENTRESS or placebo, both with OBT, and in treatment-naïve subjects who initiated ISENTRESS or efavirenz, both with emtricitabine (+) tenofovir; several were recurrent. The types and rates of specific cancers were those expected in a highly immunodeficient population (many had CD4+ counts below 50 cells/mm^3 and most had prior AIDS diagnoses). The risk of developing cancer in these studies was similar in the group receiving ISENTRESS and the group receiving the comparator.

Grade 2-4 creatine kinase laboratory abnormalities were observed in subjects treated with ISENTRESS (see Table 5). Myopathy and rhabdomyolysis have been reported; however, the relationship of ISENTRESS to these events is not known. Use with caution in patients at increased risk of myopathy or rhabdomyolysis, such as patients receiving concomitant medications known to cause these conditions.

Patients with Co-existing Conditions

Patients Co-infected with Hepatitis B and/or Hepatitis C Virus

In the randomized, double-blind, placebo-controlled trials, treatment-experienced subjects (N = 114/699 or 16%) and treatment-naïve subjects (N = 34/563 or 6%) with chronic (but not acute) active hepatitis B and/or hepatitis C virus co-infection were permitted to enroll provided that baseline liver function tests did not exceed 5 times the upper limit of normal (ULN). In general the safety profile of ISENTRESS in subjects with hepatitis B and/or hepatitis C virus co-infection was similar to that in

subjects without hepatitis B and/or hepatitis C virus co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis B and/or hepatitis C virus co-infection for all treatment groups. In treatment-experienced subjects, Grade 2 or higher laboratory abnormalities that represent a worsening Grade from baseline of AST, ALT or total bilirubin occurred in 25%, 31% and 12%, respectively, of co-infected subjects treated with ISENTRESS as compared to 8%, 7% and 8% of all other subjects treated with ISENTRESS. In treatment-naïve subjects, Grade 2 or higher laboratory abnormalities that represent a worsening Grade from baseline of AST, ALT or total bilirubin occurred in 17%, 22% and 11%, respectively, of co-infected subjects treated with ISENTRESS as compared to 4%, 4% and 3% of all other subjects treated with ISENTRESS.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of ISENTRESS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Psychiatric Disorders: anxiety, depression (particularly in patients with a pre-existing history of psychiatric illness), including suicidal ideation and behaviors, paranoia
Skin and Subcutaneous Tissue Disorders: rash, Stevens-Johnson syndrome

7 DRUG INTERACTIONS

7.1 Effect of Raltegravir on the Pharmacokinetics of Other Agents

Raltegravir does not inhibit (IC_{50}>100 µM) CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A *in vitro*. Moreover, *in vitro*, raltegravir did not induce CYP1A2, CYP2B6 or CYP3A4. A midazolam drug interaction study confirmed the low propensity of raltegravir to alter the pharmacokinetics of agents metabolized by CYP3A4 *in vivo* by demonstrating a lack of effect of raltegravir on the pharmacokinetics of midazolam, a sensitive CYP3A4 substrate. Similarly, raltegravir is not an inhibitor (IC_{50}>50 µM) of the UDP-glucuronosyltransferases (UGT) tested (UGT1A1, UGT2B7), and raltegravir does not inhibit P-glycoprotein-mediated transport. Based on these data, ISENTRESS is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or P-glycoprotein (e.g., protease inhibitors, NNRTIs, opioid analgesics, statins, azole antifungals, proton pump inhibitors and anti-erectile dysfunction agents).

In drug interaction studies, raltegravir did not have a clinically meaningful effect on the pharmacokinetics of the following: hormonal contraceptives, methadone, lamivudine, tenofovir, etravirine.

7.2 Effect of Other Agents on the Pharmacokinetics of Raltegravir

Raltegravir is not a substrate of cytochrome P450 (CYP) enzymes. Based on *in vivo* and *in vitro* studies, raltegravir is eliminated mainly by metabolism via a UGT1A1-mediated glucuronidation pathway.

Rifampin, a strong inducer of UGT1A1, reduces plasma concentrations of ISENTRESS. Therefore, the dose of ISENTRESS should be increased during coadministration with rifampin *[see Dosage and Administration (2)].* The impact of other inducers of drug metabolizing enzymes, such as phenytoin and phenobarbital, on UGT1A1 is unknown.

Coadministration of ISENTRESS with drugs that inhibit UGT1A1 may increase plasma levels of raltegravir.

Selected drug interactions are presented in Table 6 *[see Clinical Pharmacology (12.3)]*.

Table 6: Selected Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration of Raltegravir	Clinical Comment
HIV-1-Antiviral Agents		
atazanavir	↑	Atazanavir, a strong inhibitor of UGT1A1, increases plasma concentrations of raltegravir. However, since concomitant use of ISENTRESS with atazanavir/ritonavir did not result in a unique safety signal in Phase 3 studies, no dose adjustment is recommended.
atazanavir/ritonavir	↑	Atazanavir/ritonavir increases plasma

		concentrations of raltegravir. However, since concomitant use of ISENTRESS with atazanavir/ritonavir did not result in a unique safety signal in Phase 3 studies, no dose adjustment is recommended.
efavirenz	↓	Efavirenz reduces plasma concentrations of raltegravir. The clinical significance of this interaction has not been directly assessed.
etravirine	↓	Etravirine reduces plasma concentrations of raltegravir. The clinical significance of this interaction has not been directly assessed.
tipranavir/ritonavir	↓	Tipranavir/ritonavir reduces plasma concentrations of raltegravir. However, since comparable efficacy was observed for this combination relative to other ISENTRESS-containing regimens in Phase 3 studies 018 and 019, no dose adjustment is recommended.
Other Agents		
omeprazole	↑	Coadministration of medicinal products that increase gastric pH (e.g., omeprazole) may increase raltegravir levels based on increased raltegravir solubility at higher pH. However, since concomitant use of ISENTRESS with proton pump inh bitors and H2 blockers did not result in a unique safety signal in Phase 3 studies, no dose adjustment is recommended.
rifampin	↓	Rifampin, a strong inducer of UGT1A1, reduces plasma concentrations of raltegravir. The recommended dosage of ISENTRESS is 800 mg twice daily during coadministration with rifampin.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

ISENTRESS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. There are no adequate and well-controlled studies in pregnant women. In addition, there have been no pharmacokinetic studies conducted in pregnant patients.

Developmental toxicity studies were performed in rabbits (at oral doses up to 1000 mg/kg/day) and rats (at oral doses up to 600 mg/kg/day). The reproductive toxicity study in rats was performed with pre-, peri-, and postnatal evaluation. The highest doses in these studies produced systemic exposures in these species approximately 3- to 4-fold the exposure at the recommended human dose. In both rabbits and rats, no treatment-related effects on embryonic/fetal survival or fetal weights were observed. In addition, no treatment-related external, visceral, or skeletal changes were observed in rabbits. However, treatment-related increases over controls in the incidence of supernumerary ribs were seen in rats at 600 mg/kg/day (exposures 3-fold the exposure at the recommended human dose).

Placenta transfer of drug was demonstrated in both rats and rabbits. At a maternal dose of 600 mg/kg/day in rats, mean drug concentrations in fetal plasma were approximately 1.5-to 2.5-fold greater than in maternal plasma at 1 hour and 24 hours postdose, respectively. Mean drug concentrations in fetal plasma were approximately 2% of the mean maternal concentration at both 1 and 24 hours postdose at a maternal dose of 1000 mg/kg/day in rabbits.

Antiretroviral Pregnancy Registry

To monitor maternal-fetal outcomes of pregnant patients exposed to ISENTRESS, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

8.3 Nursing Mothers

Breast-feeding is not recommended while taking ISENTRESS. In addition, it is recommended that HIV-1-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV-1.

It is not known whether raltegravir is secreted in human milk. However, raltegravir is secreted in the milk of lactating rats. Mean drug concentrations in milk were approximately 3-fold greater than those in maternal plasma at a maternal dose of 600 mg/kg/day in rats. There were no effects in rat offspring attributable to exposure of ISENTRESS through the milk.

8.4 Pediatric Use

Safety and effectiveness of ISENTRESS in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of ISENTRESS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Use in Patients with Hepatic Impairment

No clinically important pharmacokinetic differences between subjects with moderate hepatic impairment and healthy subjects were observed. No dosage adjustment is necessary for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of raltegravir has not been studied *[see Clinical Pharmacology (12.3)].*

8.7 Use in Patients with Renal Impairment

No clinically important pharmacokinetic differences between subjects with severe renal impairment and healthy subjects were observed. No dosage adjustment is necessary *[see Clinical Pharmacology (12.3)].*

10 OVERDOSAGE

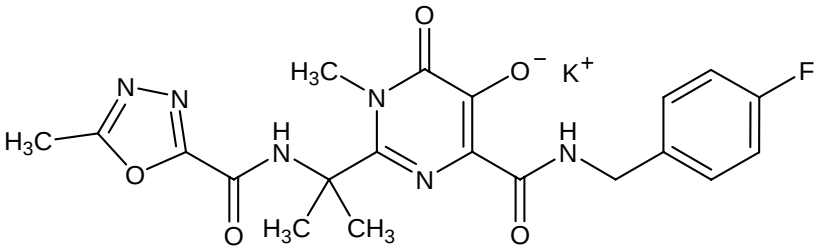
No specific information is available on the treatment of overdosage with ISENTRESS. Doses as high as 1600-mg single dose and 800-mg twice-daily multiple doses were studied in healthy volunteers without evidence of toxicity. Occasional doses of up to 1800 mg per day were taken in the clinical studies of HIV-1 infected subjects without evidence of toxicity.

In the event of an overdose, it is reasonable to employ the standard supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required. The extent to which ISENTRESS may be dialyzable is unknown.

11 DESCRIPTION

ISENTRESS contains raltegravir potassium, a human immunodeficiency virus integrase strand transfer inhibitor. The chemical name for raltegravir potassium is *N*-[(4-Fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-1-methyl-2-[1-methyl-1-[[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino]ethyl]-6-oxo-4-pyrimidinecarboxamide monopotassium salt.

The empirical formula is $C_{20}H_{20}FKN_6O_5$ and the molecular weight is 482.51. The structural formula is:



Raltegravir potassium is a white to off-white powder. It is soluble in water, slightly soluble in methanol, very slightly soluble in ethanol and acetonitrile and insoluble in isopropanol.

Each film-coated tablet of ISENTRESS for oral administration contains 434.4 mg of raltegravir potassium (as salt), equivalent to 400 mg of raltegravir (free phenol) and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, calcium phosphate dibasic anhydrous, hypromellose 2208, poloxamer 407 (contains 0.01% butylated hydroxytoluene as antioxidant), sodium stearyl fumarate, magnesium stearate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc, red iron oxide and black iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Raltegravir is an HIV-1 antiviral drug *[see Clinical Pharmacology (12.4)]*.

12.2 Pharmacodynamics

In a monotherapy study raltegravir (400 mg twice daily) demonstrated rapid antiviral activity with mean viral load reduction of 1.66 $\log_{10}$ copies/mL by Day 10.

In the randomized, double-blind, placebo-controlled, dose-ranging trial, Protocol 005, and Protocols 018 and 019, antiviral responses were similar among subjects regardless of dose.

Effects on Electrocardiogram

In a randomized, placebo-controlled, crossover study, 31 healthy subjects were administered a single oral supratherapeutic dose of raltegravir 1600 mg and placebo. Peak raltegravir plasma concentrations were approximately 4-fold higher than the peak concentrations following a 400 mg dose. ISENTRESS did not appear to prolong the QTc interval for 12 hours postdose. After baseline and placebo adjustment, the maximum mean QTc change was -0.4 msec (1-sided 95% upper CI: 3.1 msec).

12.3 Pharmacokinetics

Absorption

Raltegravir is absorbed with a T_{max} of approximately 3 hours postdose in the fasted state. Raltegravir AUC and C_{max} increase dose proportionally over the dose range 100 mg to 1600 mg. Raltegravir C_{12hr} increases dose proportionally over the dose range of 100 to 800 mg and increases slightly less than dose proportionally over the dose range 100 mg to 1600 mg. With twice-daily dosing, pharmacokinetic steady state is achieved within approximately the first 2 days of dosing. There is little to no accumulation in AUC and C_{max}. The average accumulation ratio for C_{12hr} ranged from approximately 1.2 to 1.6.

The absolute bioavailability of raltegravir has not been established.

In subjects who received 400 mg twice daily alone, raltegravir drug exposures were characterized by a geometric mean $AUC_{0\text{-}12hr}$ of 14.3 μM●hr and C_{12hr} of 142 nM.

Considerable variability was observed in the pharmacokinetics of raltegravir. For observed C_{12hr} in Protocols 018 and 019, the coefficient of variation (CV) for inter-subject variability = 212% and the CV for intra-subject variability = 122%.

Effect of Food on Oral Absorption

ISENTRESS may be administered with or without food. Raltegravir was administered without regard to food in the pivotal safety and efficacy studies in HIV-1-infected patients. The effect of consumption of low-, moderate- and high-fat meals on steady-state raltegravir pharmacokinetics was assessed in healthy volunteers. Administration of multiple doses of raltegravir following a moderate-fat meal (600 Kcal, 21 g fat) did not affect raltegravir AUC to a clinically meaningful degree with an increase of 13% relative to fasting. Raltegravir C_{12hr} was 66% higher and C_{max} was 5% higher following a moderate-fat meal compared to fasting. Administration of raltegravir following a high-fat meal (825 Kcal, 52 g fat) increased AUC and C_{max} by approximately 2-fold and increased C_{12hr} by 4.1-fold. Administration of raltegravir following a low-fat meal (300 Kcal, 2.5 g fat) decreased AUC and C_{max} by 46% and 52%, respectively; C_{12hr} was essentially unchanged. Food appears to increase pharmacokinetic variability relative to fasting.

Distribution

Raltegravir is approximately 83% bound to human plasma protein over the concentration range of 2 to 10 μM.

Metabolism and Excretion

The apparent terminal half-life of raltegravir is approximately 9 hours, with a shorter α-phase half-life (~1 hour) accounting for much of the AUC. Following administration of an oral dose of radiolabeled raltegravir, approximately 51 and 32% of the dose was excreted in feces and urine, respectively. In feces, only raltegravir was present, most of which is likely derived from hydrolysis of raltegravir-glucuronide

secreted in bile as observed in preclinical species. Two components, namely raltegravir and raltegravir-glucuronide, were detected in urine and accounted for approximately 9 and 23% of the dose, respectively. The major circulating entity was raltegravir and represented approximately 70% of the total radioactivity; the remaining radioactivity in plasma was accounted for by raltegravir-glucuronide. Studies using isoform-selective chemical inhibitors and cDNA-expressed UDP-glucuronosyltransferases (UGT) show that UGT1A1 is the main enzyme responsible for the formation of raltegravir-glucuronide. Thus, the data indicate that the major mechanism of clearance of raltegravir in humans is UGT1A1-mediated glucuronidation.

Special Populations

Pediatric

The pharmacokinetics of raltegravir in pediatric patients has not been established.

Age

The effect of age on the pharmacokinetics of raltegravir was evaluated in the composite analysis. No dosage adjustment is necessary.

Race

The effect of race on the pharmacokinetics of raltegravir was evaluated in the composite analysis. No dosage adjustment is necessary.

Gender

A study of the pharmacokinetics of raltegravir was performed in healthy adult males and females. Additionally, the effect of gender was evaluated in a composite analysis of pharmacokinetic data from 103 healthy subjects and 28 HIV-1 infected subjects receiving raltegravir monotherapy with fasted administration. No dosage adjustment is necessary.

Hepatic Impairment

Raltegravir is eliminated primarily by glucuronidation in the liver. A study of the pharmacokinetics of raltegravir was performed in subjects with moderate hepatic impairment. Additionally, hepatic impairment was evaluated in the composite pharmacokinetic analysis. There were no clinically important pharmacokinetic differences between subjects with moderate hepatic impairment and healthy subjects. No dosage adjustment is necessary for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of raltegravir has not been studied.

Renal Impairment

Renal clearance of unchanged drug is a minor pathway of elimination. A study of the pharmacokinetics of raltegravir was performed in subjects with severe renal impairment. Additionally, renal impairment was evaluated in the composite pharmacokinetic analysis. There were no clinically important pharmacokinetic differences between subjects with severe renal impairment and healthy subjects. No dosage adjustment is necessary. Because the extent to which ISENTRESS may be dialyzable is unknown, dosing before a dialysis session should be avoided.

UGT1A1 Polymorphism

There is no evidence that common UGT1A1 polymorphisms alter raltegravir pharmacokinetics to a clinically meaningful extent. In a comparison of 30 subjects with *28/*28 genotype (associated with reduced activity of UGT1A1) to 27 subjects with wild-type genotype, the geometric mean ratio (90% CI) of AUC was 1.41 (0.96, 2.09).

Drug Interactions *[see Drug Interactions (7)]*

Table 7: Effect of Other Agents on the Pharmacokinetics of Raltegravir

Coadministered Drug	Coadministered Drug Dose/Schedule	Raltegravir Dose/Schedule	Ratio (90% Confidence Interval) of Raltegravir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00			
			n	C_{max}	AUC	C_{min}
atazanavir	400 mg daily	100 mg single dose	10	1.53 (1.11, 2.12)	1.72 (1.47, 2.02)	1.95 (1.30, 2.92)
atazanavir/ritonavir	300 mg/100 mg daily	400 mg twice daily	10	1.24 (0.87, 1.77)	1.41 (1.12, 1.78)	1.77 (1.39, 2.25)
efavirenz	600 mg daily	400 mg single dose	9	0.64 (0.41,	0.64 (0.52,	0.79 (0.49,

Coadministered Drug	Coadministered Drug Dose/Schedule	Raltegravir Dose/Schedule	Ratio (90% Confidence Interval) of Raltegravir Pharmacokinetic Parameters with/without Coadministered Drug; No Effect = 1.00			
			n	C_{max}	AUC	C_{min}
				0.98)	0.80)	1.28)
etravirine	200 mg twice daily	400 mg twice daily	19	0.89 (0.68, 1.15)	0.90 (0.68, 1.18)	0.66 (0.34, 1.26)
omeprazole	20 mg daily	400 mg single dose	14 (10 for AUC)	4.15 (2.82, 6.10)	3.12 (2.13, 4.56)	1.46 (1.10, 1.93)
rifampin	600 mg daily	400 mg single dose	9	0.62 (0.37, 1.04)	0.60 (0.39, 0.91)	0.39 (0.30, 0.51)
rifampin	600 mg daily	400 mg twice daily when administered alone; 800 mg twice daily when administered with rifampin	14	1.62 (1.12, 2.33)	1.27 (0.94, 1.71)	0.47 (0.36, 0.61)
ritonavir	100 mg twice daily	400 mg single dose	10	0.76 (0.55, 1.04)	0.84 (0.70, 1.01)	0.99 (0.70, 1.40)
tenofovir	300 mg daily	400 mg twice daily	9	1.64 (1.16, 2.32)	1.49 (1.15, 1.94)	1.03 (0.73, 1.45)
tipranavir/ritonavir	500 mg/200 mg twice daily	400 mg twice daily	15 (14 for C_{min})	0.82 (0.46, 1.46)	0.76 (0.49, 1.19)	0.45 (0.31, 0.66)

12.4 Microbiology

Mechanism of Action

Raltegravir inhibits the catalytic activity of HIV-1 integrase, an HIV-1 encoded enzyme that is required for viral replication. Inhibition of integrase prevents the covalent insertion, or integration, of unintegrated linear HIV-1 DNA into the host cell genome preventing the formation of the HIV-1 provirus. The provirus is required to direct the production of progeny virus, so inhibiting integration prevents propagation of the viral infection. Raltegravir did not significantly inhibit human phosphoryltransferases including DNA polymerases α, β, and γ.

Antiviral Activity in Cell Culture

Raltegravir at concentrations of 31 ± 20 nM resulted in 95% inhibition (EC_{95}) of viral spread (relative to an untreated virus-infected culture) in human T-lymphoid cell cultures infected with the cell-line adapted HIV-1 variant H9IIIB. In addition, 5 clinical isolates of HIV-1 subtype B had EC_{95} values ranging from 9 to 19 nM in cultures of mitogen-activated human peripheral blood mononuclear cells. In a single-cycle infection assay, raltegravir inhibited infection of 23 HIV-1 isolates representing 5 non-B subtypes (A, C, D, F, and G) and 5 circulating recombinant forms (AE, AG, BF, BG, and cpx) with EC_{50} values ranging from 5 to 12 nM. Raltegravir also inhibited replication of an HIV-2 isolate when tested in CEMx174 cells (EC_{95} value = 6 nM). Additive to synergistic antiretroviral activity was observed when human T-lymphoid cells infected with the H9IIIB variant of HIV-1 were incubated with raltegravir in combination with non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, or nevirapine); nucleoside analog reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, tenofovir, zalcitabine, or zidovudine); protease inhibitors (amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, or saquinavir); or the entry inhibitor enfuvirtide.

Resistance

The mutations observed in the HIV-1 integrase coding sequence that contributed to raltegravir resistance (evolved either in cell culture or in subjects treated with raltegravir) generally included an amino acid substitution at either Q148 (changed to H, K, or R) or N155 (changed to H) plus one or more additional substitutions (i.e., L74M, E92Q, T97A, E138A/K, G140A/S, V151I, G163R, H183P, Y226C/D/F/H, S230R and D232N). Amino acid substitution at Y143C/H/R is another pathway to raltegravir resistance.

Treatment-Naïve Subjects: By Week 48 in the STARTMRK trial, the primary raltegravir resistance-associated substitutions were observed in 3 (1 with Y143R and 2 with Q148H/R) of the 6 virologic failure subjects with evaluable paired genotypic data.
Treatment-Experienced Subjects: By Week 48 in the BENCHMRK trials, at least one of the 3 primary raltegravir resistance-associated substitutions, Y143C/H/R, Q148H/K/R, and N155H, was observed in 63 (64.3%) of the 98 virologic failure subjects with evaluable genotypic data from paired baseline and raltegravir treatment-failure isolates. Some (n=18) of those HIV-1 isolates harboring one or more of the 3 primary raltegravir resistance-associated substitutions were evaluated for raltegravir susceptibility yielding a median decrease of 47.3-fold (mean 73.1 ± 60.8-fold decrease, ranging from 0.9- to 200-fold) compared to baseline isolates.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies of raltegravir in mice did not show any carcinogenic potential. At the highest dose levels, 400 mg/kg/day in females and 250 mg/kg/day in males, systemic exposure was 1.8-fold (females) or 1.2-fold (males) greater than the AUC (54 µM●hr) at the 400-mg twice daily human dose. Treatment-related squamous cell carcinoma of nose/nasopharynx was observed in female rats dosed with 600 mg/kg/day raltegravir for 104 weeks. These tumors were possibly the result of local irritation and inflammation due to local deposition and/or aspiration of drug in the mucosa of the nose/nasopharynx during dosing. No tumors of the nose/nasopharynx were observed in rats dosed with 150 mg/kg/day (males) and 50 mg/kg/day (females) and the systemic exposure in rats was 1.7-fold (males) to 1.4-fold (females) greater than the AUC (54 µM●hr) at the 400-mg twice daily human dose.

No evidence of mutagenicity or genotoxicity was observed in *in vitro* microbial mutagenesis (Ames) tests, *in vitro* alkaline elution assays for DNA breakage, and *in vitro* and *in vivo* chromosomal aberration studies.

No effect on fertility was seen in male and female rats at doses up to 600 mg/kg/day which resulted in a 3-fold exposure above the exposure at the recommended human dose.

14 CLINICAL STUDIES

Description of Clinical Studies

The evidence of durable efficacy of ISENTRESS is based on the analyses of 48-week data from an ongoing, randomized, double-blind, active-control trial, STARTMRK (Protocol 021) in antiretroviral treatment-naive HIV-1 infected adult subjects and from 2 ongoing, randomized, double-blind, placebo-controlled studies, BENCHMRK 1 and BENCHMRK 2 (Protocols 018 and 019), in antiretroviral treatment-experienced HIV-1 infected adult subjects. These efficacy results were supported by the 96-week analysis of a randomized, double-blind, controlled, dose-ranging trial, Protocol 004, in antiretroviral treatment-naïve HIV-1 infected adult subjects and by the 48-week analysis of a randomized, double-blind, controlled, dose-ranging study, Protocol 005, in antiretroviral treatment-experienced HIV-1 infected adult subjects.

Treatment-Naïve Subjects

STARTMRK (Protocol 021) is a Phase 3 study to evaluate the safety and antiretroviral activity of ISENTRESS 400 mg twice daily + emtricitabine (+) tenofovir versus efavirenz 600 mg at bedtime plus emtricitabine (+) tenofovir in treatment-naïve HIV-1-infected subjects with HIV-1 RNA >5000 copies/mL. Randomization was stratified by screening HIV-1 RNA level (≤50,000 copies/mL; and >50,000 copies/mL) and by hepatitis status.

Table 8 shows the demographic characteristics of subjects in the group receiving ISENTRESS 400 mg twice daily and subjects in the comparator group.

Table 8: Baseline Characteristics

Randomized Study Protocol 021	**ISENTRESS 400 mg Twice Daily (N = 281)**	**Efavirenz 600 mg At Bedtime (N = 282)**
Gender		
Male	81%	82%

Female	19%	18%
Race		
White	41%	44%
Black	12%	8%
Asian	13%	11%
Hispanic	21%	24%
Native American	0%	0%
Multiracial	12%	13%
Region		
Latin America	35%	34%
Southeast Asia	12%	10%
North America	29%	32%
EU/Australia	23%	23%
Age (years)		
18-64	99%	99%
≥65	1%	1%
Mean (SD)	38 (9)	37 (10)
Median (min, max)	37 (19 to 67)	36 (19 to 71)
CD4 Cell Count (cells/microL)		
Mean (SD)	219 (124)	217 (134)
Median (min, max)	212 (1 to 620)	204 (4 to 807)
Plasma HIV-1 RNA (log_{10} copies/mL)		
Mean (SD)	5 (1)	5 (1)
Median (min, max)	5 (3 to 6)	5 (4 to 6)
Plasma HIV-1 RNA (copies/mL)		
Geometric Mean	103205	106215
Median (min, max)	114000 (400 to 750000)	104000 (4410 to 750000)
History of AIDS[†]		
Yes	18%	21%
Viral Subtype		
Clade B	78%	82%
Non-Clade B[‡]	21%	17%
Baseline Plasma HIV-1 RNA		
≤100,000 copies/mL	45%	49%
>100,000 copies/mL	55%	51%
Baseline CD4 Cell Counts		
≤50 cells/mm^3	10%	11%
>50 cells/mm^3 and ≤ 200 cells/mm^3	37%	37%
>200 cells/mm^3	53%	51%
Hepatitis Status		
Hepatitis B or C Positive[§]	6%	6%

[†]Includes additional subjects identified as having a history of AIDS.

[‡]Non-Clade B Subtypes (# of subjects): Clade A (4), A/C (1), A/G (2), A1 (1), AE (29), AG (12), BF (6), C (37), D (2), F (2), F1 (5), G (2), Complex (3).

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

Notes:

ISENTRESS and Efavirenz were administered with emtricitabine (+) tenofovir

N = Number of subjects in each group.

Week 48 outcomes from Protocol 021 are shown in Table 9.

Table 9: Outcomes by Treatment Group through Week 48

Randomized Study Protocol 021	ISENTRESS 400 mg Twice Daily (N = 281)	Efavirenz 600 mg At Bedtime (N = 282)	Difference (ISENTRESS – Efavirenz) (CI[§])
Outcome at Week 48			
Subjects with HIV-1 RNA less than 50 copies/mL	87%	82%	4.7% (-1.3%, 10.6%)
Subjects with HIV-1 RNA less than 400 copies/mL	91%	88%	3.6% (-1.5%, 8.7%)
Mean CD4 cell count change from baseline (cells/mm^3)	176	150	25.8 (5.0, 46.5)
Virologic Failure (>50 copies/mL)	6%	7%	
Never suppressed through Week 48 and on study at Week 48	2%	3%	
Rebound	5%	5%	
Discontinued study drug	7%	10%	
Reasons for Discontinuation			
Death	<1%	0%	
Adverse experiences	2%	5%	
Other*	4%	5%	

[§]The 95% CI for treatment difference is adjusted by the screening HIV RNA level (<=50,000 copies/mL vs. >50,000 copies/mL) and Hepatitis B or C (negative vs. positive)
*Other includes lack of efficacy, loss to follow-up, consent withdrawn, protocol violation and other

Treatment-Experienced Subjects

BENCHMRK 1 and BENCHMRK 2 are Phase 3 studies to evaluate the safety and antiretroviral activity of ISENTRESS 400 mg twice daily in combination with an optimized background therapy (OBT), versus OBT alone, in HIV-1-infected subjects, 16 years or older, with documented resistance to at least 1 drug in each of 3 classes (NNRTIs, NRTIs, PIs) of antiretroviral therapies. Randomization was stratified by degree of resistance to PI (1PI vs. >1PI) and the use of enfuvirtide in the OBT. Prior to randomization, OBT was selected by the investigator based on genotypic/phenotypic resistance testing and prior ART history.

Table 10 shows the demographic characteristics of subjects in the group receiving ISENTRESS 400 mg twice daily and subjects in the placebo group.

Table 10: Baseline Characteristics

Randomized Studies Protocol 018 and 019	ISENTRESS 400 mg Twice Daily + OBT (N = 462)	Placebo + OBT (N = 237)
Gender		
Male	88%	89%
Female	12%	11%
Race		
White	65%	73%
Black	14%	11%
Asian	3%	3%
Hispanic	11%	8%
Others	6%	5%
Age (years)		
Median (min, max)	45 (16 to 74)	45 (17 to 70)
CD4+ Cell Count		
Median (min, max), cells/mm^3	119 (1 to 792)	123 (0 to 759)
≤50 cells/mm^3	32%	33%
>50 and ≤200 cells/mm^3	37%	36%
Plasma HIV-1 RNA		
Median (min, max), $\log_{10}$ copies/mL	4.8 (2 to 6)	4.7 (2 to 6)

>100,000 copies/mL	35%	33%
History of AIDS		
Yes	92%	91%
Prior Use of ART, Median (1st Quartile, 3rd Quartile)		
Years of ART Use	10 (7 to 12)	10 (8 to 12)
Number of ART	12 (9 to 15)	12 (9 to 14)
Hepatitis Co-infection*		
No Hepatitis B or C virus	83%	85%
Hepatitis B virus only	8%	3%
Hepatitis C virus only	8%	11%
Co-infection of Hepatitis B and C virus	1%	1%
Stratum		
Enfuvirtide in OBT	38%	38%
Resistant to ≥2 PI	97%	95%

*Hepatitis B virus surface antigen positive or hepatitis C virus ant body positive.

Table 11 compares the characteristics of optimized background therapy at baseline in the group receiving ISENTRESS 400 mg twice daily and subjects in the control group.

Table 11: Characteristics of Optimized Background Therapy at Baseline

Randomized Studies Protocol 018 and 019	ISENTRESS 400 mg Twice Daily + OBT (N = 462)	Placebo + OBT (N = 237)
Number of ARTs in OBT		
Median (min, max)	4 (1 to 7)	4 (2 to 7)
Number of Active PI in OBT by Phenotypic Resistance Test*		
0	36%	41%
1 or more	60%	58%
Phenotypic Sensitivity Score (PSS)†		
0	15%	19%
1	31%	30%
2	31%	28%
3 or more	18%	20%
Genotypic Sensitivity Score (GSS)†		
0	25%	28%
1	39%	41%
2	24%	21%
3 or more	11%	10%

*****Darunavir use in OBT in darunavir naïve subjects was counted as one active PI.

†The Phenotypic Sensitivity Score (PSS) and the Genotypic Sensitivity Score (GSS) were defined as the total oral ARTs in OBT to which a subject's viral isolate showed phenotypic sensitivity and genotypic sensitivity, respectively, based upon phenotypic and genotypic resistance tests. Enfuvirtide use in OBT in enfuvirtide-naïve subjects was counted as one active drug in OBT in the GSS and PSS. Similarly, darunavir use in OBT in darunavir-naïve subjects was counted as one active drug in OBT.

Week 48 outcomes for the 699 subjects randomized and treated with the recommended dose of ISENTRESS 400 mg twice daily or placebo in the pooled BENCHMRK 1 and 2 studies are shown in Table 12.

Table 12: Outcomes by Treatment Group through Week 48

Randomized Studies Protocol 018 and 019	ISENTRESS 400 mg Twice Daily + OBT (N = 462)	Placebo + OBT (N = 237)
Outcome at Week 48		

Subjects with HIV-1 RNA less than 400 copies/mL	72%	37%
Subjects with HIV-1 RNA less than 50 copies/mL	60%	31%
Mean CD4 cell count change from baseline (cells/mm^3)	106	44
Virologic Failure (>50 copies/mL)	36%	65%
Never suppressed through Week 48 and on study at Week 48	11%	9%
Rebound	13%	8%
Non-responder by Week 48‡	12%	48%
Discontinued study drug	4%	4%
Reasons for Discontinuation		
Death	2%	2%
Adverse Experiences	<1%	<1%
Other*	2%	1%

‡The non-responders by Week 48 were defined by the protocol as those who did not achieve > 1.0 log_{10} HIV-1 RNA reduction and <400 HIV-1 RNA copies/mL starting at Week 16 or beyond.
*Other includes lack of efficacy, loss to follow-up, consent withdrawn

The mean changes in plasma HIV-1 RNA from baseline were -2.11 log_{10} copies/mL in the group receiving ISENTRESS 400 mg twice daily and -0.96 log_{10} copies/mL for the control group.

Treatment-emergent CDC Category C events occurred in 4% of the group receiving ISENTRESS 400 mg twice daily and 5% of the control group.

Virologic responses at Week 48 by baseline genotypic and phenotypic sensitivity score are shown in Table 13.

Table 13: Virologic Response at Week 48 by Baseline Genotypic/Phenotypic Sensitivity Score

Randomized Studies Protocol 018 and 019	Percent with HIV-1 RNA <400 copies/mL at Week 48				Percent with HIV-1 RNA <50 copies/mL at Week 48			
	n	ISENTRESS 400 mg Twice Daily + OBT (N = 462)	n	Placebo + OBT (N = 237)	n	ISENTRESS 400 mg Twice Daily + OBT (N = 462)	n	Placebo + OBT (N = 237)
Phenotypic Sensitivity Score (PSS)•								
0	69	52	44	5	69	46	44	2
1	145	72	72	32	145	57	72	28
2	142	83	66	42	142	68	66	38
3 or more	85	72	48	60	85	67	48	46
Genotypic Sensitivity Score (GSS)•								
0	115	50	66	8	115	43	66	3
1	178	79	96	38	178	63	96	35
2	111	85	49	65	111	70	49	53
3 or more	51	69	23	52	51	67	23	39

•The Phenotypic Sensitivity Score (PSS) and the Genotypic Sensitivity Score (GSS) were defined as the total oral ARTs in OBT to which a subject's viral isolate showed phenotypic sensitivity and genotypic sensitivity, respectively, based upon phenotypic and genotypic resistance tests. Enfuvirtide use in OBT in enfuvirtide-naïve subjects was counted as one active drug in OBT in the GSS and PSS. Similarly, darunavir use in OBT in darunavir-naïve subjects was counted as one active drug in OBT.

16 HOW SUPPLIED/STORAGE AND HANDLING

ISENTRESS tablets 400 mg are pink, oval-shaped, film-coated tablets with “227” on one side. They are supplied as follows:

NDC 0006-0227-61 unit-of-use bottles of 60.

No. 3894

Storage and Handling

Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F). See USP Controlled Room Temperature.

17 PATIENT COUNSELING INFORMATION

[See FDA-Approved Patient Labeling.]

Patients should be informed that ISENTRESS is not a cure for HIV infection or AIDS. They should also be told that people taking ISENTRESS may still get infections or other conditions common in people with HIV (opportunistic infections). Patients should also be told that it is very important that they stay under a physician's care during treatment with ISENTRESS.

Patients should be informed that ISENTRESS does not reduce the chance of passing HIV to others through sexual contact, sharing needles, or being exposed to blood. Patients should be advised to continue to practice safer sex and to use latex or polyurethane condoms or other barrier methods to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions or blood. Patients should also be advised to never re-use or share needles.

Physicians should instruct their patients that if they miss a dose, they should take it as soon as they remember. If they do not remember until it is time for the next dose, they should be instructed to skip the missed dose and go back to the regular schedule. Patients should not take two tablets of ISENTRESS at the same time.

Physicians should instruct their patients to read the Patient Package Insert before starting ISENTRESS therapy and to reread each time the prescription is renewed. Patients should be instructed to inform their physician or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens.

Manufactured and Distributed by:
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Printed in USA

~~9795103~~

U.S. Patent Nos. US 7,169,780

Patient Information
ISENTRESS® (eye **sen** tris**)**
(raltegravir)
Tablets

Read the patient information that comes with ISENTRESS[1] before you start taking it and each time you get a refill. There may be new information. This leaflet is a summary of the information for patients. Your doctor or pharmacist can give you additional information. This leaflet does not take the place of talking with your doctor about your medical condition or your treatment.

What is ISENTRESS?

- ISENTRESS is an anti-HIV (antiretroviral) medicine used for the treatment of HIV. The term HIV stands for Human Immunodeficiency Virus. It is the virus that causes AIDS (Acquired Immune Deficiency Syndrome). ISENTRESS is used along with other anti-HIV medicines. ISENTRESS will NOT cure HIV infection.
- People taking ISENTRESS may still develop infections, including opportunistic infections or other conditions that happen with HIV infection.
- Stay under the care of your doctor during treatment with ISENTRESS.
- The safety and effectiveness of ISENTRESS in children has not been studied.

ISENTRESS must be used with other anti-HIV medicines.

How does ISENTRESS work?

- ISENTRESS blocks an enzyme which the virus (HIV) needs in order to make more virus. The enzyme that ISENTRESS blocks is called HIV integrase.
- When used with other anti-HIV medicines, ISENTRESS may do two things:
  1. Reduce the amount of HIV in your blood. This is called your "viral load".
  2. Increase the number of white blood cells called CD4 (T) cells.

- ISENTRESS may not have these effects in all patients.

Does ISENTRESS lower the chance of passing HIV to other people?

No. ISENTRESS does not reduce the chance of passing HIV to others through sexual contact, sharing needles, or being exposed to your blood.

- Continue to practice safer sex.
- Use latex or polyurethane condoms or other barrier methods to lower the chance of sexual contact with any body fluids. This includes semen from a man, vaginal secretions from a woman, or blood.
- Never re-use or share needles.

Ask your doctor if you have any questions about safer sex or how to prevent passing HIV to other people.

What should I tell my doctor before and during treatment with ISENTRESS?

Tell your doctor about all of your medical conditions. Include any of the following that applies to you:

- You have any allergies.
- You are pregnant or plan to become pregnant.

[1] Registered trademark of MERCK & CO., Inc.

- ISENTRESS is not recommended for use during pregnancy. ISENTRESS has not been studied in pregnant women. If you take ISENTRESS while you are pregnant, talk to your doctor about how you can be included in the Antiretroviral Pregnancy Registry.

- You are breast-feeding or plan to breast-feed.
  - It is recommended that HIV-infected women should not breast-feed their infants. This is because their babies could be infected with HIV through their breast milk.
  - Talk with your doctor about the best way to feed your baby.

Tell your doctor about all the medicines you take. Include the following:

- prescription medicines, including rifampin (a medicine used to treat some infections such as tuberculosis)
- non-prescription medicines
- vitamins
- herbal supplements

Know the medicines you take.

- Keep a list of your medicines. Show the list to your doctor and pharmacist when you get a new medicine.

How should I take ISENTRESS?

Take ISENTRESS <u>exactly</u> as your doctor has prescribed. The recommended dose is as follows:

- Take only one 400-mg tablet at a time.
- Take it twice a day.
- Take it by mouth.
- Take it with or without food.

Do not change your dose or stop taking ISENTRESS or your other anti-HIV medicines without first talking with your doctor.

IMPORTANT: Take ISENTRESS exactly as your doctor prescribed and at the right times of day because if you don't:

- The amount of virus (HIV) in your blood may increase if the medicine is stopped for even a short period of time.
- The virus may develop resistance to ISENTRESS and become harder to treat.
- Your medicines may stop working to fight HIV.
- The activity of ISENTRESS may be reduced (due to resistance).

If you fail to take ISENTRESS the way you should, here's what to do:

- If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule. Do NOT take two tablets of ISENTRESS at the same time. In other words, do NOT take a double dose.
- If you take too much ISENTRESS, call your doctor or local Poison Control Center.

Be sure to keep a supply of your anti-HIV medicines.

- When your ISENTRESS supply starts to run low, get more from your doctor or pharmacy.
- Do not wait until your medicine runs out to get more.

What are the possible side effects of ISENTRESS?

When ISENTRESS has been given with other anti-HIV drugs, the most common side effects included:

- nausea
- headache
- tiredness
- weakness
- trouble sleeping

Other side effects include rash, severe skin reactions, feeling anxious, depression, suicidal thoughts and actions, paranoia.

A condition called Immune Reconstitution Syndrome can happen in some patients with advanced HIV infection (AIDS) when combination antiretroviral treatment is started. Signs and symptoms of inflammation from opportunistic infections that a person has or had may occur as the medicines work to treat the HIV infection and help to strengthen the immune system. Call your doctor right away if you notice any signs or symptoms of an infection after starting ISENTRESS with other anti-HIV medicines.

Contact your doctor promptly if you experience unexplained muscle pain, tenderness, or weakness while taking ISENTRESS. This is because on rare occasions, muscle problems can be serious and can lead to kidney damage.

Tell your doctor if you have any side effects that bother you.

These are not all the side effects of ISENTRESS. For more information, ask your doctor or pharmacist.

How should I store ISENTRESS?

- Store ISENTRESS at room temperature (68 to 77°F).
- **Keep ISENTRESS and all medicines out of the reach of children.**

General information about the use of ISENTRESS

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets.

- Do not use ISENTRESS for a condition for which it was not prescribed.
- Do not give ISENTRESS to other people, even if they have the same symptoms you have. It may harm them.

This leaflet gives you the most important information about ISENTRESS.

- If you would like to know more, talk with your doctor.
- You can ask your doctor or pharmacist for additional information about ISENTRESS that is written for health professionals.
- For more information go to www.ISENTRESS.com or call 1-800-622-4477.

What are the ingredients in ISENTRESS?
Active ingredient: Each film-coated tablet contains 400 mg of raltegravir.

Inactive ingredients: Microcrystalline cellulose, lactose monohydrate, calcium phosphate dibasic anhydrous, hypromellose 2208, poloxamer 407 (contains 0.01% butylated hydroxytoluene as antioxidant), sodium stearyl fumarate, magnesium stearate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc, red iron oxide and black iron oxide.

Manufactured and Distributed by:

MERCK & CO., Inc.
Whitehouse Station, NJ 08889, USA

Revised July 2009

~~9795103~~

U.S. Patent Nos. US 7,169,780

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22 – 145/S004

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: 22-145/S-004

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

Birnkrant, Debra B.
Boucher, Robert
Connelly, Sarah
De, Swapan
El Hage, Antoine M.
Ghantous, Hanan
Himaya, Amalia
Moukhtara, Aline
O'Rear, Julian
Reynolds, Kellie S.
Rhee, Sung
Robertson, Sarah
Soon, Guoxing
Struble, Kimberly
Truffa, Melissa M.
Yuen, Ita S.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22 – 145/S004

CROSS DISCIPLINE TEAM LEADER REVIEW

CROSS DISCIPLINE TEAM LEADER REVIEW

Date	June 22, 2009
From	Kimberly Struble, PharmD
	Cross Discipline Team Leader Review
NDA/BLA # **Supplement#**	22-145 SE5 004
Applicant	Merck
Date of Submission	September 25, 2008
PDUFA Goal Date	July 24, 2009
Proprietary Name / Established (USAN) names	Isentress (raltegravir)
Dosage forms / Strength	400 mg tablet
Proposed Indication(s)	Treatment of HIV-1 infection, treatment-naïve HIV-1 infected adults
Recommended:	Approval

1. Introduction

This cross discipline team leader memorandum summarizes the main issues for NDA 22-145 (SE5 004), Merck's supplemental New Drug Application (sNDA) to support safety and efficacy for the treatment of HIV-1 infection in treatment-naïve adults. This review highlights the efficacy, safety, and virology findings.

2. Background

Isentress (raltegravir) was granted Accelerated Approval and Traditional approval on October 12, 2007, and January 29, 2009, respectively and represents the first in a new class of antiretroviral agents designed to inhibit the catalytic activity of HIV-1 integrase, an enzyme required for viral replication. The accelerated and traditional approvals were based on efficacy and safety results from two identically designed Phase 3 clinical trials (018 and 019) and one Phase 2 dose finding trial (005) in treatment-experienced patients. Statistically significant higher rates of proportion of patients with HIV-1 RNA < 400 and < 50 copies/mL were observed in patients receiving raltegravir + optimized background therapy (OBT) compared to OBT alone. Currently raltegravir is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents. The purpose of this sNDA is to expand the indication to all HIV-1 infected adults requiring therapy. The proposed indication is "raltegravir is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection." Safety and efficacy data through Week 48 were provided to support dosing in antiretroviral-naïve adults. Raltegravir given 400 mg twice daily was compared to efavirenz each in combination with emtricitabine and tenofovir. Efavirenz is a preferred agent by the DHHS treatment guidelines for antiretroviral naïve patients and represents a valid comparator. This review primarily focuses on the trial 021. The Phase 2 dosing finding trial 004 was provided as cross-reference. The datasets were provided in the traditional approval sNDA application; therefore, the data were not re-reviewed during this review cycle. Dr. Connelly's review provides safety data from this study as appropriate. The Week 96 data from this phase 2 trial were not included in labeling because few patients received the marketed raltegravir dose (approximately 40 patients) and the data does not provide additional information to what is reported from the Phase 3 trial (021).

Results from trial 021 show the safety profile in treatment-naïve patients are similar to the established safety profile in treatment-experienced patients. Additionally, raltegravir is non-inferior to the DHHS preferred treatment regimen of efavirenz, tenofovir and emtricitabine in treatment-naïve patients. Based on the favorable risk-benefit profile approval for raltegravir use in treatment-naïve patients is

recommended along with a change to broaden the indication for the treatment of HIV-1 infection without restriction to a specific adult population.

3. CMC/Device

The drug product used in the clinical trials submitted in the sNDA is identical to the product approved. No new CMC data were submitted in the sNDA.

4. Nonclinical Pharmacology/Toxicology

Not applicable. No new information submitted.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology data were submitted with the sNDA. Responses to two postmarketing commitments were submitted during the sNDA review period and reviewed separately. Results from these studies were included with the labeling changes during this sNDA review. Additionally, results from a methadone drug-drug interaction trial were reviewed and included in labeling. Please refer to section 12 for details and refer to the clinical pharmacology review by Dr. Sarah Robertson. The following postmarketing commitments were fulfilled:

- Commitment 13: Conduct an *in vitro* study (e.g. in human hepatocytes) to evaluate the relative UGT1A1 induction potency of phenytoin, phenobarbital, rifabutin, and rifampin using raltegravir as a probe substrate.
- Commitment 14: Conduct an *in vitro* study (e.g. in human hepatocytes) to evaluate the potential of raltegravir to induce CYP1A2 and CYP2B6.

6. Clinical Microbiology

Please refer to Dr. Sung Rhee's review for further details. The development of primary raltegravir resistance associated substitutions in treatment-naïve patients with virologic failure was added to the label. Raltegravir resistance-associated substitutions were observed in three (one with Y143R and two with Q148H/R) of the six virologic failure patients with evaluable paired genotypic data. The observed resistance profile is similar for treatment-naïve and treatment-experienced patients. No new substitutions were observed in trial 021.

7. Clinical/Statistical- Efficacy

The Week 48 data from trial 021 demonstrate the efficacy of raltegravir in treatment-naïve patients. Based on the time to loss of virologic response algorithm (TLOVR) over 80% of patients in both treatment groups achieved and maintained HIV RNA < 50 copies/mL. The difference between raltegravir and efavirenz based regimens was 4.7% (95% confidence interval -1.3%, 10.6%). Raltegravir is non-inferior to the preferred standard of care regimen containing efavirenz because the lower bound of the 95% confidence interval falls above the protocol specified level of -12%. The non-inferiority margin of -12% is acceptable for treatment-naïve trials.

In DAVP's guidance on HIV drug development, the noninferiority margin for comparing a third drug in regimens for HIV treatment naive patients is 10-12%. This margin is an "M2 delta", meaning the clinical treatment effect one wants to preserve compared to active controls. We have known for years, based on well-controlled superiority trials, that an "M1 delta" (the margin needed to assure that the new drug would better than placebo) for assessing comparability to a PI or NNRTI is very large (upwards of

45%--using lower confidence bounds). Very few individuals (approximately 2%) receiving only two nucleoside analogues achieve HIV RNA < 400 copies/mL. Even fewer achieve HIV RNA < 50 copies/mL. Based on this information a noninferiority margin of 10-12% is considered acceptable.

The outcomes by treatment group as presented in the package insert are included below.

Outcomes by Treatment Group through Week 48

Randomized Study Protocol 021	ISENTRESS 400 mg Twice Daily (N = 281)	Efavirenz 600 mg At Bedtime (N = 282)	Difference (ISENTRESS – Efavirenz) (CI[§])
Outcome at Week 48			
Patients with HIV-1 RNA less than 50 copies/mL	87%	82%	4.7% (-1.3%, 10.6%)
Patients with HIV-1 RNA less than 400 copies/mL	91%	88%	3.6% (-1.5%, 8.7%)
Mean CD4 cell count change from baseline (cells/mm^3)	176	150	25.8 (5.0, 46.5)
Virologic Failure (>50 copies/mL)	6%	7%	
Never suppressed through Week 48 and on study at Week 48	2%	3%	
Rebound	5%	5%	
Discontinued study drug	7%	10%	
Reasons for Discontinuation			
Death	<1%	0%	
Adverse experiences	2%	5%	
Other*	4%	5%	

[§]The 95% CI for treatment difference is adjusted by the screening HIV RNA level (<=50,000 copies/mL vs. >50,000 copies/mL) and Hepatitis B or C (negative vs. positive)

*Other includes lack of efficacy, loss to follow-up, consent withdrawn, protocol violation and other

Of note several challenges occurred with regard to Merck and Dr. Karen Qi's ability to replicate each other's analyses for treatment outcomes based on the TLOVR algorithm. The differences were minor and not clinically or statistically different. Merck agreed to include the results as calculated by FDA in the label. Please refer to Dr. Karen Qi's review for further details.

Subgroups for race, gender and age analyses were small to make definitive conclusions; however, the results from these subgroups were consistent with the overall study results.

Additionally, the mean CD4 cell count change from baseline was greater in the raltegravir group (+176 cells/mm^3) compared to the efavirenz group (+150 cells/mm^3).

8. Safety

The data submitted in this sNDA are adequate to characterize the safety profile of raltegravir in treatment-naïve patients. Safety data from trial 021 includes a total of 281 patients in receiving raltegravir for a mean of 344 days. Two deaths occurred during the trial, both in the raltegravir group. The deaths were not related to treatment (AIDS-defining illness and trauma). Similar rates between treatment groups with respect to nonfatal serious adverse events were reported. In both groups approximately 9% developed a serious adverse event, of which infections were the most commonly reported event.

Overall approximately 9% in the raltegravir group and 12% in the efavirenz group discontinued from trial 021 for any reason prior to Week 48. The most common reason for premature discontinuation was adverse events. Three percent of raltegravir-treated patients and 6% efavirenz-treated patients discontinued due to adverse events. These percentages are included in the Adverse Reaction section. Of note, the reasons for discontinuation are also included in Table 9: Outcomes by Treatment Group though Week 48 in Section 14: Clinical Studies. The rates of discontinuation due to adverse events in this table are 2% for raltegravir and 5% for efavirenz. The difference in the proportion of subjects who

discontinued due to adverse event is related to the analysis method. In the Clinical Trials section, outcomes are based on the TLOVR algorithm. For example subjects who discontinued due to adverse event may also have experienced a virologic failure and were classified as virologic failure versus classified as a discontinuation due to an adverse event based on the algorithm. Overall, no discernable pattern with respect to types of adverse events leading to treatment discontinuation was observed.

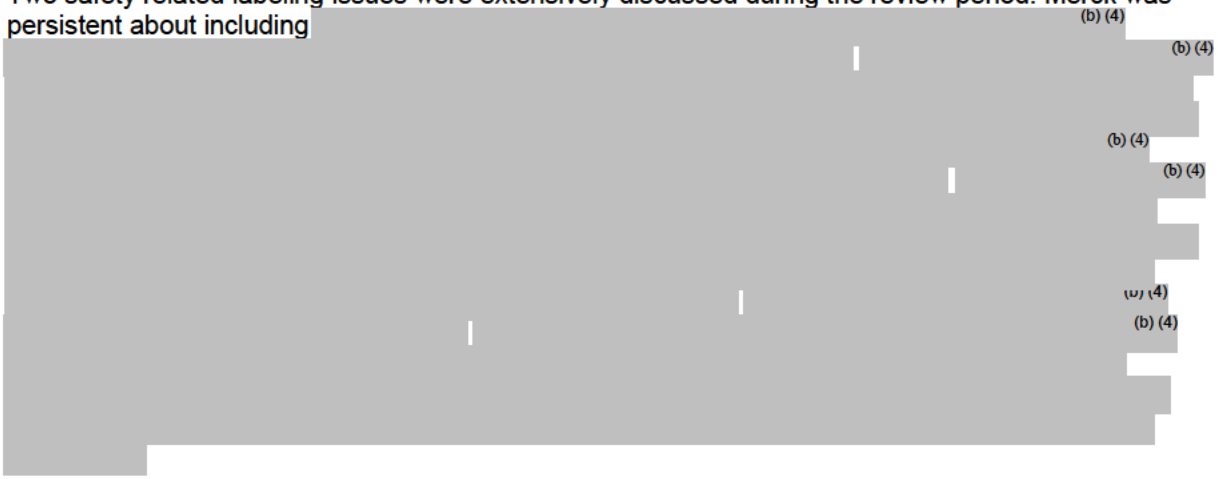
The most commonly reported adverse events occurring in ≥ 10% of raltegravir-treated patients are headache, diarrhea, nausea, nasopharyngitis, upper respiratory infection and insomnia. These events occurred at either a higher rate in the efavirenz arm or were balanced between treatment arms. Insomnia is the only treatment related moderate/severe adverse reaction occurring ≥ 2% raltegravir-treated patients and at a higher rate compared to efavirenz. Insomnia was included in section 6 of the package insert.

Dr. Connelly conducted an extensive safety review including detailed analyses for rash, hypersensitivity, immune reconstitution syndrome, hepatic and renal events, rhabdomyolysis/creatinine kinase increases, pancreatitis, dizziness, abdominal events, hypertension and psychiatric events. Based on her review of these events, no changes to the package insert are warranted. Additionally, malignancies were reviewed in detail because an imbalance was observed during accelerated approval in treatment-experienced patients. With longer follow-up, the imbalance between the two groups diminished and the identified malignancies are expected in this heavily treatment-experienced HIV population, and no apparent pattern to the types of malignancies is observed. The data from treatment-naive trial 021 show raltegravir-treated patients have lower malignancy rates compared to efavirenz-treated patients. The occurrence of malignancies in the raltegravir development program does not appear directly attributable to raltegravir. As a result the review team agreed with Merck's changes to the package insert as follows:

> Cancers were reported in treatment-experienced patients who initiated ISENTRESS or placebo, both with OBT, and in treatment-naïve patients who initiated ISENTRESS or efavirenz, both with emtricitabine (+) tenofovir; several were recurrent. The types and rates of specific cancers were those expected in a highly immunodeficient population (many had CD4+ counts below 50 cells/mm3 and most had prior AIDS diagnoses). The risk of developing cancer in these studies was similar in the group receiving ISENTRESS and the group receiving the comparator.

Of note, Merck continues an active surveillance program for malignancies as a postmarketing commitment.

Two safety related labeling issues were extensively discussed during the review period. Merck was persistent about including



I agree with the comments in Dr. Connelly's review and with the comments from DDMAC's consult. The (b) (4) is not fully characterized to date an (b) (4) s detailed in the Dr. Connelly's review insomnia occurs more frequently in the raltegravir arm of this treatment-naïve population and depression occurs with similar frequency at Weeks 8 and 48." (b) (4) owever, this is inconsistent with the Adverse Drug Reaction section of the package insert which shows moderate to severe insomnia occurred (b) (4) in the Isentress group than the efavirenz group.

Merck agreed (b) (4)

The second safety related labeling issues discussed was the Less Common Adverse Reaction subsection of the package insert. This section includes adverse drug reactions occurring in < 2% of subjects receiving raltegravir. Events are included in this section because of (1) seriousness, (2) increased frequency with raltegravir compared to efavirenz or (3) investigator's assessment of potential causality. Merck proposed to include abnormal dreams, (b) (4), fatigue (b) (4), (b) (4). With the exception of abnormal dreams and fatigue, the other adverse reactions did not fit the above definition based on Dr. Connelly's review. Merck agreed with FDA's interpretation and review and the label was amended to include abnormal dreams and fatigue in the Less Common Adverse Reaction subsection.

A review of psychiatric events, hypersensitivity, serious skin reactions including Stevens Johnson syndrome, hepatitis, hepatic failure, rhabdomyolysis and cholestasis were evaluated by Dr. Paul Gish from the Office of Safety and Epidemiology (OSE). Please refer to Dr. Gish and Connelly's review for further details. OSE recommends inclusion of insomnia, paranoia and anxiety in the ADVERSE REACTIONS, Postmarketing Experience subsection of the package insert. These events were recommended based on temporal relationship to initiation with raltegravir (< 6 weeks) and with positive dechallenge. Because insomnia was already included in the package insert based on clinical trial data, insomnia was not added to the Postmarketing Experience subsection as recommended. Further we consulted with the SEALD team and they agreed events observed in premarketing clinical trials should not be repeated in the Postmarketing Experience subsection. The Postmarketing Experience subsection is reserved for new events or concerns observed post approval.

With regard to laboratory abnormalities, no unexpected changes were seen. With the exception of bilirubin, the proportion of patients developing Grade 2-4 laboratory abnormalities were similar between treatment groups. In treatment-experienced patients a higher rate of Grade 3 and 4 bilirubin was seen in the raltegravir arm compared to control. The majority had elevated indirect bilirubin and received atazanavir as part of the background regimen. I agree with Dr. Connelly's assessment regarding the bilirubin increases observed in trial 021. "Elevated bilirubin, primarily Grade 1 and 2 and predominately indirect bilirubin, occurs more frequently in raltegravir-treated patients. The varied time to onset, lack of associated clinical AEs and resolution while continuing therapy does not support a strong causal relationship; however, the Grade 2-4 laboratory data are included in the label and further analysis will be performed with the 96-week data." As expected, co-infected patients have higher transaminases and bilirubin compared to patients without hepatitis in both groups.

A separate table for changes from baseline for lipid parameters was included. Merck analyzed the lipid data differently from the analysis used in the atazanavir label. In the atazanavir label the Week 48 mean change from baseline was calculated as the average value of the difference between Week 48 and baseline within an individual patient. Merck subtracted the baseline mean from the Week 48 mean. The method used in the atazanavir label is preferred, especially in the setting of numerous missing data points. We conducted the analyses using both methods and found the results were comparable; therefore, Merck's analysis is presented in the package insert.

Raltegravir has a favorable lipid profile compared to efavirenz. The change from baseline at Week 48 for total cholesterol and triglyceride was +10 mg/dL and -2.8 mg/dL for raltegravir compared to +32.7 mg/dL and +37.4 mg/dL for efavirenz, respectively.

9. Advisory Committee Meeting

Not applicable

10. Pediatrics

Pediatric trials are ongoing.

11. Other Relevant Regulatory Issues

No additional outstanding regulatory issues.

12. Labeling

This section summarizes the major label changes. Discussion on the label review process is included in the efficacy and safety sections above. Please refer to Amalia Himaya's review for further details.

- HIGHLIGHTS:
  - **DRUG INTERACTIONS** heading was included along with a warning about use with UGT inducers other than rifampin - Coadministration of ISENTRESS with drugs that are strong inducers of UGT1A1 may result in reduced plasma concentrations of raltegravir
  - **ADVERSE REACTIONS**: Combine treatment-naïve and treatment-experienced adverse reaction information into a single bullet point.

- Full Prescribing information.
- Section 1: **INDICATIONS AND USAGE** was changed to incorporate use in treatment-naïve patients: "ISENTRESS is indicated in combination with other anti-retroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection in adult patients. This indication is based on analyses of plasma HIV-1 RNA levels up through 48 weeks in three double-blind controlled studies of ISENTRESS. Two of these studies were conducted in clinically advanced, 3-class antiretroviral (NNRTI, NRTI, PI) treatment-experienced adults and one was conducted in treatment-naïve adults. The use of other active agents with ISENTRESS is associated with a greater likelihood of treatment response"
- Section 5.2: **WARNINGS AND PRECAUTIONS, Drug Interactions**: removal of this section because the information is sufficiently included in Section 7: **DRUG INTERACTIONS**. In addition, **DRUG INTERACTIONS** information added to HIGHLIGHTS as noted above.
- Section 6.1: **Clinical Trials Experience,** Treatment-Naïve Studies:
  - Includes 48 week safety and laboratory data from Protocol 021 as follows:

Treatment-Naïve Studies

The following safety assessment of ISENTRESS in treatment-naïve subjects is based on the randomized double-blind active controlled study of treatment-naïve subjects, STARTMRK (Protocol 021) with ISENTRESS 400 mg twice daily in combination with a fixed dose of emtricitabine 200 mg (+) tenofovir 300 mg, (N=281) versus efavirenz (EFV) 600 mg at bedtime in combination with emtricitabine (+) tenofovir, (N=282). During double-blind treatment, the total follow-up for subjects receiving ISENTRESS 400 mg twice daily + emtricitabine (+) tenofovir was 247 patient-years and 241 patient-years for subjects receiving efavirenz 600 mg at bedtime + emtricitabine (+) tenofovir.

In Protocol 021, the rate of discontinuation of therapy due to adverse reactions was 3% in subjects receiving ISENTRESS + emtricitabine (+) tenofovir and 6% in subjects receiving efavirenz + emtricitabine (+) tenofovir.

The clinical adverse drug reactions (ADRs) listed below were considered by investigators to be causally related to ISENTRESS + emtricitabine (+) tenofovir or efavirenz + emtricitabine (+) tenofovir.

Clinical ADRs of moderate to severe intensity occurring in ≥2% of treatment-naïve subjects treated with ISENTRESS and occurring at a higher rate than efavirenz are presented in Table 1.

Table 1: Adverse Reactions* of Moderate to Severe Intensity† Occurring in ≥2% of Treatment-Naïve Adult Subjects Receiving ISENTRESS and at a Higher Rate Compared to Efavirenz (48 Week Analysis)

System Organ Class, Preferred Term	Randomized Study P021	
	ISENTRESS 400 mg Twice Daily + Emtricitabine (+) Tenofovir (n = 281)‡ %	Efavirenz 600 mg At Bedtime + Emtricitabine (+) Tenofovir (n = 282)‡ %
Psychiatric Disorders		
Insomnia	4	3

*Includes adverse experiences considered by investigators to be at least possibly, probably, or definitely related to the drug
†Intensities are defined as follows: Moderate (discomfort enough to cause interference with usual activity); Severe (incapacitating with inability to work or do usual activity).
‡n = total number of subjects per treatment group

Less Common Adverse Reactions

The following ADRs occurred in <2% of subjects receiving ISENTRESS + emtricitabine (+) tenofovir. These events have been included because of their seriousness, increased frequency on ISENTRESS compared with efavirenz or investigator's assessment of potential causal relationship.
General Disorders and Administration Site Conditions: fatigue
Psychiatric Disorders: abnormal dreams

Laboratory Abnormalities

The percentages of adult subjects treated with ISENTRESS 400 mg twice daily or efavirenz in Protocol 021 with selected Grades 2 to 4 laboratory abnormalities that represent a worsening from baseline are presented in Table 2.

Table 2: Selected Grade 2 to 4 Laboratory Abnormalities Reported in Treatment-Naïve Subjects (48 Week Analysis)

Laboratory Parameter Preferred Term (Unit)	Limit	Randomized Study Protocol 021 ISENTRESS 400 mg Twice Daily + Emtricitabine (+) Tenofovir (N = 281)	Randomized Study Protocol 021 Efavirenz 600 mg At Bedtime + Emtricitabine (+) Tenofovir (N = 282)
Hematology			
Absolute neutrophil count (10^3/μL)			
Grade 2	0.75 - 0.999	3%	3%
Grade 3	0.50 - 0.749	1%	<1%
Grade 4	<0.50	<1%	0%
Hemoglobin (gm/dL)			
Grade 2	7.5 - 8.4	<1%	<1%
Grade 3	6.5 - 7.4	<1%	<1%
Grade 4	<6.5	0%	0%
Platelet count (10^3/μL)			
Grade 2	50 - 99.999	2%	0%
Grade 3	25 - 49.999	0%	<1%
Grade 4	<25	0%	.0%
Blood chemistry			
Fasting (non-random) serum glucose test (mg/dL)			
Grade 2	126 - 250	2%	3%
Grade 3	251 - 500	<1%	0%
Grade 4	>500	0%	0%
Total serum bilirubin			
Grade 2	1.6 - 2.5 x ULN	4%	0%
Grade 3	2.6 - 5.0 x ULN	<1%	0%
Grade 4	>5.0 x ULN	0%	0%
Serum aspartate aminotransferase			
Grade 2	2.6 - 5.0 x ULN	3%	4%
Grade 3	5.1 - 10.0 x ULN	1%	1%
Grade 4	>10.0 x ULN	<1%	<1%
Serum alanine aminotransferase			
Grade 2	2.6 - 5.0 x ULN	4%	6%
Grade 3	5.1 - 10.0 x ULN	<1%	2%
Grade 4	>10.0 x ULN	<1%	<1%
Serum alkaline phosphatase			
Grade 2	2.6 - 5.0 x ULN	<1%	2%
Grade 3	5.1 - 10.0 x ULN	0%	<1%
Grade 4	>10.0 x ULN	0%	0%

ULN = Upper limit of normal range

Lipids, Change from Baseline

Changes from baseline in fasting lipids are shown in Table 3.

Table 3: Lipid Values, Mean Change from Baseline, Protocol 021

Laboratory Parameter Preferred Term	ISENTRESS 400 mg Twice Daily + Emtricitabine (+) Tenofovir N = 281			Efavirenz 600 mg At Bedtime + Emtricitabine (+) Tenofovir N = 282		
			Change from Baseline at Week 48			Change from Baseline at Week 48
	Baseline Mean (mg/dL)	Week 48 Mean (mg/dL)	Mean Change (mg/dL)	Baseline Mean (mg/dL)	Week 48 Mean (mg/dL)	Mean Change (mg/dL)
LDL-Cholesterol†	97	103	6	92	108	16
HDL-Cholesterol†	38	42	4	38	48	10
Total Cholesterol†	159	169	10	156	188	33
Triglyceride†	125	122	-3	136	174	37

†Fasting (non-random) laboratory tests.

Notes:

N = Number of subjects in the treatment group. The analysis is based on all available data.

If subjects initiated or increased serum lipid-reducing agents, the last available lipid values prior to the change in therapy were used in the analysis. If the missing data was due to other reasons, subjects were censored thereafter for the analysis.

At baseline, serum lipid-reducing agents were used in 5% of subjects in the group receiving ISENTRESS and 3% in the efavirenz group. Through Week 48, serum lipid-reducing agents were used in 76% of subjects in the group receiving ISENTRESS and 86% in the efavirenz group.

- Section 6.2: **Postmarketing Experience**: addition of paranoia and anxiety
- Section 7.1 **Effect of Raltegravir on the Pharmacokinetics of Other Agents** adds information for CYP1A2, CYP2B6 and methadone.

Effect of Raltegravir on the Pharmacokinetics of Other Agents

Moreover, *in vitro*, raltegravir did not induce ***CYP1A2, CYP2B6 or*** CYP3A4.

Effect of Raltegravir on the Pharmacokinetics of Other Agents

In drug interaction studies, raltegravir did not have a clinically meaningful effect on the pharmacokinetics of the following: hormonal contraceptives, ***methadone,*** lamivudine, tenofovir, etravirine.

- Section 12.4 Microbiology was updated to include the following:

Antiviral Activity in Cell Culture

In addition, 5 clinical isolates of HIV-1 subtype B had EC_{95} values ranging from 9 to 19 nM in cultures of mitogen-activated human peripheral blood mononuclear cells.

Resistance

Treatment-Naïve Subjects: By Week 48 in the STARTMRK trial, the primary raltegravir resistance-associated substitutions were observed in 3 (1 with Y143R and 2 with Q148H/R) of the 6 virologic failure subjects with evaluable paired genotypic data.

- Section 14 **CLINICAL STUDIES** includes 48 week efficacy data from Protocol 021 as follows:

Treatment-Naïve Subjects

STARTMRK (Protocol 021) is a Phase 3 study to evaluate the safety and antiretroviral activity of ISENTRESS 400 mg twice daily + emtricitabine (+) tenofovir versus efavirenz 600 mg at bedtime plus emtricitabine (+) tenofovir in treatment-naïve HIV-1-infected subjects with HIV-1 RNA >5000

copies/mL. Randomization was stratified by screening HIV-1 RNA level (≤50,000 copies/mL; and >50,000 copies/mL) and by hepatitis status.

Table 8 shows the demographic characteristics of subjects in the group receiving ISENTRESS 400 mg twice daily and subjects in the comparator group.

Table 8: Baseline Characteristics

Randomized Study Protocol 021	**ISENTRESS 400 mg Twice Daily (N = 281)**	**Efavirenz 600 mg At Bedtime (N = 282)**
Gender		
Male	81%	82%
Female	19%	18%
Race		
White	41%	44%
Black	12%	8%
Asian	13%	11%
Hispanic	21%	24%
Native American	0%	0%
Multiracial	12%	13%
Region		
Latin America	35%	34%
Southeast Asia	12%	10%
North America	29%	32%
EU/Australia	23%	23%
Age (years)		
18-64	99%	99%
≥65	1%	1%
Mean (SD)	38 (9)	37 (10)
Median (min, max)	37 (19 to 67)	36 (19 to 71)
CD4 Cell Count (cells/microL)		
Mean (SD)	219 (124)	217 (134)
Median (min, max)	212 (1 to 620)	204 (4 to 807)
Plasma HIV-1 RNA (log_{10} copies/mL)		
Mean (SD)	5 (1)	5 (1)
Median (min, max)	5 (3 to 6)	5 (4 to 6)
Plasma HIV-1 RNA (copies/mL)		
Geometric Mean	103205	106215
Median (min, max)	114000 (400 to 750000)	104000 (4410 to 750000)
History of AIDS[†]		
Yes	18%	21%
Viral Subtype		
Clade B	78%	82%
Non-Clade B[‡]	21%	17%

Baseline Plasma HIV-1 RNA		
≤100,000 copies/mL	45%	49%
>100,000 copies/mL	55%	51%
Baseline CD4 Cell Counts		
≤50 cells/mm^3	10%	11%
>50 cells/mm^3 and ≤ 200 cells/mm^3	37%	37%
>200 cells/mm^3	53%	51%
Hepatitis Status		
Hepatitis B or C Positive[§]	6%	6%

[†]Includes additional subjects identified as having a history of AIDS.
[‡]Non-Clade B Subtypes (# of subjects): Clade A (4), A/C (1), A/G (2), A1 (1), AE (29), AG (12), BF (6), C (37), D (2), F (2), F1 (5), G (2), Complex (3).
[§]Evidence of hepatitis B surface antigen or evidence of HCV RNA by polymerase chain reaction (PCR) quantitative test for hepatitis C Virus.
Notes:
ISENTRESS and Efavirenz were administered with emtricitabine (+) tenofovir
N = Number of subjects in each group.

Week 48 outcomes from Protocol 021 are shown in Table 9.

Table 9: Outcomes by Treatment Group through Week 48

Randomized Study Protocol 021	ISENTRESS 400 mg Twice Daily (N = 281)	Efavirenz 600 mg At Bedtime (N = 282)	Difference (ISENTRESS – Efavirenz) (CI[§])
Outcome at Week 48			
Subjects with HIV-1 RNA less than 50 copies/mL	87%	82%	4.7% (-1.3%, 10.6%)
Subjects with HIV-1 RNA less than 400 copies/mL	91%	88%	3.6% (-1.5%, 8.7%)
Mean CD4 cell count change from baseline (cells/mm^3)	176	150	25.8 (5.0, 46.5)
Virologic Failure (>50 copies/mL)	6%	7%	
Never suppressed through Week 48 and on study at Week 48	2%	3%	
Rebound	5%	5%	
Discontinued study drug	7%	10%	
Reasons for Discontinuation			
Death	<1%	0%	
Adverse experiences	2%	5%	
Other*	4%	5%	

[§]The 95% CI for treatment difference is adjusted by the screening HIV RNA level (<=50,000 copies/mL vs. >50,000 copies/mL) and Hepatitis B or C (negative vs. positive)
*Other includes lack of efficacy, loss to follow-up, consent withdrawn, protocol violation and other

As mentioned in the traditional approval review, the Week 48 outcomes were to be updated based on results from the TLOVR algorithm. Below is the updated table. Week 48 outcomes for the 699 subjects randomized and treated with the recommended dose of ISENTRESS 400 mg twice daily or placebo in the pooled BENCHMRK 1 and 2 studies are shown in Table 12.

Table 12: Outcomes by Treatment Group through Week 48

Randomized Studies Protocol 018 and 019	ISENTRESS 400 mg Twice Daily + OBT (N = 462)	Placebo + OBT (N = 237)
Outcome at Week 48		
Subjects with HIV-1 RNA less than 400 copies/mL	72%	37%
Subjects with HIV-1 RNA less than 50 copies/mL	60%	31%
Mean CD4 cell count change from baseline (cells/mm^3)	106	44
Virologic Failure (>50 copies/mL)	36%	65%
Never suppressed through Week 48 and on study at Week 48	11%	9%
Rebound	13%	8%
Non-responder by Week 48‡	12%	48%
Discontinued study drug	4%	4%
Reasons for Discontinuation		
Death	2%	2%
Adverse Experiences	<1%	<1%
Other*	2%	1%

‡The non-responders by Week 48 were defined by the protocol as those who did not achieve > 1.0 $\log_{10}$ HIV-1 RNA reduction and <400 HIV-1 RNA copies/mL starting at Week 16 or beyond.

*Other includes lack of efficacy, loss to follow-up, consent withdrawn

- Other administrative changes were made for clarity and ease of use.
- The patient package insert was updated based on a DDMAC consult. Minor editorial changes were made to the patient package insert for consistency with other antiretrovirals

13 Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I concur with the assessments made by the review team and recommend approval for use of raltegravir in HIV-1 infected treatment-naïve patients.

- Risk Benefit Assessment

The data submitted provide sufficient evidence to support a favorable risk-benefit assessment for use of raltegravir in treatment-naïve patients. Raltegravir was non-inferior to efavirenz through Week 48. Efavirenz is a valid comparator and is listed as a preferred agent in the DHHS treatment guidelines. Over 80% of patients in each treatment group achieved and maintained HIV RNA < 50 copies/mL. The development of resistance was infrequent in trial 021; only three raltegravir -treated patients with virologic failure developed genotypic changes. The amino acid substitutions observed in trial 021 were similar to the substitutions previously reported in treatment-experienced patients.

No new or unexpected safety findings were seen. Insomnia was added to the Adverse Reactions section as the only moderate/severe treatment related adverse reaction occurring at a greater frequency than efavirenz. Continued ongoing review of CNS events is warranted. Compelling

cases were reported postmarketing such as depression, suicidal behaviors, anxiety and paranoia. These events are now labeled. Laboratory abnormalities were similar to efavirenz with the exception of lipids and bilirubin. Raltegravir has a favorable lipid compared to efavirenz and the results of the mean change from baseline values are included in section 6. Elevated bilirubin, primarily Grade 1 and 2 and predominately indirect bilirubin, occurs more frequently in raltegravir-treated patients. The varied time to onset, lack of associated clinical AEs and resolution while continuing therapy does not support a strong causal relationship; however, the Grade 2-4 laboratory data are included in the label and further analysis will be performed with the 96-week data.

- Recommendation for Postmarketing Risk Management Activities

RiskMaps and REMS are not required for this supplement.

- Recommendation for other Postmarketing Study Commitments

No postmarketing study commitments are required for this application

- Recommended Comments to Applicant

No additional comments to convey to the Applicant.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kimberly Struble
7/2/2009 10:22:09 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22 – 145/S004

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-145
Submission Code	SE5-004
Letter Date	September 25, 2008
Stamp Date	September 26, 2008
PDUFA Goal Date	July 24, 2009
Reviewer Name	Sarah M. Connelly, MD
Review Completion Date	June 8, 2009
Established Name	Raltegravir
(Proposed) Trade Name	ISENTRESS™
Therapeutic Class	Integrase inhibitor
Applicant	Merck
Priority Designation	S
Formulation	400 mg tablet
Dosing Regimen	400 mg, twice daily
Indication	Treatment of HIV-1 infection
Intended Population	Treatment-naïve HIV-1 infected adults

TABLE OF CONTENTS

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of raltegravir 400 mg twice daily use for HIV-1 infected treatment-naïve adults in combination with other antiretroviral agents.

Week 48 results from Protocol 021, a double-blind, randomized, placebo-controlled Phase 3 trial in 563 HIV-1 infected treatment-naïve subjects, demonstrate the antiviral activity of raltegravir is non-inferior to efavirenz, each in combination with emtricitabine /tenofovir. A total of 87% of raltegravir-treated subjects achieved the Week 48 primary endpoint of HIV-1 RNA <50 copies/mL versus 82% of efavirenz-treated subjects. Review of safety data does not identify toxicities outweighing the benefit of raltegravir use in treatment-naïve subjects. No deficiencies preclude approval.

1.2 Risk Benefit Assessment

My review supports the acceptable safety profile of raltegravir in HIV-1 infected treatment-naïve adults. The toxicity profile is similar to the profile in the treatment-experienced population. Insomnia is newly identified as a raltegravir drug-related adverse reaction of moderate-to-severe intensity occurring at a greater frequency compared with efavirenz, 4% versus 3%, respectively. No other new or unexpected safety signals with respect to cause of mortality or serious events leading to discontinuation are identified. Postmarketing safety review supports addition of paranoia and anxiety to the label.

Protocol 021 efficacy assessment demonstrates raltegravir's antiviral activity is non-inferior to efavirenz, with over 80% of subjects in both groups achieving Week 48 HIV-1 RNA <50 copies/mL.

The acceptable safety profile and established antiviral activity support approval for raltegravir use in HIV-1 infected treatment-naïve patients.

1.3 Recommendations for Postmarketing Risk Management Activities

The risk management plan for raltegravir was discussed in the clinical review of the original NDA. No additional recommendations for postmarketing risk management activities are required based on this submission.

1.4 Recommendations for other Post Marketing Study Commitments

No additional postmarketing commitments are requested with this supplement.

2 Introduction and Regulatory Background

2.1 Product Information

Generic (trade) name: Raltegravir (ISENTRESS™)
Chemical: C20H20FKN6O5
Pharmacological class: HIV integrase strand transfer inhibitor

Proposed indication: ISENTRESS is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection in adult patients

Dosing regimens: 400 mg twice daily
Dosage form: 400 mg tablet

2.2 Tables of Currently Available Treatments for Proposed Indications

There are currently 25 drugs approved for the treatment of HIV-1 infection (not including fixed dose combinations or different formulations). These drugs fall into six classes based on mechanism of action in the HIV life cycle: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion/entry inhibitors, CCR5 antagonists and integrase inhibitors (Table 2.2.A).

Table 2.2.A: Currently Approved Antiretrovirals

Drug Class	Generic Name	Trade Name
NRTI	Zidovudine (AZT)	Retrovir®
	Didanosine (ddI)	Videx®/Videx EC®
	Stavudine (d4T)	Zerit®
	Lamivudine (3TC)	Epivir®
	Abacavir	Ziagen®
	Tenofovir (TDF)	Viread®
	Emtricitabine (FTC)	Emtriva®
NNRTI	Delavirdine	Rescriptor®
	Nevirapine	Viramune®
	Efavirenz	Sustiva®
(Second Generation)	Etravirine	Intelence®
PI	Indinavir	Crixivan®
	Ritonavir	Norvir®
	Saquinavir, hard gel	Invirase®
	Saquinavir, soft gel	Fortavase®
	Nelfinavir	Viracept®
	Amprenavir	Agenerase®
	fos-amprenavir	Lexiva®
	Atazanavir (ATV)	Reyataz®
	Lopinavir/ritonavir (LPV/r)	Kaletra®
	Tipranavir (TPV)	Aptivus®
	Darunavir (DRV)	Prezista®
Fusion/Entry Inhibitor	Enfuvirtide (ENF)	Fuzeon®
CCR5 receptor antagonist	Maraviroc	Selzentry®
Integrase Inhibitor	Raltegravir	Isentress®

According to the 2008 DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents, the primary goals of antiretroviral therapy are to "reduce HIV-related morbidity and prolong survival; improve quality of life; restore and preserve immunologic function; maximally and durably suppress viral load; and prevent vertical HIV transmission". Obstacles in achieving these goals include drug side effects, drug intolerance and drug resistance. Treatment with combination therapy is often associated with drug toxicities such as fat redistribution, hyperlipidemia, hypertriglyceridemia, hyperglycemia, pancreatitis,

hepatotoxicity, rash and lactic acidosis. As noted in the DHHS Guidelines, "an overarching goal should be to select a safe and effective regimen while taking into account individual patient underlying conditions, concomitant medications, and history of drug intolerance".

2.3 Availability of Proposed Active Ingredient in the United States

The active moiety in raltegravir is currently available and marketed in the United States since accelerated approval on October 12, 2007 for use in HIV-1 infected treatment-experienced patients.

2.4 Important Safety Issues With Consideration to Related Drugs

Currently, no pharmacologically related products have received FDA approval.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Protocol 021 in HIV-1 infected treatment-naïve subjects began in September 2006 and Week 48 was completed in June 2008. The Applicant now submits the Protocol 021 48 week results as a supplemental NDA (sNDA) for approval of raltegravir in treatment-naïve adults.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Site audits by Division of Scientific Investigations (DSI) were conducted for the original raltegravir NDA application for raltegravir. The Applicant's request for a new indication in the treatment-naive HIV-infected population prompted additional site audits. The site selection process involved the raltegravir review team and Dr. Antoine El-Hage from DSI. Because international site audits were previously conducted, the current selection was restricted to United States sites. Please refer to Dr. El-Hage's DSI review for further details. Two clinical sites were inspected (Table 3.1.A) because they enrolled the second and third highest number of subjects domestically, Site 001 had four protocol violations and four premature discontinuations, and Site 0015 had five premature discontinuations. The medical records reviewed disclosed no adverse findings that would reflect negatively on the reliability of the data. In general, the trial records reviewed were found to be in order and verifiable. Therefore, the data from the inspected sites are acceptable in support of this sNDA.

Table 3.1.A: Listing of Division of Scientific Investigations Evaluation of Clinical Inspections

Name of CI and Site #	City, State	Protocol	Inspection Date	Final Classification
Richard Pollard, M.D. , Site 0015	Sacramento, CA	021	March 2009	NAI
Daniel Berger, M.D., Site 0001	Chicago, IL	021	April 2009	NAI*

Source: DSI Evaluation of Clinical Inspections for NDA 22-145 by Dr. Antoine El-Hage
*Preliminary data at the time of this review.
CI = clinical investigator
Key to Classifications
NAI = No deviation from regulations. Data acceptable.

3.2 Compliance with Good Clinical Practices

The protocol and informed consent documents were reviewed and approved by the Institutional Review Boards and Independent Ethics Committees for each of the investigational centers participating in Protocol 021. The Applicant certified these studies were conducted in compliance with the ethical principles described in the Declaration of Helsinki and in compliance with International Conference on Harmonisation Good Clinical Practice guidelines. The following table summarizes Protocol 021 protocol violations:

Table 3.2.A: Protocol 021: Protocol Violations, Double Blind Treatment Period

	Raltegravir	Efavirenz	Total
# Subjects Randomized and Treated	281	282	563
Protocol deviation for enrollment – n (%)[1]	12 (4.3)	9 (3.2)	21 (3.7)
Incorrectly stratified as HBV/HCV co-infected – n (%)	1 (0.4)	2 (0.7)	3 (0.5)
Enrolled in an Investigational Study	1 (0.4)	0	1 (0.2)
Received prior antiretroviral medication – n (%)[2]	1 (0.4)	3 (1.1)	4 (0.7)
Medication dispensing errors – n (%)[3]	5 (1.9)	0	5 (0.9)
Prematurely unblinded – n (%)	1 (0.4)	2 (0.7)	3 (0.5)
Took prohibited medication – n (%)	5 (1.9)	2 (0.7)	7 (1.2)

Source: Applicant MRL Clinical Study Report for Protocol 021
[1] Includes failure to have laboratory parameters obtained within the window prior to randomization (N=13), signs and symptoms of active infection <2 weeks prior to start of treatment (N=8)
[2] Subjects AN 23408 and AN 23422 were exposed to ART during prior pregnancies, AN 23257 received prior 3TC/AZT and LPV/r 9/03-5/04 and d4T/3TC until protocol enrollment: all of these subjects experienced virologic response. AN 24760 randomized to the efavirenz arm received a prior single dose of AZT. At Week 48 this subject did not achieve HIV-1 RNA <50 copies/mL; however, HIV-1 RNA was <400 copies/ml.
[3] All five subjects incorrectly received efavirenz for a brief period of time (AN 20007, 23317, 23370 <Week 48 visit and AN 20021, 23173 >Week 48 visit) and none experienced worsened viral load changes. Subjects AN 20007 and AN 23173 did not have temporally associated AEs. Subject AN 20021 experienced mild dehydration and myalgia during efavirenz therapy. Subject AN 23317 experienced mild dizziness and urticaria during efavirenz therapy. Subject AN 23370 experienced worsened mental disorder during efavirenz therapy leading to discontinuation.

In summary, few protocol violations were observed and do not appear to impact the overall trial conclusions.

3.3 Financial Disclosures

The Applicant examined financial data regarding significant payments and equity for all investigators per 21 CFR Part 54. A total of 312 investigators participated in Protocol 021. The Applicant provided a certification for the majority of investigators, indicating all responding investigators had no financial arrangements.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

This sNDA contains no new chemistry and manufacturing data; only a request for exclusion from the environmental assessment requirement. Please refer to Dr. Swapan De's review and to the original NDA.

4.2 Clinical Microbiology

Please refer to Dr. Sung Rhee's Microbiology review for a detailed analysis of resistance data. Phase 3 treatment-experienced data identified three primary substitutions in HIV-1 integrase: Y143C/H/R, Q148H/K/R and N155H. Each of the primary substitutions was usually accompanied by at least one secondary substitution: L74M, E92Q, T97A, E138A/K, G140A/S, V151I, G163R, H183P, Y226C/D/F/H, S230R, D232N.

The 48 week data from Protocol 021 contain six virologic failure subjects with evaluable paired genotypic samples. Primary raltegravir resistance-associated substitutions are observed in three of these subjects (1 with Y143R and 2 with Q148H/R), similar to the primary substitutions identified in the treatment-experienced data.

4.3 Preclinical Pharmacology/Toxicology

This sNDA contains no new preclinical pharmacology/toxicology data. Please refer to the original NDA review.

4.4 Clinical Pharmacology

Please refer to Dr. Sarah Robertson's Clinical Pharmacology Review. No new clinical pharmacology data are submitted with this sNDA. However, two postmarketing reports and a methadone study were separately reviewed resulting in labeling changes incorporated into this sNDA.

4.4.1 Mechanism of Action

Raltegravir inhibits the catalytic activity of HIV-1 integrase, specifically the strand transfer step.

4.4.2 Pharmacodynamics

Sparse PK sampling was not performed in Protocol 021; however, the Applicant includes an update of the previously submitted Protocol 004 PK/PD analysis using different PK parameters (geometric mean of all observed concentrations and minimum of all concentrations). Similar to prior conclusions, Protocol 004 data do not support a meaningful association between raltegravir exposure and efficacy in treatment-naïve subjects treated with raltegravir doses of 100 to 600 mg twice daily (BID) in combination with 3TC/TDF.

4.4.3 Pharmacokinetics

Postmarketing reports 013 and 014 were fulfilled with PK011 and PK012 final study report submission.

- Commitment 13: Conduct an *in vitro* study (e.g. in human hepatocytes) to evaluate the relative UGT1A1 induction potency of phenytoin, phenobarbital, rifabutin, and rifampin using raltegravir as a probe substrate.
- Commitment 14: Conduct an *in vitro* study (e.g. in human hepatocytes) to evaluate the potential of raltegravir to induce CYP1A2 and CYP2B6.

Study PK011 demonstrates phenytoin, phenobarbital, rifabutin and rifampin induce UGT1A1 mRNA expression *in vitro*. However, the results are inconclusive with respect to the relative enzyme induction potential of the four drugs using raltegravir as a probe substrate. Currently Section 2 of the label (**DOSAGE AND ADMINISTRATION**) states an increase in raltegravir dose to 800 mg BID is recommended during coadministration with rifampin based on the results of a drug interaction study conducted in healthy volunteers. No additional dosing recommendations are made for raltegravir during phenytoin, phenobarbital or rifabutin coadministration at this time, and the current precautionary statement in the label (Section 7.2) will remain unchanged.

Study PK012 indicates raltegravir is unlikely to induce CYP1A2 or CYP2B6 enzyme activity. A revision to Section 7.1 of the label is recommended to reflect the findings of this study.

> *Proposed Label:* Section 7.1 **Effect of Raltegravir on the Pharmacokinetics of Other Agents**
>
> Moreover, *in vitro*, raltegravir did not induce ***CYP1A2, CYP2B6 or*** CYP3A4.

Finally, Study 030: *A Randomized, Placebo-Controlled, 2-Period, Crossover Study in Patients Receiving Methadone Maintenance Therapy (MMT) to Evaluate the Effect of MK-0518 on Methadone Plasma Concentrations* was submitted to the IND on March 11, 2009 (SDN 1581). Study 030 indicates raltegravir does not alter methadone exposure during coadministration (reviewed separately under IND 69,928 by Dr. Robertson) and therefore supports changing the label to include methadone in the section below.

Proposed Label: Section 7.1 **Effect of Raltegravir on the Pharmacokinetics of Other Agents**

In drug interaction studies, raltegravir did not have a clinically meaningful effect on the pharmacokinetics of the following: hormonal contraceptives, ***methadone,*** lamivudine, tenofovir, etravirine.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

Protocol 021 (STARTMRK) is the pivotal trial supporting the efficacy and safety analyses in this sNDA. In addition, Protocol 004 is a Phase 2 trial in HIV-1 treatment-naïve subjects providing additional safety information. Table 5.1.A summarizes these trials.

Table 5.1.A: Clinical Trials Analyzed in this Review to Support SE5-004 Approval

Trial	Design	Raltegravir Regimens	Comparator	Background Regimen	# Enrolled and Treated	Population	Endpoint
Phase 2							
004	Part 1: 10 d Randomized Double - Blinded	100 mg bid 200 mg bid 400 mg bid 600 mg bid	Placebo	n/a	35	Treatment naïve	ΔHIV-1 RNA from B/L at Day 10
	Part 2: 48 wks plus extension Randomized Double - Blinded	100 mg bid 200 mg bid 400 mg bid 600 mg bid	Efavirenz 600 mg qhs	3TC/TDF	198	Treatment naïve	HIV-1 RNA <400 at Week 24
Phase 3							
021	Randomized Double - Blinded	400 mg bid	Efavirenz 600 mg qhs	FTC/TDF	563	Treatment naive	HIV-1 RNA <50 Week 48

5.2 Review Strategy

I conducted the clinical review of sNDA 22-145 SE5-004. Protocol 021 Week 48 data form the principal basis for characterizing the safety and efficacy of raltegravir in HIV-1 infected treatment-naïve subjects. Week 48 is defined throughout this review as ≤ Day 378 because this is the midpoint between the Week 48 (Day 336) and Week 60 (Day 420) visits. Week 8 is defined as ≤ Day 70, the midpoint between the Week 8 (Day 56) and Week 12 (Day 84) visits and Week 24 is defined as ≤ Day 196, the midpoint between the Week 24 (Day 168) and Week 32 (Day 224) visits.

Data from Protocol 004 were provided as a reference and the original datasets were included with the traditional approval sNDA; therefore, this review does not describe Protocol 004 in detail. Key safety analyses incorporate Protocol 004 data and Protocol 021 Safety Update Report (SUR) data, submitted four months after the original sNDA submission. I analyzed the submitted datasets using JMP software, reviewed subject narratives for all mortality, malignancy and important serious adverse events, and collaborated with the statistical, clinical pharmacology, microbiology and pharmacology toxicology reviewers throughout the review process. Finally, the Office of Surveillance and Epidemiology (OSE) reviewed postmarketing data in support of identified safety issues (Section 8).

5.3 Discussion of Individual Studies

Protocol 021 is an international, multicenter, double-blind, randomized, active-controlled trial comparing 400 mg BID raltegravir to 600 mg once nightly (QHS) efavirenz, each in combination with FTC/TDF, in treatment-naïve HIV-1-infected adult subjects with HIV-1 RNA >5000 copies/mL. Subjects were stratified by screening HIV-1 RNA (≤ 50,000 copies/mL or >50,000 copies/mL) and hepatitis status (positive hepatitis B surface antigen and/or hepatitis C RNA), and randomized 1:1 to one of two groups:

- Group 1 = raltegravir 400 mg BID without regard to food, and efavirenz placebo, taken QHS on an empty stomach.
- Group 2 = efavirenz 600 mg, taken QHS on an empty stomach, and raltegravir placebo, taken BID without regard to food.

Additionally, all subjects in both treatment groups took one FTC/TDF tablet with food daily with the raltegravir/placebo morning dose. A total of 67 sites participated in this trial, located in Europe, Australia, Latin America, North America and Southeast Asia. A protocol extension allows for continued double-blind observations through Week 240.

The primary endpoint is the proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 48. A 12% margin was used to define raltegravir non-inferiority to efavirenz.

Secondary Week 48 endpoints include:

- Proportion of subjects achieving HIV-1 RNA <400 copies/mL
- Change from baseline in CD4 cell count

In addition, the proportion of subjects with central nervous system (CNS) symptoms up to Week 8 is compared between the raltegravir and efavirenz groups. The Applicant defines CNS symptoms by the following MedDRA preferred terms: dizziness, insomnia, somnolence, concentration impaired, depression, nightmare, confusional state, suicidal ideation, nervous system disorder, psychotic disorder, abnormal dreams, suicide attempt, acute psychosis, delirium, depressed level of consciousness, hallucination, auditory hallucination, completed suicide, and major depression. The terms “dizziness, insomnia, somnolence, and concentration impaired” were not in the protocol and statistical analysis plan prespecified term list. The Applicant states this oversight was discovered subsequent to unblinding the data for analysis.

Virologic failure is defined as:

- Non-responders for those with (1) HIV-1 RNA >50 copies/mL at the time of discontinuation for subjects who prematurely discontinue study therapy or (2) HIV-1 RNA >50 copies/mL at Week 24
- Rebound for those with HIV-1 RNA >50 copies/mL (on two consecutive measurements at least one week apart) after initial response with HIV-1 RNA <50 copies/mL.

The major eligibility criteria for enrollment include:

- HIV-1 infected subjects at least 18 years of age
- HIV-1 RNA >5000 copies/mL
- Naïve to antiretroviral treatment
- No documented resistance to efavirenz, FTC and /or TDF
- Within 35 days prior to study treatment phase:
  - Serum creatinine ≤ 2.0x upper limit of normal (ULN)
  - Alkaline phosphatase, AST and ALT ≤ 5.0x ULN

Subjects with chronic hepatitis B virus (HBV) and/or hepatitis C virus (HCV) were allowed to enroll if clinically stable and serum AST, ALT and alkaline phosphatase values were ≤ 5 times ULN. Co-infected subjects with impaired hepatic synthetic function (e.g., hypoalbuminemia, prolonged prothrombin time) were excluded based on investigator opinion.

Table 5.3.A presents the Protocol 021 schedule of subject monitoring procedures performed during the double-blind phase:

Table 5.3.A: Protocol 021: Schedule of Monitoring Procedures

Schedule of Clinical Observations and Laboratory Measurements

	Weeks (Postinitiation of Combination Therapy)											
Visit No	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	Screen	Fasting Randomization (Day 1)	Week 2	Week 4	Week 8	Fasting Week 12	Week 16	Fasting Week 24	Week 32	Week 40	Fasting Week 48	Week 60
Obtain informed consent	X											
Review inclusion/exclusion criteria	X											
Collect medical history	X											
Perform physical exam	X[§§]	X[¶‖]	X‖	X‖	X‖	X‖	X‖	X‖	X‖	X‖	X‖	X‖
Review prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Review adverse experiences		X	X	X	X	X	X	X	X	X	X	X
Collect blood for safety	X	X[¶§]	X	X	X	X§	X	X§	X	X	X§	X
Perform pregnancy test†	X‡	X‖¶		X‡	X‡	X‡	X‡	X‡	X‡	X‡	X‡	X‡
Collect blood for HIV RNA	X	X¶	X	X	X	X	X	X	X	X	X	X
Collect blood for CD4 cell count	X	X¶	X	X	X	X	X	X	X	X	X	X
Collect plasma for viral resistance	X											
Perform DEXA scan		X¶#									X††	
Register patient visit and dispense study medication using Interactive Voice Response System (IVRS)‡‡	X	X¶	X¶¶	X	X	X	X	X	X	X	X	X
Provide/review Diary Cards		X	X	X	X	X	X	X	X	X	X	X

† For women of childbearing potential.
‡ Serum pregnancy test (central laboratory).
§ Fasting for at least 8 hours.
‖ Urine pregnancy test (central laboratory kit).
¶ Prior to first dose on Day 1.
# DEXA scan will be performed at selected sites within 7 days prior to randomization.
†† DEXA scan should be +/- 7 days of the visit date for Week 48 and Week 96.
‡‡ Study personnel will access IVRS to register patients at the screening visit. IVRS will be used to allocate drug and to manage distribution of clinical supplies.
§§ Full physical exam including vital signs.
‖‖ Directed physical exam including vital signs.
¶¶ IVRS call to register patient, supplies from V2 are re-dispensed.

Schedule of Clinical Observations and Laboratory Measurements

	Weeks (Postinitiation of Combination Therapy)					
Visit No	V13	V14	V15	U	V99	U
	Fasting Week 72	Week 84	Fasting Week 96	Viral Failure Confirmation	Fasting 14-Day Posttherapy Follow-up	Discontinuation
Collect medical history						
Perform physical exam	X‖	X‖	X‖		X‖	X‖
Review prior/concomitant medications	X	X	X		X	X
Review adverse experiences	X	X	X		X	X
Collect blood for safety	X§	X	X§		X§	X
Perform pregnancy test†	X‡	X‡	X‡		X‡	X‡
Collect blood for HIV RNA	X	X	X	X	X	X
Collect blood for CD4 cell count	X	X	X	X	X	X
Collect plasma for viral resistance				X##		X
Perform DEXA scan			X††			X†††
Provide/review Diary Cards	X	X	X			X
Register patient visit and dispense study medication using Interactive Voice Response System (IVRS)‡‡	X	X	X	X§§§		X§§§

† For women of childbearing potential.
‡ Serum pregnancy test (central laboratory).
§ Fasting for at least 8 hours.
†† DEXA scan should be +/- 7 days of the visit date for Week 48 and Week 96.
‡‡ Study personnel will access IVRS to register patients at the screening visit. IVRS will be used to allocate drug and to manage distribution of clinical supplies.
‖ Directed physical exam including vital signs.
If viral failure or relapse is confirmed (with a confirmatory HIV RNA at least one week apart), and the decision is made to discontinue the patient, plasma for resistance need not be collected again at the discontinuation visit. All other early discontinuation tests should be performed at the early discontinuation visit.
††† Patients who discontinued the study before Week 48 will undergo DEXA at their final visit, provided that visit was at or after Week 24.
§§§ IVRS called to register patient visit, no drug dispensed.

This sNDA also includes 96 week summary data from Protocol 004, a Phase 2 dose-finding trial in treatment-naïve subjects comparing raltegravir versus efavirenz, each in combination with 3TC and TDF. The Protocol 004 datasets were included with the traditional approval sNDA; therefore, this review does not describe Protocol 004 in detail. Key safety analyses incorporate Protocol 004 data.

6 Review of Efficacy

Efficacy Summary

Protocol 021 Week 48 data determine raltegravir 400 mg BID plus FTC/TDF is non-inferior to efavirenz plus FTC/TDF in HIV-1 treatment-naïve subjects using the primary HIV-1 RNA <50 copies/mL endpoint. A total of 87% raltegravir-treated subjects and 82% efavirenz-treated subjects achieved Week 48 HIV-1 RNA <50 copies/mL with a 95% confidence interval (CI) of -1.3%, 10.6%, falling above the prespecified lower 95% CI bound of -12% for non-inferiority. In addition, the proportion of raltegravir and efavirenz-treated subjects with HIV-1 RNA <400 copies/mL is similar. Tables 6.1.3.A and 6.1.4.A describe the time to loss of virologic response (TLOVR) results for HIV-1 RNA <50 and <400 copies/mL. Mean CD4 cell count increases from baseline are 176 and 150 cells/mm^3 in the raltegravir and efavirenz groups, respectively. Subgroup analyses of gender, race, age, baseline viral load and hepatitis co-infected status demonstrate comparable antiviral activity between raltegravir and efavirenz in these populations.

6.1 Indication

The current approved indication is ISENTRESS in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection in treatment-experienced adult patients who

have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents. This sNDA proposes to incorporate the Protocol 021 efficacy and safety data and revise the indication to state ISENTRESS is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adult patients.

Week 48 efficacy data from Protocol 021 support the proposed indication.

6.1.1 Demographics

The following table presents Protocol 021 demographic information (Table 6.1.1.A). A total of 689 subjects were screened for trial entry, of whom 566 were randomized and 563 received at least one study drug dose (281 raltegravir, 282 efavirenz). Sixty-seven international study centers participated with enrollment at each center ranging from 1 to 21 subjects. The majority of subjects are white (41-44%) men (81-82%) with a median age of 37 years, median baseline viral load of 5.0 $\log_{10}$ and median baseline CD4 cell count of 204-212 cells/mm^3. The overall percentage of black subjects is lower than in the Phase 3 treatment-experienced trials; however, limited to the US, the percentages are comparable to the treatment-experienced trials.

Table 6.1.1.A: Protocol 021: Baseline Characteristics

	Raltegravir N=281		**Efavirenz N=282**	
	n	**%**	**n**	**%**
Gender				
Male	227	81	231	82
Female	54	19	51	18
Race				
White	116	41	123	44
Black	33	12	23	8
US population (n/N)	16/65	25	11/76	15
Asian	36	13	32	11
Hispanic	60	21	67	24
Native American	1	<1	1	<1
Multiracial	35	12	36	13
Region				
Latin America	99	35	97	34
Southeast Asia	34	12	29	10
North America	82	29	90	32
EU/Australia	66	23	66	23
Age (years)				
18-64	279	99	278	99
≥ 65	2	1	4	1
Mean (SD)	37.6 (9.0)		36.9 (10.0)	
Median (min, max)	37 (19, 67)		36 (19, 71)	
CD4 cell count (cells/mm^3)[1]				

Mean (SD)	218.9 (124.2)		217.4 (133.5)	
Median (min, max)	212 (1, 620)		204 (4, 807)	
Plasma HIV-1 RNA (log_{10} copies/mL)				
Mean (SD)	5.0 (0.6)		5.0 (0.6)	
Median (min, max)	5.1 (2.6, 5.9)		5.0 (3.6, 5.9)	
Plasma HIV-1 RNA (copies/mL)				
Median (min, max)	114,000 (399, 750,000)		104,000 (4410, 750,000)	
History of AIDS – Yes	51	18	60	21
Hepatitis B or C Positive	18	6	16	6
Viral Subtype				
Clade B	219	78	230	82
Non-Clade B§	59	21	47	17
Missing	3	1	5	2
Baseline Plasma HIV-1 RNA (copies/mL)				
≤ 50,000	79	28	84	30
> 50,000	202	72	198	70
≤ 100,000	127	45	139	49
> 100,000	154	55	143	51
Baseline CD4 Cell Count (cells/mm^3)				
≤ 50	27	10	31	11
> 50 and ≤ 200	104	37	105	37
> 200	150	53	145	51
Missing	0	0	1	<1

Source: QHIVRNA, QCD4CC, DEMOG, DEMODATA, CLADE, LABOTHR datasets for Protocol 021
[1]Subject AN 20113 did not have a baseline CD4 cell count
‡Evidence of hepatitis B surface antigen or evidence of HCV RNA by polymerase chain reaction (PCR) quantitative test for hepatitis C Virus.
§Non-Clade B Subtypes (# of subjects): Clade A (4), A/C (1), A/G (2), A1(1), AE (29), AG (12), BF (6), C (37), D (2), F(2), F1 (5), G (2), Complex (3).
Due to rounding to the nearest whole number, some percentage totals may not equal 100.

MO Comment: The Applicant's initial "history of AIDS" definition used the preferred term "acquired immunodeficiency syndrome" in the MEDHIST dataset. I sent the Applicant a comment requesting incorporation of subjects with medical histories of CDC Category C AIDS defining conditions. The Applicant agrees with inclusion of these additional subjects and the Baseline Characteristic Table is updated accordingly.

MO Comment: The Applicant initially included subjects stratified as Hepatitis B or C positive who were not actually co-infected. I recommended the Baseline Characteristic Table include only subjects with true hepatitis co-infection and the Applicant accepts this recommendation.

6.1.2 Subject Disposition

The following table summarizes Protocol 021 discontinuations. Approximately 9% and 12% of subjects discontinued in the raltegravir and efavirenz groups, respectively, with clinical adverse events (AE) as the most common reason. Discontinuations due to AEs are described in greater detail in Section 7.3.3.

Table 6.1.2.A: Protocol 021: Disposition at Week 48

	Raltegravir		**Efavirenz**	
	n	%	n	%
Randomized	282		284	
Treated	281	99.6	282	99.3
Discontinued*	**23**	**8.2**	**34**	**12.1**
Adverse event	8	2.8	17	6.0
Clinical adverse event	8	2.8	16	5.7
Lack of efficacy	4	1.4	2	0.7
Lost to follow-up	3	1.1	7	2.5
Protocol deviation	2	0.7	0	0
Consent withdrawn	0	0	6	2.1
Other	6	2.1	2	0.7

Source: DISPOS and SPATSTT datasets for Protocol 021
*The number of treated subjects is used as the denominator for discontinuations

6.1.3 Analysis of Primary Endpoint(s)

The following sections highlight the major findings of the sNDA Statistical Review of Dr. Karen Qi. Raltegravir is non-inferior to efavirenz using the Week 48 primary endpoint of HIV-1 RNA <50 copies/mL. Based on TLOVR algorithm a total of 87% raltegravir-treated subjects and 82% efavirenz-treated subjects achieved Week 48 HIV-1 RNA <50 copies/mL with a 4.7% treatment difference and 95% confidence interval (CI) of -1.3%, 10.6%, falling above the prespecified lower 95% CI bound of -12%. Treatment response and outcomes through Week 48 are presented below. Efficacy analysis using the Week 48 "snap shot" approach produced similar results.

Table 6.1.3.A: Protocol 021: Outcomes by Treatment Group through Week 48 (TLOVR)

	Raltegravir N=281	Efavirenz N=282	Difference (Raltegravir-Efavirenz) (CI§)
Subjects with HIV-1 RNA <50 copies/mL	87%	82%	4.7% (-1.3%, 10.6%)
Virologic Failure (>50 copies/mL)^	6%	7%	
Never suppressed though Week 48 and on study at Week 48	2%	3%	
Rebound	5%	5%	
Discontinued study drug	7%	10%	
Reason for Discontinuation			
Death	<1%	0%	
Adverse Event	2%	5%	
Other*	4%	5%	

Source: Statistical Review of NDA 22-145, by Dr. Karen Qi
§The 95% CI for treatment difference is adjusted by the screening HIV RNA level (≤ 50,000 copies/mL vs. >50,000 copies/mL) and Hepatitis B or C (negative vs. positive)
^The Virologic Failure subgroup percentages do not total 6% and 7% for the raltegravir and efavirenz groups, respectively, due to rounding.
*Other includes lack of efficacy, loss to follow-up, consent withdrawn, protocol violation and other

6.1.4 Analysis of Secondary Endpoints(s)

HIV-1 RNA <400 copies/mL antiviral response rates are similar between the raltegravir and efavirenz groups. Mean CD4 cell count change from baseline is 176 and 150 cells/mm^3 in the raltegravir and efavirenz groups, respectively.

Table 6.1.4.A: Protocol 021: Secondary Outcomes by Treatment Group through Week 48

	Raltegravir N=281	Efavirenz N=282	Difference (Raltegravir-Efavirenz) (CI§)
Subjects with HIV-1 RNA <400 copies/mL*	91%	88%	3.6% (-1.5%, 8.7%)
Mean CD4 cell count change from baseline (cells/mm^3)	176	150	25.8 (5.0, 46.5)

Source: Statistical Review of NDA 22-145, by Dr. Karen Qi
*TLOVR approach
§The 95% CI for treatment difference is adjusted by the screening HIV RNA level (≤ 50,000 copies/mL vs. >50,000 copies/mL) and Hepatitis B or C (negative vs. positive)

6.1.5 Subpopulations

The following tables present Week 48 subgroup analysis of gender, race, region, age, baseline HIV-1 RNA, baseline CD4 cell count, and hepatitis status. Women achieve HIV-1 RNA <50 copies/mL response rates similar to men. Hispanic subjects have modestly higher raltegravir response rates compared with other races. Among black subjects, the raltegravir group has lower Week 48 HIV-1 RNA <50 copies/mL response; however, the CI includes zero. Higher baseline

CD4 cell count and lower baseline viral load are associated with higher response rates. In the raltegravir group, hepatitis co-infected subjects have higher response rates compared to efavirenz.

Table 6.1.5.A: Protocol 021: Subgroup Analysis for HIV-1 RNA <50 copies/mL by Treatment Group at Week 48 (TLOVR)

	Raltegravir	Efavirenz	Difference in Response Rate (95% CI)
Gender			
Female	47/54 (87%)	41/51 (80%)	6% (-7%, 21%)
Male	197/227 (87%)	191/231 (83%)	4% (-2%, 11%)
Race			
White	100/116 (86%)	102/123 (83%)	3% (-6%, 12%)
Black	26/33 (79%)	20/23 (87%)	-8% (-28%, 11%)
Asian	31/36 (86%)	27/32 (84%)	2% (-15%, 19%)
Hispanic	55/60 (92%)	54/67 (81%)	11% (-1%, 23%)
Multiracial	31/35 (89%)	28/36 (78%)	11% (-6%, 28%)
Region			
Latin America	89/99 (90%)	79/97 (81%)	5% (-1%, 18%)
Southeast Asia	30/34 (88%)	27/29 (93%)	-5% (-19%, 9%)
North America	65/82 (79%)	72/90 (80%)	-1% (-13%, 11%)
EU/Australia	60/66 (91%)	54/66 (82%)	9% (-3%, 21%)
Age			
< 37 yrs	112/129 (87%)	126/150 (84%)	3% (-4%, 11%)
≥ 37 yrs	132/152 (87%)	106/132 (80%)	7% (-2%, 15%)
Clade B			
Yes	188/219 (86%)	186/230 (81%)	5% (-2%, 12%)
No	53/59 (90%)	41/47 (87%)	3% (-10%, 15%)
Baseline HIV-1 RNA			
≤50,000 copies/mL	71/79 (90%)	68/84 (81%)	9% (-2%, 20%)
>50,000 copies/mL	173/202 (86%)	164/198 (83%)	3% (-5%, 9%)
≤100,000 copies/mL	112/127 (88%)	113/139 (81%)	7% (-2%, 15%)
>100,000 copies/mL	132/154 (86%)	119/143 (83%)	3% (-6%, 11%)
Baseline CD4 count			
≤50 cells/mm^3	21/27 (78%)	24/31 (77%)	-0.4% (-21%,22%)
>50 and ≤200 cells/mm^3	85/104 (82%)	83/105 (79%)	3% (-8%, 13%)
>200 cells/mm^3	138/150 (92%)	124/145 (86%)	6% (-1%, 14%)
>200-350 cells/mm^3	100/110 (91%)	93/109 (85%)	
>350-500 cells/mm^3	30/32 (94%)	23/26 (88%)	
>500 cells/mm^3	8/8 (100%)	8/10 (80%)*	
Hepatitis status			
HBV and/or HCV positive	18/22 (82%)	13/20 (65%)	17% (-10%, 43%)
HBV and HCV negative	226/259 (87%)	219/262 (84%)	4% (-2%, 10%)

Source: Statistical Review of NDA 22-145, by Dr. Karen Qi
*One subject lost to follow up and one subject discontinued due to elevated hepatic enzymes

7 Review of Safety

Safety Summary

Protocol 021 safety review demonstrates the overall raltegravir AE profile is similar to the established safety profile in treatment-experienced patients. The majority of Protocol 021 safety analyses are limited to the Week 48, double blind treatment period, representing 281 subjects randomized to raltegravir and 282 subjects randomized to efavirenz.

No new or unexpected safety signals with respect to causes of mortality or serious events leading to discontinuation are observed following review of the 48 week data. Insomnia occurs more frequently in raltegravir-treated subjects in both the common and drug-related AE analyses prompting inclusion of insomnia in the label.

Postmarketing reports of exacerbated depression and suicide/suicidal ideation led to inclusion of this information in the raltegravir label in January 2009. Protocol 021 review identifies depression occurring in 4% of raltegravir-treated subjects versus 5% in efavirenz-treated subjects; no suicidal AEs occur in raltegravir-treated subjects. Anxiety events are balanced between the two groups; however, postmarketing reports of anxiety support addition to the postmarketing section. Paranoia is also recommended for addition to the postmarketing section although no events occur in Protocol 021.

The Applicant performed a "Central Nervous System" analysis pooling several nervous system and psychiatric preferred terms. Their analysis favors raltegravir with fewer CNS events occurring in raltegravir-treated subject compared with efavirenz-treated subjects. (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

At the time of accelerated approval in HIV-1 treatment-experienced subjects, the raltegravir group had higher malignancy rates compared to control; however, with longer follow up the imbalance between the two groups diminished. In this sNDA, treatment-naïve raltegravir-treated subjects have lower malignancy rates compared to efavirenz-treated subjects.

AE analyses of rash, immune reconstitution syndrome, hepatic, creatine kinase, and abdominal events (b) (4). Laboratory analyses demonstrate more

raltegravir-treated subjects have Grade 1 creatinine elevations; however, only one subject had > Grade 1 creatinine and subjects were able to continue on therapy with creatinine normalization. Grade 1-2 bilirubin imbalance in the raltegravir group is also observed without current evidence for a definite causal association. Raltegravir's overall lipid profile is favorable with Week 48 mean changes from baseline of +6, +10 and -3 mg/dL for LDL, total cholesterol and triglyceride, respectively. Week 48 HDL mean change from baseline is less in the raltegravir group compared to efavirenz (+4 versus +10 mg/dL, respectively).

7.1 Methods

An AE is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporarily associated with the use of study medication, whether or not considered related to the use of the product. A serious AE (SAE) is defined as any AE occurring at any dose resulting in death, is immediately life-threatening, results in persistent or significant disability/incapacity, results in or prolongs an existing inpatient hospitalization, is a congenital anomaly/birth defect, is a cancer, is an overdose, or is deemed to be serious when, based on appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the previously listed outcomes.

AEs were monitored at each trial visit and reported in the Case Report Form (CRF). AE reports contained the following details: onset, duration, intensity, relationship to study drug, study drug action taken, outcome, association with immune reconstitution response and whether the event is classified as serious. Investigators assessed if the AE was definitely not, probably not, possibly, probably, or definitely related to study therapy. Therefore, events assessed to be possibly, probably, or definitely related to blinded or combination therapy by the investigator are referred to as treatment-emergent adverse drug reactions. Clinical AEs were graded by the investigator as mild, moderate, or severe intensity. Guidelines for grading the severity of laboratory abnormalities were based on the DAIDS criteria. AEs occurring on study treatment or within 15 days of discontinuation and SAEs occurring on treatment or within 30 days of discontinuation comprise the double-blind safety analyses. This approach differs from the Applicant because they use 14 days as the SAE cutoff.

7.1.1 Clinical Studies Used to Evaluate Safety

My integrated safety review primarily uses Protocol 021 Week 48 data. AEs and SAEs occurring outside Week 48 are generally considered separately. Causality analyses using investigator determination of drug-relatedness are applied in appropriate situations. Finally, several analyses include the Phase 2 Protocol 004 and Phase 3 treatment-experienced Protocol 018 and 019 data to maximize evaluation of uncommon, potentially clinically important AEs.

Please refer to Sections 5.1 and 5.3 for additional trial design details. Safety data are available from 563 subjects who received at least one treatment dose: 281 in the raltegravir group and 282 in the efavirenz group. The Week 48 mean raltegravir exposure is 344 days; the mean efavirenz exposure is 331 days. Total follow-up according to the Applicant is 247 patient-years for raltegravir-treated subjects and 241 patient-years for efavirenz-treated subjects.

7.1.2 Adequacy of Data

The Protocol 021 clinical data are obtained from a randomized, blinded, active-controlled trial and the overall data quality is acceptable for conducting the safety review. The frequency of clinical assessments is appropriate and consistent with other HIV trials [see Table 5.3.A]. Follow-up of enrolled subjects is acceptable with few subjects discontinuing for unknown reasons. Finally, the data is coded appropriately based upon comparison of verbatim AE terms with coded preferred MedDRA terms, Version 11.0.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

In several safety analyses, all doses in Protocol 004 are combined with Protocol 021 due to similar populations.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The 400 mg BID marketed raltegravir dose was received by 281 subjects in Protocol 021 with a mean exposure of 344 days during Week 48 analysis. An additional 41 subjects were randomized to this raltegravir dose in Protocol 004 with a mean exposure of 658 days.

7.2.2 Explorations for Dose Response

Protocol 021 uses the 400 mg BID raltegravir dose to compare to efavirenz, each in combination with FTC/TDF. No new Phase 2 dose-finding safety datasets are included in this sNDA. The Phase 2 Protocol 004 datasets were included in the traditional approval sNDA and are not re-reviewed with this supplement. In general, safety analyses of Protocol 004 did not detect clinically significant dose dependent AEs.

7.2.3 Special Animal and/or In Vitro Testing

Appropriate preclinical testing has been performed.

7.2.4 Routine Clinical Testing

The routine clinical and laboratory testing performed in Protocol 021 is adequate to assess safety (Section 5.3). The evaluations occurred at baseline, Week 2, 4, 8, 12, 16, every 8 weeks through Week 48 and then every 12 weeks through Week 96.

7.2.5 Metabolic, Clearance, and Interaction Workup

The metabolic, clearance and interaction evaluation of raltegravir has been adequate.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There are no other approved integrase inhibitors.

7.3 Major Safety Results

7.3.1 Deaths

Two subjects died in Protocol 021, both in the raltegravir group (2/281, 0.7%). The calculated mortality rate is 0.6 per 100 patient years of raltegravir exposure. The deaths were considered not related to study treatment and I agree with investigator assessment based on narrative review. One death is associated with an AIDS-defining illness and the other death resulted from trauma. Further details regarding these deaths are provided:

AN 23290 28 year old black man with baseline HIV-1 RNA 319,000 copies/mL and CD4 cell count 23 cells/mm^3. On Day 57 the subject was hospitalized with immune reconstitution syndrome (IRS) due to Kaposi's sarcoma manifested as abdominal pain, lymphadenopathy, fever, bloody stools and rectal/cecal lesions. On admission HIV-1 RNA was 103 copies/mL and CD4 cell count 155 cells/mm^3. Rectal and inguinal lymph node biopsies confirmed Kaposi's sarcoma. The subject improved; however, he required readmission on Days 71 through 79 and discontinued from the trial Day 72 due initiation of chemotherapy (bleomycin). Blood transfusions were refused for treatment of anemia and thrombocytopenia. The subject moved to another city. He died Day 106 after presenting to an emergency room with pain and hemoptysis. The cause of death was cardiopulmonary arrest, pneumonia, disseminated Kaposi's sarcoma and AIDS. The investigator assessed these events as not drug-related.

AN 23499 57 year old Asian man was found unconscious on Day 90 with a posterior head wound compatible with violence. The CT scan showed bilateral occipital lobe intracerebral hematomas. The subject died Day 96 of these injuries. The investigator assessed this event as not drug-related.

No deaths occurred during the SUR period. In Protocol 004, one subject in the efavirenz group died of gastrointestinal carcinoma on Day 679.

7.3.2 Nonfatal Serious Adverse Events

A total of 54 subjects experienced a nonfatal SAE on treatment or within 30 days of discontinuation: 26 (9.3%) in the raltegravir group and 28 (9.9%) in the efavirenz group. The

majority of these SAEs occurred during the Week 48 period (52/54, 96.3%). Most nonfatal SAEs were infections and occurred in the first 24 weeks of therapy.

Table 7.3.2.A: Protocol 021: Nonfatal Serious Adverse Events in ≥1% Raltegravir-Treated Subjects, by System Organ Class, Double Blind, Week 48 Analysis

	Week 24		Week 48	
	Raltegravir N=281	**Efavirenz N=282**	**Raltegravir N=281**	**Efavirenz N=282**
Infections and infestations – n (%)	11 (3.9)	8 (2.8)	12 (4.3)	10 (3.5)
Immune System Disorders – n (%)	4 (1.4)	2 (0.7)	4 (1.4)	2 (0.7)
Gastrointestinal Disorders – n (%)	3 (1.1)	2 (0.7)	3 (1.1)	3 (1.1)

Source: AE dataset for Protocol 021

Frequent SAEs regardless of causality reported in at least two raltegravir-treated subjects include IRS. Frequent SAEs regardless of causality reported in at least two efavirenz-treated subjects include Kaposi's sarcoma, pneumonia, IRS and appendicitis.

Drug-Related Nonfatal Serious Adverse Events

I performed a causality assessment of investigator determined drug-related nonfatal SAEs, defined as "definitely", "possibly" or "probably" related to study drug. My narrative review supports investigator assessment and identifies 10 drug-related nonfatal SAEs in 9 subjects, including 3 raltegravir-treated subjects. Table 7.3.2.B lists the drug-related nonfatal SAEs.

Table 7.3.2.B: Protocol 021: Drug-Related Nonfatal Serious Adverse Events, by Preferred Term, Double Blind, Week 48 Analysis

	Raltegravir N=281		Efavirenz N=282	
	n	%	n	%
Subjects with ≥1 Drug-Related SAE	3	1.1	6	2.1
Immune System Disorders				
Immune reconstitution syndrome	2	0.7	1	0.4
Psychiatric Disorders				
Mental disorder	1	0.4	1	0.4
Schizoaffective disorder	0	0	1	0.4
Neoplasms Benign, Malignant and Unspecified				
Kaposi's sarcoma	0	0	1	0.4
Lymphoma	0	0	1	0.4
Infections and Infestations				
Pneumocystis jiroveci pneumonia	0	0	1	0.4
Gastrointestinal Disorder				
Gastrointestinal disorder	0	0	1	0.4

Source: AE dataset for Protocol 021

Overall drug-related nonfatal SAEs are balanced between the two groups. The types of drug-related nonfatal SAEs varied and no identified pattern is observed. The SUR contains two additional raltegravir SAE cases. Details on drug-related nonfatal SAEs in raltegravir-treated subjects are summarized in Table 7.3.2.C, with IRS cases discussed further in Section 7.3.4.

Table 7.3.2.C: Protocol 021: Drug-related Nonfatal SAEs in Raltegravir-Treated Subjects through SUR

AN	Preferred Term	Onset Day	Duration (Days)	Recovered	Action (Day)	Misc
Week 48						
23321	Immune reconstitution syndrome	29	2	Yes	Continued raltegravir	
23345	Immune reconstitution syndrome	7	339	Yes	Continued raltegravir	(+)MAC
23370	(b) (4) (insomnia, vivid dreams)	76	27	Yes	D/C (90)	Hx anxiety, on alprazolam Incorrectly received EFV Day 85-90
SUR Additional Cases						
23236	Anemia	512	Ongoing	No	Continued raltegravir	(+)MAC, on valganciclovir
23291	Nausea, Aphasia, Disturbance in attention, Dizziness, Headache, Tremor, Dysphemia	447	5	Yes	Continued raltegravir	Recent cessation of cannabis use. Negative work up for etiology, recovered without treatment.

Source: AE SUR dataset for Protocol 021

MO Comment: At the time of this review, the Applicant proposes to include (b) (4) in the *Less Common Adverse Reaction* section of the label. I do not think this term merits inclusion in this label section because (b) (4) does not represent a consistent definition as outlined in the below subject narratives.

Two raltegravir-treated subjects and one efavirenz-treated subject experienced (b) (4) in Protocol 021.

AN 23370 33 year old white man with a history of anxiety randomized to the raltegravir arm. On Day 2 he experienced severe vivid dreams and dizziness associated with mild abdominal cramps. On Day 6 he experienced myalgia followed by headache and insomnia one and seven days later, respectively. All AEs with the exception of vivid dreams resolved and the subject did well until Day 61 when he experienced severe insomnia prompting medical evaluation on Day 76. On Day 76 the term (b) (4) was assigned to describe *insomnia and vivid dreams* considered related to study medication. Of note, the reported term for this event is "Physiological malfunction arising from mental factors". Alprazolam was prescribed and nine days later the subject reported the symptoms were improved, although not resolved. On that follow up visit (Day 85), efavirenz was mistakenly dispensed instead of raltegravir. Subsequently the subject experienced worsened dizziness, malaise, insomnia, tiredness and "bad quality of life" leading to trial discontinuation on Day 90.

AN 23197 42 year old white man with a history of depression and anxiety randomized to the raltegravir arm. On Day 87 the subject experienced (b) (4) considered related to study medication. This AE was associated with *dizziness, headache, memory impairment, anxiety and confusion*. All AEs continued and the subject ultimately discontinued raltegravir Day 103.

AN 20026 31 year old white man with a history of syphilitic meningitis randomized to the efavirenz arm. On Day 268 the subject experienced (b) (4) including *depersonalization, vertigo, memory disorder, irritability and nightmares*. On Day 337 efavirenz was discontinued and the symptoms resolved.

7.3.3 Dropouts and/or Discontinuations

Week 48 analysis demonstrates approximately 9% and 12% of subjects discontinued Protocol 021 in the raltegravir and efavirenz groups, respectively, with clinical AEs the most common reason (Table 6.1.3.A). A total of 8 raltegravir-treated subjects and 17 efavirenz-treated subjects discontinued due to AEs during the Week 48 analysis, and CRFs are submitted for these subjects. No pattern of discontinuation due to AEs is evident in raltegravir-treated subjects and the types of AEs leading to treatment discontinuation are consistent with the illnesses seen in this patient population. Of note, I do not include subject AN 20006 in this table. AN 20006 developed fatigue on Day 2 ultimately leading to trial discontinuation on Day 576. Because this subject remained on therapy until discontinuation, I consider this case as one occurring outside the Week 48 window.

Table 7.3.3.A: Protocol 021: Adverse Events Leading to Treatment Discontinuation, Double Blind, Week 48 Analysis

	Raltegravir N=281		Efavirenz N=282	
	n	**%**	**n**	**%**
# Subjects with any AE leading to D/C[1]	**8**	**2.8**	**17**	**6.0**
Infections and Infestations	**3**	**1.1**	**3**	**1.1**
Extrapulmonary tuberculosis	1	0.4	0	0
Hepatitis B	1	0.4	0	0
Meningitis	1	0.4	0	0
Bacteremia	0	0	1	0.4
Pneumonia	0	0	1	0.4
Pulmonary tuberculosis	0	0	1	0.4
Psychiatric Disorders	**3**	**1.1**	**3**	**1.1**
Mental disorder	2	0.7	1	0.4
Anxiety	1	0.4	0	0
Schizoaffective disorder	0	0	1	0.4
Sleep disorder	0	0	1	0.4
Immune System Disorders	**1**	**0.4**	**0**	**0**
Immune reconstitution syndrome	1	0.4	0	0
Neoplasms Benign, Malignant and Unspecified	**1**	**0.4**	**2**	**0.7**
Kaposi's sarcoma	1	0.4	1	0.4
Anal cancer	0	0	1	0.4
Nervous System Disorders	**1**	**0.4**	**2**	**0.7**
Cerebral hemorrhage	1	0.4	0	0
Dizziness	0	0	1	0.4
Dystonia	0	0	1	0.4
Skin and Subcutaneous Tissue Disorders	**0**	**0**	**5**	**1.8**
Rash	0	0	3	1.1
Dermatitis allergic	0	0	1	0.4
Drug eruption	0	0	1	0.4
Investigations	**0**	**0**	**2**	**0.7**
Elevated hepatic enzymes	0	0	2	0.7
Gastrointestinal Disorders	**0**	**0**	**1**	**0.4**
Diarrhea	0	0	1	0.4
General Disorders and Administration	**0**	**0**	**1**	**0.4**
Pain	0	0	1	0.4
Metabolism and Nutrition Disorders	**0**	**0**	**1**	**0.4**
Anorexia	0	0	1	0.4

Source: AE dataset for Protocol 021

[1] Although a subject may have had two or more clinical adverse experiences, the subject is counted only once within a category. The same subject may appear in different categories.

Further details for AE-related discontinuation in the eight raltegravir-treated subjects are provided. Section 7.3.5 provides more information on psychiatric AE analyses:

AN 20008 38 year old man with a history of anxiety developed moderate drug-related anxiety on Day 1 leading to alprazolam treatment Day 15-79 with switch to clonazepam Day 80, raltegravir discontinuation Day 87 and trial discontinuation Day 107. The subject has not recovered at the time of SUR database lock.

AN 23197 Please refer to Section 7.3.3 for details (b) (4)

AN 23290 Please refer to Section 7.3.1 for details on IRS and ultimately fatal Kaposi's sarcoma.

AN 23370 Please refer to Section 7.3.3 for details (b) (4)

AN 23436 47 year old woman with a history of "acid fast bacilli infection", esophageal candidiasis developed moderate esophagitis requiring hospitalization Day 27 leading to raltegravir discontinuation Day 29. Severe extrapulmonary tuberculosis of the brain and right axilla was diagnosed Day 40 following hospitalization for slurred speech, right facial numbness and drooling. The subject discontinued from the trial Day 94 due to extrapulmonary tuberculosis. The subject has not recovered at the time of SUR database lock.

AN 23499 Please refer to Section 7.3.1 for details on fatal cerebral hemorrhage resulting from head injury.

AN 24757 31 year old woman developed moderate chronic meningitis Day 48 determined to be chronic lymphocytic meningitis without an identified etiology. The subject was treated with antituberculosis therapy and steroids. Raltegravir was discontinued Day 57 and the subject recovered Day 96 although antituberculosis therapy continued.

AN 24762 48 year old man with chronic hepatitis B developed elevated liver enzymes Day 110 determined secondary to hepatitis B reactivation. The subject discontinued raltegravir and FTC/TDF Day 112 and discontinued the trial Day 182. Liver enzymes began to decrease by Day 133 and the subject recovered from hepatitis B reactivation Day 170.

7.3.4 Significant Adverse Events

Malignancy

At the time of accelerated approval in HIV-1 treatment-experienced subjects, the raltegravir group had higher malignancy rates compared to control (2.3 in raltegravir versus 1.9 in control, adjusted for exposure). Further analysis during traditional approval did not support a causal association between raltegravir exposure and malignancies (both raltegravir and control groups with malignancy rates of 2.1, adjusted for exposure). The initial malignancy imbalance between raltegravir and control arms appears to reflect a paucity of malignancies in control subjects rather

than an increased malignancy rate in general or an increase in a specific malignancy. With longer follow up, the imbalance between the two groups diminished, no apparent pattern to the types of malignancies is observed and the identified malignancies are expected in this heavily treatment-experienced HIV population.

The currently approved label states in the **ADVERSE REACTIONS, Clinical Trials Experience**, Adverse Events, *Regardless of Drug Relationship* section:

> Cancers were reported in treatment-experienced subjects who initiated ISENTRESS with OBT; several were recurrent. The types and rates of specific cancers were those expected in a highly immunodeficient population (many had CD4+ cell counts below 50 cells/mm^3 and most had prior AIDS diagnoses). The cancers included Kaposi's sarcoma, lymphoma, squamous cell carcinoma, hepatocellular carcinoma and anal cancer. Most subjects had other risk factors for cancer including tobacco use, papillomavirus and active hepatitis B virus infection. It is unknown if these cancer diagnoses were related to ISENTRESS use.

Table 7.3.4.A summarizes malignancies in treatment-naïve subjects from the Phase 2 and 3 studies. In Protocol 021, 0.4% of raltegravir-treated subjects versus 3.2% of efavirenz-treated subjects experienced a malignancy. One raltegravir-treated subject experienced fatal Kaposi's sarcoma as discussed in Section 7.3.1. No other malignancies occurred in raltegravir-treated subjects through the SUR reporting period. In efavirenz-treated subjects, a total of nine malignancies occurred: six Kaposi's sarcomas and one case each of anal cancer, lymphoma and bone cancer. In Protocol 004, no new malignancies occurred from the time of traditional approval. The previously reported Protocol 004 malignancies include four raltegravir-treated subjects with Kaposi's sarcoma recurrence (N=2), lymphoma (N=1) and squamous cell/basal cell carcinoma (N=1) and one efavirenz-treated subject who developed squamous cell carcinoma of the vocal cord and subsequent metastatic poorly differentiated adenocarcinoma.

Table 7.3.4.A: Malignancies in Phase 2 and 3 Treatment-Naïve Studies, through SUR

AN	Age/Sex/ Race	Term	Trial Day AE Onset	Treatment Phase	Outcome
Raltegravir 200 mg bid					
Protocol 004					
15	60/M/Hispa	B-cell lymphoma	968	Extension	Not recovered
336	44/M/White	Basal cell ca Squamous cell ca (leg)	557 557	Extension Extension	Not recovered Not recovered
Raltegravir 400 mg bid					
Protocol 004					
12	55/M/White	Kaposi's sarcoma**	409	Double-Blind	Recovered
165	35/M/White	Kaposi's sarcoma**	504	Extension	Not recovered
Protocol 021					
23290	28/M/Black	Kaposi's sarcoma	57	Double-Blind	Fatal
Efavirenz 600 mg qhs					
Protocol 004					
163	48/M/White	Squamous cell ca (Vocal cord) Metastatic adenoca	207 552	Double-Blind Extension	Recovered Fatal
Protocol 021					
20046	40/M/Hispa	B-cell lymphoma	122	Post-Study (D/C Day 94)	Not recovered
20068	42/M/White	Kaposi's sarcoma	76, 282	Double-Blind	Recovered
23178	51/M/White	Kaposi's sarcoma**	190	Double-Blind	Recovered
23211	35/M/White	Kaposi's sarcoma**	57	Double-Blind	Recovered
23213	44/M/White	Anal cancer	189	Double-Blind	Recovered
23336	43/M/Hispa	Kaposi's sarcoma**	137	Double-Blind	Recovered
23416	28/M/White	Kaposi's sarcoma	28	Double-Blind	Not recovered
23476	35/M/Multi	Kaposi's sarcoma**	137	Double-Blind	Not recovered
23500	26/M/Asian	Bone neoplasm malignant	231	Double-Blind	Not recovered

Source: AE SUR datasets for Protocols 004 and 021
SD = Study Drug, ca = carcinoma, adenoca = adenocarcinoma
** Recurrent

In treatment-experienced subjects, an additional 11 raltegravir-treated subjects experienced a malignancy since the time of traditional approval, of which four were recurrences. The expanded access and investigator initiated study programs report 87 malignancies through the time of SUR, 13 more than at the time of traditional approval. The cancers reported in the treatment-experienced trials and expanded access program remain consistent with the advanced nature of the HIV infection for this patient population and no apparent pattern to the types of malignancies is observed.

In summary, the occurrence of malignancies in the raltegravir development program does not appear directly attributable to raltegravir. Furthermore, in the treatment-naïve trials, raltegravir-treated subjects have lower malignancy rates compared to efavirenz-treated subjects. Nonetheless, an active surveillance program for malignancies has been undertaken by the Applicant as a prior postmarketing commitment. I agree with the Applicant's proposed label revision.

Proposed label revision
The Applicant's proposed labeling change in the **ADVERSE REACTIONS, Clinical Trials Experience**, Selected Adverse Experiences section related to malignancies is acceptable:

> Cancers were reported in treatment-experienced subjects who initiated ISENTRESS or placebo, both with OBT, and in treatment-naïve subjects who initiated ISENTRESS or efavirenz, both with emtricitabine (+) tenofovir; several were recurrent. The types and rates of specific cancers were those expected in a highly immunodeficient population (many had CD4+ counts below 50 cells/mm3 and most had prior AIDS diagnoses). The risk of developing cancer in these studies was similar in the group receiving ISENTRESS and the group receiving the comparator.

Rash

No cases of Stevens-Johnson syndrome or erythema multiforme are reported in Protocol 021. To allow more focused analyses of rash, I selected the following preferred terms to define "rash event": exfoliative rash, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash vesicular, drug eruption, toxic skin eruption. A total of 77 subjects experienced rash events, 8% in the raltegravir group and 20% in the efavirenz group. No rashes are SAEs. No raltegravir-treated subjects interrupted therapy due to rash, while four efavirenz-treated subjects discontinued due to rash and two efavirenz-treated subjects interrupted therapy due to rash. The majority of rash AEs are mild in intensity. Of the 30 subjects with moderate-severe rash AEs, three moderate intensity rashes occurred in raltegravir-treated subjects (1.1%) and the remaining events occurred in efavirenz-treated subjects (9.6%). Drug-related rash AEs occurred in 5 (1.8%) raltegravir-treated subjects and 41 (14.5%) efavirenz-treated subjects.

A listing of the individual preferred terms of the "rash event" definition, compared between the raltegravir and efavirenz arms, is presented in the following table (Table 7.3.4.B). Most rash AEs occurred in the first 24 weeks. The median time to rash onset and resolution is longer in raltegravir-treated subjects: 57 days (mean 111 days) in raltegravir-treated subjects versus 11 days (mean 25 days) in efavirenz-treated subjects. The median time to resolution in raltegravir-treated subjects is 34 days (mean 44 days) compared with 8.5 days (mean 25 days) in efavirenz-treated subjects. The postmarketing section of the label currently reports rash and Stevens-Johnson syndrome. This sNDA rash analysis does not support further label changes.

Table 7.3.4.B: Protocol 021: "Rash Event" Preferred Terms, Double Blind, Week 48 Analysis

	Week 24		Week 48	
	Raltegravir N=281	Efavirenz N=282	Raltegravir N=281	Efavirenz N=282
	n (%)	n (%)	n (%)	n (%)
Subjects with ≥1 Rash AE[1]	**15 (5.3)**	**55 (19.5)**	**21 (7.5)**	**56 (19.9)**
Rash	9 (3.2)	32 (11.3)	13 (4.6)	33 (11.7)
Rash erythematous	0	2 (0.7)	0	2 (0.7)
Rash generalized	0	1 (0.4)	0	1 (0.4)
Rash macular	1 (0.4)	3 (1.1)	1 (0.4)	3 (1.1)
Rash maculopapular	2 (0.7)	9 (3.2)	2 (0.7)	9 (3.2)
Rash papular	3 (1.1)	6 (2.1)	4 (1.4)	6 (2.1)
Rash pruritic	0	1 (0.4)	1 (0.4)	1 (0.4)
Rash vesicular	0	1 (0.4)	0	1 (0.4)
Drug eruption	0	2 (0.7)	0	2 (0.7)

Source: AE dataset for Protocol 021
[1] Although a subject may have had two or more clinical adverse experiences, the subject is counted only once within a category. The same subject may appear in different categories.

Hypersensitivity

Hypersensitivity is defined by the preferred terms "hypersensitivity" and "drug hypersensitivity". Two subjects were excluded from further analysis: AN 23328 with a REPTTERM "allergic reaction to antibiotics" and AN 23436 with "sulfonamide allergy". Two additional subjects experienced mild hypersensitivity: one raltegravir-treated subject and one efavirenz-treated subject. Neither event is an SAE and neither resulted in trial discontinuation. Hypersensitivity in the raltegravir-treated subject (AN 24753) was considered drug-related by the investigator and resolved within three hours.

Hypersensitivity is labeled in the Treatment-Experienced *Less Common Adverse Reactions* section. I do not recommend addition of hypersensitivity in the similar Treatment-Naïve section because only a single mild event occurred in a raltegravir-treated subject. Furthermore, no hypersensitivity events are reported in Protocol 004.

Immune Reconstitution Syndrome

Patients initiating a new potent antiretroviral regimen may develop an inflammatory response to an underlying opportunistic infection or noninfectious agent as their immune function improves. Protocol 021 required investigators to evaluate the association of each AE with an immune reconstitution response. My analysis differs from the Applicant because I include AN 20046 (randomized to the efavirenz group, who was diagnosed with lymphoma within 30 days of efavirenz discontinuation).

A total of 29 subjects experienced an AE related to IRS as determined by the investigator: 17 raltegravir, 12 efavirenz with a mean time of onset of 22 and 23 days, respectively. There is no imbalance between the two groups overall. One raltegravir-treated subject with an IRS-related AE died (Section 7.3.1). Four raltegravir-treated subjects experienced non-fatal SAEs of IRS compared with three efavirenz-treated subjects (two IRS, one lymphoma). The following table lists IRS-related AEs by preferred term:

Table 7.3.4.C: Protocol 021: Immune Reconstitution Response: Associated Preferred Terms, Double Blind, Week 48 Analysis

	Raltegravir N=281		Efavirenz N=282	
	n	**%**	**n**	**%**
Subjects with ≥1 Immune Reconstitution Related Event	17	6.0	12	4.3
Ear and Labyrinth Disorders				
Motion sickness	0	0	1	0.4
Gastrointestinal Disorders				
Diarrhea	1	0.4	0	0
Gastritis	2	0.7	0	0
Nausea	0	0	1	0.4
Periodontitis	1	0.4	0	0
General Disorders and Administration Site Conditions				
Pyrexia	0	0	1	0.4
Immune System Disorders				
Immune reconstitution syndrome	5	1.8	2	0.7
Infections and Infestations				
Body tinea	1	0.4	0	0
Folliculitis	2	0.7	0	0
Herpes simplex	1	0.4	1	0.4
Herpes zoster	2	0.7	2	0.7
Onychomycosis	1	0.4	0	0
Oral herpes	0	0	1	0.4
Perianal abscess	1	0.4	0	0
Respiratory tract infection	1	0.4	0	0
Tuberculosis gastrointestinal	1	0.4	0	0
Upper respiratory tract infection	2	0.7	0	0
Injury, Poisoning and Procedural Complications				
Skin injury	1	0.4	0	0
Neoplasms Benign, Malignant and Unspecified				
B-cell lymphoma	0	0	1	0.4
Skin papilloma	1	0.4	0	0
Nervous System Disorders				
Headache	1	0.4	1	0.4
Psychiatric Disorders				
Depression	1	0.4	0	0

Insomnia	1	0.4	0	0
Nightmare	1	0.4	1	0.4
Reproductive System and Breast Disorders				
Epididymitis	0	0	1	0.4
Respiratory, Thoracic and Mediastinal Disorders				
Pharyngolaryngeal pain	1	0.4	0	0
Skin and Subcutaneous Tissue Disorders				
Rash	2	0.7	0	0
Rash papular	0	0	1	0.4
Rosacea	0	0	1	0.4

Source: AE dataset for Protocol 021

The current label contains **Immune Reconstitution Syndrome** in the **WARNINGS AND PRECAUTIONS** section and I do not recommend additional labeling changes based on Protocol 021 review.

Hepatic Events

Mouse and rat carcinogenicity studies detected focal liver necrosis. In eight day intravenous toxicity studies dogs dosed with ≥100 mg/kg raltegravir had liver enzyme elevation (without corresponding histopathological changes). The systemic exposure at this dose was about 12-fold the AUC value at the clinical raltegravir 400 mg BID dose. The current label includes hepatitis in the Treatment-Experienced *Less Common Adverse Reaction* section due to 11 hepatic SAEs in the Phase 2 and 3 trials, with one hepatitis event assessed as possibly related to study therapy.

My Protocol 021 hepatic analyses use the following preferred terms to define "hepatic event", recognizing the laboratory-related AEs do not have prespecified grading criteria: abdominal pain upper, hepatic congestion, hepatitis, hepatomegaly, hepatosplenomegaly, ALT increased, AST increased, blood alkaline phosphatase increased, blood bilirubin increased, GGT increased. Of note, these are similar terms used in the traditional approval review, omitting terms not occurring in Protocol 021.

A total of 72 hepatic events occurred in 48 subjects during the Week 48, double-blind phase. The following table (Table 7.3.4.D) presents the results of this analysis. Hepatic events occurred in approximately 8% of raltegravir-treated subjects and 10% in efavirenz-treated subjects.

Table 7.3.4.D: Protocol 021: Hepatic Events, Double Blind, Week 48 Analysis

Preferred Term	Raltegravir N=281 n (%)		Efavirenz N=282 n (%)	
	n	%	n	%
Subjects with ≥1 Hepatic Event[1]	**21**	**7.5**	**27**	**9.6**
AST increased	13	4.6	14	5.0
ALT increased	9	3.2	13	4.6
Abdominal pain upper	5	1.8	8	2.8
Blood alkaline phosphatase increased	2	0.7	5	1.8
Hepatomegaly	2	0.7	0	0
Hepatitis	0	0	1	0.4

Source: AE dataset for Protocol 021
[1] Although a subject may have had two or more clinical adverse experiences, the subject is counted only once within a category. The same subject may appear in different categories.

One efavirenz-treated subject experienced SAEs of increased AST and alkaline phosphatase ultimately leading to trial discontinuation. There were no other SAEs and no additional hepatic AEs leading to trial discontinuation. All clinical hepatic AEs are mild or moderate intensity.

Twenty-three subjects experienced drug-related hepatic events: 8 (2.8%) in the raltegravir group and 15 (5.3%) in the efavirenz group. Of those events in raltegravir-treated subjects, the majority are laboratory-related (N=6) with the remaining two subjects experiencing upper abdominal pain. No raltegravir-treated subjects required study drug interruption. One raltegravir-treated subject with upper abdominal pain (AN 23279) had continued symptoms at the time of the SUR database lock despite omeprazole and metoclopromide initiation on Day 15; however, this subject entered the trial with an active history of epigastric pain

Outside the 48 week, double-blind phase there are no SAEs or trial discontinuations due to hepatic AEs.

Laboratory Data
Table 7.3.4.E shows the rates of AST, ALT, alkaline phosphatase and bilirubin abnormalities from Protocol 021 during the Week 48, double-blind phase. Overall, the rates of liver enzyme elevations are similar between the raltegravir and efavirenz arms. Six raltegravir-treated subjects have Grade 3 or 4 AST/ALT values. Two subjects were co-infected with HCV (AN 23383 and 24760), one subject with chronic HBV experienced HBV reactivation (AN 24762), and one subject was newly diagnosed with HCV (AN 20027). The two remaining subjects had isolated elevated liver enzymes with resolution on therapy and had no pertinent past medical history, concomitant AEs or new initiation of medications.

Elevated bilirubin only occurs in the raltegravir arm (5.7%, N=16) and most are Grade 1 or 2 (94%, 15/16). The majority of subjects with elevated total bilirubin levels have elevated or upper limit of normal indirect bilirubin (81%, 13/16). The median time to maximum treatment-emergent bilirubin elevation is 223 days (range 14-337 days), bilirubin normalized in all but two

subjects by Week 48 and in most cases the elevated levels are intermittent. No subjects with elevated bilirubin experienced SAEs within two weeks of the elevated value and all subjects continued dosing. All subjects are men with a median age of 39 years: 10 are white, four are hispanic, one is black and one is multicultural. Evaluation of prior and current medical history does not provide a common predisposing etiology: one subject was HCV co-infected (AN 24760), one subject ultimately was diagnosed with cholecystitis (AN 20003), one subject started valganciclovir four days prior to bilirubin elevation (AN 20071), one subject had a prior history of elevated bilirubin (AN 20071), one subject was bitten by a dog two weeks prior to bilirubin elevation and received HBV vaccination one week prior to bilirubin elevation (AN 20106), one subject started zopiclone, hydroxyzine and escitalopram 10 days prior to bilirubin elevation and experienced mild diarrhea eight days prior to bilirubin elevation (AN 23240).

The traditional approval raltegravir sNDA for treatment-experienced subjects found a higher rate of Grade 3/4 total bilirubin in the raltegravir arm compared to control. The majority of subjects with elevated total bilirubin levels had elevated indirect bilirubin (86%, 25/29), and all of these subjects were receiving ATV as part of the OBT. The remaining four subjects had an alternative explanation for hyperbilirubinemia: occurrence in the setting of shock for two subjects and in the setting of transient viral hepatitis reactivation for two subjects.

In summary, elevated bilirubin, primarily Grade 1 and 2 and predominately indirect bilirubin, occurs more frequently in raltegravir-treated subjects. The varied time to onset, lack of associated clinical AEs and resolution while continuing therapy does not support a strong causal relationship; however, the Grade 2-4 laboratory data are included in the label and further analysis will be performed with the 96 week data.

Table 7.3.4.E: Protocol 021: Grade 1 – 4 AST, ALT, Alkaline Phosphatase, Total Bilirubin Laboratory Data, Double Blind, Week 48 Analysis

Laboratory Parameter	Limit	Treatment Arm			
		Raltegravir N=281		Efavirenz N=282	
		n	%	n	%
ALT					
Grade 1	1.25-2.5 x ULN	43	15.3	50	17.7
Grade 2	2.6-5.0 x ULN	12	4.3	15	5.3
Grade 3	5.1-10.0 x ULN	1	0.4	5	1.8
Grade 4	>10.0 x ULN	2	0.7	1	0.4
AST					
Grade 1	1.25-2.5 x ULN	39	13.9	44	15.6
Grade 2	2.6-5.0 x ULN	8	2.8	11	3.9
Grade 3	5.1-10.0 x ULN	3	1.1	4	1.4
Grade 4	>10.0 x ULN	2	0.7	1	0.4
Alkaline Phosphatase					
Grade 1	1.25-2.5 x ULN	26	9.3	46	16.3
Grade 2	2.6-5.0 x ULN	2	0.7	7	2.5
Grade 3	5.1-10.0 x ULN	0	0	1	0.4
Grade 4	>10.0 x ULN	0	0	0	0
Total Bilirubin					
Grade 1	1.1-1.5 x ULN	6	2.1	0	0
Grade 2	1.6-2.5 x ULN	9	3.2	0	0
Grade 3	2.6-5.0 x ULN	1	0.4	0	0
Grade 4	>5.0 x ULN	0	0	0	0

Source: LABCHEM datasets for Protocol 021. ULN = upper limit of normal.

.

Evaluation for Potential Hy's Law Cases

"Hy's Law" is the observation 10-50% of patients with hepatocellular jaundice will have fatal liver failure/transplantation (Zimmerman HJ. Hepatotoxicity (New York: Appleton-Century Crofts), 1978; Bjornsson and Olsson, Hepatology 2005;42:481-9). Hy's Law is operationally defined as:

- AST and/or ALT $\geq$ 3x ULN
- Total bilirubin $\geq$ 2x ULN
- No evidence of obstruction (with a relatively normal alkaline phosphatase)
- No evidence of another cause

One raltegravir-treated subject met initial laboratory screening criteria (AN 24760); however, this subject was HCV co-infected and therefore does not satisfy Hy's Law.

Summary

Hepatic events occurred in approximately 8% of raltegravir-treated subjects, similar to the efavirenz group. No hepatic-related SAEs occurred in raltegravir-treated subjects and all

subjects with hepatic events continued the trial. Laboratory data analysis detects a Grade 1-2 bilirubin imbalance in the raltegravir group without current evidence for a definite causal association. I do not recommend further labeling changes based on this hepatic analysis. The Applicant continues to monitor liver enzyme elevations and related clinical events in clinical studies and postmarketing reports as part of the company's pharmacovigilance plan. In addition, a post-authorization safety study will monitor hepatic encephalopathy and raltegravir discontinuation where liver toxicity is listed as one of the reasons for discontinuation. Please refer to Section 8 for OSE review of postmarketing hepatic cases.

Rhabdomyolysis/Creatine Kinase Elevations

The current label states in the **ADVERSE REACTIONS, Clinical Trials Experience**, Adverse Events, *Regardless of Drug Relationship* section:

> Grade 2-4 creatine kinase laboratory abnormalities were observed in subjects treated with ISENTRESS (see Table 5). Myopathy and rhabdomyolysis have been reported; however, the relationship of ISENTRESS to these events is not known. Use with caution in patients at increased risk of myopathy or rhabdomyolysis, such as patients receiving concomitant medications known to cause these conditions.

There are no reported rhabdomyolysis cases in Protocol 021. Using the preferred terms "myalgia, muscular weakness and myopathy", 6 (2.1%) raltegravir-treated subjects and 13 efavirenz-treated subjects (4.6%) have potential creatine kinase (CK)-related AEs during the Week 48 period. The median onset time is 46 days in the raltegravir group and 92 days in the efavirenz group. No cases are SAEs and all are mild or moderate intensity. One raltegravir-treated subject briefly interrupted therapy for three days without recurrence upon restart. Two raltegravir and four efavirenz cases are considered drug-related. Outside the Week 48 period, three additional subjects had myalgia (raltegravir=2, efavirenz=1), including one raltegravir-treated subject with severe myalgia on Day 449 resolving after five days while continuing study therapy and considered unrelated to study therapy. In addition, subject AN 24760 with a history of HCV developed moderate muscular weakness and intermittent paresthesia Day 282 and had continued symptoms. On Day 378 the subject experienced Grade 2 CK elevation associated with elevated erythroid sedimentation rate and ultimately was admitted with an SAE of severe inflammatory myopathy Day 425 requiring treatment with steroids and immunoglobulin. Raltegravir was continued, the investigator did not consider this AE related to study treatment: this subject recovered after 16 days.

CK values were not routinely collected in Protocol 021; however, CK values are being collected in the ongoing once daily versus BID raltegravir treatment-naïve trial (Protocol 071) and will be evaluated upon data submission for review.

I think the current language in the label is acceptable and do not recommend changes based on review of this supplement.

Renal Events

My renal analyses in Protocol 021 use the following clinical preferred terms to define "renal event": nephrolithiasis, renal colic, renal failure, renal pain and urinary calculus. Of note, these are similar terms used in the traditional approval review, omitting terms not occurring in Protocol 021. Only one raltegravir-treated subject experienced a renal event (mild unrelated renal colic) versus six efavirenz-treated subjects.

Laboratory Data
Table 7.3.4.F contains Protocol 021 creatinine data. More raltegravir-treated subjects have elevated Grade 1 creatinine compared with efavirenz-treated subjects, and one subject has Grade 2. The median time to maximum treatment-emergent creatinine elevation is 105 days (range 15-275 days) and creatinine normalized in most subjects (92%, 12/13) while continuing therapy. Two subjects had SAEs within 14 days of creatinine elevation: AN 23177 was admitted with acute pyelonephritis and AN 23370 developed moderate drug-related mental disorder including vivid dreams as noted in Section 7.3.3 ultimately leading to trial discontinuation. No subjects interrupted therapy due to elevated creatinine levels. Evaluation of prior and current medical history does not provide a common predisposing etiology: one subject had a history of hyperglycemia (AN 23487), one subject was HBV co-infected (AN 21582) and one subject was newly diagnosed with HCV (AN 20027).

Table 7.3.4.F: Protocol 021: Grade 1 – 4 Creatinine Laboratory Data, Double Blind, Week 48 Analysis

Laboratory Parameter	Limit	Treatment Arm			
		Raltegravir N=281		Efavirenz N=282	
		n	%	n	%
Grade 1	1.1-1.3 x ULN	12	4.3	2	0.7
Grade 2	1.4-1.8 x ULN	1	0.4	2	0.7
Grade 3	1.9-3.4 x ULN	0	0	0	0
Grade 4	≥3.5x ULN	0	0	0	0

Source: LABCHEM datasets for Protocol 021. ULN = upper limit of normal.

Summary
There is no imbalance between the two groups in terms of clinical renal events. More raltegravir-treated subjects have Grade 1 creatinine elevations. Tenofovir increases the raltegravir C_{max} approximately 60%. Interestingly, raltegravir does not increase tenofovir concentrations. Perhaps the Grade 1 creatinine elevations are the result of an uncharacterized drug-drug interaction with tenofovir. However, only one subject had ≥ Grade 2 creatinine and subjects were able to continue on therapy with creatinine normalization. Therefore, I think the current labeling information is acceptable.

Pancreatitis

One raltegravir-treated subject with a history of chronic pancreatitis experienced three episodes of pancreatitis on Days 146, 406 and 421. The last episode was ongoing at the time of the SUR; however, the prior two episodes resolved while continued study therapy. No other pancreatitis cases are reported. Although amylase and lipase were not routinely collected in this protocol, there are no ≥ Grade 2 amylase or lipase laboratory values. Therefore, the data do not support a causal relationship between raltegravir and pancreatitis.

Dizziness

Dizziness occurs in 8% raltegravir-treated subjects and in 36% efavirenz-treated subjects (Section 7.4.1). Median onset is two days in the raltegravir group and three days in the efavirenz group. Four (1.4%) raltegravir-treated and 20 (7.1%) efavirenz-treated subjects experienced moderate or severe dizziness; however, no subjects in the raltegravir group had an SAE or discontinued study medication. Outside of the Week 48 period one raltegravir-treated subject (AN 23291) experienced an SAE of dizziness associated with tremor, nausea, dysphemia, aphasia, headache and lack of attention on Day 447 believed secondary to discontinuation of marijuana abuse within the preceding two weeks. This subject recovered without further intervention. Therefore, although the label lists dizziness in the Treatment-Experienced *Less Common Adverse Reaction* section, I do not believe the current Protocol 021 data support a causal relationship between raltegravir and dizziness for this treatment-naïve population.

Abdominal Events

Preclinical data detected gastric mucosal irritation in rodents and the current label includes abdominal pain and gastritis in the **ADVERSE REACTIONS, Clinical Trials Experience** Treatment-Experienced *Less Common Adverse Reaction* section based on review of the traditional approval sNDA. I performed an analysis in Protocol 021 using the following preferred terms based on the MedDRA SMQ "Gastrointestinal nonspecific inflammation" to define "abdominal event": duodenitis, gastritis, esophagitis, reflux esophagitis. In addition, I included the preferred terms abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, epigastric discomfort, gastrointestinal pain and stomach discomfort in the analysis.

A total of 61 subjects experienced 67 abdominal events in Protocol 021 and the rates are balanced between the two groups. Median time of abdominal event onset is 18 days for raltegravir-treated subjects versus 33 days for efavirenz-treated subjects.

Table 7.3.4.G: Protocol 021: Abdominal Events, Double Blind, Week 48 Analysis

	Raltegravir N=281		Efavirenz N=282	
	n	%	n	%
Subjects with ≥1 Abdominal Event[1]	**29**	**10.3**	**32**	**11.3**
Any Abdominal Pain	*23*	*8.2*	*28*	*9.9*
Abdominal discomfort	2	0.7	2	0.7
Abdominal pain	16	5.7	15	5.3
Abdominal pain lower	0	0	3	1.1
Abdominal pain upper	5	1.8	8	2.8
Abdominal tenderness	2	0.7	1	0.4
Gastritis	6	2.1	4	1.4
Esophagitis	1	0.4	0	0
Stomach discomfort	0	0	2	0.7

Source: AE dataset for Protocol 021
[1] Although a subject may have had two or more clinical adverse experiences, the subject is counted only once within a category. The same subject may appear in different categories.

Drug-related abdominal events occur in 3.2% (9/281) of raltegravir-treated subjects versus 4.3% (12/282) of efavirenz-treated subjects. Drug-related abdominal events in the raltegravir group include abdominal pain/tenderness (N=6) and gastritis (N=3). All drug-related abdominal events are mild to moderate intensity and none are SAEs. One efavirenz-treated subject interrupted therapy, the remainder of subjects recovered while continuing study therapy.

One subject in the raltegravir group experienced an abdominal SAE of esophagitis during the double-blind period. Subject AN 23436 had a history of esophageal candidiasis and was hospitalized with moderate esophagitis Day 27 lasting 41 days. This AE was not considered drug-related and the subject recovered while continuing raltegravir.

My abdominal event analysis does not support additional raltegravir labeling changes.

Hypertension

In the traditional approval sNDA, hypertension (HTN) was reported more frequently in the raltegravir arms of the Phase 2 and 3 clinical trials. The majority of subjects with HTN AEs had a prior cardiovascular history and objective analyses of systolic (SBP) and diastolic blood pressures (DBP) did not support a causal association.

An analysis of HTN and treatment-emergent blood pressure elevation was performed for Protocol 021. Preferred terms of "Hypertension" and/or "blood pressure increased" are reported in approximately 3% in each group. Time to onset varied and no raltegravir drug-related events or SAEs occurred. One raltegravir-treated subject (AN 23496) with a history of HTN on baseline antihypertensive therapy interrupted study therapy on Day 29 for 38 days due to

uncontrolled HTN during which time new blood pressure medications were started. This subject recovered Day 57 and resumed therapy Day 66.

Additionally, I performed an analysis of treatment-emergent blood pressure elevation using the DAIDS criteria to assign grade (Tables 7.3.4.H and 7.3.4.I). Seven raltegravir-treated subjects experienced Grade 3 SBP and /or DBP elevation: five had a HTN history and four were on baseline antihypertensive therapy. Three subjects required initiation of new antihypertensive agents. All but one subject recovered.

Table 7.3.4.H: Protocol 021: Treatment-Emergent Systolic Blood Pressure Elevations, Double Blind, Week 48 Analysis

Grade[1]	**Raltegravir N=281**	**Efavirenz N=282**
	n (%)	n (%)
1 (>140-159 mmHg)	25 (8.9)	41 (14.5)
2 (≥160-179 mmHg)	10 (3.6)	8 (2.8)
3 (≥180 mmHg)	4 (1.4)	0 (0)

Source: VITALS dataset for Protocol 021
[1] Grades are defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. December, 2004

Table 7.3.4.I: Protocol 021: Treatment-Emergent Diastolic Blood Pressure Elevations, Double Blind, Week 48 Analysis

Grade[1]	**Raltegravir N=281**	**Efavirenz N=282**
	n (%)	n (%)
1 (>90-99 mmHg)	31 (11.0)	25 (8.9)
2 (≥100-109 mmHg)	14 (5.0)	19 (6.7)
3 (≥110 mmHg)	5 (1.8)	2 (0.7)

Source: VITALS dataset for Protocol 021
[1] Grades are defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. December, 2004

Similar to traditional approval, this Protocol 021 analysis does not support a causal association between raltegravir and HTN.

7.3.5 Submission Specific Primary Safety Concerns

Psychiatric Events

Traditional approval review of the Phase 2 and 3 data did not support a causal relationship between raltegravir and depression or suicidal-related events; however, postmarketing reports of exacerbated depression and suicide/suicidal ideation led to inclusion of this information in the raltegravir label in the **ADVERSE REACTIONS, Postmarketing Experience** section: *depression (particularly in patients with a pre-existing history of psychiatric illness), including*

suicidal ideation and behaviors. Inclusion of these terms in the package insert was initiated by the Applicant through a Changes Being Effected (CBE) supplement. Therefore, I performed additional analysis of psychiatric events in Protocol 021.

Depression and Suicidal Adverse Events

An analysis for events associated with depression and suicide is limited to the following Protocol 021 preferred terms based on the MedDRA SMQ for "Depression and suicide/self-injury": anhedonia, depressive symptom, depressed mood, depression, major depression, suicidal behavior and suicidal ideation. The following table presents the preferred terms by treatment group: no imbalance is noted. Approximately half the subjects in each group have a prior psychiatric history. Median time to onset is 91 days compared to 98 days for the raltegravir and efavirenz groups, respectively. Of note, the median time to onset for the Phase 2 and treatment-experienced Phase 3 population was similar in the raltegravir group, 84 days, compared to 152 days in control. Study therapy continued in all subjects and the majority of depression and suicide-related AEs are mild to moderate intensity, with the exception of two efavirenz-treated subjects with severe suicidal ideation and/or depression. Approximately 30% of these AEs are drug-related in raltegravir-treated subjects and 40% in efavirenz-treated subjects.

Table 7.3.5.A: Protocol 021: Depression and Suicidal AEs, Double Blind, Week 48 Analysis

Preferred Term	**Raltegravir N=281**	**Efavirenz N=282**
	n (%)	n (%)
Subjects with ≥1 AE[1]	**14 (5.0)**	**22 (7.8)**
Depression	11 (3.9)	15 (5.3)
Major Depression	1 (0.4)	0
Depressed Mood	2 (0.7)	5 (1.8)
Anhedonia	0	1 (0.4)
Depressive Symptom	0	1 (0.4)
Suicidal Behavior	0	1 (0.4)
Suicidal Ideation	0	1 (0.4)

Source: AE dataset for Protocol 021

[1] Although a subject may have had two or more clinical adverse experiences, the subject is counted only once within a category. The same subject may appear in different categories.

One subject in each group had an SAE of depression. The raltegravir-treated subject (AN 23327) is a 39 year old man with a history of reactive depression. On Day 152 the subject was hospitalized with psychosis after taking lysergic acid diethylamide (LSD). After 10 days the subject recovered and he was transferred to a depression clinic where he began valproate and reboxetine for worsened reactive depression and was discharged Day 238. The event was not considered drug-related by the investigator. No additional SAEs occurred in raltegravir-treated subjects in the SUR. Please refer to Section 8 for the OSE assessment of postmarketing cases.

Anxiety

An analysis for events associated with anxiety was limited to the following Protocol 021 preferred terms based on the MedDRA high level group term for "Anxiety disorders and symptoms": agitation, anxiety, anxiety disorder, nervousness, panic attack, panic disorder, stress. The following table presents the preferred terms by treatment group: no imbalance is noted. Approximately half the subjects in each group have a prior psychiatric history. Median time to onset in raltegravir-treated subjects is longer, 90 days, compared to 32 days for efavirenz-treated subjects. Four raltegravir-treated and seven efavirenz-treated subjects initiated therapy for anxiety-associated symptoms. Approximately 30% of these AEs are drug-related in raltegravir-treated subjects and 40% in efavirenz-treated subjects. All anxiety-related AEs are mild to moderate intensity and no anxiety-related SAEs are reported. One raltegravir-treated subject discontinued therapy: as noted in Section 7.3.3, a 38 year old man with a history of anxiety was randomized to the raltegravir arm and developed moderate drug-related anxiety on Day 1 leading to alprazolam treatment Day 15-79 with switch to clonazepam Day 80, raltegravir discontinuation Day 87 and trial discontinuation Day 107. The subject has not recovered at the time of SUR database lock.

My analysis does not detect any imbalance of anxiety-related AEs between the two treatment groups and no SAEs are reported. One raltegravir-treated subject discontinued therapy due to continued anxiety; however, this subject did have a prior psychiatric history making causality assessment difficult. Given the current available Protocol 021 clinical data, I do not recommend [redacted] (b) (4) OSE review of postmarketing cases does support addition of anxiety to the postmarketing label section. Please refer to Section 8 for the OSE assessment of postmarketing cases. Further analysis of anxiety events will be performed with the 96 week treatment-experienced and treatment-naïve data.

Table 7.3.5.B: Protocol 021: Anxiety-Related AEs, Double Blind, Week 48 Analysis

Preferred Term	**Raltegravir N=281**	**Efavirenz N=282**
	n (%)	n (%)
Subjects with ≥1 AE[1]	**12 (4.3)**	**14 (5.0)**
Anxiety	9 (3.2)	7 (2.5)
Anxiety disorder	1 (0.4)	0
Agitation	1 (0.4)	0
Nervousness	1 (0.4)	2 (0.7)
Panic attack	1 (0.4)	3 (1.1)
Panic disorder	0	1 (0.4)
Stress	0	1 (0.4)

Source: AE dataset for Protocol 021

[1] Although a subject may have had two or more clinical adverse experiences, the subject is counted only once within a category. The same subject may appear in different categories.

Insomnia

Adverse drug reaction analysis finds moderate-severe insomnia occurring in 4% raltegravir-treated and 3% efavirenz-treated subjects (Section 7.4.1). Further insomnia analysis is performed to better characterize this association using the following preferred terms: insomnia, sleep disorder. The following table presents the preferred terms by treatment group: there is no imbalance between the groups. Subject AN 23370 is the only subject with an insomnia-related SAE (Section 7.3.2). Approximately 15% subjects in each group have a prior insomnia history. Median time to onset in raltegravir-treated subjects is four times longer, 28 days, compared to 6 days for efavirenz-treated subjects. The majority of insomnia-related AEs are mild to moderate intensity (97%) and resolve on study therapy (60%). One raltegravir-treated subject (AN 23370) and one efavirenz-treated subject discontinued therapy for severe insomnia.

Table 7.3.5.C: Protocol 021: Insomnia-Related AEs, Double Blind, Week 48 Analysis

Preferred Term	**Raltegravir N=281**	**Efavirenz N=282**
	n (%)	n (%)
Subjects with ≥1 AE[1]	**31 (11.0)**	**32 (11.3)**
Insomnia	30 (10.7)	29 (10.3)
Sleep disorder	1 (0.4)	3 (1.1)

Source: AE dataset for Protocol 021

[1] Although a subject may have had two or more clinical adverse experiences, the subject is counted only once within a category. The same subject may appear in different categories.

OSE review of postmarketing reports also detects insomnia cases (Section 8) and I think this additional data further supports a causal relationship between raltegravir and insomnia, noting the majority of subjects successfully continue on therapy. Further analysis of insomnia events will be performed with the 96 week treatment-experienced and treatment-naïve data.

Central Nervous System Analysis: Applicant Definition

The Applicant evaluated central nervous system (CNS) AEs as a secondary endpoint in Protocol 021. CNS AEs were originally defined by the following preferred terms: depression, nightmare, confusional state, suicidal ideation, nervous system disorder, psychotic disorder, abnormal dreams, suicide attempt, acute psychosis, delirium, depressed level of consciousness, hallucination, auditory hallucination, completed suicide, and major depression. Additional terms not included in the statistical analysis plan because of an oversight were also included: dizziness, insomnia, somnolence, and concentration impaired. The Applicant uses the Week 8 and Week 48 time points for their analysis.

I am able to replicate the Applicant's findings (Table 7.3.5.D) with minor differences attributed to trial window determination differences. Four CNS events are SAEs, three in efavirenz-treated subjects and one in a raltegravir-treated subject (AN 23327 described under *Depression and Suicidal Adverse Events*).

Table 7.3.5.D: Protocol 021: Central Nervous System AEs using Applicant Definition[1], Double Blind[2]

	Raltegravir N=281		Efavirenz N=282	
	n	%	n	%
Week 8	**60**	**21.4**	**149**	**52.8**
Insomnia	22	7.8	22	7.8
Abnormal dreams	20	7.1	31	11.0
Dizziness	16	5.7	99	35.1
Nightmare	7	2.5	13	4.6
Depression	5	1.8	6	2.1
Major depression	1	0.4	0	0.0
Somnolence	2	0.7	17	6.0
Hallucination, visual	0	0.0	1	0.4
Nervous system disorder	0	0.0	1	0.4
Week 48	**73**	**26.0**	**166**	**58.9**
Insomnia	30	10.7	29	10.3
Dizziness	22	7.8	102	36.2
Abnormal dreams	20	7.1	37	13.1
Depression	11	3.9	15	5.3
Major depression	1	0.4	0	0.0
Nightmare	7	2.5	13	4.6
Somnolence	3	1.1	22	7.8
Confusional state	1	0.4	1	0.4
Psychotic disorder	1	0.4	0	0.0
Hallucination, visual	0	0.0	1	0.4
Nervous system disorder	0	0.0	2	0.7
Suicidal ideation	0	0.0	1	0.4

Source: AE dataset for Protocol 021

[1] Applicant Definition: depression, nightmare, confusional state, suicidal ideation, nervous system disorder, psychotic disorder, abnormal dreams, suicide attempt, acute psychosis, delirium, depressed level of consciousness, hallucination, auditory hallucination, completed suicide, and major depression. Additional terms not included in the statistical analysis plan because of an oversight were also included: dizziness, insomnia, somnolence, and concentration impaired.

[2] Although a subject may have had two or more clinical adverse experiences, the subject is counted only once within a category. The same subject may appear in different categories.

The Applican [redacted] (b) (4) The following comment was sent:

We do not agree with [redacted] (b) (4)

The Applicant responded they disagree with this recommendation because (b) (4)

[redacted]

”

The Applicant’s rationale does not alter my opinion because I do not think th (b) (4)

[redacted]

As detailed above, insomnia occurs more frequently in the raltegravir arm of this treatment-naïve population and depression occurs with similar frequency at Weeks 8 and 48. DDMAC also recommends deletion of this paragraph with the rationale (b) (4)

[redacted]

Ongoing discussion with respect tc (b) (4) continues at the time of this review. Further CNS analysis will be performed on the treatment-experienced and treatment-naïve 96 week Phase 3 data along with future treatment-naïve trials.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

All Cause

Clinical AEs (e.g., not laboratory AEs) are common in trial subjects, occurring in ≥ 90% of all subjects receiving either 400 mg raltegravir BID or efavirenz, each in combination with FTC/TDF (Table 7.4.1.A). Minimal AE profile changes exist between Week 24 and 48 and rates increased similarly for individual AEs between treatment groups over time. The majority of AEs are mild to moderate intensity. The most common AEs occurring in ≥ 10% of raltegravir-treated subjects are headache, diarrhea, nausea, nasopharyngitis, upper respiratory infection and insomnia and are either higher in the efavirenz arm or balanced between treatment arms. Clinical AEs reported in raltegravir-treated subjects with ≥ 2% greater frequency over efavirenz are bolded and include dyspepsia and night sweats.

Table 7.4.1.A: Protocol 021: Clinical Adverse Experiences Reported in ≥ 2% of Raltegravir-Treated Subjects Without Regard to Causality, Double Blind

	Week 24				Week 48			
Preferred Term	**Raltegravir N=281**		**Efavirenz N=282**		**Raltegravir N=281**		**Efavirenz N=282**	
	n	%	n	%	n	%	n	%
Subjects with one or more AE[1]	232	82.6	266	94.3	253	90.0	271	96.1
Headache	43	15.3	59	20.9	56	19.9	62	22.0
Diarrhea	30	10.7	52	18.4	39	13.9	60	21.3
Nausea	37	13.2	32	11.3	39	13.9	34	12.1
Nasopharyngitis	21	7.5	19	6.7	34	12.1	30	10.6
URI	20	7.1	25	8.9	34	12.1	31	11.0
Insomnia	23	8.2	27	9.6	30	10.7	29	10.3
Cough	18	6.4	19	6.7	24	8.5	23	8.2
Dizziness	21	7.5	101	35.8	22	7.8	102	36.2
Pyrexia	16	5.7	22	7.8	22	7.8	24	8.5
Abnormal dreams	20	7.1	35	12.4	20	7.1	37	13.1
Vomiting	13	4.6	20	7.1	18	6.4	24	8.5
Abdominal pain	14	5.0	11	3.9	16	5.7	15	5.3
Dyspepsia	**14**	**5.0**	**7**	**2.5**	**16**	**5.7**	**10**	**3.5**
Fatigue	14	5.0	29	10.3	16	5.7	30	10.6
Arthralgia	11	3.9	8	2.8	16	5.7	13	4.6
Influenza	9	3.2	20	7.1	16	5.7	27	9.6
Pharyngolaryngeal pain	8	2.8	8	2.8	13	4.6	9	3.2
Rash	9	3.2	32	11.3	13	4.6	33	11.7
Asthenia	8	2.8	11	3.9	12	4.3	11	3.9
Back pain	7	2.5	7	2.5	12	4.3	13	4.6
Bronchitis	6	2.1	11	3.9	12	4.3	15	5.3
Depression	7	2.5	11	3.9	11	3.9	15	5.3
Pharyngitis	9	3.2	12	4.3	11	3.9	17	6.0
Sinusitis	9	3.2	5	1.8	11	3.9	11	3.9
Acne	8	2.8	5	1.8	10	3.6	5	1.8
Flatulence	9	3.2	15	5.3	10	3.6	16	5.7
Herpes zoster	5	1.8	5	1.8	10	3.6	10	3.5
Anorexia	9	3.2	9	3.2	9	3.2	11	3.9
Anxiety	8	2.8	6	2.1	9	3.2	7	2.5
Genital herpes	6	2.1	10	3.5	9	3.2	10	3.5
Hypertension	7	2.5	4	1.4	8	2.8	8	2.8
Nasal congestion	7	2.5	4	1.4	8	2.8	6	2.1
Night sweats	**7**	**2.5**	**1**	**0.4**	**8**	**2.8**	**1**	**0.4**
Pruritus	7	2.5	10	3.5	8	2.8	11	3.9
Dermatitis	4	1.4	5	1.8	7	2.5	8	2.8

Lymphadenopathy	5	1.8	3	1.1	7	2.5	4	1.4
Nightmare	7	2.5	13	4.6	7	2.5	13	4.6
Pain	7	2.5	2	0.7	7	2.5	3	1.1
Skin lesion	3	1.1	3	1.1	7	2.5	3	1.1
Folliculitis	4	1.4	4	1.4	6	2.1	5	1.8
Gastritis	6	2.1	3	1.1	6	2.1	4	1.4
GERD	5	1.8	3	1.1	6	2.1	3	1.1
Migraine	3	1.1	0	0	6	2.1	1	0.4
Neck pain	6	2.1	2	0.7	6	2.1	2	0.7
Paresthesia	5	1.8	3	1.1	6	2.1	5	1.8
Productive cough	3	1.1	2	0.7	6	2.1	3	1.1

Source: AE SUR dataset for Protocol 021
[1] Although a subject may have had two or more clinical adverse experiences, the subject is counted only once within a category. The same subject may appear in different categories.
URI- upper respiratory tract infection, GERD – gastroesophageal reflex disease

Drug-Related

Drug-related clinical AE (adverse drug reactions, ADRs) analysis is performed for Protocol 021, limited to the Week 48, double-blind phase. Investigators assessed if the AE is definitely not, probably not, possibly, probably, or definitely related to study therapy (blinded therapy or combination therapy) or open-label FTC/TDF alone. ADRs are those events the investigators assess as possibly, probably, or definitely related to study therapy. Table 7.4.1.B displays Protocol 021 ADRs of moderate to severe intensity occurring in the Week 48, double-blind phase. Insomnia is the only ADR occurring ≥ 2% raltegravir-treated subjects and at a higher frequency compared to efavirenz. ADR analysis using all intensities yields similar results.

Table 7.4.1.B: Protocol 021: Clinical Adverse Drug Reactions of Moderate-Severe Intensity Reported in ≥ 1% of Raltegravir-Treated Subjects, Double Blind, Week 48 Analysis

	Raltegravir N=281		**Efavirenz N=282**	
	n	**%**	**n**	**%**
Subjects with one or more ADR[1]	45	16.0	87	30.9
Preferred Term				
Headache	11	3.9	13	4.6
Insomnia	10	3.6	9	3.2
Nausea	8	2.8	10	3.5
Abnormal dreams	4	1.4	5	1.8
Dizziness	4	1.4	18	6.4
Fatigue	4	1.4	7	2.5
Diarrhea	3	1.1	8	2.8
Nightmare	3	1.1	3	1.1

Source: AE SUR dataset for Protocol 021
[1] Although a subject may have had two or more clinical adverse experiences, the subject is counted only once within a category. The same subject may appear in different categories.

Less Common Adverse Reactions

Section 6.1 **Clinical Trials Experience**, Treatment-Naïve Studies, *Less Common Adverse Reactions* incorporates adverse drug reactions (ADR) occurring "in <2% of subjects receiving ISENTRESS + emtricitabine (+) tenofovir. These events have been included because of their seriousness, increased frequency on ISENTRESS compared with efavirenz or investigator's assessment of potential causal relationship". At the time of this review, (b) (4) abnormal dreams (b) (4) fatigue, (b) (4) With the exception of abnormal dreams and fatigue, I do not think these terms merit inclusion in this label section and have outlined my rationale below.

Abnormal Dreams: The occurrence of abnormal dreams in the common AE and moderate-severe ADR analyses is greater in efavirenz-treated subjects. Median time to onset in both treatment groups is <5 days. Raltegravir-treated subjects have a longer median duration (47 days) compared with efavirenz-treated subjects (15 days); however, the range is similar between the two groups. Four raltegravir-treated and five efavirenz-treated subjects experienced moderate or severe intensity abnormal dreams; however, both severe events occur in the raltegravir group. There are no SAEs or study medication discontinuations due to abnormal dreams. In the treatment-experienced Protocols 018 and 019 four raltegravir-treated and three-placebo treated subjects experienced abnormal dreams: none are associated with SAE or trial discontinuation. I do not believe the current data support a strong causal relationship between raltegravir and abnormal dreams; however, because severe events occurred only in raltegravir-treated subjects, inclusion of abnormal dreams in this section is acceptable.

(b) (4)

Fatigue: Fatigue occurs in approximately twice as many efavirenz-treated subjects as in raltegravir-treated subjects in both the common AE and moderate-severe ADR analyses. Median time to onset is longer in the raltegravir group, 37 days, compared with 2 days in the efavirenz group. Six raltegravir-treated and eight efavirenz-treated subjects experienced moderate or severe intensity fatigue. All severe events occur in the raltegravir group (N=3), including one subject with an active history of fatigue. There are no fatigue-related SAEs and no raltegravir discontinuations due to fatigue. I do not believe the current Protocol 021 data support a strong causal relationship between raltegravir and fatigue; however, because severe fatigue occurred only in raltegravir-treated subjects, inclusion of fatigue in this section is acceptable.

(b) (4)

Immune Reconstitution Syndrome: Because immune reconstitution syndrome is listed in the Section 5.1 **Warnings and Precautions**, (b) (4)

(b) (4)

7.4.2 Laboratory Findings

Guidelines for grading the severity of laboratory abnormalities are based on Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Experiences from December 2004. This Protocol 021 laboratory analysis includes all subjects who had both a baseline and an on-treatment or final laboratory measurement. A subject is included in the analysis as having a Grade X treatment-emergent laboratory value if the highest grade during double-blind treatment is X and this grade is worse than baseline. The following table presents my Week 48 treatment-emergent laboratory value analysis. Discrepancies between the Applicant and FDA analyses occur due to differences in determination of trial visit window; however, because these discrepancies were small and the derived conclusions from each analysis are similar, the Applicant's analysis is in the label. Of note, creatine kinase was not collected and amylase and lipase were not routinely collected in Protocol 021.

Increased treatment-emergent laboratory values in the raltegravir group noted for bilirubin is discussed in more detail in Section 7.3.4.

Table 7.4.2.A: Protocol 021: Treatment-Emergent Laboratory Abnormalities Reported, Double Blind, Week 48 Analysis

Laboratory Parameter	Limit	Treatment Arm			
		Raltegravir N=281		Efavirenz N=282	
		n	%	n	%
Chemistry Laboratory Values					
Fasting (non-random) serum glucose (mg/dL)					
Grade 2	126-250	5	1.8	8	2.8
Grade 3	251-500	1	0.4	0	0
Grade 4	>500	0	0	0	0
Serum ALT (IU/L)					
Grade 2	2.6-5.0 x ULN	12	4.3	15	5.3
Grade 3	5.1-10.0 x ULN	1	0.4	5	1.8
Grade 4	>10.0 x ULN	2	0.7	1	0.4
Serum AST (IU/L)					
Grade 2	2.6-5.0 x ULN	8	2.8	11	3.9
Grade 3	5.1-10.0 x ULN	3	1.1	4	1.4
Grade 4	>10.0 x ULN	2	0.7	1	0.4
Serum Alkaline Phosphatase (IU/L)					
Grade 2	2.6-5.0 x ULN	2	0.7	7	2.5
Grade 3	5.1-10.0 x ULN	0	0	1	0.4
Grade 4	>10.0 x ULN	0	0	0	0
Total Serum Bilirubin (mg/dL)					
Grade 2	1.6-2.5 x ULN	9	3.2	0	0
Grade 3	2.6-5.0 x ULN	1	0.4	0	0
Grade 4	>5.0 x ULN	0	0	0	0
Serum Creatinine (mg/dL)					
Grade 2	1.4-1.8 x ULN	1	0.4	2	0.7
Grade 3	1.9-3.4 x ULN	0	0	0	0
Grade 4	≥3.5 x ULN	0	0	0	0
Serum Amylase (IU/L)[†]					
Grade 2	1.6-2.0 x ULN	0	0	0	0
Grade 3	2.1-5.0 x ULN	0	0	0	0
Grade 4	>5.0 x ULN	0	0	0	0
Serum Lipase (IU/L)[§]					
Grade 2	1.6-3.0 x ULN	0	0	0	0
Grade 3	3.1-5.0 x ULN	0	0	1	5.3
Grade 4	>5.0 x ULN	0	0	0	0
Serum Albumin (g/dL)					
Grade 2	2.0-2.9	8	2.8	5	1.8
Grade 3	<2.0	0	0	0	0

Serum Bicarbonate (mEq/L)					
Grade 2	11.0-15.9	3	1.1	0	0
Grade 3	8.0-10.9	0	0	0	0
Grade 4	<8.0	0	0	0	0
Serum Calcium, high* (mg/dL)					
Grade 2	11.6-12.5	0	0	0	0
Grade 3	12.6-13.5	0	0	0	0
Grade 4	>13.5	0	0	0	0
Serum Calcium, low* (mg/dL)					
Grade 2	7.0-7.7	2	0.7	0	0
Grade 3	6.1-6.9	0	0	0	0
Grade 4	<6.1	0	0	0	0
Serum Phosphorous (mg/dL)					
Grade 2	2.0-2.4	18	6.4	38	13.5
Grade 3	1.0-1.9	2	0.7	5	1.8
Grade 4	<1.0	0	0	0	0
Serum Potassium, high (mEq/L)					
Grade 2	6.1-6.5	0	0	1	0.4
Grade 3	6.6-7.0	0	0	0	0
Grade 4	>7.0	0	0	0	0
Serum Potassium, low (mEq/L)					
Grade 2	2.5-2.9	0	0	2	0.7
Grade 3	2.0-2.4	0	0	0	0
Grade 4	<2.0	0	0	0	0
Serum Sodium, high (mEq/L)					
Grade 2	151-154	0	0	0	0
Grade 3	155-159	0	0	0	0
Grade 4	≥160	0	0	0	0
Serum Sodium, low (mEq/L)					
Grade 2	125-129	2	0.7	2	0.7
Grade 3	121-124	1	0.4	0	0
Grade 4	≤120	1	0.4	0	0
Lipid Laboratory Values					
Fasting Serum Cholesterol (mg/dL)					
Grade 1	200-239	46	16.4	51	18.1
Grade 2	240-300	17	6.0	38	13.5
Grade 3	>300	0	0	7	2.5
Fasting LDL Cholesterol (mg/dL)**					
Grade 1	130-159	33	11.7	43	15.3
Grade 2	160-190	15	5.3	29	10.3
Grade 3	>190	3	1.1	9	3.2
Fasting Triglyceride (mg/dL)					
Grade 2	500-750	0	0	7	2.5

Grade 3	751-1200	1	0.4	0	0
Grade 4	>1200	0	0	2	0.7
Hematologic Laboratory Values					
Absolute Neutrophil Count (10^3/microL)					
Grade 2	0.75-0.999	8	2.8	9	3.2
Grade 3	0.50-0.749	4	1.4	2	0.7
Grade 4	<0.50	1	0.4	0	0
Hemoglobin (gm/dL)					
Grade 2	7.5-8.4	2	0.7	1	0.4
Grade 3	6.5-7.4	2	0.7	2	0.7
Grade 4	<6.5	0	0	0	0
Platelet Count (10^3/microL)					
Grade 2	50-99.999	3	1.1	0	0
Grade 3	25-49.999	0	0	1	0.4
Grade 4	<25	0	0	0	0
White Blood Cell (10^3/microL)					
Grade 2	1.5-1.999	2	0.7	1	0.4
Grade 3	1.0-1.499	0	0	0	0
Grade 4	<1.0	0	0	0	0

Source: FDAREQ11 and LABCHEM datasets for Protocol 021, ULN = upper limit of normal
*Corrected for albumin
†Number of subjects with lipase values: raltegravir group = 15, efavirenz group = 19
§Number of subjects with amylase values: raltegravir group = 14, efavirenz group = 19
**Efavirenz group=281

An analysis of mean changes from baseline in hematologic and chemistry laboratory values is performed for Protocol 021. "Baseline" is defined as Visit 2.0, "Week 12" as Visit 6.0, "Week 24" as Visit 8.0 and "Week 48" as Visit 11. Therefore, this analysis does not capture data obtained outside these visit windows leading to minor differences between the Applicant's and my results.

Table 7.4.2.B summarizes the analysis of laboratory mean changes from baseline.

Table 7.4.2.B: Protocol 021: Change from Baseline for Selected Laboratory Tests, Double Blind, Week 48 Analysis

	Raltegravir			Efavirenz		
	N	**Mean BL Value**	**Mean Change from BL**	**N**	**Mean BL Value**	**Mean Change from BL**
Chemistry						
AST (IU/L)						
Week 24	263	31.0	-4.1	258	31.4	-3.3
Week 48	251	31.1	-3.5	239	31.8	-2.4
ALT (IU/L)						
Week 24	263	33.5	-5.1	258	33.5	-1.5
Week 48	252	33.5	-3.2	242	33.9	-0.5
Bilirubin (mg/dL)						
Week 24	264	0.5	0.1	260	0.5	-0.1
Week 48	253	0.5	0.1	244	0.5	-0.2
Creatinine (mg/dL)						
Week 24	263	0.9	0	259	0.9	0
Week 48	254	0.9	0	244	0.9	0
Hematology						
WBC (10^3/microL)						
Week 24	259	4.8	0.8	258	5.0	0.6
Week 48	246	4.8	1.0	237	4.9	0.9
Hemoglobin (gm/dL)						
Week 24	259	13.5	0.9	257	13.5	0.7
Week 48	245	13.6	1.1	237	13.5	1.0
Platelet (10^3/microL)						
Week 24	248	215.9	38.8	252	220.3	45.3
Week 48	232	214.5	45.1	226	218.6	51.4
ANC (10^3/microL)						
Week 24	260	2.7	0.5	258	2.8	0.5
Week 48	246	2.7	0.7	235	2.7	0.7

Source: LABCHEM and LABHEM datasets for Protocol 021

Lipids

Table 7.4.2.C is the Applicant's proposed lipid table for inclusion in the label **ADVERSE REACTIONS, Clinical Trials Experience** Treatment-Naïve Studies *Lipids, Change from Baseline* section (Table 3 in the proposed label). The Applicant's mean change from baseline is determined by subtracting the baseline mean from the Week 48 mean. This approach differs from the atazanavir label where Week 48 mean change from baseline was calculated as the average value of the difference between Week 48 and baseline within an individual subject. Dr. Qi performed both analyses with comparable results; therefore, we

accept the Applicant's proposed lipid value table for inclusion in the label with recommendations to round the lipid values and percentages to the nearest whole number. In addition, we recommend changing the last sentence to be consistent with the analyses used in the atazanavir label to describe the use of lipid-reducing agents: "At baseline, serum lipid-reducing agents were used in 5% subjects in the ISENTRESS group and 3% in the efavirenz group. Through Week 48, serum lipid-reducing agents were used in 6% in the ISENTRESS group and 6% in the efavirenz group."

Table 7.4.2.C: Lipid Values, Mean Change from Baseline, Protocol 021

Laboratory Parameter Preferred Term	ISENTRESS 400 mg Twice Daily + Emtricitabine (+)Tenofovir N = 281			Efavirenz 600 mg At Bedtime + Emtricitabine (+) Tenofovir N = 282		
			Change from Baseline at Week 48			Change from Baseline at Week 48
	Baseline Mean (mg/dL)	Week 48 Mean (mg/dL)	Mean Change (mg/dL)	Baseline Mean (mg/dL)	Week 48 Mean (mg/dL)	Mean Change (mg/dL)
LDL-Cholesterol†	[redacted] (b) (4)					
HDL-Cholesterol†						
Total Cholesterol†						
Triglyceride†						

†Fasting (non-random) laboratory tests.

Notes:

N = Number of subjects in the treatment group. The analysis is based on all available data.

If subjects initiated or increased serum lipid-reducing agents, the last available lipid values prior to the change in therapy were used in the analysis. If the missing data was due to other reasons, subjects were censored thereafter for the analysis.
At baseline serum lipid-reducing agents were used in [redacted] (b) (4) (5%) in the ISENTRESS group and [redacted] (b) (4) (3%) in the efavirenz group. [redacted] (b) (4) .

7.4.3 Vital Signs

Please refer to Section 7.3.4 for blood pressure analysis. Review of remaining vital signs does not identify clinically relevant differences between the treatment groups.

7.4.4 Electrocardiograms (ECGs)

In a randomized, placebo-controlled, crossover trial, 31 healthy subjects were administered a single oral supratherapeutic dose of raltegravir 1600 mg and placebo. Peak raltegravir plasma concentrations were approximately 4-fold higher than the peak concentrations following a 400 mg dose. Raltegravir did not appear to prolong the QTc interval for 12 hours postdose. After baseline and placebo adjustment, the maximum mean QTc change was -0.4 msec (1-sided 95% upper Cl: 3.1 msec). Please refer to the original NDA clinical review for additional details.

ECGs were not routinely collected in Protocol 021. There were no episodes of PR interval or QT prolongation reported as AEs.

7.4.5 Special Safety Studies

No special safety studies were submitted with this application.

7.4.6 Immunogenicity

Raltegravir is a small molecule, not a peptide; therefore, development of immunogenicity directed against raltegravir was not specifically evaluated.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Only the 400 mg BID raltegravir dose was used in Protocol 021. No new Phase 2 dose-finding safety datasets are included in this sNDA.

7.5.2 Time Dependency for Adverse Events

Evaluation of time dependency for adverse events is integrated in the safety analyses.

7.5.3 Drug-Demographic Interactions

Age

In the raltegravir group (median age 37, range 19-67), 267 subjects (95%) are between 19-55 years, 12 subjects (4%) are between 56-64 years, and 2 subjects (1%) are 65 years or older.

In the efavirenz group (median age 36, range 19-71), 267 subjects (95%) are between 19-55 years, 11 subjects (4%) are between 56-64 years, and 4 subjects (1%) are 65 years or older.

No SAEs or discontinuations due to AE occurred in subjects ≥ 65 years old.

Gender

The majority of subjects in Protocol 021 are men (81%). There are 227 men and 54 women receiving raltegravir and 231 men and 51 women receiving efavirenz. The overall frequency of AEs (all intensities, regardless of causality) is similar within each of the treatment groups.

- Raltegravir: women 87%, men 91%
- Efavirenz: women 94%, men 97%

Comparing the raltegravir-treated men and raltegravir-treated women, the following AEs have a difference of >5%:

- Diarrhea: women 6%, men 16%
- Dizziness: women 2%, men 9%
- Headache: women 11%, men 21%
- Vomiting: women 11%, men 5%

Comparing the efavirenz-treatment men and efavirenz-treated women, the following AEs have a difference of >5%:

- Abdominal pain: women 14%, men 3%
- Cough: women 18%, men 6%
- Diarrhea: women 14%, men 23%
- Dizziness: women 29%, men 38%
- Headache: women 27%, men 21%
- Pruritus: women 10%, men 3%
- Pyrexia: women 4%, men 10%

Comparing the raltegravir-treated men and efavirenz-treated men, no AEs have >5% difference.

Comparing the raltegravir-treated women and efavirenz-treated women, the following AEs have a difference of >5% in the raltegravir group:

- Nasopharyngitis: raltegravir 15%, efavirenz 6%
- Pharyngolaryngeal pain: raltegravir 6%, efavirenz 0%

Race

The overall AE frequency (all grades, regardless of causality) by race is similar within each treatment group.

A few differences in AEs stratified by race are observed. In the raltegravir group:

- Nausea highest in black subjects (24%) compared with white (14%), Hispanic (8%) and Asian (11%) subjects.
- Cough and dizziness highest in Asian subjects (22%, 22%) compared with white (7%, 9%), black (12%, 3%) and Hispanic (7%, 8%) subjects.
- Insomnia and vomiting highest in white subjects (14%, 9%), compared with black (6%, 3%), Hispanic (8%, 0%) and Asian subjects (6%, 8%).

7.5.4 Drug-Disease Interactions

Hepatitis co-infection

A total of 6% of subjects (35/563) are co-infected with HBV and/or HCV in Protocol 021, 18 in the raltegravir group and 17 in the efavirenz group. Hepatitis co-infected status is defined as a positive hepatitis B surface antigen and/or positive hepatitis C (HCV) PCR. I include one additional subject, AN 24742. This subject had a positive HCV antibody with a negative HCV PCR; however the medical history included (+) HCV status. Table 7.5.4.A summarizes AST, ALT, and bilirubin laboratory values in this population. Co-infected subjects have higher transaminases and bilirubin compared to subjects without hepatitis in both groups; however, no discontinuations are related laboratory abnormalities. In addition, raltegravir-treated co-infected subjects have slightly higher ALT and bilirubin compared to efavirenz-treated co-infected subjects; however, the small numbers preclude further causality assessment.

Table 7.5.4.A: Protocol 021: Select Laboratory Data in Subjects with Hepatitis Co-infection, Double Blind, Week 48 Analysis

	Raltegravir-Treated Subjects			Efavirenz-Treated Subjects	
Laboratory Parameter	**HBV/HCV Co-infected N=18 (%)**	**Non Co-infected N=263 (%)**		**HBV/HCV Co-infected N=17 (%)**	**Non Co-infected N=265 (%)**
Serum ALT					
Grade 2	4 (22.2)	8 (3.0)		1 (5.9)	14 (5.3)
Grade 3	0	1 (0.4)		1 (5.9)	4 (1.5)
Grade 4	1 (5.6)	1 (0.4)		1 (5.9)	0
Serum AST					
Grade 2	1 (5.6)	7 (2.7)		2 (11.8)	9 (3.4)
Grade 3	1 (5.6)	2 (0.8)		0	4 (1.5)
Grade 4	1 (5.6)	1 (0.4)		1 (5.9)	0
Total Bilirubin					
Grade 2	2 (11.1)	7 (2.7)		0	0
Grade 3	0	1 (0.4)		0	0
Grade 4	0	0		0	0

Source: LABOTHR and LABCHEM datasets for Protocol 021

Analysis of common AEs in hepatitis co-infected subjects versus non co-infected subjects is presented in the following table (Table 7.5.4.B). Reports of insomnia, back pain and conjunctivitis are greater in raltegravir-treated HBV/HCV co-infected subjects versus both efavirenz-treated HBV/HCV co-infected subjects and non co-infected subjects; however, given the small sample size, these differences are not clinically significant.

Table 7.5.4.B: Protocol 021: Clinical Adverse Events in ≥ 2 Raltegravir-Treated Subjects with Hepatitis Co-infection, Double Blind, Week 48 Analysis

	Raltegravir-Treated Subjects		Efavirenz-Treated Subjects	
Preferred Term	**HBV/HCV Co-infected N=18 (%)**	**Non Co-infected N=263 (%)**	**HBV/HCV Co-infected N=17 (%)**	**Non Co-infected N=265 (%)**
Insomnia	**4 (22.2)**	**26 (9.9)**	**1 (5.9)**	**28 (10.6)**
Back pain	**3 (16.7)**	**9 (3.4)**	**2 (11.8)**	**11 (4.2)**
Upper respiratory infection	3 (16.7)	31 (11.8)	4 (23.5)	27 (10.2)
Abnormal dreams	2 (11.1)	18 (6.8)	3 (17.6)	34 (12.8)
Conjunctivitis	**2 (11.1)**	**3 (1.1)**	**1 (5.9)**	**6 (2.3)**
Cough	2 (11.1)	22 (8.4)	3 (17.6)	20 (7.5)
Headache	2 (11.1)	54 (20.5)	5 (29.4)	57 (21.5)
Nasopharyngitis	2 (11.1)	32 (12.2)	0	30 (11.3)

Source: LABOTHR and AE datasets for Protocol 021

7.5.5 Drug-Drug Interactions

Proton pump inhibitors (PPI) increase raltegravir plasma levels and the mechanism for increasing raltegravir plasma concentration is likely because higher pH increases raltegravir solubility. Therefore, I performed an analysis combining PPI and H2-receptor antagonist use (omeprazole, pantoprazole, esomeprazole, lansoprazole, rabeprazole, ranitidine, famotidine, nizatidine, cimetidine) to further explore a potential relationship between higher raltegravir concentration and clinical AEs. Only AEs occurring on concomitant therapy or within 14 days of stopping concomitant therapy are included; therefore, if a subject received concomitant therapy at any point during the 48 week period but an AE occurred >14 days after stopping this therapy, the AE is not captured in my analysis. Of note, the original NDA did not establish correlation between higher measured raltegravir plasma concentrations and clinical AEs and the sNDA for treatment-experienced subjects demonstrated similar AEs in raltegravir-treated subjects with and without PPI and/or H2-receptor antagonist use.

In this Protocol 021 analysis, observed AEs are similar in raltegravir-treated subjects with and without PPI and/or H2-receptor antagonist use, with headache and dyspepsia being the most common. Drug-related AEs of moderate to severe intensity occurred in 4% of raltegravir-treated subjects receiving PPI and/or H2-receptor antagonist versus 18% not on PPI and/or H2-receptor antagonist. Therefore, concomitant raltegravir and PPI and/or H2-receptor antagonist use is not associated with an altered safety profile in this population.

Table 7.5.5.A: Protocol 021: Concomitant Proton Pump Inhibitor and/or H2-receptor Antagonist Use and Clinical Adverse Events in ≥5% Raltegravir-Treated Subjects Double Blind, Week 48 Analysis

	Raltegravir Treated Subjects			Efavirenz Treated Subjects	
Preferred Term	**PPI and/or H2 Blocker N=47 (%)**	**No PPI or H2 Blocker N=234 (%)**		**PPI and/or H2 Blocker N=55 (%)**	**No PPI or H2 Blocker N=227 (%)**
Headache	4 (9)	47 (20)		3 (5)	46 (20)
Dyspepsia	3 (6)	8 (3)		1 (2)	5 (2)

Source: AE and CONXCLP datasets for Protocol 021

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

Discussion of malignancies in the raltegravir treatment-naïve Phase 2 and 3 studies with additional treatment-experienced and expanded access program cases is presented in Section 7.3.4. An active surveillance program for malignancies and other potential adverse events has been undertaken by the Applicant as a prior postmarketing commitment.

7.6.2 Human Reproduction and Pregnancy Data

Please refer to the traditional approval sNDA for additional details. Pregnancy was an exclusion criterion in Protocol 021, and any subject who became pregnant had to immediately discontinue study medication.

Based on pregnancy data available through the SUR, in utero exposure to raltegravir occurred in two subjects.

- AN 20028 reported her pregnancy to the investigator Day 77 after stopping therapy Day 75. This subject delivered a live, term birth at 38 weeks.
- AN 20065 had a positive urine pregnancy test at Visit 13 (Day 560). Further information is not available at the time of database lock.

Three efavirenz-treated subjects became pregnant: two of the pregnancies were electively terminated (AN 20031 and 23334) and one pregnancy resulted in first trimester fetal loss (AN 23479).

Based on the available data, the effects of in utero exposure to raltegravir remain unknown. The Antiretroviral Pregnancy Registry has been established to monitor birth outcomes of pregnancy exposures to antiretroviral products.

7.6.3 Pediatrics and Effect on Growth

Pediatric studies of raltegravir are ongoing. In the studies submitted with this NDA no clinical assessment on growth has been performed.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Raltegravir has no potential for drug withdrawal or abuse. No subjects in Protocol 021 overdosed on raltegravir. Human experience of acute raltegravir overdose is limited and, to date, no adverse events have occurred with raltegravir overdose.

7.7 Additional Submissions

The Applicant submitted the SUR on January 21, 2009. The original sNDA cut-off date for safety assessments was June 5, 2008 for Protocol 021. The SUR cut-off date for safety assessments was August 29, 2008. As mentioned in Section 7.1.1, the SUR data were used for key safety analyses.

In addition, the Applicant provided several responses to FDA requests for information throughout the review. Pertinent information provided through these responses is incorporated into the review.

8 Postmarketing Experience

Review of psychiatric events, hypersensitivity, serious skin reactions including Stevens Johnson syndrome, hepatitis, hepatic failure, rhabdomyolysis and cholestasis were evaluated by the Office of Safety and Epidemiology (OSE). Conclusions of their review based on a February 4, 2009 AERS database search are summarized below.

Psychiatric Events (N=36)

- *Depression or suicidality (N=19)*
  - A history of psychiatric illness is reported in 9 cases, including 5 patients on concomitant psychiatric medication
  - Concomitant etravirine or efavirenz in 4 cases
  - Onset 1 week to 3.5 months after starting raltegravir
  - Hospitalization in 5 patients, including 4 with a psychiatric history
  - One death; however, it is not clear if the death is related to a psychiatric event because the patient was bedridden following a femur fracture, experienced depression and died.
  - Dechallenge in 8 patients: recovered (N=2), recovered with added/altered psychiatric medication (N=2), did not recover (N=1), unknown (N=3)
  - Continued raltegravir in 6 patients: recovered (N=2), recovered with added/altered psychiatric medication (N=2), unknown (N=2)
  - 3 cases with temporal relationship to raltegravir administration and with positive dechallenge

- "*Other" psychiatric events (N=17)*
  - Insomnia (N=6), paranoia (N=4), anger/disorientation (N=1), anxiety (N=1), panic attack (N=1), compulsive sexual behavior (N=1), expressive language disorder (N=1), mental status changes (N=1), psychosis (N=1)
  - A history of psychiatric illness is reported in 6 cases
  - Hospitalization in 2 patients (panic attack and paranoia), both in patients with a psychiatric history
  - Dechallenge in 6 patients: recovered (N=4: insomnia (2), paranoia (1), psychosis (1)), recovered with added/altered psychiatric medication (N=1: paranoia), unknown (N=1)
  - Continued raltegravir in 5 patients: recovered (N=1: panic attack), recovered with added/altered psychiatric medication (N=1: anger/disorientation), not recovered (N=3: insomnia (2), anxiety (1))
  - 3 cases with temporal relationship to raltegravir administration and with positive dechallenge (insomnia, paranoia, anxiety)

- Based on cases of a documented temporal relationship with starting raltegravir (<6 weeks) and with positive dechallenge, OSE recommends *insomnia, paranoia* and *anxiety* should be added to the label under **ADVERSE REACTIONS, Postmarketing Experience** section.
  MO Comment: Based on Protocol 021 analyses, insomnia is included in the adverse reaction section and therefore will not be included in the postmarketing section.

Hypersensitivity (N=14)
There are four new cases of hypersensitivity reactions (angioedema-1, hypersensitivity with rash-1, rash with eosinophila-1, drug rash with eosinophilia and systemic symptoms (DRESS) with oropharyngeal swelling-1) since the last review at the time of traditional approval sNDA for a total of 14 cases. In all four new cases (including two deaths) a causal association between the events and raltegravir cannot be established because the events appear more likely due to an underlying condition such as immune reconstitution or concomitant medications associated with hypersensitivity reactions (e.g., etravirine, abacavir, benazepril).

Hypersensitivity is currently labeled under **ADVERSE REACTIONS**, **Clinical Trials Experience**. Based on the clinical characteristics of the new AERS cases the current labeling appears adequate. No labeling changes regarding hypersensitivity are recommended at this time. Although the postmarketing cases are confounded there is one concerning report from the previous review of a severe drug-induced hypersensitivity syndrome described by the reporter as atypical drug induced hypersensitivity syndrome (DIHS). This 39 year old woman had a history of sulfa allergy and Stevens Johnson syndrome with dapsone. Three weeks after starting raltegravir, darunavir and enfuvirtide she developed a diffuse maculopapular rash over 80% of her body, hypotension, fever and transaminitis requiring hospitalization. The patient improved and was subsequently rechallenged with raltegravir plus etravirine, AZT and 3TC. Two weeks later, similar symptoms developed, again requiring hospitalization. Antiretroviral therapy was stopped, steroids were initiated and the patient improved.

OSE will continue to closely monitor postmarketing reports with raltegravir for any new cases of serious hypersensitivity reactions (e.g. DRESS, DIHS).

Serious skin reactions (N=7)
There are two new cases of Stevens-Johnson syndrome since the last review at the time of traditional approval sNDA for a total of seven cases of serious skin reactions (Stevens-Johnson syndrome-6, acute generalized pustulosis-1). One of the two new cases appears causally related to raltegravir due to a positive rechallenge. Currently Stevens-Johnson syndrome is labeled under **ADVERSE REACTIONS**, **Postmarketing Experience**. At this time the current labeling appears adequate, however as OSE continues to monitor for serious skin reactions, if the frequency or qualitative nature of the cases evolve, labeling changes (such as elevation to **WARNINGS AND PRECAUTIONS**) may be needed.

Hepatitis/hepatic failure/cytolytic hepatitis (N=27)
There are 14 new cases of hepatitis, hepatic failure, or cytolytic hepatitis since the last review at the time of traditional approval sNDA for a total of 27 cases. Three of the new cases are in patients co-infected with hepatitis B or hepatitis C and 11 report no co-infection for a total of 12 cases in co-infected patients and a total of 15 cases without reported co-infection with hepatitis B or hepatitis C, respectively. In all the new cases the events appear more likely due to factors other than raltegravir, such as concomitant medication (e.g. darunavir, tipranavir) or an underlying condition. As such, a causal association between the events and raltegravir cannot be established. Hepatitis is currently labeled under **ADVERSE REACTIONS**, **Clinical Trials Experience**. Hepatic failure and cytolytic hepatitis are unlabeled. Based on the clinical characteristics of the new cases the current labeling appears adequate. No labeling changes regarding hepatitis, hepatic failure or cytolytic hepatitis are recommended at this time.

Rhabdomyolysis/elevated creatine kinase (N=17)
There are six new cases of rhabdomyolysis (N=1), increased CPK with myalgia (N=1), or increased CPK (N=4) since the last review at the time of traditional approval sNDA for a total of 17 cases. In all six new cases a causal association between the events and raltegravir cannot be established because the patient recovered and continued on raltegravir therapy or the report provides insufficient information. Rhabdomyolysis and increased CPK are currently labeled under Adverse Reactions-Clinical Trials Experience. Based on the clinical characteristics of the AERS cases the current labeling appears adequate. No labeling changes regarding rhabdomyolysis or elevated creatine kinase are recommended at this time.

Cholestasis (N=5)
There are two new cases of hepatitis cholestatic since the last review at the time of traditional approval sNDA for a total of five cases. Both new cases are also included under the hepatic section. In both new cases a causal association between the events and raltegravir cannot be established because the events appear more likely due to an underlying condition such as lithiasis of the bile duct or cancer. Cholestasis is currently unlabeled. Based on the clinical characteristics of the two new cases no labeling changes regarding cholestasis are recommended at this time.

9 Appendices

9.1 Labeling Recommendations

The following highlights the notable labeling changes (as of June 4, 2009):

- HIGHLIGHTS:
  - Add **DRUG INTERACTIONS** heading and include warning about use with UGT inducers other than rifampin
  - **ADVERSE REACTIONS**: Combine treatment-naïve and treatment-experienced adverse reaction information into a single bullet point.
- Section 1: **INDICATIONS AND USAGE** changed to incorporate use in treatment-naïve patients: "ISENTRESS is indicated in combination with other anti-retroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection in adult patients. This indication is based on analyses of plasma HIV-1 RNA levels up through 48 weeks in three double-blind controlled studies of ISENTRESS. Two of these studies were conducted in clinically advanced, 3-class antiretroviral (NNRTI, NRTI, PI) treatment-experienced adults and one was conducted in treatment-naïve adults."
- Section 1: **INDICATIONS AND USAGE,** Section 8.4: **Pediatric Use and** Section 12.3: **Pharmacokinetics,** Special Populations *Pediatric* removal of "less than 16 years of age". In Protocol 021 subjects were required to be >18 years and in Protocols 018 and 019 only five subjects were <18 years.
- Section 5.2: **WARNINGS AND PRECAUTIONS, Drug Interactions**: removal of this section because the information is sufficiently included in Section 7: **DRUG INTERACTIONS**. In addition, **DRUG INTERACTIONS** information added to HIGHLIGHTS as noted above.
- Section 6.1: **Clinical Trials Experience,** Treatment-Naïve Studies:
  - Includes 48 week safety and laboratory data from Protocol 021.
  - Inclusion of Lipids values, Mean Change from Baseline table
  - Ongoing discussion regarding inclusion of *CNS Events* and *Less Common Adverse Reactions* sections.
- Section 6.2: **Postmarketing Experience**: addition of paranoia and anxiety
- Section 7.1 **Effect of Raltegravir on the Pharmacokinetics of Other Agents** adds information for CYP1A2, CYP2B6 and methadone.
- Section 12.4 **Microbiology**, Antiviral Activity in Cell Culture includes information pertaining to HIV-1 subtypes. Resistance includes Protocol 021 48 week resistance data. Current negotiations are ongoing regarding the specific number of virologic failure subjects.
- Section 14 **CLINICAL STUDIES**
  - Includes 48 week efficacy data from Protocol 021
  - Updated with TLOVR efficacy table for Protocols 018 and 019 (Table 12).
- Other administrative changes were made for clarity and ease of use.

Pending issues at the time of review:

Package Insert:

- Recommend revision of the proposed [redacted] (b) (4) "tenofovir 300 mg" to convey the more commonly used tenofovir dosage
- Determination of the specific number of virologic failure subjects in Section 12.4
- Ongoing discussion regarding inclusion of [redacted] (b) (4) and *Less Common Adverse Reactions* sections
- Lipids values, Mean Change from Baseline table:
  - Recommendation to round the lipid values and percentages to the nearest whole number
  - Recommendation to modify statement of lipid-lowering agent use to be consistent with the atazanavir label
- Removal of the proposed sentence from Section 14: [redacted] (b) (4) We believe the treatment difference and confidence intervals in Table 9: Outcomes by Treatment Group through Week 48 provide adequate comparison information.

Patient Package Insert: Incorporation of DDMAC recommendations as summarized below.

- **What is ISENTRESS?** Statements that ISENTRESS [redacted] (b) (4) are promotional in nature and may be used in promotional material to misleadingly suggest a guarantee of efficacy, e.g., that treatment with ISENTRESS [redacted] (b) (4) Please revise the text, for example "ISENTRESS is an anti-HIV (antiretroviral) medicine used for the treatment of HIV".
- **How does ISENTRESS work?** Recommend retention of the word "may" due to concern this statement will be used in promotional material to imply a guarantee of efficacy. Recommend deletion of the phrase [redacted] (b) (4)
- **What are the possible side effects of ISENTRESS?**
  - *A condition called Immune Reconstitution Syndrome can happen in some patients with advanced HIV infection (AIDS) when combination antiretroviral treatment is started. Signs and symptoms of inflammation from opportunistic infections that a person has or had may occur as the medicines work to* [redacted] (b) (4) *Call your doctor right away if you notice any signs or symptoms of an infection after starting ISENTRESS with other anti-HIV medicines.*

  The underlined statement is promotional in nature and may be used in promotional material to misleadingly suggest a guarantee of efficacy and/or overstate the efficacy, e.g., that treatment with ISENTRESS wil[redacted] (b) (4) Please revise the underlined text.

  - *Contact your doctor promptly if you experience unexplained muscle pain, tenderness, or weakness while taking ISENTRESS.*

Recommend adding "This is because on rare occasions, muscle problems can be serious, including muscle breakdown resulting in kidney damage." This statement is similar to the PPI for Vytorin.

- *Tell your doctor if you have any side effect that bothers you or* (b) (4)

This statement minimizes risks associated with ISENTRESS because it implies patients should expect their side effects (b) (4) Please revise this phrase and also make "side effect" plural.

Please refer to the approval letter for the final label.

9.2 Advisory Committee Meeting

No advisory committee meeting was held for this naïve efficacy supplement.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sarah Connelly
6/8/2009 04:19:42 PM
MEDICAL OFFICER

Kimberly Struble
6/8/2009 05:12:36 PM
MEDICAL OFFICER

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22-145 **Applicant: Merck** **Stamp Date: September 26, 2008**

Drug Name: Raltegravir **NDA/BLA Type: NDA**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			No link to narratives – SAEs, deaths are linked to Protocol 021CSR document
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?		x		Not needed because one pivotal study used to support safety and efficacy in treatment-naïve patients. Additional data from phase 2 study (n=50 patients at to be marketed dose) Similar format to experienced indication
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?		x		See above
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			Section 2.5.6 of Clinical Overview
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	x			505 (b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Protocol 004 Study Title: Multicenter, Double-Blind, Randomized,	X			Used same dose in treatment naïve and treatment experienced patients. Dose was determined and

	Content Parameter	Yes	No	NA	Comment
	Dose Ranging Study to Compare the Safety and Activity of Raltegravir Plus Tenofovir and Lamivudine (3TC) Versus Efavirenz Plus Tenofovir and Lamivudine (3TC) in ART Naive, HIV-Infected Patients Sample Size: 198 Arms: 100, 200, 400, 600 raltegravir BID vs EFV, each combined with 3TC and tenofovir Location in submission: Part of the Accelerated Approval				verified as part of end of phase 2 meeting and in accelerated approval review. Also Protocol 005 supported dose ranging. In this submission, there is a PK/PD assessment M5 Section 5.3.4.2
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 A Multicenter, Double-Blind, Randomized, Active-Controlled Study to Evaluate the Safety and Antiretroviral Activity of MK-0518 Versus Efavirenz in Treatment Naïve HIV-Infected Patients, Each in Combination With TRUVADA™ (Protocol 021) Indication: HIV-infected naive patients Pivotal Study #2 n/a Indication:	x			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		x		No definitive "rationale"; however, this data is representative of what was studied in the treatment-experienced studies. In addition, during accelerated approval, there was no indication of genetic response differences and HIV RNA was used as an objective efficacy parameter. Therefore, use of treatment-naïve

	Content Parameter	Yes	No	NA	Comment
					subjects in US and non-US subjects to support dosing in treatment-naïve patients is acceptable. 69 total centers: 67 randomized subjects. 18 US, 3 Canada; 19 EU and Australia; 19 Latin America; 8 SE Asia US N=142 (25%)
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?				Not with this submission. Prior QT study part of accelerated approval and evaluated by the QT team.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	x			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	x			"REPTTERM" in AE dataset
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			x	First in class drug
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data			x	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	requested by the Division during pre-submission discussions?				
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			x	At the time of accelerated approved for treatment-experienced patients: (1) Deferral of pediatric studies 4wks-18yo until 6/30/11 (2) Waiver for birth-4wks because "too few pediatric subjects to study in this age group with this disease".
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		x		Similar data was submitted to support accelerated approval in treatment-experienced patients.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			For deaths and AEs associated with d/c. Not for SAEs (same for accelerated approval)
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			36 investigators did not return the information
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all	x			In Protocol 021 CSR

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?				and in Clinical Overview

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _Yes, Traditional Approval_

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Sarah Connelly 11/6/08

Reviewing Medical Officer Date

Clinical Team Leader Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sarah Connelly
11/24/2008 11:53:24 AM
MEDICAL OFFICER

Kimberly Struble
12/5/2008 02:24:13 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22 – 145/S004

CHEMISTRY REVIEW(S)

NDA 22-145
ISENTRESS™ (raltegravir potassium) Tablets
Efficacy Supplement SE5-004
Document Date: 25-SEP-2008

Reviewer: SWAPAN K. DE, Ph.D.

Office of New Drug Chemistry
Division of Post-Marketing Evaluation
Division IV, Branch VIII

Reviewed for Division of Aniviral Products

NDA 22-145/SE5-004

Background:

The supplement to the NDA proposes to expand use of the drug product beyond the approved indication, to include Isentress in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced adult patient who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents. This supplement contains data to justify that MK-0518 has potent and durable antiretroviral and immunologic effects and is well tolerated in treatment-naïve patients and is comparable to other approved drug product (Efavirenz).

Chemistry Information Submitted in Supplement:

The only chemistry and manufacturing information submitted in the supplement is Environmental Assessment. No CMC related changes are proposed in the updated labeling section.

In this section, the sponsor requests an exclusion from the requirement for an Environment Assessment, and provides a Claim for a Categorical Exclusion from the requirement for an Environmental Assessment, pursuant to 21 CFR 25.31(b).

Evaluation:

Acceptable. The supplement meets the requirements of a categorical exclusion under 21 CFR §25.31(b) because the estimated concentration of the active drug substance at the point of entry, referred to as the Expected Introduction Concentration (EIC), into the aquatic environment will be below 1 part per billion (ppb).

Conclusion:

From a CMC perspective, this supplement may be approved.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Swapan De
4/24/2009 09:02:03 AM
CHEMIST
SE-5 004 CMC EA review

Hasmukh Patel
4/24/2009 12:02:53 PM
CHEMIST

CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: **Applicant:** **Stamp Date:**

Drug Name: **NDA/BLA Type:**

On **initial** overview of the NDA/BLA application for filing:
NI = No Information

	Content Parameter	Yes	No	Comment
1	Is the section legible, organized, indexed, and paginated adequately?			NI
2	Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)?			NI
3	Is a statement provided to indicate whether each manufacturing or testing site is ready for inspection or, if not, when it will be ready?			NI
4	Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)?			Categorical Exclusion - OK [under 21 CFR §25.31(b)]
5	Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)?			NI
6	Is information on the Drug Product provided as required in 21 CFR 314.50(d)(1)(ii)?			NI
7	If applicable, has all information requested during the IND phases and at the pre-NDA meetings been included?			CMC Information contained in the original, approved NDA.
8	Have draft container labels and package insert been provided?	X		
9	Have all DMF References been identified?			NI
10	Is information on the investigational formulations included?			NI
11	Is information on the methods validation included?			NI
12	If applicable, is documentation on the sterilization process validation included?			NI

IS THE CMC SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from chemistry, manufacturing, and controls perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Allan Fenselau 03-NOV-2008

Reviewing Chemist Date

Team Leader/Supervisor Date

File name: 5_Chemical Manufacturing Controls (CMC) Filing Checklist for NDA_BLA or Supplement 010908

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Allan Fenselau
11/7/2008 08:45:26 AM
CHEMIST

I think Fileability approvals need your sign-off, but it's been so long...

Hasmukh Patel
11/7/2008 12:30:39 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22 – 145/S004

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-145**
SERIAL NUMBER:	**SE5-004**
DATE RECEIVED BY CENTER:	**9/26/08**
PRODUCT:	**ISENTRESS™**
INTENDED CLINICAL POPULATION:	**HIV-infected patients**
SPONSOR:	**Merck & Co., Inc.**
DOCUMENTS REVIEWED:	**Electronic**
REVIEW DIVISION:	**Division of Antiviral Products (HFD-530)**
PHARM/TOX REVIEWER:	**Ita Yuen, PhD**
PHARM/TOX SUPERVISOR:	**Hanan Ghantous, PhD, DABT**
DIVISION DIRECTOR:	**Debra Birnkrant, MD**
PROJECT MANAGER:	**Amalia Himaya, BS**

Date of review submission to Division File System (DFS): **May 12, 2009**

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

Yes

B. Recommendation for nonclinical studies

None.

C. Recommendations on labeling

No change was made in the sections of label which contain nonclinical pharmacology/toxicology data

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

No new nonclinical pharmacology/toxicology studies were included in this NDA submission.

B. Pharmacologic activity

Please see Dr. Sung Rhee's review.

C. Nonclinical safety issues relevant to clinical use

None.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ita Yuen
5/12/2009 10:07:10 AM
PHARMACOLOGIST

Hanan Ghantous
5/13/2009 03:57:53 PM
PHARMACOLOGIST

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22145 **Applicant: Merck** **Stamp Date: 9/26/2008**

Drug Name: Raltegravir **NDA/BLA Type: Efficacy Supplement**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?			Not applicable since no new pharmacology/toxicology data submitted
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			Not applicable
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			Not applicable
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?			Not applicable
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			Not applicable
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?			Not applicable
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			Not applicable
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			Not applicable

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	√		The changes in the "Carcinogenesis, Mutagenesis, Impairment of Fertility" section are under negotiation with the sponsor.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	√		
11	Has the applicant addressed any abuse potential issues in the submission?		√	Not applicable
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?		√	

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Ita Yuen 12/1/08

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ita Yuen
12/2/2008 01:54:35 PM
PHARMACOLOGIST

Hanan Ghantous
12/2/2008 02:43:23 PM
PHARMACOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22 – 145/S004

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

NDA/Serial Number:	N22145
Drug Name:	Isentress™ (raltegravir potassium) 400 mg tablets, administered twice daily (bid)
Indication(s):	Treatment of HIV-1 infection in combination with other antiretroviral agents in treatment-naïve patients
Applicant:	Merck Research Laboratories
Date(s):	Submission date: 9/25/2008 PDUFA date: 7/25/2009
Review Priority:	Standard
Biometrics Division:	DB4
Primary Statistical Reviewer:	Karen Qi, Ph.D.
Concurring Reviewers:	Greg Soon, Ph.D.
Medical Division:	Division of Antiviral Products (DAVP)
Medical Reviewer:	Sarah Connelly, M.D.
Project Manager:	Amalia Himaya

Table of Contents

LIST OF TABLES

List of Figures

EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

In October of 2007, the Agency approved raltegravir 400 mg administered orally, twice daily (b.i.d.) with or without food, in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced patients with HIV-1 replication despite ongoing antiretroviral therapy. In September of 2008, Merck submitted Week 48 data from one pivotal Phase III trial (i.e., Study 021) to seek the approval of raltegravir 400 mg administer orally, b.i.d. in combination with TRUVADA™ in the treatment-naïve HIV-1 infected patients.

After reviewing the efficacy results based on the 48 week data from Study 021 in treatment-naïve patients, the statistical reviewer concluded that raltegravir 400 mg b.i.d. demonstrated non-inferior at Week 48 to efavirenz 600 mg, once daily at bedtime (q.h.s.), each in combination of TRUVADA™.

1.2 Brief Overview of Clinical Studies

Study 021 is a multicenter, double-blind, randomized, non-inferiority study to evaluate the safety, tolerability and efficacy of raltegravir 400 mg b.i.d. compared with efavirenz 600 mg q.h.s. when each was given in combination with TRUVADA™ among treatment-naïve HIV-infected patients of 18 years of age or older with plasma HIV RNA >5000 copies/mL. The study was conducted in Latin America, North America, Europe, Australia, and Southeast Asia. The primary efficacy hypothesis was that the proportion of patients achieving HIV RNA below 50 copies/mL at Week 48 in the raltegravir treatment group was noninferior to that in the efavirenz treatment group, each in combination with TRUVADA™. The non-inferiority margin was 12%.

In total, 566 patients were randomized in a 1:1 ratio to receive either raltegravir 400 mg, b.i.d. (n=282) or efavirenz 600 mg, q.h.s. (n=284), each given in combination with TRUVADA™. The randomization was stratified by screening HIV RNA level (<=50,000 or >50,000 copies/mL) and hepatitis B or C infection status at screening. The duration of the study was 96 weeks. The primary efficacy endpoint was the proportion of patients with HIV RNA level below 50 copies/mL at Week 48. In this sNDA, the applicant only submitted the initial 48 week data from the Study 021.

1.3 Statistical Issues and Findings

To evaluate the robustness of the efficacy results of Study 021 in the treatment-naïve patients, the statistical reviewer used different rules of assigning viral load when the results from different assays were available for a given visit (i.e., standard, ultrasensitive and dilution assays), different definitions of visit windows for measurements of HIV RNA level and CD4 counts, and different approaches to impute missing data. After adopting the rules, the reviewer further computed the proportion of patients with HIV RNA below 50 copies/mL and the proportion of patients with HIV RNA below 400 copies/mL at Week 48 using both the snap shot approach and the TLOVR algorithm. The snap shot approach classified patients as responders or non-responders based on

the HIV RNA level at Week 48. If the patients discontinued the study treatment before Week 48 or did not have the HIV RNA value at Week 48 even after the missing HIV RNA was imputed, they were considered as non-responders in the snap shot analysis. On the other hand, the TLOVR algorithm defined the patients as the responders if the patients maintained at least two HIV RNA measurements below 50 copies/mL for the endpoint of proportion of patients with HIV RNA below 50 copies/mL at Week 48 (or at least two HIV RNA measurements below 400 copies/mL for the endpoint of proportion of patients with HIV RNA below 400 copies/mL at Week 48) without virologic rebound or treatment discontinuation. The results from the reviewer's snap shot and TLOVR varied slightly from the applicant's results, but they did not change the conclusion that both the proportion of patients with HIV RNA below 50 copies/mL and the proportion of patients with HIV RNA below 400 copies/mL in the raltegravir group were slightly higher than those in the efavirenz group. Additionally, the reviewer calculated the change from baseline in $\log_{10}$ HIV RNA and change from baseline in CD4 cells at Week 48. Again the results showed that the raltegravir had similar results to the efavirenz with respect to these two endpoints.

The subgroup analyses for the primary efficacy endpoint with patient demographics and baseline disease characteristics demonstrated that there was no apparent treatment by subgroup interaction. However, the magnitudes of the treatment differences in the following subgroups were large. But the sample sizes in these subgroups were not big enough to make the final conclusions.

1) Among the black patients, the proportion of patients with HIV RNA below 50 copies/mL at Week 48 in the raltegravir group was about 8% lower than that in the efavirenz group.

2) Among the patients with positive HBV and/or HCV, approximately 17% more raltegravir-treated patients achieved HIV RNA below 50 copies/mL at Week 48 than the efavirenz-treated patients.

3) Among the patients with HIV RNA below 50,000 copies/mL at screening, approximately 12% more patients in the raltegravir group had HIV RNA below 50 copies/mL at Week 48 than those in the efavirenz group.

2. INTRODUCTION

2.1 Overview

The HIV integrase is one of the three HIV-1 enzymes required for viral replication and catalyzes the stepwise process resulting in the integration of the HIV deoxyribonucleic acid (DNA) into the genome of the host cell. Merck has been developing raltegravir, the first HIV integrase strand transfer inhibitor, to treat HIV-infected patients. In October of 2007, the Agency approved raltegravir 400 mg administered orally, twice daily (b.i.d.) with or without food, in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced patients with HIV-1 replication despite ongoing antiretroviral therapy. In September of 2008, Merck submitted Week 48 data from one pivotal Phase III trial (i.e., Study

021) to seek the approval of raltegravir 400 mg administer orally, b.i.d. in combination of TRUVADA™ in the treatment-naïve HIV-1 infected patients.

In this review report, we will review the Week 48 efficacy results from Study 021 that was conducted in the treatment-naïve patients.

2.2 Data Sources

The application was electronic and can be found in FDA internal network drive of \\cdsesub1\evsprod\nda022145\0094.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy of Study 021

3.1.1 Study Design

Study 021 is a multicenter, double-blind, randomized, non-inferiority study to evaluate the safety, tolerability and efficacy of raltegravir 400 mg b.i.d. compared with efavirenz 600 mg q.h.s. when each was given in combination with TRUVADA™ among treatment-naïve HIV-infected patients of 18 years of age or older with plasma HIV RNA >5000 copies/mL. The study was conducted in Latin America, North America, Europe, Australia, and Southeast Asia. The primary efficacy hypothesis was that the proportion of patients achieving HIV RNA below 50 copies/mL at Week 48 in the raltegravir treatment group was noninferior to that in the efavirenz treatment group, each in combination with TRUVADA™. The non-inferiority margin was 12%.

In total, 566 patients were randomized in a 1:1 ratio to receive either raltegravir 400 mg, b.i.d. (n=282) or efavirenz 600 mg, q.h.s. (n=284), each given in combination with TRUVADA™. The randomization was stratified by screening HIV RNA level (<=50,000 or >50,000 copies/mL) and hepatitis B or C infection status. The duration of the study was 96 weeks.

3.1.2 Efficacy Assessments

The plasma HIV RNA and CD4 cell counts were determined at Screening, Randomization (Day 1), Weeks 2, 4, 8, 12, 16, 24, 32, 40, 48, 60, 72, 84, 96, viral failure, discontinuation and at the 14-day post-therapy follow-up.

3.1.3 Efficacy Endpoints

The primary efficacy endpoint was the proportion of patients achieving HIV RNA < 50 copies/mL at Week 48. The secondary efficacy endpoints at Week 48 included the proportion of patients with HIV RNA <400 copies/mL, change from baseline in $\log_{10}$ HIV RNA, and change from baseline in CD4 cells counts.

3.1.4 Patient Disposition, Demographic and Baseline Characteristics

Table 1 displays patient disposition. A total of 566 patients were randomized, of whom 563 received at least one dose of assigned treatment regimen (raltegravir: 281; placebo: 282). Twenty-four out of 281 patients (9%) discontinued the study in the raltegravir group versus 35 out of 282 patients (12%) in the efavirenz group. In both groups, the most common reason for discontinuation was clinical adverse event. Specifically, 3% of raltegravir-treated patients and 6% of efavirenz-treated patients withdrew study due to clinical adverse event. The other reasons causing discontinuation in the raltegravir group were lack of efficacy (1%), consent withdrawn (<1%), lost to follow-up (1%), protocol violation (1%) and other (2%). In the efavirenz group, the other reasons included lack of efficacy (1%), laboratory adverse event (<1%), consent withdrawn (2%), lost to follow-up (2%) and other (1%).

Table 1: Patient Disposition

	Raltegravir 400 mg bid N (%)	**Efavirenz 600 mg qhs N (%)**
Total Entered	282	284
Never Treated	1	2
Treated	281 (100)	282 (100)
Discontinued	24 (9)	35 (12)
Lack of efficacy	4 (1)	2 (1)
Clinical adverse experience	8 (3)	17 (6)
Laboratory adverse experience	0 (0)	1 (<1)
Consent withdrawn	1 (<1)	6 (2)
Lost to follow-up	3 (1)	7 (2)
Protocol deviation	2 (1)	0 (0)
Other	6 (2)	2 (1)

Source: Clinical Study Report for Study 021, Section 10, Table 10-3.

As shown in Table 2 below, the patient demographics and baseline characteristics were balanced between the two treatment groups. A majority of patients were male (81%). Approximately 43% of the patients were white. The mean age (± standard deviation (SD)) of patients was 37 (± 10) years old. Most of the patients were treated in Latin America (35%), North America (31%) and Europe/Australia (23%). About 15% of patients had history of AIDS. One of the stratified factors in the randomization was hepatitis B or C coinfection status: approximately 7% of the patients in both treatment groups were hepatitis B and/or C positive. The mean baseline CD4 cell count (± SD) was 208 (± 129) cells/microL, and the mean baseline HIV RNA (± SD) was 5.0 (± 0.6) $\log_{10}$ copies/mL. About 80% of the patients were infected with Clade B virus.

Table 2: Patient Demographics and Baseline Characteristics (Randomized and Treated)

	Raltegravir 400 mg bid (N = 281)	Efavirenz 600 mg qhs (N = 282)	Total (N = 563)
Gender – n (%)			
Female	227 (81)	231 (82)	458 (81)
Male	54 (19)	51 (18)	105 (19)
Race – n (%)			
White	116 (41)	123 (44)	239 (43)
Black	33 (12)	23 (8)	56 (10)
Asian	36 (13)	32 (11)	68 (12)
Hispanic	60 (21)	67 (24)	127 (23)
Native American	1 (0.4)	1 (0.4)	2 (0.4)
Multiracial	35 (13)	36 (13)	7 (13)
Region – n (%)			
Latin America	99 (35)	97 (34)	196 (35)
Southeast Asia	34 (12)	29 (10)	63 (11)
North America	82 (29)	90 (32)	172 (31)
EU/Australia	66 (24)	66 (23)	132 (23)
Age			
mean (SD)	38 (9.0)	37 (10)	37 (10)
median (min, max)	37 (19, 67)	36 (19, 71)	37 (19, 71)
History of AIDS – n (%)			
Yes	40 (14)	42 (15)	82 (15)
Clade B – n (%)			
Yes	219 (78)	230 (82)	449 (80)
No	59 (21)	47 (17)	106 (19)
missing	3 (1)	5 (2)	8 (1)
Baseline HIV RNA (log_{10} copies/mL)			
mean (SD)	5.0 (0.6)	5.0 (0.6)	5.0 (0.6)
median (min, max)	5.1 (2.6, 5.9)	5.0 (3.6, 5.9)	5.0 (2.6, 5.9)
Baseline CD4 count (cells/microL)			
mean (SD)	219 (124)	217 (134)	218 (129)
median (min, max)	212 (1, 620)	204 (4, 807)	208 (1, 807)
Stratum – n (%)			
Screening HIV RNA ≤50,000 copies/mL	74 (26)	80 (28)	154 (27)
HBV or HCV positive	20 (7)	19 (7)	39 (7)

Source: Clinical Study Report for Study 021, Section 10, Table 10-4.

3.1.5 Statistical Methodologies

The efficacy analyses were based on the full analysis set which included the randomized patients who received at least one dose of study medication. For the primary efficacy endpoint of the proportion of patients with HIV RNA below 50 copies/mL at Week 48, a non-completer = failure (NC=F) approach was used to impute the missing data. All monotone missing values after premature discontinuations were filled in as failures regardless of the reason for discontinuation and the success/failure status at the time of discontinuation. The proportions were computed within strata (screen HIV RNA >50,000 copies/mL or HIV RNA <=50,000 copies/mL) and then combined using weights proportional to the size of each stratum. The 95% confidence intervals (CIs) and p-values for non-inferiority for treatment differences in percent response were calculated using Miettinen and Nurminen's method with weights proportional to the size of each stratum. In addition to NC=F approach, the missing data was also imputed using treatment related discontinuations = failure (TRD=F) and observed failure (OF) approaches. The detailed description of TRD=F and OF approaches are as follows:

- Observed Failure (OF): Patients who prematurely discontinued the assigned treatment due to lack of efficacy were considered as failures thereafter.

- Treatment-Related Discontinuation = Failure (TRD=F): Patients who prematurely discontinued the assigned treatment due to lack of efficacy or adverse experiences were considered as failures thereafter.

Also, time-to-loss-of-virologic-response (TLOVR) which measures the durability was also estimated using Kaplan-Meier product-limit estimates and graphically displayed, and the log rank test was applied to this time-to-event data.

The OF approach, which considered the pure antiretroviral effect of the treatment, was used for the calculations of change from baseline in HIV RNA and change from baseline in CD4 cell counts. Under this approach, baseline values were carried forward for patients who discontinued assigned therapy due to lack of efficacy.

3.1.6 Applicant's Results and Conclusion

Table 3 summarizes the applicant's results for primary efficacy endpoint. The applicant's analyses demonstrated that, regardless of imputation approaches of missing data, the proportion of patients with HIV RNA below 50 copies/mL at Week 48 in the raltegravir group was slightly higher than that in the efavirenz group. And the lower bounds of 95% CIs for the treatment difference (raltegravir – efavirenz) were greater than -12%. Therefore raltegravir was non-inferior to efavirenz by 12% at Week 48.

Table 3: Applicant's Results for Primary Efficacy Endpoint at Week 48 (Randomized and Treated)

	Response by Treatment Group Responder / Evaluable[1] n/N (%)		Treatment Diffience (raltegravir – efavirenz)	
Proportion of patients with HIV RNA below 50 copies/mL at Week 48	**Raltegravir 400 mg bid (N = 281)**	**Efavirenz 600 mg qhs (N = 282)**	**Difference (95% CI)[2]**	**p-value[2]**
Non-Completer=Failure (NC=F)	241/280 (86)	230/281 (82)	4 (-1.9, 10.3)	<0.001
Treatment-Related Disc.=Failure (TRD=F)	241/271 (89)	230/274 (84)	5 (-0.8, 10.8)	<0.001
Observed Failure (OF)	241/263 (92)	230/258 (89)	3 (-2.6, 7.7)	<0.001

Source: Clinical Study Report for Study 021, Section 11, Table 11-3.
[1]Evaluable patient number in each treatment group according to different missing data approaches.
[2]The 95% CIs and p-values for treatment differences were calculated using Miettinen and Nurminen's method with weights proportional to the size of each stratum (screen HIV RNA >50,000 copies/mL or <=50,000 copies/mL). A 95% CI on the difference excluding a decrease of 12 percentage points or more and associated 1-sided p-value <= 0.025 implies that the difference is statistically significantly less than the pre-specified clinical relevant decrease of 12 percentage points and allows for a conclusion of non-inferiority.

The applicant further showed that there appeared no treatment difference between the two treatment groups with respect to the secondary efficacy endpoints at Week 48 including the proportion of patients with HIV RNA <400 copies/mL, change from baseline in $\log_{10}$ HIV RNA, and change from baseline in CD4 cells counts. The applicant's results for the secondary efficacy endpoints are displayed in Table 4 below.

Finally, the applicant demonstrated that raltegravir treatment group showed non-inferior antiretroviral efficacy over time compared with efavirenz with respect to the proportion of patients with HIV RNA below 50 copies/mL, the proportion of patients with HIV RNA below 400 copies/mL, change from baseline in $\log_{10}$ HIV RNA and change from baseline in CD4 cells (Figure 1 to Figure 4).

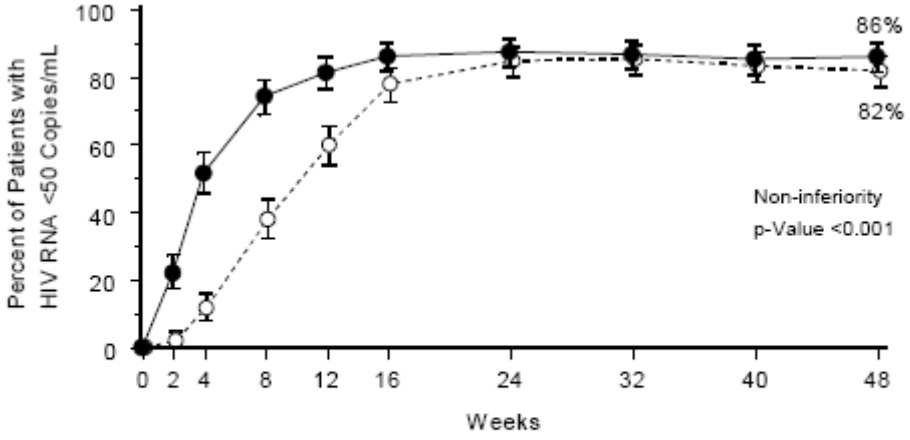
Based on the primary and secondary efficacy analyses, the sponsor concluded that raltegravir had non-inferior efficacy at Week 48 to efavirenz.

Table 4: Applicant's Results for Secondary Efficacy Endpoints at Week 48 (Randomized and Treated)

Week 48	Raltegravir 400 mg bid (N=281)	Efavirenz 600 mg qhs (N=282)	Treatment Difference (95% CI) [1]
Proportion of patients with HIV RNA <400 copies/mL – # of responders / # of evaluable patients (%)[2]	252/280 (90%)	241/281 (86%)	4% (-1%, 10%)
Change from baseline in log_{10} HIV RNA[3]			
n	263	257	0.0
mean (SD)	-2.5 (0.8)	-2.5 (0.7)	(-0.1, 0.1)
Change from baseline in CD4 counts[3]			
n	258	251	26
mean (SD)	189 (124)	163 (121)	(4, 47)

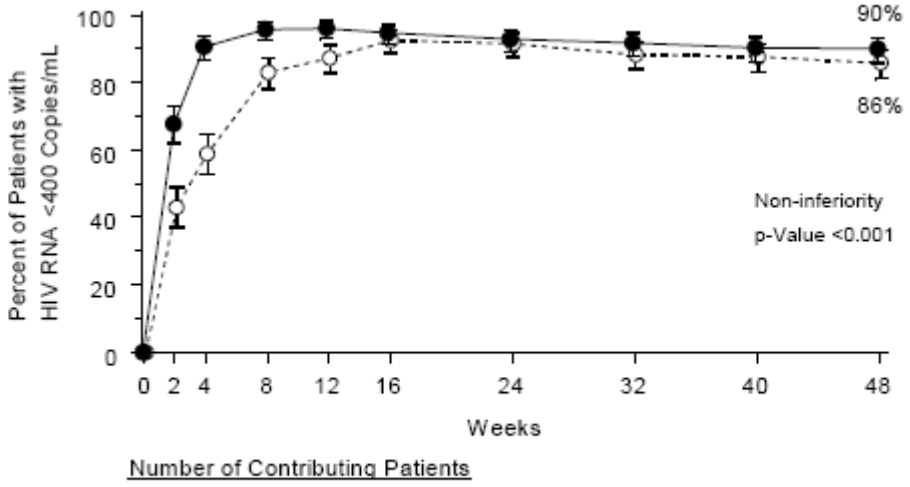
Sources: Clinical Study Report for Study 021, Section 11, Tables 11-4, 11-5, 11-6 and 14-15.
[1]For binary endpoints, the 95% CIs were calculated based on Miettinen and Nurminen's method with weights proportional to the size of each stratum (screen HIV RNA > 50,000 copies/mL or <=50,000 copies/mL). For continuous endpoints, the 95% CIs were calculated based on the t-distribution.
[2]The Noncompleter=Failure (NC=F) approach was applied to handle missing data. Specifically, all missing values after premature discontinuation regardless of the reasons were considered as failures; and intermittent missing values due to a missed or skipped visit or due to and inadequate were also regarded as failures unless immediately flanked by 2 successes which were excluded in the analysis.
[3]The Observed Failure (OF) approach was applied to handle missing data. Specifically, OF carried the baseline values for patients who discontinued assigned therapy due to lack of efficacy and excluded other missing values.

Figure 1: Proportion of Patients Achieving HIV RNA <50 copies/mL (95% CI) Over Time (NC=F Approach)



Sources: Clinical Study Report for Study 021, Section 11, Figure 11-2.

Figure 2: Proportion of Patients Achieving HIV RNA <400 copies/mL (95% CI) Over Time (NC=F Approach)

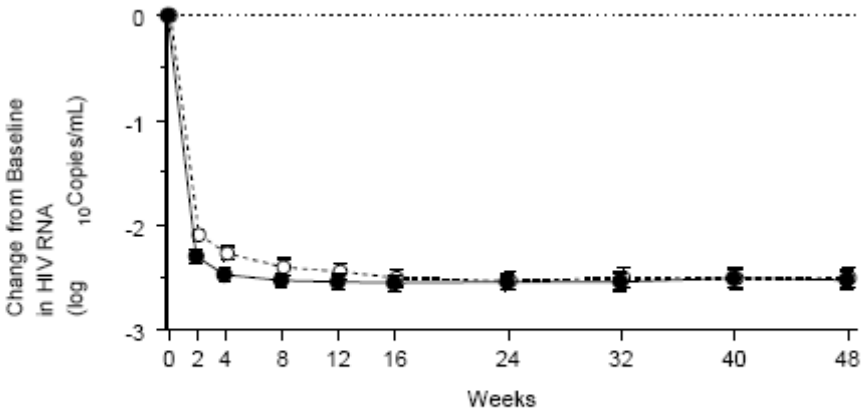


Number of Contributing Patients

●	MK-0518 400 mg b.i.d.	281	279	281	279	281	279	278	280	280
○	Efavirenz 600 mg q.h.s.	282	282	282	282	281	282	280	281	281

Sources: Clinical Study Report for Study 021, Section 11, Figure 11-2.

Figure 3: Change From Baseline in Log_{10} HIV RNA (95% CI) Over Time (OF Approach)

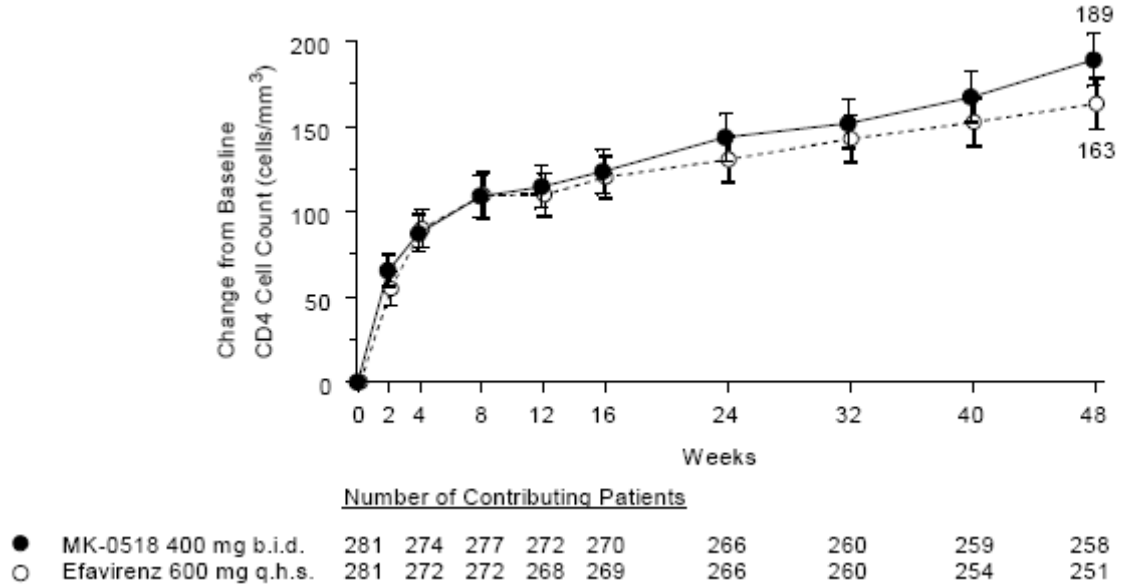


Number of Contributing Patients

●	MK-0518 400 mg b.i.d.	281	278	277	273	272	264	262	264	263
○	Efavirenz 600 mg q.h.s.	282	273	275	271	272	268	260	259	257

Sources: Clinical Study Report for Study 021, Section 14, Figure 14-1.

Figure 4: Change From Baseline in CD4 Cells Count (95% CI) Over Time (OF Approach)



Sources: Clinical Study Report for Study 021, Section 11, Figure 11-4.

3.1.7 Reviewer's Comments

The statistical reviewer conducted additional analyses to evaluate the robustness of the efficacy results. First of all, the reviewer used different rules of assignment of HIV viral load when the results from different assays were available for a given visit (i.e., standard, ultrasensitive and dilution assays), different definitions of visit windows for measurements of HIV RNA level and CD4 counts and different approaches to impute missing data. The detailed differences between the reviewer's and the applicant's rules are listed in Table 5 in next page.

After adopting the rules, the reviewer further computed the proportion of patients with HIV RNA below 50 copies/mL and the proportion of patients with HIV RNA below 400 copies/mL at Week 48 using both the snap shot approach and the TLOVR algorithm. The snap shot approach classified patients as responders or non-responders based on the HIV RNA level at Week 48. If the patients discontinued the study treatment before Week 48 or did not have the HIV RNA value at Week 48 even after the missing HIV RNA was imputed by the rule described in Table xx, they were considered as non-responders in the snap shot analysis. On the other hand, the TLOVR algorithm defined the patients as the responders if the patients maintained at least two HIV RNA measurements below 50 copies/mL for the endpoint of proportion of patients with HIV RNA below 50 copies/mL at Week 48 (or at least two HIV RNA measurements below 400 copies/mL for the endpoint of proportion of patients with HIV RNA below 400 copies/mL at Week 48) without virologic rebound or treatment discontinuation. The results from the reviewer's snap shot and TLOVR varied slightly from the applicant's results shown in Table 3, but they did not change the

conclusion that both the proportion of patients with HIV RNA below 50 copies/mL and the proportion of patients with HIV RNA below 400 copies/mL in the raltegravir group were slightly higher than those in the efavirenz group. Meanwhile, to be consistent with the efficacy displays in the label of other HIV-1 drugs, the results based on the TLOVR algorithm were supposed to be presented in the label. However, the applicant did not correctly implement the TLOVR algorithm in the initial submission and the subsequent responses to the Division's query on March 9, 2009. Therefore, the reviewer's TLOVR results are displayed in the label. Additionally, the reviewer calculated the change from baseline in $\log_{10}$ HIV RNA and change from baseline in CD4 cells at Week 48. Again the results showed that the raltegravir had similar results to the efavirenz with respect to these two endpoints. Table 6 and Table 7 below summarize the statistical reviewer's analysis results.

Table 5: Rules Used by Applicant and Reviewer in Efficacy Analysis

	Applicant	Reviewer
Assignment of results from 3 HIV RNA assays	1. Endpoints of proportion of patients with HIV RNA level < 400 copies/mL • Results from the standard assays were used. 2. Endpoints of proportion of patients with HIV RNA level < 50 copies/ mL • If HIV RNA was < 400 copies/mL by standard assay, then ultrasensitive assay was also performed. • Results from the ultrasensitive assay were used if the assay was done; results from the standard assay were used if otherwise. 3. Endpoint of change from baseline • If HIV RNA =750,000 copies/mL by standard assay, then dilution assay was also carried out. • If dilution assay was done, then the minimum value of the standard assay and the dilution assay was used. • If the result from the standard assay was reported as "< 400 copies/mL HIV RNA detected", then it was imputed as "399 copies/mL"; if the result from the standard assay was reported as "< 400 copies/mL HIV RNA undetected", then it was imputed as "200 copies/mL".	1. If the ultrasensitive assay was done in addition to the standard assay, then use the minimum value of 399 copies/mL and the results from the ultrasensitive assay. 2. If the result from the standard assay was <400 copies/mL then impute it as "399 copies/mL". If the result from the ultrasensitive assay was < 50 copies/mL, then impute it as "49 copies/mL". 3. If the dilution assay was performed in addition to the standard assay, then use the maximum value of 750,001 and the result from the dilution assay.
Visit window for measurements of HIV RNA and CD4 count	In the datasets, there was a variable using integers to indicate the scheduled visits, e.g., 2.0=baseline, 3.0=Week 2, 4.0=Week 4, 5.0=Week 8, 6.0=Week 12, 7.0=Week 16, 8.0=Week 24; and using non-integers for the off-scheduled visits, e.g., 7.1, 22.2. The measurements at the scheduled visits were used, and those from off-scheduled visits were not used.	1. The measurements from all visits including scheduled and off-scheduled were used. 2. Use the mid-point between two consecutively scheduled visits as the dividing point except for the baseline, which is specified as follows: Visit — Visit window in days Baseline — <=1 Week 2 — (2, 21) Week 4 — (22, 42) Week 8 — (43, 70) Week 12 — (41, 98) Week 16 — (99, 140) Week 24 — (141, 196) Week 32 — (197, 252) 3. If more than one measurement was available with a visit window, then the one closest to the expected visit date was used.

to be continued

Table 5: Rules Used by Applicant and Reviewer in Efficacy Analysis (Cont.)

	Applicant	Reviewer
Missing data imputation	The following four approaches were used to analyze the proportions of patients achieving HIV RNA < 400 copies/mL and < 50 copies/mL at a certain visit. 1. The missing values were not imputed. The proportions were calculated as the number of responders divided by the total number of treated patients. 2. Observed failure: patients who discontinued the assigned treatment due to lack of efficacy were considered as failure thereafter. 3. Treatment-related discontinuation = failure: patients who discontinued the assigned treatment due to lack of efficacy or AE were considered as failures thereafter. 4. Non-completer = failure: patients who discontinued the assigned treatment regardless of reasons were considered as failures thereafter.	For the patients who withdrew from the study regardless of reasons or discontinued the assigned treatment and switched to the open label raltegravir treatment, the following rules were used: 1) they were regarded as failures thereafter for the binary endpoints such as proportion of patients with HIV RNA less than 400 copies/mL or 50 copies/mL at Week 48; and 2) they were considered as no change from baseline in HIV RNA or CD4 count. For the patients who did not withdrew from the study and did not discontinue the assigned blind treatment, if the measurement at a visit was missing and the one at next visit was available, then the one at the next visit was used; and if the one at the next visit was missing as well, then the one at the previous visit was carried forwards. For example, if a patient did not have HIV RNA value at Week 48, but had one at Week 60, then the one at Week 60 was used to impute the missing measurement at Week 48. If HIV RNA at Week 60 was missing as well, then Week 40 RNA level was carried forwards to Week 48.

Table 6: Reviewer's Results for Key Efficacy Endpoints at Week 48 Based on Snap Shot Approach

Week 48	Raltegravir 400 mg bid (N=281)	Efavirenz 600 mg qhs (N=282)	Treatment Difference (95% CI) [1]
Proportion of patients with HIV RNA <50 copies/mL – n (%)[2]	241 (86%)	231 (82%)	4% (-2%, 10%)
Proportion of patients with HIV RNA <400 copies/mL – n (%)[2]	253 (90%)	245 (87%)	3% (-2%, 8%)
Change from baseline in log_{10} HIV RNA[2] **n** **mean (SD)**	 281 -3.0 (1.1)	 282 -2.9 (1.2)	-0.1 (-0.3, 0.1)
Change from baseline in CD4 counts[2] **n** **mean (SD)**	 280 176 (128)	 181 150 (124)	25.8 (5.0, 46.5)

[1]For binary endpoints, the 95% CIs were calculated based on the chi-squared test. For continuous endpoints, the 95% CIs were calculated based on t-test.
[2]If the subject discontinued from the study for any reason, he was considered as having HIV RNA >= 50 copies/mL, HIV RNA >=400 copies/mL, no change from baseline in log10 HIV RNA and no change from baseline in CD4 counts at Week 48.

Table 7: Reviewer's Results for Key Efficacy Endpoints at Week 48 Based on TLOVR Algorithm

	Raltegravir 400 mg Twice Daily (N = 281)	Efavirenz 600 mg At Bedtime (N = 282)	Difference (ISENTRESS – Efavirenz) (CI*)
Outcome at Week 48			
Subjects with HIV-1 RNA less than 50 copies/mL	87%	82%	4.7% (-1.3%, 10.6%)
Subjects with HIV-1 RNA less than 400 copies/mL	91%	88%	3.6% (-1.5%, 8.7%)
Virologic Failure (>50 copies/mL) **Never suppressed through Week 48 and on study at Week 48** **Rebound**	6% 2% 5%	7% 3% 5%	
Discontinued study drug	7%	10%	
Reasons for Discontinuation			
Death **Adverse experiences** **Other**	<1% 2% 4%	0% 5% 5%	

* The 95% CI for treatment difference is adjusted by the screening HIV RNA level (<=50,000 copies/mL vs. >50,000 copies/mL) and Hepatitis B or C (negative vs. positive)

3.2 Evaluation of Safety

When reviewing the label, there was a question about how to calculate the mean change from baseline at Week 48 in LDL, HDL, total cholesterol and triglyceride. The applicant's approach to calculate the mean change from baseline at Week 48 was to subtract the baseline mean from the Week 48 mean. This was different from the approach presented in the label for Atazanavir, where the mean change from baseline at Week 48 was calculated as the average value of the difference between Week 48 and baseline within the individual patient. In general, if there is no missing data at both baseline and Week 48, the two algorithms lead to the same results. However, there were some missing data, and the results could vary. Therefore, the statistical reviewer carried out the analyses to compare the results between the two approaches.

Also, the applicant used the following 2 rules to determine the analysis dataset and to impute the missing data in the analysis:

1) If subjects initiated or increased serum lipid-reduction agents, the last available lipid values prior to the change in therapy were used in the analysis.
2) If the missing data was due to other reasons, subjects were censored thereafter for the analysis.

Based on Rule 1, the 21 patients used serum lipid-reducing agents at baseline (13 in raltegravir and 8 in efavirenz group) were excluded in the calculation of baseline means and Week 48 means because there were no measurements prior to taking serum lipid-reducing agents available for these subjects in the database. Also, for the 15 patients who initiated the lipid-reducing agent after baseline through Week 48 (3 in raltegravir and 12 in efavirenz group), the last available lipid values prior to the therapy were carried forwards as the values for Week 48. Rule 2 excluded the subjects who did not take lipid-reduction agents but had missing data at either baseline or Week 48 from the analysis.

The statistical reviewer could not reproduce the baseline means and Week 48 means presented by the sponsor (20). However, the differences between the sponsor's and the reviewer's results (Table 9) were within 1 unit for all parameters except for the Week 48 mean for triglyceride for which the difference was 2.8 units. In addition, there were about 10% subjects who did not have Week 48 values due to other reasons including withdrawal from study in both groups. But the means change from baseline at Week 48 for all parameters obtained based on the two algorithms were very close – all within 1-unit difference.

Of note, it stated that "values obtained after initiation of serum lipid-reducing agents were not included in these analyses" in the Atazanavir label. It is not clear whether the last available measurements prior to the serum lipid-reducing agents were carried forwards for the subjects who received serum lipid-reducing agents in the analysis (i.e., LOCF approach). In this submission, the applicant used the LOCF approach, i.e., Rule 1 described above.

Table 8: Applicant's Results for Lipids

	Raltegravir (N=281)			Efavirenz (N=282)		
			Change from baseline at Week 48			Change from baseline at Week 48
	Baseline mean	Week 48 mean	Mean change[1]	Baseline mean	Week 48 mean	Mean Change[1]
LDL-cholesterol	97.0	103.0	5.9	92.4	108.5	16.1
HDL-cholesterol	38.4	42.5	4.2	37.8	47.8	10.0
Total cholesterol	159.4	169.4	10.0	155.8	188.4	32.7
Triglyceride	124.7	121.9	-2.8	136.2	173.6	37.4

Sources: Table 3 in label.
[1]mean change = Week 48 mean – baseline mean.

Table 9: Reviewer's Results for Lipids

	Raltegravir (N=281)				Efavirenz (N=282)			
			Change from baseline at Week 48				Change from baseline at Week 48	
	Baseline mean	Week 48 mean	Mean change[1]	Within subject mean change[2]	Baseline mean	Week 48 mean	Mean Change[1]	Within subject mean change[2]
LDL-cholesterol	96.3 (n=264)	102.9 (n=235)	6.6	6.2 (n=232)	91.8 (n=267)	109.0 (n=228)	17.2	16.2 (n=225)
HDL-cholesterol	38.8 (n=267)	42.6 (n=238)	3.8	4.0 (n=237)	37.8 (n=271)	47.9 (n=240)	10.1	10.2 (n=238)
Total cholesterol	159.3 (n=268)	169.6 (n=241)	10.3	10.2 (n=241)	155.3 (n=272)	188.4 (n=240)	33.1	32.7 (n=239)
Triglyceride	123.9 (n=268)	122.2 (n=241)	-1.7	-1.5 (n=241)	135.8 (n=272)	170.8 (n=240)	35.0	35.0 (n=239)

[1]mean change = Week 48 mean – baseline mean.
[2]Within subject mean change was only for subjects who had measurements at both baseline and Week 48. It was the average value of the difference between Week 48 and baseline for the individual subject.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Both the applicant and the statistical reviewer performed the subgroup analyses for the primary efficacy endpoint with respective to patient demographic and baseline disease characteristics. The applicant used OF to impute the missing data and the Miettinen and Nurminen's method to calculate the 95% CIs for the treatment differences within each subgroup. On the other hand, the statistical reviewer employed the same approaches as those for the efficacy analyses in the subgroup analyses, i.e., the TLOVR algorithm and the snap shot approach. The reviewer also calculated the 95% CIs without stratification for the treatment differences within the subgroup. The

reviewer's subgroup analyses results from the two approaches were similar. Table 10 summarizes the reviewer's subgroup analyses based on the TLOVR algorithm. Also, the response rates in the applicant's subgroup analysis were slightly elevated compared with the reviewer's results. This was because the denominator in the OF approach used by the applicant did not included all randomized and treated patients but excluded the patients who discontinued the assigned treatment due to the reasons other than lack of efficacy.

Nevertheless, all these subgroup analyses demonstrated that there was no apparent interaction between the treatment by the subgroup. However, the magnitudes of the treatment differences in the following subgroups were large in the reviewer's subgroup analyses. But the sample sizes in these subgroups were not big enough to make the final conclusions.

1) Among the black patients, the proportion of patients with HIV RNA below 50 copies/mL at Week 48 in the raltegravir group was about 8% lower than that in the efavirenz group.

2) Among the patients with positive HBV and/or HCV, approximately 17% more raltegravir-treated patients achieved HIV RNA below 50 copies/mL at Week 48 than the efavirenz-treated patients.

3) Among the patients with HIV RNA below 50,000 copies/mL at screening, approximately 12% more patients in the raltegravir group had HIV RNA below 50 copies/mL at Week 48 than those in the efavirenz group.

Additionally, there were only 12 patients in the subgroup of patients with HIV RNA $\leq$50,000 and positive HBV and/or HCV at screening. Among these 12 patients, 7 were in the raltegravir group and 5 in the efavirenz group. However, all the 7 raltegravir-treated patients achieved HIV RNA less than 50 copies/mL at Week 48 while only 1 out 5 did so among the efavirenz-treated patients. Nevertheless, the sample size was too small to conclude that raltegravir was significantly superior to efavirenz in this subgroup or that there was significant interaction between the treatment and the subgroups classified by HIV RNA and HBVand/or HCV status at screening.

Table 10: Reviewer's Subgroup Analysis for HIV RNA <50 copies/mL at Week 48 (TLOVR)

	Raltegravir 400 mg bid	Efavirenz 600 mg qhs	Difference in Response Rate (95% CI)
Gender			
Female	47/54 (87%)	41/51 (80%)	6% (-7%, 21%)
Male	197/227 (87%)	191/231 (83%)	4% (-2%, 11%)
Race			
White	100/116 (86%)	102/123 (83%)	3% (-6%, 12%)
Black	26/33 (79%)	20/23 (87%)	-8% (-28%, 11%)
Asian	31/36 (86%)	27/32 (84%)	2% (-15%, 19%)
Hispanic	55/60 (92%)	54/67 (81%)	11% (-1%, 23%)
Multiracial	31/35 (89%)	28/36 (78%)	11% (-6%, 28%)
Region			
Latin America	89/99 (90%)	79/97 (81%)	5% (-1%, 18%)
Southeast Asia	30/34 (88%)	27/29 (93%)	-5% (-19%, 9%)
North America	65/82 (79%)	72/90 (80%)	-1% (-13%, 11%)
EU/Australia	60/66 (91%)	54/66 (82%)	9% (-3%, 21%)
Age			
< 37 yrs	112/129 (87%)	126/150 (84%)	3% (-4%, 11%)
>=37 yrs	132/152 (87%)	106/132 (80%)	7% (-2%, 15%)
Clade B			
Yes	188/219 (86%)	186/230 (81%)	5% (-2%, 12%)
No	53/59 (90%)	41/47 (87%)	3% (-10%, 15%)
Baseline HIV RNA			
≤50,000 copies/mL	71/79 (90%)	68/84 (81%)	9% (-2%, 20%)
>50,000 copies/mL	173/202 (86%)	164/198 (83%)	3% (-5%, 9%)
≤100,000 copies/mL	112/127 (88%)	113/139 (81%)	7% (-2%, 15%)
>100,000 copies/mL	132/154 (86%)	119/143 (83%)	3% (-6%, 11%)
Baseline CD4 count			
≤50 cells/mm^3	21/27 (78%)	24/31 (77%)	-0.4% (-21%, 22%)
>50 and ≤200 cells/mm3	85/104 (82%)	83/105 (79%)	3% (-8%, 13%)
>200 cells/mm3	138/150 (92%)	124/145 (86%)	6% (-1%, 14%)
Hepatitis status			
HBV and/or HCV positive	18/22 (82%)	13/20 (65%)	17% (-10%, 43%)
HBV and HCV negative	226/259 (87%)	219/262 (84%)	4% (-2%, 10%)
Screening HIV RNA (one of two stratification factors for randomization)			
≤50,000 copies/mL	66/74 (89%)	62/80 (78%)	12% (1%, 23%)
>50,000 copies/mL	178/207 (86%)	170/202 (84%)	2% (-5%, 9%)
HBV or HCV positive (one of two stratification factors for randomization)			
Yes	16/20 (80%)	14/19 (74%)	6% (-20%, 33%)
No	228/261 (87%)	218/263 (83%)	4% (-2%, 11%)
Combination of 2 stratification factors			
HIV RNA ≤50,000, HBV and HCV Neg.	59/67 (88%)	61/75 (81%)	7% (-5%, 18%)
HIV RNA ≤50,000, HBV and/or HCV Pos.	7/7 (100%)	1/5 (20%)	80% (45%, 100%)
HIV RNA >50,000, HBV and HCV Neg.	169/194 (87%)	157/188 (84%)	4% (-3%, 11%)
HIV RNA >50,000, HBV and/or HCV Pos.	9/13 (69%)	13/14 (93%)	-24% (-52%, 5%)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

To evaluate the robustness of the efficacy results of Study 021 in the treatment-naïve patients, the statistical reviewer used different rules of assigning of viral load when the results from different assays were available for a given visit (i.e., standard, ultrasensitive and dilution assays), different definitions of visit windows for measurements of HIV RNA level and CD4 counts, and different approaches to impute missing data. After adopting the rules, the reviewer further computed the proportion of patients with HIV RNA below 50 copies/mL and the proportion of patients with HIV RNA below 400 copies/mL at Week 48 using both the snap shot approach and the TLOVR algorithm. The snap shot approach classified patients as responders or non-responders based on the HIV RNA level at Week 48. If the patients discontinued the study treatment before Week 48 or did not have the HIV RNA value at Week 48 even after the missing HIV RNA was imputed, they were considered as non-responders in the snap shot analysis. On the other hand, the TLOVR algorithm defined the patients as the responders if the patients maintained at least two HIV RNA measurements below 50 copies/mL for the endpoint of proportion of patients with HIV RNA below 50 copies/mL at Week 48 (or at least two HIV RNA measurements below 400 copies/mL for the endpoint of proportion of patients with HIV RNA below 400 copies/mL at Week 48) without virologic rebound or treatment discontinuation. The results from the reviewer's snap shot and TLOVR varied slightly from the applicant's results, but they did not change the conclusion that both the proportion of patients with HIV RNA below 50 copies/mL and the proportion of patients with HIV RNA below 400 copies/mL in the raltegravir group were slightly higher than those in the efavirenz group. Additionally, the reviewer calculated the change from baseline in $\log_{10}$ HIV RNA and change from baseline in CD4 cells at Week 48. Again the results showed that the raltegravir had similar results to the efavirenz with respect to these two endpoints.

The subgroup analyses for the primary efficacy endpoint with patient demographics and baseline disease characteristics demonstrated that there was no apparent treatment by subgroup interaction. However, the magnitudes of the treatment differences in the following subgroups were large. But the sample sizes in these subgroups were not big enough to make the final conclusions.

1) Among the black patients, the proportion of patients with HIV RNA below 50 copies/mL at Week 48 in the raltegravir group was about 8% lower than that in the efavirenz group.

2) Among the patients with positive HBV and/or HCV, approximately 17% more raltegravir-treated patients achieved HIV RNA below 50 copies/mL at Week 48 than the efavirenz-treated patients.

3) Among the patients with HIV RNA below 50,000 copies/mL at screening, approximately 12% more patients in the raltegravir group had HIV RNA below 50 copies/mL at Week 48 than those in the efavirenz group.

5.2 Conclusions and Recommendations

After reviewing the efficacy results based on the 48 week data from Study 021 in treatment-naïve patients, the statistical reviewer concluded that raltegravir 400 mg b.i.d. was non-inferior in efficacy at Week 48 to efavirenz 600 mg q.h.s., each in combination with TRUVADA™.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Karen Qi
6/8/2009 02:41:48 PM
BIOMETRICS

Greg Soon
6/8/2009 03:52:13 PM
BIOMETRICS

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 22145 S-004 **Applicant: Merck** **Stamp Date:**

Drug Name: raltegravir **NDA/BLA Type: NDA**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	✓			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	✓			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	✓			No subgrp for safety
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	✓			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	✓			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	✓			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	✓			
Appropriate references for novel statistical methodology (if present) are included.	✓			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	✓			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	✓			

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Reviewing Statistician	11/7/08 Date
Supervisor/Team Leader	11/7/08 Date

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Karen Qi
6/26/2009 02:14:43 PM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22 – 145/S004

MICROBIOLOGY REVIEW(S)

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

MICROBIOLOGY REVIEW

NDA: 22-145 **SN**: SE5-004 **DATE REVIEWED:** 05/21/09

Microbiology Reviewer: Sung S. Rhee, Ph.D.

NDA #: 22-145 **Serial #:** SE5-004

Applicant Name and Address: Merck & Co., Inc.
One Merck Drive, P.O. Box 100
Whitehouse Station, NJ 08889-0100

Reviewer's Name(s): Sung S. Rhee, Ph.D.

Initial Submission Dates:

Correspondence Date: September 25, 2008
CDER Receipt Date: September 25, 2008
Reviewer Receipt Date: September 29, 2008
Review Complete Date: May 21, 2009
DAVP Action Date: July 24, 2009
PDUFA Date: July 24, 2009

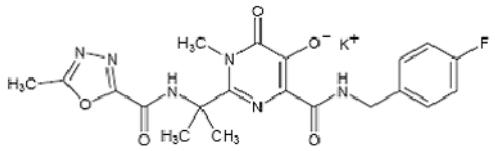
Related/Supporting Documents: IND 69,928

Product Name(s):

Proprietary: ISENTRESS™
Non-Proprietary/USAN: Raltegravir potassium
Code Name/Number: MK-0518

Chemical Name: N-[(4-fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-1-methyl-2-[1-methyl-1-[[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino]ethyl]-6-oxo-4-pyrimidinecarboxamide monopotassium salt

Structural Formula:



Raltegravir (RAL)

Molecular Formula: $C_{20}H_{20}FKN_6O_5$
Molecular Weight: 482.51

Dosage Form(s): 400 mg tablet
Route(s) of Administration: Oral
Indication(s): Treatment of HIV-1 infection in combination with other antiretroviral agents in adult patients
Recommended Dosage: 400 mg twice daily
Dispensed: Rx _X_ **OTC** ___ **(Discipline relevant)**

Abbreviations: Abbreviations: AE, adverse event; ARV, antiretroviral; BID, *bis in die* (twice a day); CONDO, drug-sensitive control subtype B virus; EC_{50}, 50% effective concentration; EC_{95}, 95% effective concentration; EFV, efavirenz; FTC, emtricitabine; FTC^r, emtricitabine resistance; HIV-1, human immunodeficiency virus type 1; HIV-2, human immunodeficiency virus type 2; IC_{50}, 50% inhibitory concentration; IN, integrase; INSTI, HIV-1 integrase strand transfer inhibitor; LAM, lamivudine; LLOQ, lower limit of

quantification; OBT, optimized background therapy; PCR, polymerase chain reaction; QD, once daily; QHS, once nightly; RAL, raltegravir; RAL^r, raltegravir resistance; RT, reverse transcriptase; RT-PCR, reverse transcriptase polymerase chain reaction; RTV, resistance test vector; sNDA, supplemental new drug application; TDF, tenofovir disoproxil fumarate; ULOQ, upper limit of quantification

---

Table of Contents

List of Tables

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

MICROBIOLOGY REVIEW

NDA: 22-145 **SN**: SE5-004 **DATE REVIEWED:** 05/21/09

Microbiology Reviewer: Sung S. Rhee, Ph.D.

EXECUTIVE SUMMARY

Raltegravir (MK-0518, ISENTRESS^{TM}) is an HIV-1 integrase (IN) inhibitor that specifically inhibits the strand transfer reaction of HIV-1 IN, and thereby prevents the covalent insertion, or integration, of unintegrated linear HIV-1 DNA into the host cell genome that forms the provirus. The integration of viral DNA into host chromosomal DNA is one of the essential steps in the HIV-1 life cycle.

Originally, raltegravir 400 mg BID for the oral tablet formulation was approved for the treatment of HIV-1 infection in combination with other antiretroviral agents in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents by the FDA on October 13, 2006 (NDA 22-145). Three independent raltegravir resistance pathways, through the emergence of Y143C/H/R, Q148H/K/R, or N155H substitutions within the HIV-1 integrase protein, were identified in this treatment-experienced HIV-1-infected population. These 3 amino acid substitutions were highly associated with virologic failure and virologic rebound to raltegravir therapy, detectable in 64% and 67% of evaluable virologic failures and rebounders, respectively, at Week 48. Each of the 3 primary substitutions was usually accompanied by one or more of the 11 secondary substitutions, L74M/R, E92Q, T97A, E138A/K, G140A/S, V151I, G163R, H183P, Y226C/D/F/H, S230N/R, and D232N.

This supplemental NDA provides the 48-week data from the Phase 3 non-inferiority study (Protocol 021) in treatment-naïve HIV-1-infected subjects of raltegravir compared to efavirenz, both in combination with TRUVADA^{TM}. By Week 48, raltegravir (+TRUVADA) showed non-inferior antiviral efficacy to efavirenz (+TRUVADA): 86% of raltegravir recipients were suppressed with plasma HIV-1 RNA <50, compared to 82% of efavirenz recipients. Emergence of previously identified primary raltegravir resistance-associated substitutions, Y143R (in one rebounder) and Q148H/R (in 2 non-responders), were observed in 3 subjects, out of 6 raltegravir-treatment failures whose paired genotypic data of baseline and failure isolates were currently available.

1. Recommendations

1.1. Recommendation and Conclusion on Approvability

Approval of this supplemental NDA for ISENTRESS^{TM} 400 mg BID for the treatment of HIV-1 infection in combination with other antiretroviral agents in treatment-naïve, adult patients is recommended with respect to Clinical Microbiology.

1.2. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, If Approvable: None

2. Summary of OAP Microbiology Assessments

2.1. Nonclinical Microbiology

Raltegravir inhibits the HIV-1 IN-catalyzed strand transfer with an IC_{50} value of 2 to 7 nM in a biochemical reaction. Raltegravir did not significantly inhibit human

phosphoryltransferases including DNA polymerases α, β, and γ. Raltegravir exhibited antiviral activity against HIV-1 clinical isolates in human peripheral blood mononuclear cells with IC_{95} values ranging from 6 to 50 nM. Isolates tested included various HIV-1 subtypes, A to F, and both NSI (nonsyncytia inducing M-tropic) and SI (syncytia inducing T-tropic) viruses that use the co-receptors CCR5 and CXCR4, respectively. Raltegravir also inhibited replication of an HIV-2 isolate when tested in CEMx174 cells (EC_{95} value = 6 nM). Raltegravir exerted additive to synergistic antiviral effects when combined with each of 18 FDA-approved antiretroviral drugs: NNRTIs delavirdine, efavirenz, or nevirapine; NRTIs abacavir, didanosine, lamivudine, stavudine, tenofovir, zalcitabine, or zidovudine; PIs amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, or saquinavir; or the fusion inhibitor enfuvirtide.

Antiviral activity of raltegravir against HIV-1 non-B subtype clinical isolates was further assessed in cell culture in a single-cycle infection assay (Monogram Biosciences PhenoSense® Integrase assay). The mean IC_{50} value of raltegravir against the tested 23 non-B subtype isolates representing 5 subtypes (A, C, D, F, and G) and 5 circulating recombinant forms (AE, AG, BF, BG, and cpx) was 7.1 ± 1.7 nM (5-12 nM; median = 7 nM), with the mean fold-change in IC_{50} values of 0.9 ± 0.2 (0.7-1.6; median = 0.9 fold-change) compared to the subtype B control virus. Thus, raltegravir appears to be active against various non-B subtype HIV-1 isolates with IC_{50} values similar to that of subtype B isolates.

2.2. Clinical Microbiology

Three independent primary pathways to raltegravir resistance, through the emergence of Y143C/H/R, Q148H/K/R, or N155H substitutions within the HIV-1 integrase protein, were previously identified. By Week 48, in the treatment-experienced HIV-1-infected population (Phase 3 studies 018 and 019), these 3 primary raltegravir resistance-associated substitutions were observed to emerge in 63 (64%) of the 98 evaluable, raltegravir-treatment virologic failures and in 52 (67%) of the 85 evaluable virologic rebounders. Overall, the probability of incurring genotypic resistance (emergence of at least one of the 3 primary substitutions) to raltegravir in Year 1 was calculated to be 14.4%. Each of the 3 primary substitutions were usually accompanied by one or more of the 11 secondary substitutions, L74M, E92Q, T97A, E138A/K, G140A/S, V151I, G163R, H183P, Y226C/D/F/H, S230N/R, and D232N. Of note, in the previous cell-based phenotypic studies using a single-cycle HIV-1 infection assay, Y143C/H/R, Q148H/K/R, and N155H substitutions were shown to reduce susceptibility to raltegravir by 2-10 fold, 24-46 fold, and 13 fold, respectively. Addition of reported secondary substitutions to the primary substitutions appeared to increase resistance (e.g., addition of E92Q to Y143R, G140S to Q148H, E92Q to N155H decreased susceptibility to raltegravir from >10-fold to 215-fold, 24-fold to 521-fold, 13-fold to 64-fold, respectively; E92Q and G140S, by themselves conferred 3-fold and 2-fold reduced susceptibility, respectively).

By Week 48, in the treatment-naïve HIV-1-infected population (Phase 3 study 021), raltegravir (+TRUVADA) showed non-inferior antiviral efficacy to efavirenz (+TRUVADA) based on virologic suppression (measured by proportions of subjects achieving HIV-1 RNA levels <50 copies/mL and <400 copies/mL): 86% (241/281) and

90% (253/281) of raltegravir recipients were suppressed with plasma HIV-1 RNA <50 and <400 copies/mL compared to 82% (231/282) and 87% (245/282) of efavirenz recipients, respectively.

There were 27 raltegravir (+TRUVADA)-treated subjects (10%) who experienced virologic failure by Week 48, compared to 12% of the efavirenz (+TRUVADA)-treated subjects. A greater proportion of those raltegravir-treatment failures experienced virologic rebound (63% [17/27]), compared to those with suboptimal suppression of HIV-1 replication (non-response; 37% [10/27]), suggesting that raltegravir-containing regimens can potently suppress HIV-1 replication but such response may not be durable. In contrast, no differences between the rates of virologic rebound and non-response were observed in efavirenz recipients (each 50% [17/34]).

Out of 6 failures whose paired genotypic data of baseline and failure isolates were currently available, previously identified primary raltegravir resistance-associated substitutions, Y143R (in one rebounder) and Q148H/R (in 2 non-responders), were detected in 3 subjects. Similar observations for genotypic raltegravir resistance were made in the Phase 2 study 004. By Week 96, 50% (3/6) of the evaluable raltegravir (+TDF/LAM) treatment-failures developed the Y143C (n=1, rebounder) or N155H (n=2, non-responders) primary raltegravir resistance-associated substitutions.

3. Administrative

3.1. Reviewer's Signature(s)

_____
Sung S. Rhee, Ph.D.
Microbiologist

3.2. Concurrence

_____ Date: _____
HFD-530/MicroTL/J. O'Rear

CC:
HFD-530/NDA # 22145
HFD-530/Division File
HFD-530/PM/A. Himaya

OAP MICROBIOLGY REVIEW

1. Introduction and Background

Raltegravir (RAL; MK-0518, ISENTRESS^{TM}) is an HIV-1 integrase strand transfer (INSTI) inhibitor that specifically inhibits the strand transfer reaction of HIV-1 integrase (IN), and thereby prevents the covalent insertion (or integration) of unintegrated linear HIV-1 DNA into the host cell genome that forms the provirus. The integration of viral DNA into host chromosomal DNA is an essential step in the HIV-1 life cycle. RAL 400 mg BID for the oral tablet formulation was approved for the treatment of HIV-1 infection in combination with other antiretroviral agents in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents by the FDA on October 13, 2006 (NDA 22-145, Phase 3 studies 018 and 019).

In treatment-experienced adult subjects (Studies 018 and 019), RAL plus optimized background therapy (OBT) showed superior antiviral efficacy to placebo plus OBT by Week 48. In the censored, as-treated analysis, 73% and 64% of RAL (+OBT) recipients were suppressed with plasma HIV-1 RNA <400 copies/mL and <50 copies/mL, respectively, compared to 37% and 32% of placebo (+OBT)-treated subjects (Microbiology review N022145.SE7-001). Higher rates of virologic failure by Week 48 were observed in the subgroup of subjects with higher baseline viral load in both RAL and placebo-treated subjects. Treatment failure of the RAL recipients was largely due to treatment-emergent virologic rebound (87% of the RAL + OBT virologic failures), rather than due to the suboptimal suppression of HIV-1 replication (non-response to the treatment; 13%). In contrast, no significant differences between the rates of virologic non-response (55% of the placebo + OBT virologic failures) and rebound (45%) were observed in placebo recipients. The number of subjects experiencing virologic rebound has increased at Week 48, compared to Week 16, by 64% (n=58 to 95 subjects) and 47% (n=43 to 63 subjects) in RAL and placebo recipients, respectively. These results indicated that RAL-containing regimens can suppress HIV-1 replication but such response may not be durable.

The paired genotypic analysis of the pre-treatment and on-treatment samples of 98 evaluable subjects, out of the 109 virologic failures to RAL (+OBT) treatment in the 2 Phase 3 studies (018 and 019), identified 3 amino acid substitutions at positions 143 (Y143C/H/R), 148 (Q148H/K/R), and 155 (N155H) in HIV-1 IN to be primarily associated with RAL treatment virologic failure and rebound. These 3 primary RAL resistance (RAL^{r})-associated substitutions emerged on RAL in 63 (64%) of the 98 evaluable virologic failures and in 52 (67%) of the 85 evaluable virologic rebounders. Furthermore, these 3 primary substitutions appeared to emerge independently as separate pathways to RAL resistance. Each of the 3 primary substitutions were usually accompanied by one or more of the 11 secondary substitutions, L74M, E92Q, T97A, E138A/K, G140A/S, V151I, G163R, H183P, Y226C/D/F/H, S230R, and D232N. Of the 63 subjects with emerging primary RAL^{r}-associated substitutions, these 11 secondary substitutions were found in 46 subjects (73%).

This supplemental NDA (sNDA) for RAL 400 mg BID provides primarily the 48-week

datasets from the Phase 3 non-inferior study (Protocol 021) in treatment-naïve HIV-1-infected subjects of RAL compared to efavirenz (EFV), both in combination with TRUVADA™. In addition, the applicant included the 96-week supportive and long-term data from a Phase 2 dose-ranging trial (Protocol 004), RAL at 4 dose levels (100, 200, 400, and 600 mg) versus EFV, both administered with tenofovir (TDF) and lamivudine (LAM) in treatment-naïve HIV-1-infected subjects.

2. Materials and Methods

2.1. Quantification of Plasma HIV-1 RNA Levels

Plasma HIV-1 RNA levels were quantified using an COBAS Amplicor HIV-1 Monitor Test (Roche, version 1.5) that received marketing approval from FDA (BP950005) on March 2, 1999 as an *in vitro* nucleic acid amplification test for the quantification of HIV-1 RNA in human plasma. According to the manufacturer, the Amplicor HIV-1 Monitor Test yielded a specificity of >99.5%, reducing false positive results when tested in a large seronegative population of over 500 samples. It could distinguish 0.5 $\log_{10}$ copies/mL differences. In addition, this test utilizes a primer set designed to detect non-B subtypes (HIV-1 Group M), providing reliable viral load measurement of HIV-1 subtypes A-G.

The Roche Amplicor HIV-1 Monitor Test was used with either the standard processing procedure or the ultrasensitive processing procedure. In the standard processing procedure, HIV-1 RNA was isolated directly from plasma by lysis of virus particles with a chaotropic agent followed by precipitation of the RNA with alcohol. HIV-1 RNA can be quantified by this procedure over the range of 400 (2.60 $\log_{10}$, lower limit of quantification [LLOQ]) to 750,000 (5.88 $\log_{10}$, upper limit of quantification [ULOQ]) copies/mL. When HIV-1 RNA levels were <400 copies/mL by the standard processing procedure, the applicant employed the ultrasensitive processing procedure where HIV-1 viral particles are first pelleted from the plasma specimen by high speed ultracentrifugation followed by lysis of the pelleted virus particles with a chaotropic agent and precipitation of the HIV-1 RNA with alcohol. This procedure was reported by the manufacturer to quantify viral loads as low as 50 copies/mL 95% of the time. For specimens containing high levels of HIV-1 RNA (≥750,000 copies/mL), diluted samples were requantified.

2.2. Nucleotide Sequence Analysis of the HIV-1 Integrase Coding Region

(b) (4)

(b) (4)

(b) (4)

(b) (4)

3. Nonclinical Microbiology: Antiviral Activity of Raltegravir against HIV-1 Non-B Subtype Clinical Isolates

Please refer to the Microbiology review NDA022145.000 and NDA022145.SE7-001 for the nonclinical microbiology of RAL, including mechanism of action, antiviral activity in cell culture against wild-type HIV-1 and variants harboring RAL^r-associated substitutions within the integrase protein, cytotoxicity, combination antiviral activity relationships with FDA-approved antiretrovirals, and cross-resistance with other investigational HIV-1 integrase strand transfer inhibitors (INSTIs).

In this sNDA package for RAL, the applicant included a study report, Reference 750, that assessed the cell culture antiviral activity of RAL against non-B subtype HIV-1 clinical isolates using the Monogram Biosciences PhenoSense® Integrase assay as previously described (Fransen *et al.*, 2005, presented at the 12th Conference on Retroviruses and Opportunistic Infections meeting, Abstract #725). (b) (4)

A total of 23 non-B subtype clinical isolates was tested (Table 1): subtypes A1 (5 isolates), C (4 isolates), D (2 isolates), F (2 isolates), G (1 isolate), and circulating recombinant forms CRF01_AE (3 isolates), CRF12_BF (2 isolates), CRF14_BG (2 isolates), CRF02_AG (1 isolate), and CRF06_cpx (1 isolate). The mean IC_{50} value of RAL against the tested 23 non-B subtype isolates was 7.1 ± 1.7 nM, ranging from 5 to 12 nM (median = 7 nM), with the mean fold-change in IC_{50} values of 0.9 ± 0.2, ranging from 0.7 to 1.6 (median = 0.9 fold-change) compared to the subtype B control virus (CNDO). Thus, RAL appears to be active against various non-B subtype HIV-1 isolates with IC_{50} values similar to that of subtype B isolates. Indeed, these cell-culture results were confirmed in Phase 3 Study 021 (STARTMRK trial in treatment-naïve HIV-1-

infected subjects) where the applicant observed RAL-treatment virologic failure in the non-B subtype-infected subpopulation with a similar frequency (7%; Table 2), compared to the corresponding overall study population (10%) or the subtype B-infected population (11%).

Table 1: Raltegravir Antiviral Activity against 23 Non-B Subtype HIV-1 Clinical Isolates Tested in the Monogram PhenoSense® Integrase Assay

Virus Subtype	Virus Accession Number[†]	Raltegravir IC_{50} (nM)	Raltegravir Fold-Change IC_{50}[‡]
Subtype A1	5142679	6	0.77
Subtype A1	5142680	12	1.55
Subtype A1	5142681	6	0.78
Subtype CRF01_AE	5142682	6	0.84
Subtype CRF01_AE	5142683	7	0.94
Subtype A1	5142684	7	0.94
Subtype A1	5142685	7	0.99
Subtype CRF01_AE	5142686	6	0.79
Subtype C (Africa)	5142687	8	1.01
Subtype C (Africa)	5142688	7	0.96
Subtype C (Africa)	5142689	7	0.91
Subtype C (Africa)	5142690	8	1.02
Subtype D	5142691	6	0.75
Subtype D	5142692	5	0.69
Subtype F	5142693	7	0.97
Subtype CRF12_BF	5142694	6	0.80
Subtype CRF12_BF	5142695	7	0.89
Subtype F	5142696	7	0.96
Subtype CRF02_AG	5142697	6	0.80
Subtype CPX_06	5142698	8	1.06
Subtype CRF14_BG	5142699	6	0.77
Subtype CRF14_BG	5142700	12	1.60
Subtype G	5142701	7	0.97

Data shown were generated by Monogram Biosciences, Inc., using an investigational phenotypic assay. Test viruses contained the RNase H and Integrase coding sequences from primary HIV-1 isolates of the indicated subtypes. [†] Monogram's accession number for each test virus. [‡]The fold-change IC_{50} value indicates the change in IC_{50} relative to the control (wild-type subtype B) virus.

4. Clinical Microbiology

4.1. Antiviral Efficacy

Protocol 021 (STARTMRK trial) is a multicenter, double-blind, randomized, active-controlled, phase 3, non-inferior study of RAL 400 mg BID compared to EFV 600 mg QHS, when both are administered in combination with TRUVADA® QD, in treatment-naïve HIV-1-infected subjects with HIV-1 RNA >5000 copies/mL. A total of 563 subjects were randomized in a 1:1 ratio to receive one of the 2 treatments for 240 weeks. By the June-05-2008 data cut-off, all of the 563 treated subjects had Week 48 data (i.e., either completed the Week 48 visit or had the potential to experience Week 48 visits for those who discontinued before Week 48).

The 48-week overall efficacy data demonstrated that RAL (+TRUVADA) was non-inferior

to EFV (+TRUVADA) based on virologic suppression (measured by proportions of subjects achieving HIV-1 RNA levels <50 copies/mL and <400 copies/mL) and on immunological effect (measured by changes from baseline in $CD4^+$ T cell count). As summarized in Table 2, at Week 48, 86% (241/281) and 90% (253/281) of RAL (+TRUVADA) recipients were suppressed with plasma HIV-1 RNA <50 and <400 copies/mL, respectively, as quantified by the Roche COBAS AMPLICOR HIV-1 Monitor Ultrasensitive (version 1.5) and Standard assays (version 1.5). In the EFV (+TRUVADA) population, the rates of virologic suppression to <50 and to <400 HIV-1 RNA copies/mL were 82% (231/282) and 87% (245/282), respectively. Please refer to the reviews by Medical Officer Sarah Connelly, M.D. and Statistician Karen Qi, Ph.D. for a detailed analysis of the efficacy of RAL 400 mg BID.

Table 2: Key Efficacy Outcomes in Evaluable and As-Treated Population

	RAL 400 mg BID (+ TRUVADA)	**EFV 600 mg QHS** (+ TRUVADA)
Mean HIV-1 RNA in $\log_{10}$ copies/mL at baseline, (range; median)[1]	5 ± 0.6 (2.7 - 5.9; 5)	5 ± 0.6 (3.6 - 5.9; 5)
Subjects with HIV-1 RNA <50 copies/mL at Week 48, n (%)[1]	241/281 (85.8%)[2]	231/282 (81.9%)[2]
Subjects with HIV-1 RNA <400 copies/mL at Week 48, n (%)[1]	253/281 (90%)[2]	245/282 (86.9%)[2]
Mean decrease in $\log_{10}$ copies/mL HIV-1 RNA at Week 48 from baseline[1]	3.0 ± 1.1[2]	2.9 ± 1.2[2]
Mean increase in $CD4^+$ T cell counts at Week 48 from baseline[1]	176 ± 128[2]	150 ± 124[2]
Virologic Failure at Week 48[3,4]	**27/281 (9.6%)**	**34/274**[3] **(12.4%)**
• Non-response[5], n (%) • Virologic Rebound[6], n (%)	10/281 (3.6%) 17/281 (6%)	17/274 (6.2%) 17/274 (6.2%)
• Baseline HIV-1 RNA <100,000 copies/mL, n (%) • Baseline HIV-1 RNA ≥100,000 copies/mL, n (%)	9/127 (7.1%) 18/154 (11.7%)	17/134 (12.7%) 17/140 (12.1%)
• Infected with HIV-1 subtype B, n (%) • Infected with HIV-1 non-B subtypes, n (%)	23/219 (10.5%) 4/59 (6.8%)	32/222 (14.4%) 2/47 (4.2%)

[1]For subjects who discontinued assigned treatment regardless of reasons, they were considered as failures to achieve virologic suppression (HIV-1 RNA <50 and <400 copies/mL) and to have no changes in HIV-1 RNA levels and $CD4^+$ T cell counts at Week 48.
[2]Data source: Statistical Review and Evaluation by Karen Qi, Ph.D., Table 6
[3]Subjects (n=8, all treated with EFV + TRUVADA) who discontinued assigned treatment at or before Week 2 were excluded from the virologic failure and resistance analyses.
[4]Virologic failure was defined as having either virologic non-response or virologic rebound.
[5]Virologic non-response was defined as (1) HIV-1 RNA >50 copies/mL at the time of discontinuation for subjects who prematurely discontinue study therapy or (2) HIV-1 RNA >50 copies/mL at Week 24.
[6]Virologic rebound was defined as HIV-1 RNA >50 copies/mL on 2 consecutive measurements at least 1 week apart after initial response with HIV-1 RNA <50 copies/mL.

The virologic failure and resistance analyses were performed in the censored, as-treated subject population (n=555), excluding 8 subjects from the as-treated population who received ≤2 weeks of assigned treatment. All 8 excluded subjects were treated with EFV (+TRUVADA) and discontinued their treatment due to clinical AE (n=5), loss to follow-up (n=2), and consent withdrawn (n=1) at or before Week 2. At the time of discontinuation, none suppressed HIV-1 RNA levels to <50 copies/mL. Virologic failure

was defined as having either virologic non-response or virologic rebound:

- Virologic non-response was defined as (1) HIV-1 RNA >50 copies/mL at the time of discontinuation for subjects who prematurely discontinue study therapy or (2) HIV-1 RNA >50 copies/mL at Week 24.
- Virologic rebound was defined as HIV-1 RNA >50 copies/mL on 2 consecutive measurements at least 1 week apart after initial response with HIV-1 RNA <50 copies/mL.

Of the 281 RAL (+TRUVADA) recipients (treatment-naïve) in the censored, as-treated analysis (Table 2), 27 subjects (10%) experienced virologic failure by Week 48, comparable to 12% (34/274) of the subjects treated with EFV (+TRUVADA). Treatment failure of the RAL recipients was largely due to treatment-emergent virologic rebound (Table 2): a greater proportion of those RAL-treatment failures experienced virologic rebound (63% [17/27]) compared to those with suboptimal suppression of HIV-1 replication (non-response; 37% [10/27]). In contrast, no differences between the rates of virologic rebound and non-response were observed in EFV recipients (each 50% [17/34]; Table 2). Similarly, virologic rebound-associated treatment failure was also observed more frequently in RAL-treated, treatment-experienced subjects (Studies 018 and 019): most (87%) of the RAL (+ OBT) treatment failures at Week 48 experienced virologic rebound, whereas no significant differences between the rates of virologic non-response (55% of the placebo + OBT virologic failures) and rebound (45%) were observed in placebo recipients. These results indicated that RAL-containing regimens can potently suppress HIV-1 replication but such response is not durable.

In addition, virologic failure was more frequently observed in the subgroup of RAL (+TRUVADA)-treated subjects with baseline viral RNA levels ≥100,000 copies/mL than those with <100,000 copies/mL (12% versus 7%; Table 2). In contrast, consistent efficacy was observed in EFV (+TRUVADA) recipients, regardless of baseline HIV-1 levels (12% versus 13%; Table 2). Plasma HIV-1 RNA levels at Baseline were comparable between the 2 treatment groups, both with mean and median values of 100,000 copies/mL (Table 2).

4.2. Clinical Resistance Analyses

To date, 3 amino acid substitutions at positions 143 (Y143C/H/R), 148 (Q148H/K/R), and 155 (N155H) in HIV-1 IN have been identified as primary RAL resistance (RAL^r)-associated substitutions in the paired genotypic analysis of the pre-treatment and RAL-treatment failure isolates (Microbiology reviews N022145.000. and N022145.SE7-001). Recent molecular modeling studies by Loizidou *et al*. (2009) indicated there are 2 different groups of amino acid residues around the active site of IN interacting with RAL, implying a differential binding mode of RAL, one leading to the Y143 and another to the N155 and Q148 resistance pathway.

Previously, in the treatment-experienced HIV-1-infected population (Phase 3 studies 018 and 019), these 3 primary substitutions were observed to emerge on RAL in 63 (64%) of the 98 evaluable virologic failures and in 52 (67%) of the 85 evaluable virologic rebounders by Week 48 (Microbiology review N022145.SE7-001). Furthermore, these 3

substitutions appeared to emerge independently as separate pathways to RAL resistance. The probability of incurring genotypic resistance (emergence of at least one of the 3 primary substitutions) to RAL in Year 1 was calculated to be 14.4% in treatment-experienced HIV-1-infected subjects. Each of the 3 primary substitutions were usually accompanied by one or more of the 11 secondary substitutions, L74M, E92Q, T97A, E138A/K, G140A/S, V151I, G163R, H183P, Y226C/D/F/H, S230R, and D232N. Of the 63 subjects with emerging primary RAL^r-associated substitutions, these 11 secondary substitutions were also found in 46 subjects (73%).

Of the 281 RAL (+TRUVADA)-treated, treatment-naïve HIV-1-infected subjects in the censored, as-treated analysis of STARTMRK trial (Study 021), 27 subjects showed evidence of virologic failure by Week 48 (Table 2) and 10 of those 27 subjects had plasma HIV-1 RNA levels >400 copies/mL at the time of virologic failure or at Week 48 (or at the time of discontinuation). The population genotypic sequencing of the HIV-1 IN domain was only performed in failure isolates with HIV-1 RNA >400 copies/mL, due the limit of the assay's threshold of around HIV-1 RNA 400 copies/mL. As of the genotypic data cut-off date (August 27, 2008), the applicant obtained paired baseline and on-treatment genotypic data from 6 of the 10 evaluable Year-1 RAL-treatment failures whose failure isolates had HIV-1 RNA >400 copies/mL.

As summarized in Table 3, the emergence of the primary RAL^r-associated substitutions (highlighted in yellow; Y143R and Q148H/R) was observed in 3 of those 6 failures: Subjects 20094 (rebounder), 23261 (non-responder), and 23304 (non-responder), all of whom were infected with HIV-1 subtype B. Of note, no naturally occurring polymorphic substitutions at Y143, Q148, and N155 were detectable in 22 subjects (13 RAL and 9 EFV recipients) with submitted baseline genotypic data. Recently, Rhee *et al*. (2008) also found very rarely substitutions at these 3 amino acid positions when 741 ARV-naïve HIV-1 group M IN sequences were analyzed: Y143H was present in 3 subtype C isolates and 1 subtype D isolate as a naturally occurring polymorphism; Q148H (subtype G) and Q148K (CRF02_AG) were each present in one isolate; and N155H was present in one subtype B.

Subject 20094 (Table 3) achieved virologic suppression (HIV-1 RNA <50 copies/mL) at Week 4 but virologic breakthrough was eventually observed at Week 24. The subject's rebound isolate collected at Week 24 harbored the Y143R primary RAL^r-associated substitution with the pre-existing baseline L74M change (L74M was identified as a secondary substitution frequently accompanying each of the 3 primary RAL^r-associated substitutions). In cell culture, the Y143R substitution displayed a significant reduction in RAL susceptibility of >10-fold, and the addition of L74M, which by itself conferred no reduction in susceptibility to RAL, decreased susceptibility to >20-fold (Microbiology review N022145.SE7-001). L74M was reported to be present in isolates (<1%) from untreated persons (Rhee *et al*., 2008). In addition, the signature emtricitabine resistance (FTC^r)-associated substitution, rtM184I in the HIV-1 RT domain (IAS-USA, 2008), was also detected in his rebound isolate. The subject discontinued from treatment at Week 32 due to lack of efficacy.

Subjects 23261 and 23304 (Table 3) did not responded to RAL treatment, both with a <1.0 $\log_{10}$ HIV-1 RNA reduction from Baseline at the time of early discontinuation (at

Weeks 17 and 12, respectively). When virus samples collected at their last treatment visits were genotyped, the Q148H/R primary RAL^r-associated substitution was detectable in both subjects together with the secondary G140S substitution. In cell culture, the Q148H/R substitution conferred 24- and 27-fold reduced susceptibility to RAL, respectively, and the addition of G140S to Q148 variants increased resistance to 405-fold (G140S/Q148R) to 521-fold (G140S/Q148H; Microbiology review N022145.000). G140S alone conferred 2-fold reduced susceptibility, respectively. In Year 1 in the treatment-experienced HIV-1-infected population (Phase 3 studies 018 and 019), the G140S + Q148H/R double substitutions were frequently observed among the RAL-treatment failure subjects with the emerging primary RAL^r-associated substitutions (16/63 [25.4%]). Subject 23261 also developed the rtM184V substitution while on TRUVADA.

Table 3: Resistance Analysis of 10 Evaluable Raltegravir-Treatment Failure Subjects in STARTMRK trial (Study 021)

Subject ID	Virologic Response	Baseline Isolate		Failure Isolate				
		Subtype	Viral Load[1]	Week	Viral Load[1]	Substitutions in HIV-1 IN		FTC/TDF Resistance-Associated Substitutions in HIV-1 RT[2]
						# of changes	Substitutions	
20073	Rebound	B	4.5	35	4.2	1	A105A/T	None
20082	Rebound	C	5.5	24	3.1	4	F1I, K14R, K240K/I, A278A/S	No paired genotypic data available
20094	Rebound	B	4.7	24[4]	2.8	3	(L74M)[3], Y143R, R224R/W, L242L/F	M184I
23261	Non-response	B	5.6	17[4]	5.2	2	G140S, Q148H, (V151I)[3]	M184V
23304	Non-response	B	5.3	12[4]	4.9	4	V31V/I, G140S, Q148R, V165V/I	No paired genotypic data available
23374	Rebound	B	5	26[4]	3.3	2	A21A/T, S24S/N,	None
20083	Rebound	B	5.1	48	2.9	-	No paired genotypic data available	No paired genotypic data available
23194	Rebound	B	5.8	24	2.8	-	No paired genotypic data available	No paired genotypic data available
				40	4	-		M184M/I
23436	Non-response	B	5.4	4[4]	2.7	-	No paired genotypic data available	No paired genotypic data available
24757	Non-response	C	5.9	4[4]	2.7	-	No paired genotypic data available	No paired genotypic data available

[1]HIV-1 RNA, $\log_{10}$ copies/mL
[2]TDF and FTC resistance-associated substitutions in HIV-1 RT: K65R, K70E, M184V/I (IAS-USA, 2008)
[3]RAL^r-associated secondary amino acid substitutions, L74M and V151I, were detected in 2 subjects' pretreatment virus samples and persisted through RAL treatment.
[4]Early discontinuation

The remaining 3 subjects, 20073, 20082, and 23374 (Table 3), with paired genotypic data achieved early virologic suppression (HIV-1 RNA to <50 copies/mL) by Weeks 4, 4, and 2, respectively, but failed to maintain suppression through Week 48. Subject 20073 had virologic breakthrough at Week 35, and Subjects 20082 and 23374 at Week 24. No detectable primary RAL^r-associated substitutions were observed in their failure isolates collected at the time of virologic rebound (Subjects 20073 and 20082) or at 2-weeks post-failure (Subject 23374). However, other amino acid substitutions (at 1 to 4 residues/subject; Table 3) in the HIV-1 IN proteins were present in all 3 subjects' failure

isolates compared to their respective baseline sequences: F1I (conserved), K14R (polymorphic), A21A/T (polymorphic), S24S/N (polymorphic), A105A/T (conserved), K240K/I (conserved), and A278A/S (polymorphic), each substitution occurring only once. These substitutions may be clinically significant in response to RAL treatment but infrequent occurrences preclude making definitive conclusions. Of these 7 residues, 3 residues, F1, A105, and K240, are conserved among HIV-1 isolates. Changes at residues F1 and A105 are particularly interesting, since HIV-1 variants harboring F1L (n=1) or A105V (n=1) substitutions were also detected in 2 of the 31 RAL-treatment failures with no evidence of emerging 3 primary substitutions (Study 018 in the treatment-experienced HIV-1-infected population). It is, thus, recommended to evaluate the contribution of these amino acid substitutions to RAL resistance. Of note, conserved residues were identified by levels of amino acid sequence variations occurring in the general population by Heckett *et al*. (2005): frequencies of <2% were considered conserved in the phylogenetic analysis of 497 HIV-1 group M isolates (76 subtype A, 81 subtype B, 70 subtype C, 43 subtype D, 15 subtype F, 10 subtype G, 1 subtype H, 48 CRF01_AE, 97 CRF02_AG, 56 MOSAIC).

Similarly, primary RAL^r-associated substitutions also observed in 50% (3/6) of the evaluable RAL (+TDF/LAM) treatment-failures with genotypic data in Phase 2 studies 004-01 and 004-10 by Week 96 (Table 4). According to the applicant, virologic failure occurred in 6 (3.8%) of 160 subjects in the RAL (+TDF/LAM) treatment group and in 2 (5.3%) of 38 subjects in the EFV (+TDF/LAM) treatment group by Week 96. When drug resistance testing (Monogram Biosciences) was conducted on viruses collected from all 6 subjects experiencing virologic failure to RAL treatment (3 non-responders and 3 rebounders; Table 4), the Y143C (n=1, rebounder) or N155H (n=2, non-responders) primary RAL^r-associated substitutions were detectable in 3 subjects. In cell culture, the N155H and Y143C substitutions conferred 13- and 2-fold reduced susceptibility to RAL, respectively, (Microbiology reviews N022145.000 and N022145.SE7-001). In addition, these 3 subjects' failure isolates also harbored rtM184I/V ± rtK65R substitutions in the HIV-1 RT domain, conferring reduced susceptibility to LAM ± TDF (Table 4; IAS-USA, 2008).

Table 4: Resistance Analysis of 6 Evaluable Raltegravir-Treatment Failure Subjects in Studies 004-001 and 004-010

Treatment Group	Allocation Number	Virologic Failure Type	MK-0518 Sensitivity		3TC Sensitivity		TDF Sensitivity		EFV Sensitivity	
			Known Resistance Mutations	Genotype Interpretation	Resistance Mutations	Geno/Pheno Interpretation	Resistance Mutations	Geno/Pheno Interpretation	Resistance Mutations	Geno/Pheno Interpretation
MK-0518 100 mg b.i.d.										
MK-0518 200 mg b.i.d.										

(b) (4)

[§]Subjects 000345, 000363, and 000399 achieved >1.0 $\log_{10}$ decrease in HIV RNA at the nadir.
[‡]Subject 000018 had virologic failure after week 48.

Study 004-01 was a multicenter, double-blind, randomized, 2-part dose-ranging (RAL 100, 200, 400, or 600 mg BID) study to compare the safety and antiviral activity of RAL (+TDF/LAM) versus EFV (+TDF/LAM) in ART-naïve, HIV-1-infected subjects: Part 1 (10-day period of RAL monotherapy versus placebo) and Part 2 (48-week period of RAL/TDF/LAM combination therapy versus EFV/TDF/LAM). Subjects who completed the Week-48 visit of the original Study 004-01 were given the option to continue in the double-blind extension (Study 004-010). Subjects who randomized to any dose of RAL in the original study continued in extension on RAL at 400 mg BID, and subjects who randomized to EFV in the original study continued on EFV in the extension. Both open-label drugs, TDF 300 mg QD and LAM 300 mg QD continued unchanged in the extension. Virologic failure was defined in this study as having either virologic non-response or virologic rebound:

- Virologic non-response: (1) HIV-1 RNA >400 copies/mL at the time of discontinuation for subjects who prematurely discontinue study therapy OR (2) HIV-1 RNA >400 copies/mL at Week 24
- Virologic rebound: (1) confirmed HIV-1 RNA >400 copies/mL after initial response with HIV-1 RNA <400 copies/mL OR (1) confirmed >1.0 $\log_{10}$ increase in HIV-1 RNA above nadir level).

5. Conclusion

Approval of this supplemental NDA for ISENTRESS^{TM} 400 mg BID for the treatment of HIV-1 infection in combination with other antiretroviral agents in treatment-naïve adult patients is recommended with respect to Clinical Microbiology. By Week 48, raltegravir plus TRUVADA showed non-inferior antiviral efficacy to efavirenz plus TRUVADA in the studied treatment-naïve HIV-1-infected subject population (Study 021 STARTMRK trial). In the as-treated analysis, 86% and 90% of raltegravir (+TRUVADA) recipients were suppressed with plasma HIV-1 RNA <50 copies/mL and <400 copies/mL, respectively, compared to 82% and 87% of efavirenz (+TRUVADA)-treated subjects.

In the censored, as-treated population where subjects who received ≤2 weeks of raltegravir treatment were excluded, 27 of the 281 RAL (+TRUVADA) recipients experienced virologic failure by Week 48: 63% of the 27 failures experienced virologic rebound. Ten of the 27 raltegravir-treatment failures had plasma HIV-1 RNA levels >400 copies/mL at the time of virologic failure or at Week 48 (or at the time of discontinuation), and their baseline and on-treatment virus samples were genotyped for raltegravir resistance analyses. Paired genotypic data were successfully generated from 6 of the 10 evaluable failures. Previously identified primary RAL^{r}-associated substitutions, Y143R and Q148H/R, were detected in 3 (2 non-responders and 1 rebounder) of those 6 failures.

6. Recommendations

- Evaluate the contribution of F1I/L, A105T/V, and F1I + K240I substitutions to raltegravir resistance (including cell culture raltegravir susceptibility and replication capability) by site-directed mutagenesis. These substitutions of highly conserved amino acid residues among HIV-1 isolates were detectable in 2 subjects' rebound

isolates with no evidence of emerging 3 primary raltegravir resistance-associated substitutions.

7. Updated Package Insert: Section 12.4. MICROBIOLOGY

7.1. Mechanism of Action

Raltegravir inhibits the catalytic activity of HIV-1 integrase, an HIV-1-encoded enzyme that is required for viral replication. Inhibition of integrase prevents the covalent insertion, or integration, of unintegrated linear HIV-1 DNA into the host cell genome preventing the formation of the HIV-1 provirus. The provirus is required to direct the production of progeny virus, so inhibiting integration prevents propagation of the viral infection. Raltegravir did not significantly inhibit human phosphoryltransferases including DNA polymerases α, β, and γ.

7.2. Antiviral Activity in Cell Culture

Raltegravir at concentrations of 31 $\pm$ 20 nM resulted in 95% inhibition (EC_{95}) of viral spread (relative to an untreated virus-infected culture) in human T-lymphoid cell cultures infected with the cell-line adapted HIV-1 variant H9IIIB. In addition, 5 clinical isolates of HIV-1 subtype B had EC_{95} values ranging from 9 to 19 nM in cultures of mitogen-activated human peripheral blood mononuclear cells. In a single-cycle infection assay, raltegravir inhibited infection of 23 HIV-1 isolates representing 5 non-B subtypes (A, C, D, F, and G) and 5 circulating recombinant forms (AE, AG, BF, BG, and cpx) with EC_{50} values ranging from 5 to 12 nM. Raltegravir also inhibited replication of an HIV-2 isolate when tested in CEMx174 cells (EC_{95} value = 6 nM).

Additive to synergistic antiretroviral activity was observed when human T-lymphoid cells infected with the H9IIIB variant of HIV-1 were incubated with raltegravir in combination with non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, or nevirapine); nucleoside analog reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, tenofovir, zalcitabine, or zidovudine); protease inhibitors (amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, or saquinavir); or the entry inhibitor enfuvirtide.

7.3. Resistance

The mutations observed in the HIV-1 integrase coding sequence that contributed to raltegravir resistance (evolved either in cell culture or in subjects treated with raltegravir) generally included an amino acid substitution at either Q148 (changed to H, K, or R) or N155 (changed to H) plus one or more additional substitutions (i.e., L74M, E92Q, T97A, E138A/K, G140A/S, V151I, G163R, H183P, Y226C/D/F/H, S230R, and D232N). Amino acid substitution at Y143C/H/R is another pathway to raltegravir resistance.

- Treatment-Naïve Subjects: By Week 48 in the STARTMRK trial, primary raltegravir resistance-associated substitutions were observed in 3 (1 with Y143R and 2 with Q148H/R) of the 6 virologic failure subjects with evaluable paired genotypic data.

- Treatment-Experienced Subjects: By Week 48 in the BENCHMRK trials, at least one of the 3 primary raltegravir resistance-associated substitutions, Y143C/H/R, Q148H/K/R, and N155H, was observed in 63 (64.3%) of the 98 virologic failure subjects with evaluable genotypic data from paired baseline and raltegravir treatment-failure isolates. Some (n=18) of those HIV-1 isolates harboring one or more of the 3 primary raltegravir resistance-associated substitutions were evaluated for raltegravir susceptibility yielding a median decrease of 47.3-fold (mean 73.1 ± 60.8-fold decrease, ranging from 0.9- to 200-fold) compared to baseline isolates.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sung Rhee
5/28/2009 11:54:59 AM
MICROBIOLOGIST

Julian O Rear
5/28/2009 12:01:37 PM
MICROBIOLOGIST

MICROBIOLOGY FILING CHECKLIST FOR NDA or Supplement

NDA Number: 22-145 **Applicant: Merck** **Stamp Date: 09/26/2008**

Drug Name: Raltegravir **NDA Type: sNDA**

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comments
1	Is the virology information (nonclinical and clinical) provided and described in different sections of the NDA organized in a manner to allow substantive review to begin?	X		
2	Is the virology information (nonclinical and clinical) indexed, paginated and/or linked in a manner to allow substantive review to begin?	X		
3	Is the virology information (nonclinical and clinical) legible so that substantive review can begin?	X		
4	On its face, has the applicant submitted cell culture data in necessary quantity, using necessary clinical and non-clinical strains/isolates, and using necessary numbers of approved current divisional standard of approvability of the submitted draft labeling?	X		
5	Has the applicant submitted any required animal model studies necessary for approvability of the product based on the submitted draft labeling?			NA
6	Has the applicant submitted all special/critical studies/data requested by the Division during pre-submission discussions?			NA
7	Has the applicant submitted the clinical virology datasets in the appropriate format as described in the relevant guidance documents and are the datasets complete?	X		
8	Has the applicant used standardized or nonstandardized methods for virologic outcome measures? If nonstandardized methods were used, has the applicant included complete details of the method, the name of the laboratory where actual testing was done and performance characteristics of the assay in the laboratory where the actual testing was done?	X		
9	Has the applicant submitted draft labeling consistent with current regulation, divisional and Center policy, and the design of the development package?	X		
10	Has the applicant submitted annotated microbiology draft labeling consistent with current divisional policy, and the design of the development package?	X		
11	Have all the study reports, published articles, and other references been included and cross-referenced in the	X		

MICROBIOLOGY FILING CHECKLIST FOR NDA or Supplement

	Content Parameter	Yes	No	Comments
	annotated draft labeling or summary section of the submission?			
12	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	

IS THE MICROBIOLOGY SECTION OF THE APPLICATION FILEABLE? __YES____

If the NDA is not fileable from the microbiology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Sung Rhee 11/05/2008

Reviewing Microbiologist Date

Microbiology Team Leader Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sung Rhee
12/3/2008 10:50:14 AM
MICROBIOLOGIST

Julian O Rear
12/3/2008 11:39:41 AM
MICROBIOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22 – 145/S004

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	22-145
Submission Date(s)	September 25, 2008 (SE5) November 13, 2008 (4F)
Brand Name	ISENTRESS
Generic Name	Raltegravir
Primary Reviewer	Sarah Robertson, Pharm.D.
Team Leader	Kellie Reynolds, Pharm.D.
OCP Division	DCP4
OND Division	DAVP
Applicant	Merck
Submission Type; Code	SE5 (004) 4F (000)
Formulation; Strength	400 mg tablets
Indication(s)	Treatment of HIV-1 infection in treatment-experienced adults (Approved) and treatment-naïve adults (Proposed)

1. EXECUTIVE SUMMARY

Raltegravir tablets were approved on October 12, 2007 for the treatment of HIV-1 in treatment-experienced adults. This supplement (SE5-004) proposes to expand the indication to treatment-naïve adults. The 48-week results from Phase 3 trial 021, which evaluated the safety and efficacy of raltegravir 400 mg BID relative to efavirenz (both in combination with tenofovir/emtricitabine) in treatment-naïve patients, are submitted in support of the supplement. No new clinical pharmacology data are submitted, and no sparse PK sampling was performed in Study 021. However, included in the supplement is an update of the PK/PD analysis in treatment-naïve patients from Phase 2 trial 004 which was submitted with the original NDA. A reanalysis was conducted using different PK parameters than those evaluated in the original report. The results of the reanalysis are consistent with previous conclusions. Namely, there is no meaningful association between raltegravir exposure and efficacy in the treatment-naïve population treated with doses of 100 to 600 mg BID in combination with tenofovir/lamivudine in Study 004.

Final study reports for in vitro studies PK011 and PK012 were submitted in fulfillment of postmarketing commitments 13 and 14, as relayed in the October 12, 2007 approval letter:

Commitment 13: Conduct an in vitro study (e.g. in human hepatocytes) to evaluate the relative UGT1A1 induction potency of phenytoin, phenobarbital, rifabutin, and rifampin using raltegravir as a probe substrate.

Commitment 14: Conduct an in vitro study (e.g. in human hepatocytes) to evaluate the potential of raltegravir to induce CYP1A2 and CYP2B6.

The results of Study PK011 demonstrated that phenytoin, phenobarbital, rifabutin and rifampin all induce UGT1A1 mRNA expression in vitro. However, the results were inconclusive with respect to the relative enzyme induction potential of the four drugs using raltegravir as a probe substrate. Therefore, no dosing recommendations can be made for raltegravir during phenytoin,

phenobarbital or rifabutin coadministration at this time, and the current precautionary statement in the label (section 7.2) will remain unchanged. The Sponsor will not be asked to repeat the study, as the clinical applicability of any obtained results is likely to be unclear. Results from Study PK012 indicate that raltegravir is unlikely to induce CYP1A2 or CYP2B6 enzyme activity in vivo. A revision to Section 7.1 of the label is recommended to reflect the findings of this study.

An additional change to the label is recommended at this time based on the results of drug interaction study 030, submitted to the IND on March 11, 2009 (SDN 1581). The results of the study indicate raltegravir does not alter methadone exposure during coadministration (study reviewed separately under IND 69,928).

1.1 Recommendations

Supplement SE05-004 is acceptable from a clinical pharmacology perspective.

The Sponsor has fulfilled post-marketing commitments 13 and 14. A revision to the product label is recommended (Section 7, DRUG INTERACTIONS), as follows:

7.1 Effect of Raltegravir on the Pharmacokinetics of Other Agents

Raltegravir does not inhibit (IC50>100 μM) CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A *in vitro*. Moreover, *in vitro*, raltegravir did not induce CYP1A2, CYP2B6 or CYP3A4.

In drug interaction studies, raltegravir did not have a clinically meaningful effect on the pharmacokinetics of the following: hormonal contraceptives, methadone, lamivudine, tenofovir, etravirine.

2. SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

In vitro metabolism studies PK011 and PK 012 are reviewed in detail in Section 3 of this review. In summary, the results of Study PK011 demonstrated that phenytoin, phenobarbital, rifabutin and rifampin all induce UGT1A1 mRNA expression in vitro. However, the results were inconclusive with respect to the relative enzyme induction potential of the four drugs. An increase in raltegravir dose to 800 mg BID is recommended during coadministration with rifampin based on the results of a drug interaction study conducted in healthy volunteers. No dosing recommendation can be made during coadministration with phenytoin, phenobarbital or rifabutin based on the results of PK011, and the precautionary statement in the label will remain unchanged. Results from Study PK012 indicate that raltegravir is unlikely to induce CYP1A2 or CYP2B6 enzyme activity in vivo.

Study 004 was a Phase 2 multi-center, double-blind, randomized, 2-part dose-ranging study in HIV-infected, treatment-naïve patients. Part I of the study evaluated 10 days of raltegravir monotherapy at 4 different doses (100, 200, 400 and 600 mg BID) versus placebo in 35 patients. Part II evaluated the same 4 doses in combination with tenofovir/lamivudine versus efavirenz in combination with tenofovir/lamivudine for 48 weeks in 198 patients. Intensive PK sampling was performed on Day 10 in all patients in Part I. Sparse PK samples were collected from all patients in Part II at Weeks 4, 8 and 16 (single sample, irrespective of dose) and Week 12 (single sample, immediately pre-dose).

A PK/PD analysis of the data from Part I was included in the original NDA. Available data from Part I suggested a possible association between short-term antiretroviral activity and C_{12h} values. However, all doses of raltegravir were associated with potent antiretroviral activity and it was not possible to differentiate between the doses studied in Part I on the basis of HIV RNA decline at Day 10. A PK/PD analysis of the dataset from Phase 2 was also conducted and submitted with the original NDA. In this analysis, the geometric mean (GM) of observed C_{12h} values for each patient, the minimum observed C_{12h} value, and the model-predicted steady-state AUC_{0-12} and C_{12h} (fed and fasted) values were examined. There were insufficient treatment failures to allow a formal association analysis for the primary PK parameter, GM C_{12hr}. A formal statistical analysis for the occurrence of HIV RNA <50 copies/mL did not show an association with any of the observed C_{12h} values. The model-predicted AUC_{0-12} and C_{12h} parameters were available for most patients, which allowed formal association analyses with HIV RNA <400 copies/mL and the occurrence of virologic failure. There was no evidence to suggest any PK/PD association.

In the current submission, the PK/PD analysis from Part II of Study 004 is updated with 2 additional, non-model-based exposure estimates: Geometric mean of all observed concentrations (GM All) and minimum of all observed concentrations (Cmin). GM All was evaluated in the exploratory data analysis of Phase 1, 2 and 3 PK data submitted in the original NDA and was found to correlate with measured AUC (Figure 1).

Figure 1. Relationship between measured AUC vs. GM All computed over the dosing interval in subjects receiving multiple doses of raltegravir (full-profile data from Studies 004, 017, 026, 035 and 036)

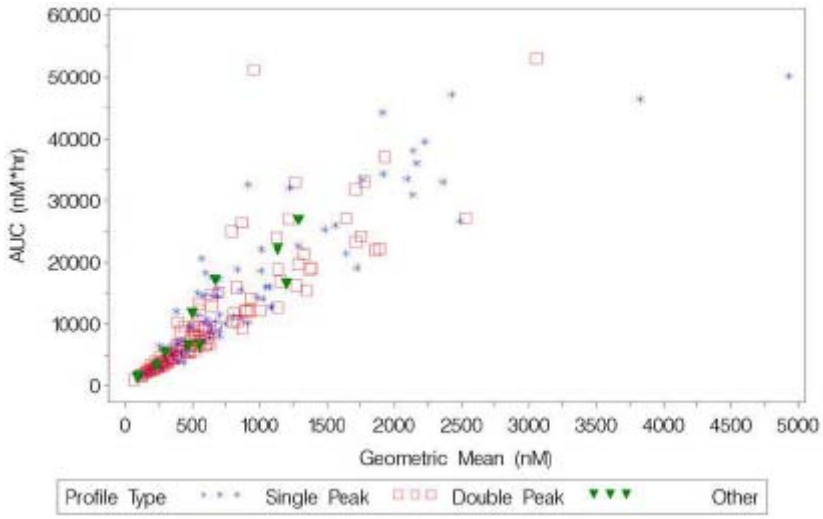


FIGURE SOURCE: Final study report for the Analysis of Raltegravir Plasma Concentration Data from Phase 1, 2 and 3 Studies (48 Week Analysis)

In general, the PK data collected in Part II demonstrates a general trend of increasing concentrations with increasing dose. However, considerable overlap of PK values is observed, particularly between the 200 mg and 400 mg doses. This is consistent with the large degree of

intersubject and interoccasion variability observed for raltegravir in other studies. The exploratory PK parameters GM All and Cmin were evaluated for a formal association with 4 efficacy response parameters (HIV RNA < 400 copies/mL, HIV RNA < 50 copies/mL, virologic failure and change from baseline HIV RNA at Week 48). No associations were observed for GM All or Cmin and any of the response parameters, except for HIV RNA < 400 copies/mL. However, the association between GM All and Cmin with HIV RNA < 400 copies/mL went in the opposite direction as would be expected (a higher GM All or Cmin decreased the probability of having an HIV RNA < 400). This paradoxical relationship was found to be driven by one outlier. In summary, the results of this re-analysis confirm previous data demonstrating a lack of a meaningful PK/PD association over the range of doses evaluated in this treatment-naïve population.

3. INDIVIDUAL STUDY REVIEWS

PK011 – In Vitro Evaluation of the Relative UGT1A1 Induction Potency of Rifampin, Rifabutin, Phenobarbital and Phenytoin using Raltegravir as a Probe Substrate

Introduction

The potential for rifampin, rifabutin, phenobarbital, and phenytoin to induce UDP-glucuronsyl transferase 1A1 (UGT1A1) enzyme activity using raltegravir as the probe was evaluated in cryopreserved human hepatocytes (n=4).

Methods

Cryopreserved human hepatocytes were obtained from (b) (4) (Lot 4069) and (b) (4) Hepatocytes were thawed according to the standard procedures as outlined by the supplier, (b) (4) Hepatocytes were plated onto 48-well collagen-I coated plates in CP plating medium supplemented with antibiotics. One set of plates was utilized to assess changes in UGT1A1 mRNA expression, while the parallel set of plates was used to evaluate UGT1A1 enzyme activity using raltegravir as the probe substrate. Once attached, hepatocytes were overlaid with Matrigel and maintained in the incubation medium supplemented with antibiotics (HI medium) at 37ºC, 95% humidity, and 5% CO_2.

Stock solutions of rifampin (50 mM), rifabutin (50 mM), phenytoin (200 mM) and phenobarbital (1000 mM) were prepared in DMSO. Serial dilutions of the stock solutions were performed to give rifampin (0.1-50 mM), rifabutin (0.1-50 mM), phenytoin (1-200 mM) and phenobarbital (10-1000 mM) in DMSO. Dosing solutions were prepared by diluting DMSO stock solutions 1000-fold in HI medium. Dosing solution for the vehicle control (DMSO) was prepared by diluting DMSO 1000-fold in HI medium to give a final concentration of 0.1%.

Cell culture treatments were initiated by replacing HI medium with dosing solution (0.2 mL/well, n=3) for each condition. Cultures were maintained at 37ºC, 95% humidity, and 5% CO_2 for the duration of the 48 hr exposure. Wells were aspirated and replenished with fresh dosing solution after 24 hrs. At the end of the exposure, one set of plates was aspirated and stored at -70ºC until RNA isolation, while functional activity studies were conducted on the other set of plates.

Raltegravir Glucuronidation Activity

Following the 48-hr incubation period, hepatocytes were washed twice with HBSS. The cells were then incubated with 10 µM ^{3}H-raltegravir prepared in HBSS for 120 min at 37°C and 95:5 O_2:CO_2. The formation of M2, the phenolic glucuronide of raltegravir, was shown to be linear up to 120 min. The reactions were stopped by addition of acetonitrile and the mixtures centrifuged at 3000 rpm for 10 min. The supernatants were transferred into a clean 96 well plate, and the solvent was evaporated to dryness under nitrogen at 40°C. Samples were reconstituted in 150 µL 20% (v/v) acetonitrile in water, and were analyzed by HPLC- β-RAM.

RNA Isolation and Quantitation

Cell cultures frozen at -70ºC were thawed to room temperature and total RNA was isolated. Samples were treated with RNase-free DNase and eluted with 80 µL water. Reverse transcription of RNA (~50 ng of each sample) to cDNA was conducted using High Capacity cDNA Reverse Transcription Kit (b) (4) PCR reactions for UGT1A1 were prepared by adding an aliquot of cDNA (3 µL) to a reaction mixture containing (b) (4) target gene primer and probe and endogenous control 18S ribosomal RNA primers and probe. PCR amplification conditions were as follows: 1 cycle at 50ºC, 2 min; 1 cycle at 95ºC, 10 min; 40 cycles at 95ºC, 15 sec and 40 cycles at 60ºC, 1 min. PCR amplified cDNAs were detected by real-time fluorescence on an (b) (4) Sequence Detection System (b) (4). Quantitation of the target cDNA in treated samples versus DMSO control

samples was calculated after correcting for the 18S ribosomal RNA in each sample (ΔCt) using the following equation: Fold change = $2^{-\Delta\Delta Ct}$.

Results

Changes in UGT1A1 mRNA expression for hepatocytes treated with rifampin, rifabutin, phenobarbital and phenytoin were 0.8 to 5.1-fold, 0.5 to 3.6-fold, 0.3 to 5.5-fold and 0.3- to 7.3-fold, respectively (Table 1). Rifampin 10 μM produced a statistically significant increase in UGT1A1 mRNA expression in all four lots of hepatocytes, while a statistically significant increase was observed in three of the four lots of hepatocytes treated with phenobarbital 1000 μM and phenytoin (50-200 μM). Rifabutin produced a statistically significant increase in mRNA in two of four lots at concentrations of 0.1-10 μM. Overall, the results indicate that all four compounds induce UGT1A1 mRNA expression.

UGT1A1 enzyme activity levels in hepatocytes treated with rifampin, rifabutin, phenobarbital, and phenytoin were 0.6 to 1.1-fold, 0.3 to 1.1-fold, 0.8 to 1.5-fold, and 0.9 to 1.5-fold that of DMSO control, respectively. The investigators report that a significant increase in the induction potency of the four test compounds may not have been observed due to intersubject variability and a low UGT1A1 induction window.

Table 1. Effect of Test Compounds on UTG1A1 mRNA Expression in Cryopreserved Human Hepatocytes After 48-Hr Treatment

		KQG	4069	HIE	LOF
Treatment	[uM]	UGT1A1 mRNA			
		Fold[a]	Fold[a]	Fold[a]	Fold[a]
Rifampin	0.1	0.8	1.6	4.1*	2.1*
	0.5	1.8	2.3	2.9*	2.6*
	1	1.6	2.6*	4.3*	1.6
	5	1.6	3.5*	5.0*	1.7
	10	2.5*	4.0*	5.1*	1.8*
	20	1.2	2.6*	4.2*	1.3
	50	1.1	2.9*	4.4*	0.9
Rifabutin	0.1	1.7	1.8	1.7*	3.2*
	0.5	0.9	3.6*	2.2*	1.5
	1.0	0.8	2.6	2.3*	1.4
	5.0	0.6	2.3*	2.9*	1.6
	10.0	0.9	2.3*	2.0*	1.3
	20.0	1.1	1.9*	1.8	1.3
	50.0	0.5	0.6	1.4	0.6
Phenobarbital	10	0.3	0.8	1.0	0.9
	25	0.4	0.9	1.3	0.6
	50	0.4	1.0	1.4	1.0
	125	0.7	1.5	1.8	1.3
	250	0.6	1.5	2.8*	1.3
	500	1.3	1.5	3.9*	1.1
	1000	1.5	3.9*	5.5*	3.3*
Phenytoin	1	0.5	1.2	1.6	0.8
	5	0.6	1.6	2.1*	1.0
	10	0.3	0.9	1.8*	1.0
	25	0.5	2.3*	2.7*	1.9
	50	0.6	4.1*	2.7*	2.2*
	100	0.8	3.5*	3.4*	2.4*
	200	0.6	3.2*	7.3*	3.3*

[a] Fold change of target gene mRNA compared to vehicle control (DMSO).

* $P < 0.05$ using the student's *t*-test.

Conclusion

The results of the mRNA analysis indicate that rifampin, rifabutin, phenytoin and phenobarbital all induce UGT1A1 mRNA expression. However, the results of the enzyme activity assessment, in which raltegravir was used as the probe substrate, were inconclusive in determining the relative induction potential of the four drugs. It is unclear why there was no induction of activity, given the finding of induced mRNA expression. Inclusion of a probe substrate, in addition to raltegravir, may have helped with the interpretation. Incubation time may have been too short for full protein translation of UGT1A1 enzyme.

PK012 – Evaluation of Raltegravir as an Inducer of CYP2B6 and CYP1A2 in Cryopreserved Human Hepatocytes

Introduction

The potential for raltegravir to induce CYP2B6 and CYP1A2 mRNA and enzyme activities was evaluated in cryopreserved human hepatocytes (n=3).

Methods

Cryopreserved human hepatocytes were obtained from (b) (4) (Lot 4069) and (b) (4) Hepatocytes were thawed according to the standard procedures supplied by (b) (4) and plated onto 48-well collagen-I coated plates in CP plating medium supplemented with antibiotics. Once attached, hepatocytes were overlaid with Matrigel and maintained in HI incubation medium supplemented with antibiotics (HI medium) at 37ºC, 95% humidity, and 5% CO_2.

A stock solution (10 mM) of raltegravir was prepared in DMSO. Serial dilutions of the 10 mM stock were performed to give 10, 1, and 0.1 mM stock solutions in DMSO. Dosing solutions were prepared by diluting DMSO stock solutions 1000-fold in HI medium. Dosing solutions for the positive controls rifampin and omeprazole were prepared by diluting stock solutions (10 mM rifampin and 50 mM omeprazole in DMSO) 1000-fold in HI medium to give final concentrations of 10 µM rifampin and 50 µM omeprazole. Dosing solution for the vehicle control (DMSO) was prepared by diluting DMSO 1000-fold in HI medium to give a final concentration of 0.1%.

Cell culture treatments were initiated by replacing HI medium with dosing solution (0.2 mL/well, n=3) for each condition. Cultures were maintained at 37ºC, 95% humidity, and 5% CO_2 for the duration of the 48-hr exposure. Wells were aspirated and replenished with fresh dosing solution after 24 hrs. At the end of the exposure, incubations were conducted with probe substrates bupropion and phenacetin. Plates were then aspirated and stored at -70ºC until RNA isolation.

Bupropion-Hydroxylase Assay

Cell cultures were assayed for the hydroxylation of the CYP2B6 substrate bupropion to hydroxybupropion following the 48-hr exposure to test compounds. Wells were aspirated, rinsed with Hanks Balanced Salt Solution (HBSS) containing HEPES (10 mM) then incubated with 85 µL bupropion (100 µM in HBSS). Cells were incubated at 37ºC, 95% humidity, and 5% CO_2 for 1 hour. Reactions were terminated by transferring 75 µL of the incubation to a 96-well microtiter plate and adding 25 µL acetonitrile containing cortisone (600 ng/mL, internal standard).

Phenacetin-O-Deethylase Assay

Cell cultures were assayed for the *O*-deethylation of the CYP1A2 substrate phenacetin to acetaminophen following the 48-hr exposure to test compounds. Wells were aspirated, rinsed with HBSS containing HEPES (10 mM) then incubated with 85 µL phenacetin (100 µM in HBSS). Cells were incubated at 37ºC, 95% humidity, and 5% CO_2 for 1 hour. Reactions were terminated by transferring 75 µL of the incubation to a 96-well microtiter plate and adding 25 µL acetonitrile containing cortisone (600 ng/mL, internal standard).

Quantitation of the phenacetin and bupropion metabolites was conducted by LC-MS/MS. Activities were calculated using the peak area ratio of hydroxybupropion or acetaminophen to cortisone and reported as fold change over vehicle control.

RNA Isolation and Quantitation

Cell cultures frozen at -70ºC were thawed to room temperature and total RNA was isolated using an (b) (4) according to the manufacturer's protocol. Samples were treated with RNase-free DNase, as described in the protocol and eluted with 80 µL water.

Reverse transcription of RNA (~50 ng of each sample) to cDNA was conducted using High Capacity cDNA Reverse Transcription Kit [redacted] PCR reactions for target genes (CYP2B6 and CYP1A2) were prepared by adding an aliquot of cDNA (3 µL) to a reaction mixture containing [redacted] target gene primers and probe and endogenous control 18S ribosomal RNA primers and probe. PCR amplification conditions were as follows: 1 cycle at 50ºC, 2 min; 1 cycle at 95ºC, 10 min; 40 cycles at 95ºC, 15 sec; 40 cycles at 60ºC, 1 min. PCR amplified cDNAs were detected by real-time fluorescence on an [redacted] Sequence Detection System [redacted]. Quantitation of the target cDNA in treated samples versus DMSO control samples was calculated after correcting for the 18S ribosomal RNA in each sample (ΔCt) using the following equation: Fold change = $2^{-\Delta\Delta Ct}$.

Results

The effect of 48-hr exposure to raltegravir (0.1, 1 and 10 µM) and positive control inducers, rifampin (10 µM) and omeprazole (50 µM) on CYP2B6 and CYP1A2 are reported below in Tables 1 and 2. Rifampin induced CYP2B6 mRNA and enzyme activity by 2.2 to 4.1-fold and 1.5 to 6.7-fold, respectively, in the three donors tested. No significant increase in CYP2B6 mRNA or enzyme activity was observed after treatment with raltegravir (0.1-10 µM). Omeprazole induced CYP1A2 mRNA and enzyme activity by 11.2 to 32.6-fold and 1.8 to 5.3-fold, respectively, in the three donors tested. No significant increase in CYP1A2 mRNA or enzyme activity was observed after treatment with raltegravir (0.1-10 µM).

Table 1. Effect of Raltegravir on CYP2B6 mRNA and Enzyme Activity

		4069				DXP				KQG			
Treatment	µM	mRNA		Activity		mRNA		Activity		mRNA		Activity	
		Fold[a]	% of PC[c]	Fold[b]	% of PC[c]	Fold[a]	% of PC[c]	Fold[b]	% of PC[c]	Fold[a]	% of PC[c]	Fold[b]	% of PC[c]
Rifampin	10	2.2	100.0	2.2	100.0	4.1	100.0	6.7	100.0	3.5	100.0	1.5	100.0
Raltegravir	0.1	0.6	n.d.	0.6	n.d.	0.7	n.d.	1.2	4.2	0.4	n.d.	0.3	n.d.
	1	0.7	n.d.	0.6	n.d.	1.3	8.5	1.6	10.8	0.9	n.d.	0.3	n.d.
	10	0.6	n.d.	0.6	n.d.	1.3	9.9	1.4	6.9	0.6	n.d.	0.3	n.d.

[a] The mean fold change of target gene mRNA compared to vehicle control (DMSO).
[b] The mean fold change of target gene enzyme activity compared to vehicle control (DMSO).
[c] Percent of positive control (rifampin, 10 µM) corrected for the vehicle control (DMSO).
n.d. = not determined (response is less that vehicle control thus percentage is less than zero).

Table 2. Effect of Raltegravir on CYP1A2 mRNA and Enzyme Activity

		4069				DXP				KQG			
Treatment	µM	mRNA		Activity		mRNA		Activity		mRNA		Activity	
		Fold[a]	% of PC[c]	Fold[b]	% of PC[c]	Fold[a]	% of PC[c]	Fold[b]	% of PC[c]	Fold[a]	% of PC[c]	Fold[b]	% of PC[c]
Omeprazole	50	32.6	100.0	1.8	100.0	17.2	100.0	5.3	100.0	11.2	100.0	3.4	100.0
Raltegravir	0.1	0.4	n.d.	0.8	n.d.	1.2	1.3	0.9	n.d.	0.7	n.d.	1.3	0.1
	1	2.2	3.9	0.9	n.d.	0.8	n.d.	1.0	0.3	1.0	0.0	1.1	0.0
	10	1.0	0.1	0.8	n.d.	1.8	5.0	1.0	n.d.	0.8	n.d.	0.9	n.d.

[a] The mean fold change of target gene mRNA compared to vehicle control (DMSO).
[b] The mean fold change of target gene enzyme activity compared to vehicle control (DMSO).
[c] Percent of positive control (omeprazole, 50 µM) corrected for the vehicle control (DMSO).
n.d. - not determined (response is less that vehicle control thus percentage is less than zero).

Conclusion

Raltegravir did not induce either CYP2B6 or CYP1A2 mRNA expression or enzyme activity over a concentration range of 0.1 – 10 μM.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sarah M. Robertson
4/14/2009 11:27:37 AM
BIOPHARMACEUTICS

Kellie Reynolds
4/14/2009 11:31:32 AM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22-145 **Applicant: MERCK** **Stamp Date:**

Drug Name: Raltegravir **NDA/BLA Type: SE5-004**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
Criteria for Refusal to File (RTF)				
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			NA (Commercial product was used in the phase 3 study)
2	Has the applicant provided metabolism and drug-drug interaction information?			No additional data are needed for this supplement
Criteria for Assessing Quality of an NDA				
	Data			
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			NA
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			NA
	Studies and Analyses			
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			NA (relevant data were reviewed at the time of original NDA submission)
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?			NA
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?	X		
8	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			NA (relevant data were reviewed at the time of original NDA submission)
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			The pediatric study is ongoing.
10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?		X	The pediatric study is ongoing.
11	Is the appropriate pharmacokinetic information submitted?			No pharmacokinetic data were obtained in the Phase III Protocol 021. All known relevant raltegravir clinical pharmacology and biopharmaceutical data (using the current approved tablet formulation) should

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA/BLA or Supplement

				apply to the HIV treatment naïve population.
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X		No pharmacokinetic data were obtained in the Phase III Protocol 021. The sponsor updated PK/PD analysis using 48 week data of a Phase II study (P004) in HIV treatment naïve population.
	General			
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?	X		
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X		
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	X		
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			NA (No new Clin Pharm/Biopharmaceutical studies were conducted for this supplement).
17	Was the translation from another language important or needed for publication?		X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ____Yes____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

No pharmacokinetic data were obtained in the Phase III Protocol 021. The sponsor updated PK/PD analysis using 48 week data of a Phase II study (P004) in HIV treatment naïve population. No new findings were reported.

We agree with the sponsor that all relevant raltegravir clinical pharmacology and biopharmaceutical data (using the current approved tablet formulation) should apply to the HIV treatment naïve population.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA/BLA or Supplement

Derek Zhang	11/04/2008
Reviewing Clinical Pharmacologist	Date
Kellie Reynolds	11/04/2008
Team Leader/Supervisor	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Derek Zhang
12/4/2008 11:19:29 AM
BIOPHARMACEUTICS

Kellie Reynolds
12/4/2008 04:39:57 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22 – 145/S004

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Antiviral Products

Application Number: 22-145 SE5-004

Name of Drug: ISENTRESS (raltegravir potassium) 400 mg tablets

Applicant: Merck & Co., Inc.
126 E. Lincoln Ave
P.O. Box 2000, RY33-212
Rahway, NJ 07065-0900

Materials Reviewed:

Submission Dates: June 26, 2009

Receipt Dates: June 26, 2009

Submission Dates of Structured Product Labeling (SPL): September 25, 2008

Type of Labeling Reviewed: Word

FDA's January 29, 2009, approved package insert (PI) and patient package insert (PPI), NDA 22-145 SE7-001

Background and Summary:

This efficacy supplement, submitted on September 25, 2008, expands the patient population for raltegravir to include treatment of HIV-1 in treatment-naïve subjects based on the 48 week data from Protocol 021. Merck and FDA agreed on the PI and PPI labels submitted on June 26, 2009. These were compared to the most recent approved PI and PPI dated January 29, 2009 (NDA 22-145/SE7-001).

Review of Package Insert:

I. Overview of Highlights Section:
A. In RECENT MAJOR CHANGES section:

1. (b) (4)

2. (b) (4)

B. The INDICATIONS AND USAGE section was revised to expand the adult patient population for the treatment of HIV infection. The last sentence was also revised stating safety and efficacy have not been established in pediatric patients only. This section now reads:

ISENTRESS® is a human immunodeficiency virus integrase strand transfer inhibitor (HIV-1 INSTI) indicated:

- *In combination with other antiretroviral agents for the treatment of HIV-1 infection in adult patients (1).*

The safety and efficacy of ISENTRESS have not been established in pediatric patients (1).

C. In ADVERSE REACTIONS section, the first bullet item was revised. *Insomnia* was added as one of the most common adverse reactions and "…higher exposure adjusted rate compared to placebo…" was replaced with "…higher rate than the comparator…"

D. DRUG INTERACTIONS section was added and reads as follow:

- *Coadministration of ISENTRESS with drugs that are strong inducers of UGT1A1 may result in reduced plasma concentrations of raltegravir (7.2).*

II. Full Prescribing Information: CONTENTS*
A. Subsection 5.2, Drug Interactions, was deleted.

III. Full Prescribing Information (FPI):
A. Section 1 was revised and now reads:

ISENTRESSi is indicated in combination with other anti-retroviral agents for the treatment of human immunodeficiency virus (HIV-1) infection in adult patients.

This indication is based on analyses of plasma HIV-1 RNA levels up through 48 weeks in three double-blind controlled studies of ISENTRESS. Two of these studies were conducted in clinically advanced, 3-class antiretroviral (NNRTI, NRTI, PI) treatment-experienced adults and one was conducted in treatment-naïve adults.

The use of other active agents with ISENTRESS is associated with a greater likelihood of treatment response [see Clinical Studies (14)].

The safety and efficacy of ISENTRESS have not been established in pediatric patients.

B. Subsection 5.2 was deleted.

C. Subsection 6.1 was revised as follows:

1. Addition of <u>Treatment-Naive Studies</u> subheading containing the 48 week safety data from Protocol 21. This reads as follow:

<u>Treatment-Naïve Studies</u>

The following safety assessment of ISENTRESS in treatment-naïve subjects is based on the randomized double-blind active controlled study of treatment-naïve subjects, STARTMRK (Protocol 021) with ISENTRESS 400 mg twice daily in combination with a fixed dose of emtricitabine 200 mg (+) tenofovir 300 mg, (N=281) versus efavirenz (EFV) 600 mg at bedtime

in combination with emtricitabine (+) tenofovir, (N=282). During double-blind treatment, the total follow-up for subjects receiving ISENTRESS 400 mg twice daily + emtricitabine (+) tenofovir was 247 patient-years and 241 patient-years for subjects receiving efavirenz 600 mg at bedtime + emtricitabine (+) tenofovir.

In Protocol 021, the rate of discontinuation of therapy due to adverse reactions was 3% in subjects receiving ISENTRESS + emtricitabine (+) tenofovir and 6% in subjects receiving efavirenz + emtricitabine (+) tenofovir.

The clinical adverse drug reactions (ADRs) listed below were considered by investigators to be causally related to ISENTRESS + emtricitabine (+) tenofovir or efavirenz + emtricitabine (+) tenofovir. Clinical ADRs of moderate to severe intensity occurring in ≥2% of treatment-naïve subjects treated with ISENTRESS and occurring at a higher rate than efavirenz are presented in Table 1.

Table 1: Adverse Reactions* of Moderate to Severe Intensity† Occurring in ≥2% of Treatment-Naïve Adult Subjects Receiving ISENTRESS and at a Higher Rate Compared to Efavirenz (48 Week Analysis)

System Organ Class, Preferred Term	Randomized Study Protocol 021	
	ISENTRESS 400 mg Twice Daily + Emtricitabine (+) Tenofovir (n = 281)‡ %	Efavirenz 600 mg At Bedtime + Emtricitabine (+) Tenofovir (n = 282)‡ %
Psychiatric Disorders		
Insomnia	4	3

*Includes adverse experiences considered by investigators to be at least poss bly, probably, or definitely related to the drug
†Intensities are defined as follows: Moderate (discomfort enough to cause interference with usual activity); Severe (incapacitating with inability to work or do usual activity).
‡n = total number of subjects per treatment group

Less Common Adverse Reactions

The following ADRs occurred in <2% of subjects receiving ISENTRESS + emtricitabine (+) tenofovir. These events have been included because of their seriousness, increased frequency on ISENTRESS compared with efavirenz or investigator's assessment of potential causal relationship.

General Disorders and Administration Site Conditions: fatigue

Psychiatric Disorders: abnormal dreams

Laboratory Abnormalities

The percentages of adult subjects treated with ISENTRESS 400 mg twice daily or efavirenz in Protocol 021 with selected Grades 2 to 4 laboratory abnormalities that represent a worsening from baseline are presented in Table 2.

Table 2: Selected Grade 2 to 4 Laboratory Abnormalities Reported in Treatment-Naïve Subjects (48 Week Analysis)

Laboratory Parameter Preferred Term (Unit)	Limit	Randomized Study Protocol 021 ISENTRESS 400 mg Twice Daily + Emtricitabine (+) Tenofovir (N = 281)	Efavirenz 600 mg At Bedtime + Emtricitabine (+) Tenofovir (N = 282)
Hematology			
Absolute neutrophil count ($10^3/\mu L$)			
Grade 2	0.75 - 0.999	3%	3%
Grade 3	0.50 - 0.749	1%	<1%

Grade 4	<0.50	<1%	0%
Hemoglobin (gm/dL)			
Grade 2	7.5 - 8.4	<1%	<1%
Grade 3	6.5 - 7.4	<1%	<1%
Grade 4	<6.5	0%	0%
Platelet count ($10^3/\mu L$)			
Grade 2	50 - 99.999	2%	0%
Grade 3	25 - 49.999	0%	<1%
Grade 4	<25	0%	.0%
Blood chemistry			
Fasting (non-random) serum glucose test (mg/dL)			
Grade 2	126 - 250	2%	3%
Grade 3	251 - 500	<1%	0%
Grade 4	>500	0%	0%
Total serum bilirubin			
Grade 2	1.6 - 2.5 x ULN	4%	0%
Grade 3	2.6 - 5.0 x ULN	<1%	0%
Grade 4	>5.0 x ULN	0%	0%
Serum aspartate aminotransferase			
Grade 2	2.6 - 5.0 x ULN	3%	4%
Grade 3	5.1 - 10.0 x ULN	1%	1%
Grade 4	>10.0 x ULN	<1%	<1%
Serum alanine aminotransferase			
Grade 2	2.6 - 5.0 x ULN	4%	6%
Grade 3	5.1 - 10.0 x ULN	<1%	2%
Grade 4	>10.0 x ULN	<1%	<1%
Serum alkaline phosphatase			
Grade 2	2.6 - 5.0 x ULN	<1%	2%
Grade 3	5.1 - 10.0 x ULN	0%	<1%
Grade 4	>10.0 x ULN	0%	0%

ULN = Upper limit of normal range-

Lipids, Change from Baseline

Changes from baseline in fasting lipids are shown in Table 3.

Table 3: Lipid Values, Mean Change from Baseline, Protocol 021

Laboratory Parameter Preferred Term	ISENTRESS 400 mg Twice Daily + Emtricitabine (+) Tenofovir N = 281			Efavirenz 600 mg At Bedtime + Emtricitabine (+) Tenofovir N = 282		
			Change from Baseline at Week 48			Change from Baseline at Week 48
	Baseline Mean (mg/dL)	Week 48 Mean (mg/dL)	Mean Change (mg/dL)	Baseline Mean (mg/dL)	Week 48 Mean (mg/dL)	Mean Change (mg/dL)
LDL-Cholesterol†	97	103	6	92	108	16
HDL-Cholesterol†	38	42	4	38	48	10
Total Cholesterol†	159	169	10	156	188	33
Triglyceride†	125	122	-3	136	174	37

†Fasting (non-random) laboratory tests.

Notes:

N = Number of subjects in the treatment group. The analysis is based on all available data.

If subjects initiated or increased serum lipid-reducing agents, the last available lipid values prior to the change in therapy were used in the analysis. If the missing data was due to other reasons, subjects were censored thereafter for the analysis.

At baseline, serum lipid-reducing agents were used in 5% of subjects in the group receiving ISENTRESS and 3% in the efavirenz group. Through Week 48, serum lipid-reducing agents were used in 6% of subjects in the group receiving ISENTRESS and 6% in the efavirenz group.

2. In Treatment-Experienced Studies subheading, Adverse Events *Regardless of Drug Relationship* was renamed, revised and relocated immediately after Table 5 (previously Table 2). Specifically, Adverse Events was renamed Selected Adverse Events containing revision in the first paragraph:

Cancers were reported in treatment-experienced subjects who initiated ISENTRESS or placebo, both with OBT, and in treatment-naïve subjects who initiated ISENTRESS or efavirenz, both with emtricitabine (+) tenofovir; several were recurrent. The types and rates of specific cancers were those expected in a highly immunodeficient population (many had CD4+ counts below 50 cells/mm^3 and most had prior AIDS diagnoses). The risk of developing cancer in these studies was similar in the group receiving ISENTRESS and the group receiving the comparator.

3. Patients with Co-existing Conditions was updated to include findings from both treatment-experienced and treatment-naïve studies. This now reads:

Patients Co-infected with Hepatitis B and/or Hepatitis C Virus

In the randomized, double-blind, placebo-controlled trials, treatment-experienced subjects (N = 114/699 or 16%) and treatment-naïve subjects (N = 34/563 or 6%) with chronic (but not acute) active hepatitis B and/or hepatitis C virus co-infection were permitted to enroll provided that baseline liver function tests did not exceed 5 times the upper limit of normal (ULN). In general the safety profile of ISENTRESS in subjects with hepatitis B and/or hepatitis C virus co-infection was similar to that in subjects without hepatitis B and/or hepatitis C virus co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis B and/or hepatitis C virus co-infection for all treatment groups. In treatment-experienced subjects, Grade 2 or higher laboratory abnormalities that represent a worsening Grade from baseline of AST, ALT or total bilirubin occurred in 25%, 31% and 12%, respectively, of co-infected subjects treated with ISENTRESS as compared to 8%, 7% and 8% of all other subjects treated with ISENTRESS. In treatment-naïve subjects, Grade 2 or higher laboratory abnormalities that represent a worsening Grade from baseline of AST, ALT or total bilirubin occurred in 17%, 22% and 11%, respectively, of co-infected subjects treated with ISENTRESS as compared to 4%, 4% and 3% of all other subjects treated with ISENTRESS.

D. In subsection 6.2, anxiety and paranoia were added in the *Psychiatric Disorders section*. This *section* was also moved to precede *Skin and Subcutaneous Tissue Disorders*.

E. In subsection 7.1, CYP1A2 and CYP2B6 were added in the group of enzymes not induced by raltegravir *in vitro.* In addition, methadone was deleted from the list of drugs raltegravir is not expected to pharmacokinetically effect. Instead, methadone was added to the list of drugs raltegravir did not have a *clinically meaningful* pharmacokinetic effect on.

F. In subsection 8.4, "less than 16 years of age" was removed from the sentence.

G. Subsection 12.4 was revised as follows:

1. Under Antiviral Activity in Cell Culture, the second and third sentences now reads:
In addition, 5 clinical isolates of HIV-1 subtype B had EC_{95} values ranging from 9 to 19 nM in cultures of mitogen-activated human peripheral blood mononuclear cells. In a single-cycle infection assay, raltegravir inhibited infection of 23 HIV-1 isolates representing 5 non-B

subtypes (A, C, D, F, and G) and 5 circulating recombinant forms (AE, AG, BF, BG, and cpx) with EC_{50} values ranging from 5 to 12 nM.

2. Under Resistance, findings in *Treatment-Naïve Subjects* were added and differentiated from *Treatment-Experienced Subjects*.

H. Section 14 was revised as follows:

1. Description of Clinical Studies was revised and now reads:

The evidence of durable efficacy of ISENTRESS is based on the analyses of 48-week data from an ongoing, randomized, double-blind, active-control trial, STARTMRK (Protocol 021) in antiretroviral treatment-naive HIV-1 infected adult subjects and from 2 ongoing, randomized, double-blind, placebo-controlled studies, BENCHMRK 1 and BENCHMRK 2 (Protocols 018 and 019), in antiretroviral treatment-experienced HIV-1 infected adult subjects. These efficacy results were supported by the 96-week analysis of a randomized, double-blind, controlled, dose-ranging trial, Protocol 004, in antiretroviral treatment-naïve HIV-1 infected adult subjects and by the 48-week analysis of a randomized, double-blind, controlled, dose-ranging study, Protocol 005, in antiretroviral treatment-experienced HIV-1 infected adult subjects.

2. Treatment-Naïve Subjects information was added, located after Description of Clinical Studies:

STARTMRK (Protocol 021) is a Phase 3 study to evaluate the safety and antiretroviral activity of ISENTRESS 400 mg twice daily + emtricitabine (+) tenofovir versus efavirenz 600 mg at bedtime plus emtricitabine (+) tenofovir in treatment-naïve HIV-1-infected subjects with HIV-1 RNA >5000 copies/mL. Randomization was stratified by screening HIV-1 RNA level (≤50,000 copies/mL; and >50,000 copies/mL) and by hepatitis status.

Table 8 shows the demographic characteristics of subjects in the group receiving ISENTRESS 400 mg twice daily and subjects in the comparator group.

Table 8: Baseline Characteristics

Randomized Study Protocol 021	ISENTRESS 400 mg Twice Daily (N = 281)	Efavirenz 600 mg At Bedtime (N = 282)
Gender		
Male	81%	82%
Female	19%	18%
Race		
White	41%	44%
Black	12%	8%
Asian	13%	11%
Hispanic	21%	24%
Native American	0%	0%
Multiracial	12%	13%
Region		
Latin America	35%	34%
Southeast Asia	12%	10%
North America	29%	32%
EU/Australia	23%	23%
Age (years)		
18-64	99%	99%
≥65	1%	1%
Mean (SD)	38 (9)	37 (10)
Median (min, max)	37 (19 to 67)	36 (19 to 71)

CD4 Cell Count (cells/microL)		
Mean (SD)	219 (124)	217 (134)
Median (min, max)	212 (1 to 620)	204 (4 to 807)
Plasma HIV-1 RNA (log_{10} copies/mL)		
Mean (SD)	5 (1)	5 (1)
Median (min, max)	5 (3 to 6)	5 (4 to 6)
Plasma HIV-1 RNA (copies/mL)		
Geometric Mean	103205	106215
Median (min, max)	114000 (400 to 750000)	104000 (4410 to 750000)
History of AIDS[†]		
Yes	18%	21%
Viral Subtype		
Clade B	78%	82%
Non-Clade B[‡]	21%	17%
Baseline Plasma HIV-1 RNA		
≤100,000 copies/mL	45%	49%
>100,000 copies/mL	55%	51%
Baseline CD4 Cell Counts		
≤50 cells/mm^3	10%	11%
>50 cells/mm^3 and ≤ 200 cells/mm^3	37%	37%
>200 cells/mm^3	53%	51%
Hepatitis Status		
Hepatitis B or C Positive[§]	6%	6%

[†]Includes additional subjects identified as having a history of AIDS.

[‡]Non-Clade B Subtypes (# of subjects): Clade A (4), A/C (1), A/G (2), A1 (1), AE (29), AG (12), BF (6), C (37), D (2), F (2), F1 (5), G (2), Complex (3).

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

Notes:

ISENTRESS and Efavirenz were administered with emtricitabine (+) tenofovir

N = Number of subjects in each group.

Week 48 outcomes from Protocol 021 are shown in Table 9.

Table 9: Outcomes by Treatment Group through Week 48

Randomized Study Protocol 021	ISENTRESS 400 mg Twice Daily (N = 281)	Efavirenz 600 mg At Bedtime (N = 282)	Difference (ISENTRESS – Efavirenz) (CI[§])
Outcome at Week 48			
Subjects with HIV-1 RNA less than 50 copies/mL	87%	82%	4.7% (-1.3%, 10.6%)
Subjects with HIV-1 RNA less than 400 copies/mL	91%	88%	3.6% (-1.5%, 8.7%)
Mean CD4 cell count change from baseline (cells/mm^3)	176	150	25.8 (5.0, 46.5)
Virologic Failure (>50 copies/mL)	6%	7%	
Never suppressed through Week 48 and on study at Week 48	2%	3%	
Rebound	5%	5%	
Discontinued study drug	7%	10%	
Reasons for Discontinuation			
Death	<1%	0%	
Adverse experiences	2%	5%	
Other*	4%	5%	

[§]The 95% CI for treatment difference is adjusted by the screening HIV RNA level (<=50,000 copies/mL vs. >50,000 copies/mL) and Hepatitis B or C (negative vs. positive)

*Other includes lack of efficacy, loss to follow-up, consent withdrawn, protocol violation and other

3. *Treatment-Experienced Subjects* information was also revised as follows:

a. Table 7 was renamed Table 12 and revised. This now reads:

Table 12: Outcomes by Treatment Group through Week 48

Randomized Studies **Protocol 018 and 019**	ISENTRESS 400 mg Twice Daily + OBT (N = 462)	Placebo + OBT (N = 237)
Outcome at Week 48		
Subjects with HIV-1 RNA less than 400 copies/mL	72%	37%
Subjects with HIV-1 RNA less than 50 copies/mL	60%	31%
Mean CD4 cell count change from baseline (cells/mm^3)	106	44
Virologic Failure (>50 copies/mL)	36%	65%
Never suppressed through Week 48 and on study at Week 48	11%	9%
Rebound	13%	8%
Non-responder by Week 48‡	12%	48%
Discontinued study drug	4%	4%
Reasons for Discontinuation		
Death	2%	2%
Adverse Experiences	<1%	<1%
Other*	2%	1%

‡The non-responders by Week 48 were defined by the protocol as those who did not achieve > 1.0 $\log_{10}$ HIV-1 RNA reduction and <400 HIV-1 RNA copies/mL starting at Week 16 or beyond.
*Other includes lack of efficacy, loss to follow-up, consent withdrawn

b. The paragraph immediately after Table 12 was also revised and now reads:
The mean changes in plasma HIV-1 RNA from baseline were -2.11 $\log_{10}$ copies/mL in the group receiving ISENTRESS 400 mg twice daily and -0.96 $\log_{10}$ copies/mL for the control group.

c. Table 8 was renamed Table 13 and revised. This now reads:

Table 13: Virologic Response at Week 48 by Baseline Genotypic/Phenotypic Sensitivity Score

Randomized Studies **Protocol 018 and 019**	Percent with HIV-1 RNA <400 copies/mL at Week 48				Percent with HIV-1 RNA <50 copies/mL at Week 48			
	n	ISENTRESS 400 mg Twice Daily + OBT (N = 462)	n	Placebo + OBT (N = 237)	n	ISENTRESS 400 mg Twice Daily + OBT (N = 462)	n	Placebo + OBT (N = 237)
Phenotypic Sensitivity Score (PSS)*								
0	69	52	44	5	69	46	44	2
1	145	72	72	32	145	57	72	28
2	142	83	66	42	142	68	66	38
3 or more	85	72	48	60	85	67	48	46
Genotypic Sensitivity Score (GSS)*								
0	115	50	66	8	115	43	66	3
1	178	79	96	38	178	63	96	35
2	111	85	49	65	111	70	49	53
3 or more	51	69	23	52	51	67	23	39

*The Phenotypic Sensitivity Score (PSS) and the Genotypic Sensitivity Score (GSS) were defined as the total oral ARTs in OBT to which a subject's viral isolate showed phenotypic sensitivity and genotypic sensitivity, respectively, based upon phenotypic and genotypic resistance tests. Enfuvirtide use in OBT in enfuvirtide-naïve subjects was counted as one active drug in OBT in the GSS and PSS. Similarly, darunavir use in OBT in darunavir-naïve subjects was counted as one active drug in OBT.

I. Other minor changes were made in the label including, but not limited to, renaming of table numbers and changing the word HIV to HIV-1 (see attached annotated copy of the label, Attachment 1).

Review of Patient Package Insert:

I. "What is ISENTRESS?" section was revised as follows:

A. In consultation with the Division of Drug Marketing, Advertising, and Communications (DDMAC), the first bullet item now reads:

- *ISENTRESS is an anti-HIV (antiretroviral) medicine used for the treatment of HIV. The term HIV stands for Human Immunodeficiency Virus. It is the virus that causes AIDS (Acquired Immune Deficiency Syndrome). ISENTRESS is used along with other anti-HIV medicines. ISENTRESS will NOT cure HIV infection.*

B. In the last bullet item, "less than 16 years of age" was removed from the sentence.

II. In "How does ISENTRESS work?" section, the second bullet item was revised in consultation with DDMAC:

- *When used with other anti-HIV medicines, ISENTRESS may do two things:*
  1. Reduce the amount of HIV in your blood. This is called your "viral load".
  2. Increase the number of white blood cells called CD4 (T) cells.

III. "What are the possible side effects of ISENTRESS?" section contains the following revision:

A. In the "When ISENTRESS has been given with other anti-HIV drugs, the most common side effects:" subsection, *trouble sleeping* was added.

B. In the "Other side effects" subsection, *feeling anxious* and *paranoia* were added. In addition, the following paragraphs were revised, in consultation with DDMAC:

A condition called Immune Reconstitution Syndrome can happen in some patients with advanced HIV infection (AIDS) when combination antiretroviral treatment is started. Signs and symptoms of inflammation from opportunistic infections that a person has or had may occur as the medicines work to treat the HIV infection and help to strengthen the immune system. Call your doctor right away if you notice any signs or symptoms of an infection after starting ISENTRESS with other anti-HIV medicines.

Contact your doctor promptly if you experience unexplained muscle pain, tenderness, or weakness while taking ISENTRESS. This is because on rare occasions, muscle problems can be serious and can lead to kidney damage.

Tell your doctor if you have any side effects that bother you.

Conclusion:

It will be conveyed to the applicant that labeling is acceptable, and an approval letter should be sent.

{See appended electronic signature page}
Amalia Himaya
Regulatory Project Manager

Supervisory Comment/Concurrence:

{See appended electronic signature page}
Karen Winestock
Chief, Project Management Staff
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Attachments: PI and PPI submitted by Merck on June 26, 2009, compared to the last approved labels on January 29, 2009.

Drafted: Himaya 6/21/09
Revised/Initialed: Winestock eso 6/25/09
Finalized: 6/30/09
Filename:v: DAVP/CSO/Himaya/NDA/22145/SE5-004/CSO review 22145_SE5004.doc

23 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amalia Himaya
6/30/2009 04:36:29 PM
CSO

Karen Winestock
7/2/2009 09:02:02 AM
CSO

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: June 1, 2009

TO: Amalia Himaya, Regulatory Project Manager
Sarah Connelly, M. D., Medical Officer
Division of Antiviral Drug Products

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

FROM: Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-145/SE5-004

APPLICANT: Merck &Co., Inc.

DRUG: Isentress (raltegravir) Tablets

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of HIV-1 infection

CONSULTATION REQUEST DATE: December 18, 2008

DIVISION ACTION GOAL DATE: July 24, 2009

PDUFA DATE: July 26, 2009

I. BACKGROUND:

The sponsor, Merck &Co, Inc. has submitted a supplemental new drug application for marketing approval of MK-0158 when compared with efavirenz when each is given in combination with Truvada for treatment-naïve HIV–infected patients, 18 years of age and older, with HIV RNA >5000 copies/mL. The duration of the study for a given subject is 96 weeks.

The review division requested inspection of protocol 021-00: **"**A multi-center, double-blind, randomized, active-controlled study to evaluate the safety and antiviral activity of Mk-0158 versus efavirenz in the treatment-naïve HIV-1 infected patients, each in combination with truvada." The sponsor submitted results from protocol 021-00 in support of NDA 21-145SE5 004.

The primary objective of study protocol 021-00 was to evaluate the antiviral activity, safety and tolerability of MK0158 400 mg b.i.d. compared with efavirenz 600mg q.h.s., each in combination therapy with truvada, as measured by proportion of patients achieving HIV RNA < 50 copies/mL and assessed by review of the following parameters at week 48: Proportion of patients achieving HIV RNA <400 copies/mL, and change from baseline in CD4 counts. The inspection targeted two domestic clinical investigators who enrolled a relatively large number of subjects.

II. RESULTS (by protocol/site):

Name of CI, site #and location	Protocol and # of subjects	Inspection Dates	Final Classification
Richard Pollard, M.D UC Davis Medical Ctr. 4150 V Ste G500 Sacramento, CA 95817	Protocol 021-00 14 subjects	3/9-13/08	NAI
Daniel S. Berger, M.D Northstar Medical Ctr. 2835 N. Sheffield Ave Suite 500 Chicago, IL60657	Protocol 021-00 16 subjects	4/28- 5/13/09	Pending (Preliminary classification NAI)

Key to Classifications
NAI = No deviations
VAI = Deviation(s) from regulations
OAI = Significant deviations for regulations. Data unreliable.
Pending = Preliminary classification based on e-mail communication from the field; EIR has not been received from the field and complete review of EIR is pending.

Protocol 021-00

1. Richard Pollard, M.D.
   Sacramento, CA 95817

   At this site, a total of 15 subjects were screened; one subject was reported as screen failure; 14 subjects were randomized, and the study is still ongoing. Informed consent for all subjects was verified to be signed by subjects prior to enrollment. There were no subjects enrolled prior to IRB approval of the protocol and informed consent.

   The medical records/source data for 14 subjects were reviewed in depth including drug accountability records and the source data were compared to case report forms and data listings, including primary efficacy measures and adverse events.

   The medical records reviewed disclosed no adverse findings that would reflect negatively on the reliability of the data. In general, the study records reviewed were found to be in order and verifiable. There were no limitations to this inspection.

   The data appear acceptable in support of the pending application.

2. Daniel S. Berger, M.D.
   Chicago, IL 60657

   Observations noted below are based on an e-mail summary statement from the field investigator; the EIR for this inspection is currently pending. An inspection addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

   At this site, a total of 22 subjects were screened, 5 subjects were reported as screen failures, and 17 subjects were randomized. Informed consent for all subjects was verified.

   The medical records/source data for 8 subjects were reviewed in depth, including drug accountability records, laboratory records, IRB records, and source documents were compared to data listings, including primary efficacy endpoints and adverse events. Adverse events experienced by subjects were reported to the IRB and the sponsor within the required time frames. Our investigation found that subject 013 was hospitalized for psychiatric condition which was reported.

The medical records reviewed disclosed no adverse findings that would reflect negatively on the reliability of the data. In general, the records reviewed were found to be verifiable. There were no known limitations to this inspection.

The data appear acceptable in support of the pending application.

OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The inspection of Drs. Pollard and Berger revealed no significant problems that would adversely impact data acceptability. Please note that the observations noted for Dr. Berger is based on e-mail summary statements from the field investigators; the EIR for that inspection is currently pending. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the EIRs.

The data submitted from the inspected sites are acceptable in support of the pending application.

{*See appended electronic signature page}*

Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

{*See appended electronic signature page*}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Antoine El-Hage
6/4/2009 07:23:21 AM
PHARMACOLOGIST

Constance Lewin
6/4/2009 02:44:01 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Internal Consult

Pre-decisional Agency Information

To: Amalia Himaya
Division of Anti-Viral Products (DAVP)

From: Lynn Panholzer, PharmD
Aline Moukhtara, RN
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Date: May 15, 2009

Re: Isentress (raltegravir) Tablets, NDA 22-145/SE5-004
Labeling Review: Package Insert, Patient Package Insert

Thank you for forwarding this consult request to DDMAC. The following comments are based on the draft package insert (PI) and patient package insert (PPI) submitted by Merck & Co., Inc. on May 8, 2009, available at \\CDSESUB1\EVSPROD\NDA022145\0135.

Package Insert

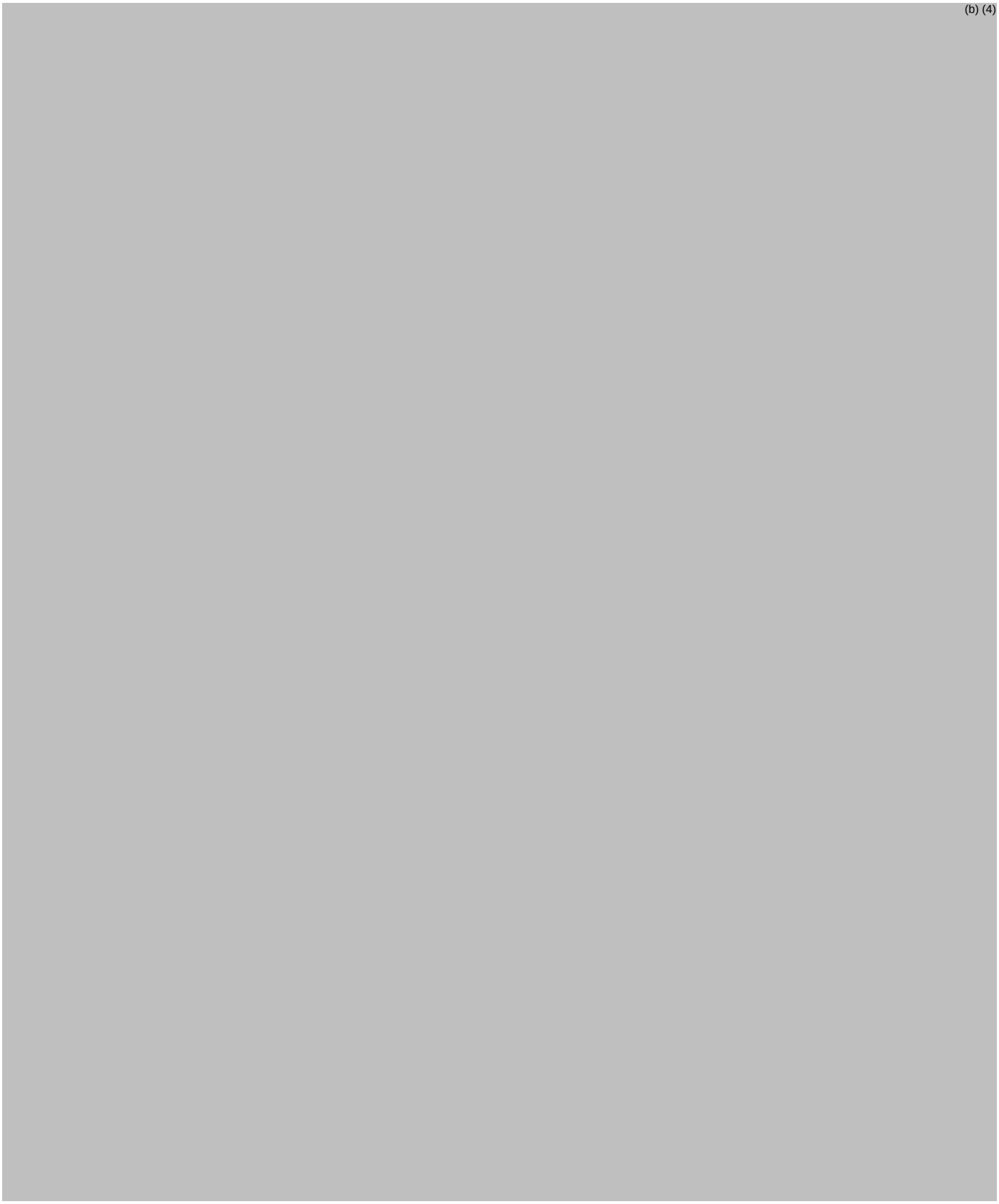
HIGHLIGHTS

WARNINGS AND PRECAUTIONS

DDMAC Comments:
We note the deletion from HIGHLIGHTS of the drug interaction between Isentress and strong inducers of UGT1A1, including rifampin. However, this drug interaction still appears in the WARNINGS AND PRECAUTIONS section of the Full Prescribing Information (b) (4)). Some companies are using the risk sections of Highlights as their "fair balance," i.e., risk information, in promotional materials. Therefore, omission from the Highlights section may mean that this risk is not conveyed in promotional materials for Isentress. Although the DOSAGE AND ADMINISTRATION section of HIGHLIGHTS provides the adjusted Isentress dosing when co-administered with rifampin, dosing information is generally not included in presentations of risk in promotional materials. Therefore, this dosing information will not serve to communicate in promotional materials the risk associated with administration of Isentress with rifampin and other strong UGT1A1 inducers. Even in those pieces where dosing is presented, dosing with rifampin will not communicate the reason for the dosing adjustment or that there may be interactions with other UGT1A1 inducers. Was this interaction deemed not significant enough to include any longer in HIGHLIGHTS? If

warranted by the significance of the risk, we recommend that you consider adding the UGT1A1 drug interaction information back to the WARNINGS AND PRECAUTIONS section of HIGHLIGHTS.

(b) (4)



3 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lynn Panholzer
5/15/2009 11:37:29 AM
DDMAC PROFESSIONAL REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Richard Pollard, M.D.
1500 21st Street
Sacramento, CA 95817

Dear Dr. Pollard:

The purpose of this letter is to inform you of the findings of a Food and Drug Administration (FDA) inspection conducted at your site. This inspection is part of FDA's Bioresearch Monitoring Program, which evaluates the research conduct and ensures that the rights, safety, and welfare of human study subjects are protected. Between March 9 and 13, 2009, Ms. Shelly H. Beausoleil and Ms. Jane M. Kreis, representing the FDA, met with you to review your conduct of a clinical investigation (protocol 021-00 entitled "A multicenter, double-blind, randomized, active-controlled study to evaluate the safety and antiretroviral activity of MK-05118 versus efavirenz in treatment-naïve HIV-1 infected patients, each in combination with truvada") of the investigational drug MK-0518 (raltegravir potassium), performed for Merck & Co., Inc.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigators Beausoleil and Kreis during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 51, Rm. 5354
10903 New Hampshire Avenue
Silver Spring, MD 20993

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Constance Lewin

4/21/2009 10:59:40 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: April 17, 2009

To: Debra Birnkrant, MD, Division Director
Division of Antiviral Products (DAVP)

Thru: Robert Boucher, MD, MPH, Deputy Director
for
Ann McMahon, MD, MS, Acting Director

Melissa M. Truffa, RPh, Safety Evaluator Team Leader
Division of Pharmacovigilance (DPV) II

From: Paula Gish, RPh, Safety Evaluator
Division of Pharmacovigilance (DPV) II

Subject: Psychiatric events

Drug Name(s): Isentress (raltegravir, aka MK0518)

NDA Numbers: NDA 22-145

Applicant/sponsor: Merck

OSE RCM #: 2009-662

EXECUTIVE SUMMARY

This review summarizes cases of psychiatric events in association with raltegravir reported to FDA's Adverse Event Reporting System (AERS) as of February 4, 2009. Currently depression and suicidality (particularly in patients with a pre-existing history of psychiatric illness) are labeled under **Adverse Reactions - postmarketing**. Despite the labeling DAVP and DPV II decided it was important to review all AERS cases of psychiatric events to determine if there were any characteristics from these cases that are not currently labeled.

We reviewed 36 cases of psychiatric events reported in the AERS database in association with raltegravir as of February 4, 2009. Nineteen of the 36 cases report depression or suicidality and 17 cases report other psychiatric events (e.g. insomnia, anxiety, paranoia, psychosis). Fifteen of the 36 cases report a history of psychiatric illness. Only 4 of the 36 cases report concomitant etravirine or efavirenz (HIV medications associated with psychiatric events). There are 7 hospitalizations and one death; however, it is not clear if the death is related to a psychiatric event.

Although causality is difficult to determine due to the high background rate of depression for HIV patients, there are three cases of depression or suicidality with a temporal relationship to raltegravir administration with positive dechallenge. In addition there are three cases of unlabeled events (insomnia, paranoia, anxiety) with a temporal relationship to raltegravir administration with positive dechallenge. Based on these six cases a causal contribution from raltegravir to the events of depression, suicidality, insomnia, paranoia and anxiety cannot be excluded.

The current labeling for depression or suicidality appears adequate at this time. However, we recommend updating the **Adverse Reactions-postmarketing** section to include the following terms: *insomnia, paranoia, anxiety.*

1 INTRODUCTION

This review summarizes cases of psychiatric events in association with raltegravir reported to FDA's Adverse Event Reporting System (AERS) as of February 4, 2009.

In September 2008 an article was published in AIDS that described 4 cases of worsening depression in association with raltegravir in patients with pre-existing depression.[1] In January 2008 the sponsor added the following statement to the raltegravir US package insert under Adverse Reactions - Postmarketing experience (section 6.2) *"psychiatric disorders: depression (particularly in patients with a pre-existing history of psychiatric illness), including suicidal ideation and behaviors*. Despite the labeling DAVP and DPV

[1] Harris M et al. Exacerbation of depression associated with starting raltegravir: a report of four cases. AIDS 2008;22:1890-1892.

II decided it was important to review all AERS cases of psychiatric events to determine if there were any characteristics from these cases that are not currently labeled.

Isentress™ (raltegravir, formerly MK0518) is a human immunodeficiency virus integrase strand transfer inhibitor (HIV-1 INSTI) indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced adult patients with resistance to multiple antiretroviral agents. It was approved on October 12, 2007 based on 24-week data from 2 randomized, double-blind, placebo-controlled trials in antiretroviral treatment-experienced adults, and is the first integrase strand transfer inhibitor approved for use in the United States.

2 SEARCH CRITERIA

As of February 4, 2009 the AERS database contained a total of 571 adverse event reports (including reports submitted prior to approval date) listing raltegravir as a suspect drug.

The AERS database was searched on February 4, 2009 for reports listing raltegravir as a suspect drug and all MedDRA Preferred Terms listed under the System Organ Class (SOC): *psychiatric disorders*

The results include reports submitted prior to the October 2007 approval date (e.g. reports from clinical trials and early access programs for raltegravir).

3 AERS DATA RESULTS

The search retrieved 60 (crude count) adverse event reports in AERS as of February 4, 2009. Twenty-four of the 60 were excluded due to the following: duplicate reports (8), MK0518 clinical trial report (1) (case #6376759), event occurred prior to raltegravir (1) (case #6741227), the events did not appear to be psychiatric events (4) (such as "eating disorder" due to nausea and vomiting), the psychiatric event appeared to be due to underlying medical conditions (10) (such as altered mental status due to AIDS related dementia).

Nineteen of the remaining 36 cases report depression or suicidality and 17 report other psychiatric events (such as insomnia, paranoia, anxiety, psychosis). All 36 cases are detailed in Table 1 in the appendix. Cases #1-19 in Table 1 report depression or suicidality events and cases #20-36 report other psychiatric events.

3.1 **Depression or suicidality (n=19)**

Nineteen of the 36 cases of psychiatric events report depression or suicidality. The MedDRA Preferred Terms relating to psychiatric events are summarized below:

MedDRA Preferred Terms reported (# cases):
Depression (9)
Depression/agitation (3)
Depression/suicidal ideation (2)
Depression/irritability (1)
Depression/suicidal ideation/psychosis/paranoia (1)
Depression/suicide attempt (1)
Suicide attempt/psychosis/agitation/anger (1)
Suicide ideation (1)

Temporal Relationship and Psychiatric History:
A temporal relationship was documented in 13 of the 19 cases reporting depression or suicidality and ranged from 1 week to 3.5 months after starting raltegravir. Nine of the 19 report a history of depression or bipolar disorder, and ten cases do not report psychiatric history. Five of the 9 patients with a psychiatric history report concomitant psychiatric medications:

- fluoxetine-2
- citalopram/bupropion/quetiapine/risperidone/clonazepam-1
- bupropion/clonazepam/quetiapine/sertraline/valproic acid/zopiclone-1
- trazodone-1

Of the six cases reporting suicidality (suicide ideation-3, suicide ideation/psychosis/paranoia-1, suicide attempt-1, suicide attempt/psychosis/agitation/anger-1), four of these cases report a psychiatric history and two do not report psychiatric history.

Outcome: There are 5 hospitalizations due to the events (depression-1, suicide ideation-1, suicide ideation/psychosis/paranoia -1, suicide attempt-1, suicide attempt/psychosis/agitation/anger-1). Four of the 5 hospitalization cases report a history of depression and one does not report psychiatric history.

One death is reported but it is unclear if the death is related to a psychiatric event.

Eight of the 19 cases report raltegravir was discontinued due to events (outcome: recovered-2, recovered with alteration or addition of psychiatric medications-2, did not recover-1, unknown-3). Six cases report raltegravir was not discontinued (outcome: recovered-2, recovered with alteration or addition of psychiatric medications-2, unknown-2). Five cases do not report if raltegravir was discontinued or not (outcome: recovered-1, did not recover-1, unknown-3).

Concomitant Medications: Four of the 19 cases report concomitant etravirine (2) or efavirenz (2). Etravirine and efavirenz are HIV medications associated with psychiatric events. One patient was treated with efavirenz for more than 3 years prior to the events and the other three do not report duration of therapy. All four of these cases also report history of depression or bipolar disorder.

3.2 Other psychiatric events (n=17)
Seventeen of the 36 cases of psychiatric events report other psychiatric events. The MedDRA Preferred Terms relating to psychiatric events are summarized below:

MedDRA Preferred Terms reported (# cases):
Insomnia (6)
Paranoia/anxiety (3)
Paranoia/hallucination (1)
Anger/disorientation (1)
Anxiety (1)
Panic attack (1)
Compulsive sexual behavior (1)
Expressive language disorder (1)
Mental status changes (1)
Psychosis (1)

Temporal Relationship and Psychiatric History:
A temporal relationship is documented in 8 of the 17 cases of other psychiatric events. Time to onset ranges from 1 day (for insomnia) to 3 months (for paranoia with hallucination). Six of the 17 report a history of psychiatric illness (drug addiction or abuse-2, depression/anxiety-2, depression/attention deficit disorder/anxiety-1, depression/suicidality with Atripla-1). Ten of the 17 cases do not report psychiatric history. One case of insomnia reports the patient had "no history of insomnia". Three of the six cases with a psychiatric history report concomitant psychiatric meds:

- Risperdal/Klonopin/Celexa/Ritalin/Effexor
- Celexa
- Wellbutrin XL

Outcome: There are 2 hospitalizations due to the psychiatric events (panic attack-1, paranoia/anxiety-1). Both cases report a psychiatric history (crack cocaine abuse-1, depression/anxiety-1).

Six of the 17 cases report raltegravir had to be discontinued due to events. Four of these cases report the patients recovered (insomnia-2, paranoia/anxiety-1, psychosis-1), one reports the patient recovered with the addition of Zyprexa (paranoia/hallucination-1), and one outcome is unknown (paranoia/anxiety-1).

Five cases report raltegravir was not discontinued due to the events. One of these 5 cases reports the patient recovered (panic attack-1), one reports the patient recovered after altering psychiatric medications (anger/disorientation-1), three cases report the patients have not recovered (insomnia-2, anxiety-1).

Six cases do not report any intervention or outcome information (insomnia-2, paranoia/anxiety-1, mental status changes-1, expressive language disorder-1, compulsive sexual behavior-1).

Concomitant Medications: No cases report concomitant etravirine or efavirenz (HIV drugs associated with psychiatric events). One case (paranoia/hallucination) reports the patient had smoked Salvia, a plant with hallucinogenic properties.

4 DISCUSSION

The prevalence of depression in HIV patients is higher than the general population and is estimated at 22% for major depression and 5% for dysthymic disorder.[2] The high background rate makes causality assessment difficult. In addition, causality to raltegravir appears unclear in the majority of cases because: the events resolved without discontinuation of raltegravir, the cases are confounded by illicit drug use (for example one patient had smoked Salvia, a plant with hallucinogenic properties), or the cases do not provide sufficient information to make a causality assessment.

However, there are six cases of psychiatric events with a documented temporal relationship (< 6 weeks after beginning raltegravir therapy) that report a positive dechallenge. These psychiatric events include depression (cases #2, #10, #16), suicidal ideation (cases #2, #16), insomnia (cases #31, #32), paranoia (case #25), and anxiety (case #25). Four of these 6 cases report a history of depression and two cases (#31, #32) do not report psychiatric or medical history information.

Although causality is difficult to determine due to the high background rate of depression for HIV patients, a causal contribution from raltegravir to the events of depression, suicidality, insomnia, paranoia, and anxiety cannot be excluded.

5 CONCLUSION

The current label is adequate for depression and suicidality, however several unlabeled events *(insomnia, paranoia, anxiety)* report a strong temporal relationship to raltegravir with positive dechallenge and should also be included in the label.

6 RECOMMENDATIONS

No changes to the label regarding depression or suicidality are suggested at this time. However, we recommend updating the **Adverse Reactions-postmarketing** section to include the following terms: *insomnia, paranoia, anxiety.*

[2] Rabkin J. HIV and Depression: 2008 Review and Update. Current HIV/AIDS Reports 2008;5:163-171.

APPENDIX

Table 1
Raltegravir
Postmarketing cases of psychiatric events
N=36
AERS data as of 02/04/09

Ref #	AERS case # Mfr # Location Date initially received	Age/ sex	MedDRA PTs	Raltegravir duration/ ARV Concomitant medications	Med History	Intervention/ Outcome	Description/Comments
1	6554110 CTU 324393 US 2/5/2008	64M	Agitation, depression	Raltegravir x 1 month Nevirapine, darunavir, ritonavir (duration unk)	nr	nr	Verbatim: I'm concerned about raltegravir. I have had two patients begun on raltegravir who have developed sudden depression. The onset seemed sudden. I sit on a list serve with other HIV clinicians and although a large list of clinicians representing many, many patients with HIV they have reported at least 5 other patients with agitation or depression soon after beginning raltegravir. In some cases, including my second case raltegravir substituted for another HIV med thus being the only newly introduced medication.
2	6622369 US-MERCK-0804USA03967 US 4/23/2008	33M	Depression, suicidal ideation	Raltegravir x 1 month nr	Hx depression	Event resolved without dc'ing raltegravir, then recurred, recovered after dc'd raltegravir and increased fluoxetine	Physician reported therapy with enfuvirtide was dropped and the patient was placed on raltegravir on 29-Nov-2007. It was reported that within the first month of taking raltegravir (approximately December 2007) the patient felt depressed with suicidal thoughts. It was reported that the patient's symptoms were "pretty serious", but they passed. Therapy with raltegravir was continued. On 11-MAR-2008, the patient reported that his depression had reoccurred. All ARV medications including raltegravir were discontinued. The physician increased the patient's fluoxetine from 20 mg to 40 mg.
3	6706269 WAES 0803USA03832 US	Male (age unk)	Depression, irritability	Raltegravir < 2 mos nr	No "real" hx of depression nr	Placed on escitalopram, outcome unk	Patient was recently switched from enfuvirtide to raltegravir. Within 2 mos went from non-depressed to irritable and clearly depressed. There were no precipitating issues. The physician reported the drug is working great for him. He remains undetectable. The patient was not

Table 1
Raltegravir
Postmarketing cases of psychiatric events
N=36
AERS data as of 02/04/09

Ref #	AERS case # Mfr # Location Date initially received	Age/ sex	MedDRA PTs	Raltegravir duration/ ARV Concomitant medications	Med History	Intervention/ Outcome	Description/Comments
	5/15/2008						suicidal. "more irritable than anything". Pt treated with Lexapro, outcome unknown.
4	6706399 WAES 0802USA02896 US 5/15/2008	Age, sex unk	Agitation, depression, liver function test abnormal	Raltegravir (duration unk) Nevirapine (< 2 weeks)	nr	Dc'd raltegravir, outcome unk	Patient was placed on therapy with raltegravir, subsequently experienced depression and agitation and had a rise in LFTS thought to be due to nevirapine which pt had commenced a couple weeks earlier. Raltegravir was dc'd but physician planned to recommence therapy with raltegravir "soon"
5	6706401 WAES 0802USA02959 US 5/15/2008	Age, sex unk	Depression	Raltegravir (duration unk) nr	nr	2 pts marked depression, recovered after raltegravir dc'd	Physician reported two patients placed on therapy with raltegravir and subsequently experienced marked depression. After stopping the drug the depression reversed.
6	6708265 WAES 0802USA04556 US 5/15/2008	Age, sex unk	Agitation, depression	Raltegravir (duration unk) nr	nr	Cont'd raltegravir, resolved	Physician reported pt placed on therapy with raltegravir. Subsequently the patient experienced depression and agitation. Pt continued on raltegravir and depression resolved.
7	6736229 US-MERCK-0808USA03215 Canada 8/25/2008	48M	Depression, suicidal ideation, suicide attempt,	Raltegravir x 2.5-3.5 mos Etravirine, darunavir, ritonavir x 2.5-3.5 mos	Hx depression, chronic knee pain, hypercholesterolemia, peripheral neuropathy, and bipolar disorder.	Hospitalized for suicidal ideation on (b) (6) after beginning raltegravir), dc'd medications (date unk), restarted same	48 year old male who, on Feb 11, 2008, was placed on therapy with raltegravir, 400 mg, twice a day. In May 2008, the patient experienced depression and, in June 2008, he experienced suicidal ideation. The patient had follow-up in mid-March with 100% compliance to drugs and an undetectable viral load. The patient started to feel depressed and became non-compliant in May 2008. (b) (6) the patient was admitted

Table 1
Raltegravir
Postmarketing cases of psychiatric events
N=36
AERS data as of 02/04/09

Ref #	AERS case # Mfr # Location Date initially received	Age/ sex	MedDRA PTs	Raltegravir duration/ ARV Concomitant medications	Med History	Intervention/ Outcome	Description/Comments
				Bactrim DS, azithromycin x 2.5-3.5 mos, Percocet (duration unk)		medications end of July 08 because depression did not improve after medications were dc'd	to psychiatry for severe suicidal ideations. The patient was "restarted on the same meds again" from 28-JUL-2008 (date of drug interruption not reported). Depression did not improve upon stopping the drug.
8	6753908 Dup 6870587 CA-MERCK-0809CAN00002 Dup CA-BRISTOL-MYERS SQUIBB COMPANY-14457303 Literature Harris M, Larsen G, Montaner JSG. Exacerbation of depression associated with starting raltegravir: a report of four cases. AIDS 2008;22(14):1890-2. Canada 9/11/2008	44M	Depressive symptom, depression, paranoid personality disorder, psychomotor skills impaired, suicidal ideation, tearfulness, anxiety, depression suicidal, psychotic disorder	Raltegravir x 1 mos Atazanavir, ritonavir, tenofovir, emtricitabine (duration unk) citalopram, bupropion, clonazepam, quetiapine, risperidone (duration unk)	Hx depression, hx worsening depression with efavirenz	Hospitalized for suicidal risk, psychosis, depression, anxiety, resolved after increased doses of risperidone, buproprion, clonazepam. Quetiapine was switched to zopiclone, did not dc raltegravir, patient was discharged 1 mos later and continues on raltegravir	It was reported in a published article a 44 year old male with depression (diagnosed in 2006) on 26-JUN-2007 was placed on therapy with raltegravir. On 02-JUN-2006 the patient's symptoms of depression exacerbated (worsening of a pre-existing condition) by efavirenz and improved after efavirenz was discontinued on 22-MAY-2007. As of 26-JUN-2007 blood helper/inducer cell lymphocyte count was 310 cells/±1 and plasma HIV viral RNA quantification test was <50 copies/mL. On 23-JUL-2007 the patient was depressed, tearful, suicidal, with paranoid ideation and psychomotor slowing when he presented to his family doctor. (b) (6) the patient experienced psychosis, depression with suicidal risk and anxiety and was hospitalized. Therapy with raltegravir continued. It was reported that the patient's doses of risperidone, bupropion and clonazepam were increased, citalopram was continued, quetiapine was discontinued and the patient commenced zopiclone. It was reported that psychiatric symptoms improved after discharge on (b) (6) and that patient remained stable on raltegravir as of 22-MAY-2008. The authors concluded that "at this time,

Table 1
Raltegravir
Postmarketing cases of psychiatric events
N=36
AERS data as of 02/04/09

Ref #	AERS case # / Mfr # / Location / Date initially received	Age/ sex	MedDRA PTs	Raltegravir duration/ ARV / Concomitant medications	Med History	Intervention/ Outcome	Description/Comments
							the mechanism by which raltegravir may have contributed to the observed psychiatric decompensation remains unknown. Pending further study, caution and close monitoring is advised when starting raltegravir in patients with a history of depression who are currently under treatment with antidepressant and other psychotropic medications. Two patients had simply replaced enfuvirtide with raltegravir, a strategy that has demonstrated virological success." ***The article also discussed the experience of three other patients: male patient aged 54 years - WAES 0809CAN00001; male patient aged 55 years - WAES 0809CAN00003 and male patient aged 40 years - WAES 0809CAN00004***
9	6753911 Dup 6870591 CA-MERCK-0809CAN00001 Dup CA-BRISTOL-MYERS SQUIBB COMPANY-14455729 Literature Harris M, Larsen G, Montaner JSG. Exacerbation of depression associated with starting raltegravir: a report of four cases. AIDS 2008;22(14):1890-2	54M	Drug interaction, depression	Raltegravir x 1 week Efavirenz, lamivudine, lopinavir, ritonavir, atazanavir (x > 3 years) Bupropion, clonazepam, quietiapine, sertraline, valproic acid, zopiclone (duration unk)	Hx bipolar disorder longstanding, depression	Incr valproic acid, continued on raltegravir, resolved	54 year old male with bipolar disorder (long standing) on 20-JUN-2007 was placed on therapy with raltegravir. ON 05-JUN-2007 the patient was doing well and his bipolar disorder was stable. As of 20-JUN-2007 blood helper/inducer cell lymphocyte count was 340 cells/mm3 and plasma HIV viral RNA quantification test was <50 copies/mL. On 27-JUN-2007 the patient experienced increased depression/severe depression and drug interaction. Therapy with raltegravir continued. On 27-JUN-2007 the patient was seen by his family doctor reporting increased depression (worsening of a pre-existing condition). The dose of valproic acid was increased by his psychiatrist. For the next month the patient experienced severe depression to the point where he had no "strength to get out of bed". The symptoms resolved gradually and by 24-AUG-2007 the patient felt better. As of 14-MAR-2007 the patient recovered from increased depression/severe depression (reported as the

Table 1
Raltegravir
Postmarketing cases of psychiatric events
N=36
AERS data as of 02/04/09

Ref #	AERS case # Mfr # Location Date initially received	Age/ sex	MedDRA PTs	Raltegravir duration/ ARV Concomitant medications	Med History	Intervention/ Outcome	Description/Comments
	Canada 9/11/2008						patient's mood was stable while still receiving raltegravir).
10	6760542 WAES 0804USA03858 US 8/14/2008	44M	Depression	Raltegravir < 1 month Efavirenz abacavir lamivudine (duration unk) Prozac (duration unk)	Hx depression, sulfa, penicillin allergy	Dc'd raltegravir, improved	Pt was placed on therapy with raltegravir on 29-Nov-2007. In December the patient developed depression, which lasted several weeks. The patient notified the physician after it had remitted in mid-January 2008. On 12-Mar-2008 the patient again developed depression and was seen in the physician's office on 12-Mar-2008. Raltegravir was discontinued. As of 17-Apr-2008 the patient's condition was improved. There were no symptoms or treatments reported. There were no lab or diagnostic studies performed. At the time of reporting the patient was recovering.
11	6760571 WAES 0804USA04019 US 8/14/2008	64M	Depressive symptom, hepatic enzyme increased	Raltegravir x < 2 weeks nr	nr	Continued raltegravir, symptoms passed	A 64 year old male was placed on therapy with raltegravir on 21-Dec-2007. Within two weeks , on approximately 04-Jan-2008 the patient developed depression like symptoms. The symptoms passed and the patient continued taking raltegravir. On 12-Jn-2008 the patient developed increased liver enzymes (results not reported). On 25-Jan-2008 the physician dc'd all patient's medications including raltegravir. No other information was reported.
12	6777216 US-MERCK-0809USA04944 US 10/2/2008	Male (age unk)	Depression, general symptom, mental status changes	Raltegravir < 3 months Lamivudine, zidovudine (duration unk)	Hx depression	Hospitalized for depression, unclear if dc'd raltegravir, resolved	A male with depression who, in approximately June 2008, was placed on therapy with raltegravir (dose and indication not reported). Subsequently, the patient experienced change in baseline depression and also experienced a "medical condition" (unspecified) that required hospitalization for a short time. Therapy was stopped (?) on 23-SEP-2008 after the patient had been on it for about three months. Follow-up

Table 1
Raltegravir
Postmarketing cases of psychiatric events
N=36
AERS data as of 02/04/09

Ref #	AERS case # Mfr # Location Date initially received	Age/ sex	MedDRA PTs	Raltegravir duration/ ARV Concomitant medications	Med History	Intervention/ Outcome	Description/Comments
							information was received from a nurse practitioner on 31-DEC-2008 indicating that she felt that this "was not a true AE". The patient had been on lots of medication and had many medical issues prior to raltegravir initiation. During the usage, the patient had a change in his mental status. He continued raltegravir (also reported as stopped on 23-SEP-2008) but the mental concern resolved.
13	6783478 US-MERCK-0810USA01019 US 10/9/2008	40M	Bedridden, death, depression, femur fracture, viral load increased	Raltegravir (duration not reported) nr	nr	nr Death	Information has been received from a health professional concerning a 40 year old male was placed on therapy with raltegravir 400 mg, twice a day (duration not reported). No concomitant medications were reported. On an unspecified date, the patient experienced a fractured femur, became bedridden, and died (date not reported) while on therapy with raltegravir. The patient sought unspecified medical attention. Follow-up information was received from a health professional on 29-OCT-2008 indicating that she did not think that raltegravir potassium had anything to do with the patient's death. The patient had been in a home and very depressed. It was uncertain whether the patient was definitely taking raltegravir. It had been prescribed for him but his viral load was very high.
14	6788124 CTU 351002 US 9/29/2008	42M	Depression	Raltegravir x 2 weeks nr	Hx depression	nr	Verbatim: I began taking raltegravir -Isentress- on July 25, 2008. Within a couple of weeks I relapsed into a significant bout of depression. I have been under medical treatment for depression for nearly two decades. I have read reports that there is a possible link between raltegravir and depression relapses, so I thought I would take the time to report my own experiences.
15	6789995 Dup 6867765 Dup 6778332	42F	Pneumonia, pancytopenia, pyrexia,	Raltegravir x 1 week after	Hx depression, HIV, cytomegalovirus DNA	Did not dc raltegravir, outcome unknown	The patient was treated with darunavir (dose unknown)) initiated on 05-AUG-2008. On 28-AUG-2008, darunavir was stopped due to rash.

Table 1
Raltegravir
Postmarketing cases of psychiatric events
N=36
AERS data as of 02/04/09

Ref #	AERS case # Mfr # Location Date initially received	Age/ sex	MedDRA PTs	Raltegravir duration/ ARV Concomitant medications	Med History	Intervention/ Outcome	Description/Comments
	Dup 6895518 Dup 6896232 US-JNJFOC-20081001983 Dup WAES 0812USA01814 Dup WAES 0809USA01998 Dup A0765514A Dup US-GILEAD-2009-0019920 Enrolled in an NIH sponsored study A5241 "The optimised treatment that includes or omits NRTIs (options) trial: A randomised strategy study for HIV-1 infected treatment experienced subjects using the cPSS to select an effective regimen" in AUG-2005: EAE# 2008-1044 US 10/17/2008		pancreatitis, immune reconstitution syndrome, nephritis interstitial, diarrhoea, hepatotoxicity, anorexia, asthenia, cheilitis, depression, gastric ulcer, gastrointestinal disorder, gastrointestinal mucosal disorder, hiatus hernia, hypersensitivity, oesophageal candidiasis, rash, weight decreased,	restarting Darunavir, ritonavir, etravirine, zidovudine, tenofovir, emtricitabine Dextromethorphan for cough, fluconazole for oral thrush, lomotil, ibuprofen, azithromycin, pentamidine for pneumocystis jiroveci pneumonia, pantoprazole, hydroxyzine, dronabinol, famotidine, ondansetron hydrochloride, dexamethasone, prochlorperazine edisylate, potassium chloride, trazodone, and docusate.	test positive (Polymerase chain reaction), nephrolithiasis, pancreatitis and smoker (20 pack years), GERD, hypothyroidism. Hx hives when taking lopinavir/ritonavir, tattoo on 16-AUG-2008, No previous history of: liver disease, drug addiction, herbal medication intake, tendency to bleed or alcohol abuse. The patient had a family history of breast cancer, diabetes and hypercholesterolemia.		(b) (6) the patient was hospitalized with a diagnosis of grade 4 pancreatitis and remaining ARV was discontinued (b) (6) the patient was diagnosed with immune reconstitution inflammatory syndrome and treated for presumed PJP. Patient experienced acute renal failure due to drugs (acute interstitial nephritis) versus hypoperfusion and increased liver function tests and bilirubin. Her serum albumin also became low. APTT and APT were prolonged. On (b) (6), the patient re-admitted to hospital with grade 4 possible hepatotoxicity, cachechia and mild respiratory distress, blood test results for hepatitis A, B C and E were all negative. The polymerase chain reaction test for cytomegalovirus was positive, On 06-NOV-2008, the patient was restarted on darunavir, TMC125 (etravirine), raltegravir, ritonavir, zidovudine and Truvada (tenofovir + emtricitabine). On 07-NOV-2008, the patient experienced low grade fever followed by progressive weakness and depression on Nov 14, she was withdrawn from her family and required assistance for all activities of daily living. The patient also received pentamidine at an outpatient clinic on the same day. (b) (6) the patient was hospitalised as she presented with a two-week history of progressive weakness, severe anorexia, diarrhoea and lip sores. On 09-DEC-2008, treatment with zidovudine was permanently withdrawn.
16	6802257 US-MERCK-0810USA04941	42M	Depression, feeling abnormal, suicidal ideation	Raltegravir x 4-6 weeks	Hx depression but was in remission for years and not on medication	Hospitalized for suicidal ideation, raltegravir dc'd and treated with	Information has been received from a physician concerning a 42 year old white male with anxiety who was placed on therapy with raltegravir, 400 mg, BID (duration not reported) after having "failed (with) other antiretrovirals". Within about

Table 1
Raltegravir
Postmarketing cases of psychiatric events
N=36
AERS data as of 02/04/09

Ref #	AERS case # Mfr # Location Date initially received	Age/ sex	MedDRA PTs	Raltegravir duration/ ARV Concomitant medications	Med History	Intervention/ Outcome	Description/Comments
	US 11/3/2008			darunavir, ritonavir, emtricitabine, tenofovir (duration unk)		escitalopram, much improved but not fully recovered	4-6 weeks after starting raltegravir potassium, the patient began "feeling different and not himself" and became profoundly depressed. The patient had suicidal ideation and admitted to the psychiatric unit of the hospital (b) (6) The physician reported the patient was better, much improved off therapy with raltegravir but still depressed. The patient was started on therapy with escitalopram.
17	6872863 JP-MERCK-0812USA04900 Japan 1/5/2009	Age, sex unk	Suicidal ideation	Raltegravir (duration not reported) nr	nr	nr	Initial information has been received from a pharmacist concerning a patient (age, sex unknown). No information concerning the patient's concurrent condition, medical history or concomitant medications was obtained. Reportedly, the patient had suicidal ideation while on therapy with raltegravir (dosage, indication unknown). The outcome of the suicidal ideation was not reported. The reporting pharmacist did not assess the relationship between the suicidal ideation and raltegravir, or the serious criteria of the suicidal ideation. Upon internal review, the suicidal ideation was determined as an other important medical event. Follow up information is not expected.
18	6831427 WAES 0809USA01429 US 11/14/2008	54M	Depression	Raltegravir x 19 days Emtricitabine, tenofovir (duration not reported)	nr	Raltegravir dc'd Outcome unk	A physician reported a 54 year old male patient was placed on raltegravir therapy on 8/14/08. The physician stated he contacted the patient "two weeks" after the start of therapy. The patient had taken himself off of raltegravir on 9/2/08 because it made him depressed. Outcome is unknown.
19	6893650 (b) (6)	59M	Agitation, irritability, overdose, suicide attempt, anger,	Raltegravir (duration not reported)	nr	Hospitalized, raltegravir dc'd	Information has been received from a physician concerning a male patient who was placed on therapy with raltegravir (duration not reported). Subsequently the patient experienced "psychotic

Table 1
Raltegravir
Postmarketing cases of psychiatric events
N=36

AERS data as of 02/04/09

Ref #	AERS case # Mfr # Location Date initially received	Age/ sex	MedDRA PTs	Raltegravir duration/ ARV Concomitant medications	Med History	Intervention/ Outcome	Description/Comments
	0901USA03380 US 1/27/2009		multiple drug overdose, psychotic disorder	Emtricitabine, tenofovir (duration not reported) Pneumococcal vaccine		Outcome unk	episodes" .The patient was hospitalized, at unspecified facility. Therapy with raltegravir potassium was discontinued. At the time on the report on 22-JAN-2009 the patient was not recovered. Additional information has been received from a Physician's office who reported on 13-NOV-2008 the patient was vaccinated with pneumococcal 23v polysaccharide vaccine. On 23-NOV-2008 patient seemed agitated and angry. On (b) (6) the patient overdosed on 270 diazepam (VALIUM) tablets and unknown amount of trazodone. He was taken to the hospital and admitted into lock down for approximately 5 days because he attempted suicide. Physician recommended to the patient see a psychiatrist. Physician did not think the vaccine had anything to do with the psychotic episodes. Additional information is not expected.
20	6661718 WAES 0805PRT00008 Portugal 5/27/2008	38M	Hallucination, hallucination auditory, paranoia, paranoid personality disorder	Raltegravir x 3 mos Emtricitabine, tenofovir, zidovudine x 3 mos Sulfa/tmp, zolpidem (duration unk)	Drug addiction	Dc 'd raltegravir, began Zyrprexa, recovered then restarted raltegravir, outcome unk	Patient had also smoked Salvia which may cause hallucination
21	6685347 WAES 0711USA03799 US	60M	Chromaturia, clumsiness, dizziness, fatigue, headache, insomnia, malaise, nausea	Raltegravir x duration unk Lamivudine, zidovudine,	Blood sugar increased, jaundice, penicillin allergy, diabetes	Event continues	Insomnia after evening dose, also dizziness clumsiness (tripping)

Table 1
Raltegravir
Postmarketing cases of psychiatric events
N=36
AERS data as of 02/04/09

Ref #	AERS case # Mfr # Location Date initially received	Age/ sex	MedDRA PTs	Raltegravir duration/ ARV Concomitant medications	Med History	Intervention/ Outcome	Description/Comments
	2/14/2008			tenofovir (duration unk)			
22	6685417 WAES 0712USA01642 US 2/14/2008	Female (age unk)	Psychotic disorder	Raltegravir (duration unk) Stavudine, enfuvirtide, other unspecified therapy (duration unk)	nr	Lowered dose, then dc'd raltegravir altogether, patient recovered	Became psychotic
23	6706191 WAES 0801USA02783 US 5/15/2008	55M	Anger, disorientation, dizziness, hypokinesia	Raltegravir x 8 days Abacavir, lamivudine, zidovudine, tenofovir (duration unk) Risperdal, Klonopin, Celexa, Ritalin, Effexor	Depression, attention deficit disorder, anxiety	Increased Risperdal to 2mg tid, increased Effexor to 150mg QD and dc'd Ritalin, patient returned to baseline a few days later	Reported dizziness and disorientation, then next day "rage attack" at psychiatrist visit that was "uncharacteristic for the patient" and lasted several hours
24	6713294 US-MERCK-0807USA05025 US	Female (age unk)	Panic attack	Raltegravir x 2 mos Emtricitabine, tenofovir, ritonavir,	Drug abuse (crack cocaine)	Hospitalized, continued on raltegravir, recovered	

Table 1
Raltegravir
Postmarketing cases of psychiatric events
N=36
AERS data as of 02/04/09

Ref #	AERS case # Mfr # Location Date initially received	Age/ sex	MedDRA PTs	Raltegravir duration/ ARV Concomitant medications	Med History	Intervention/ Outcome	Description/Comments
	7/29/2008			darunavir (duration unk) Celexa (duration unk)			
25	6759530 US-MERCK-0808USA02676 US 9/15/2008	40F	Anxiety, fear, hypoaesthesia, paranoia	Raltegravir < 2 mos Nevirapine, unboosted atazanavir (duration unk)	Hx depression, anxiety	Dc'd raltegravir, hospitalized for 5 days, patient recovered	Felt like "I wanted to tear the place apart" and "my house felt very strange to me" and "total body numbness", "fear of the unknown", "extreme anxiety"
26	6760337 US-MERCK-0809USA01417 US 9/16/2008	37M	Expressive language disorder	Raltegravir Emtricitabine, tenofovir	nr	Intervention, outcome unk	Trouble "word finding"
27	6760593 WAES 0804USA06214 US 8/14/2008	Age, sex unk	Anorexia, diarrhoea, feeling abnormal, insomnia	Raltegravir (duration unk) Emtricitabine, tenofovir (duration unk)	nr	Intervention, outcome unk	Wakes up in middle of night
28	6761549 WAES 0807USA00425	44U	Fatigue, insomnia, vasodilatation	Raltegravir x 1 day nr	Hx depression, suicidality with Atripla (efavirenz,	Ambien CR, problem continues	78 hours with no sleep, shaky wired fatigued within minutes of taking raltegravir

Table 1
Raltegravir
Postmarketing cases of psychiatric events
N=36
AERS data as of 02/04/09

Ref #	AERS case # Mfr # Location Date initially received	Age/ sex	MedDRA PTs	Raltegravir duration/ ARV Concomitant medications	Med History	Intervention/ Outcome	Description/Comments
	US 8/14/2008				emtricitabine, tenofovir)		
29	6831411 WAES 0808USA04948 US 11/14/2008	38M	Insomnia	Raltegravir (duration unk) nr	No hx of insomnia	Intervention, outcome unk	
30	6831438 WAES 0809USA01658 US 11/14/2008	Age, sex unk	Anxiety, paranoia	Raltegravir (duration unk) nr	nr	Intervention, outcome unk	
31	6831705 WAES 0807USA03893 US 11/14/2008	Age, sex unk	Insomnia	Raltegravir x 1 day nr	nr	Dc'd raltegravir, recovered promptly	
32	6831712 WAES 0807USA05326 US	Age, sex unk	Insomnia	Raltegravir x 1 day nr	nr	Dc'd raltegravir, recovered promptly	

Table 1
Raltegravir
Postmarketing cases of psychiatric events
N=36
AERS data as of 02/04/09

Ref #	AERS case # Mfr # Location Date initially received	Age/ sex	MedDRA PTs	Raltegravir duration/ ARV Concomitant medications	Med History	Intervention/ Outcome	Description/Comments
	11/14/2008						
33	6831717 WAES 0807USA05640 US 11/14/2008	Age, sex unk	Mental status changes	Raltegravir (duration unk) nr	nr	Intervention, outcome unk	Clinic health care professional reports very subtle changes in the mental status of patients when they started therapy with raltegravir. Mood changes, irritability and depression that affected each pt slightly differently
34	6831767 WAES 0808USA02784 US 11/14/2008	Age, sex unk	Anxiety, paranoia	Raltegravir (duration unk) nr	nr	Dc'd raltegravir, outcome unk	
35	6831795 WAES 0808USA04673 US 11/14/2008	Male (age unk)	Anxiety, formication	Raltegravir < 18 days Emtricitabine, tenofovir (duration unk) Wellbutrin XL (duration unk)	Hx depression/anxiety	Treated with Xanax, has not recovered	
36	6831931 WAES 0810USA01796 US	Age, sex unk	Compulsive sexual behaviour	Raltegravir (duration unk) nr	nr	Intervention, outcome unk	

Table 1
Raltegravir
Postmarketing cases of psychiatric events
N=36
AERS data as of 02/04/09

Ref #	AERS case # Mfr # Location Date initially received	Age/ sex	MedDRA PTs	Raltegravir duration/ ARV Concomitant medications	Med History	Intervention/ Outcome	Description/Comments
	11/14/2008						

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Paula Gish
4/17/2009 10:45:54 AM
DRUG SAFETY OFFICE REVIEWER

Melissa Truffa
4/17/2009 10:56:46 AM
DRUG SAFETY OFFICE REVIEWER

Robert M Boucher
4/17/2009 11:04:41 AM
MEDICAL OFFICER

NDA/BLA REGULATORY FILING REVIEW

(Including Memo of Filing Meeting)

Application Information		
NDA # 22-145 BLA#	NDA Supplement #:S- 004 BLA STN #	Efficacy Supplement Type SE- 5
Proprietary Name: Isentress Established/Proper Name: Raltegravir Potassium Dosage Form: Tablets Strengths: 400 mg		
Applicant: Merck Agent for Applicant (if applicable):		
Date of Application: 9/25/08 Date of Receipt: 9/26/08 Date clock started after UN:		
PDUFA Goal Date: 7/24/09	Action Goal Date (if different):	
Filing Date: 12/9/08 Date of Filing Meeting: 11/7/08		
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed Indication(s): Treatment of HIV-1 infection (in combination with other retroviral agents) in treatment-naïve adult patients.		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***Refer to Appendix A for further information.***	☐ 505(b)(1) ☐ 505(b)(2) ☒ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.***	☒ Standard ☐ Priority ☐ Tropical disease Priority review voucher submitted
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☒ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 69928, 75635, and 77787	
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒ YES ☐ NO
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.***	☒ YES ☐ NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	☒ YES ☐ NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ora/compliance_ref/aiplist.html*** **If yes**, explain: **If yes**, has OC/DMPQ been notified of the submission? **Comments**:	☐ YES ☒ NO ☐ YES ☐ NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	☒ YES ☐ NO
User Fee Status **Comments:**	☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).*	
Exclusivity	
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II,***	☐ YES ☒ NO ☐ YES ☐ NO

Office of Regulatory Policy (HFD-007) **Comments**:	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.* **Comments**:	☐ YES # years requested: ☒ NO
If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***): Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***	☒ Not applicable ☐ YES ☐ NO
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
	☒ **Not applicable**
1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☐ NO
2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).	☐ YES ☐ NO
3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*	☐ YES ☐ NO

4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:	☐ YES ☐ NO

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Format and Content	
Do not check mixed submission if the only electronic component is the content of labeling (COL). **Comments**:	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	
If electronic submission: paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)? ***Forms*** *include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.* **Comments**:	☒ YES ☐ NO
If electronic submission, does it follow the eCTD guidance? (*http://www.fda.gov/cder/guidance/7087rev.pdf*) **If not,** explain (e.g., waiver granted):	☒ YES ☐ NO

Form 356h: Is a signed form 356h included? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.*** Are all establishments and their registration numbers listed on the form? **Comments**:	☒ YES ☐ NO ☐ YES ☒ NO
Index: Does the submission contain an accurate comprehensive index? **Comments**:	☒ YES ☐ NO
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain:	☒ YES ☐ NO
Controlled substance/Product with abuse potential: Abuse Liability Assessment, including a proposal for scheduling, submitted? Consult sent to the Controlled Substance Staff? **Comments**:	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
BLAs/BLA efficacy supplements only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	 ☐ YES ☐ NO
Patent Information (NDAs/NDA efficacy supplements only)	
Patent information submitted on form FDA 3542a? **Comments**:	☒ YES ☐ NO
Debarment Certification	
Correctly worded Debarment Certification with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.***	☒ YES ☐ NO

Note: *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"* **Comments**:	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
Field Copy Certification: that it is a true copy of the CMC technical section (***applies to paper submissions only***) ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☒ Not Applicable (*electronic submission or no CMC technical section*) ☐ YES ☐ NO
Financial Disclosure	
Financial Disclosure forms included with authorized signature? ***Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.* **Comments**:	☒ YES ☐ NO
Pediatrics	
PREA ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.* Are the required pediatric assessment studies or a full waiver of pediatric studies included? **If no,** is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included? • ***If no, request in 74-day letter.*** • **If yes**, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) **Comments**: Expansion of an indication into a new population is not considered a new indication.	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
BPCA (NDAs/NDA efficacy supplements only):	

Is this submission a complete response to a pediatric Written Request? ***If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).*** **Comments**:	☐ YES ☒ NO
Prescription Labeling	
Check all types of labeling submitted. **Comments**:	☐ **Not applicable** ☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use ☐ MedGuide ☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)
Is electronic Content of Labeling submitted in SPL format? ***If no, request in 74-day letter.*** **Comments**:	☒ YES ☐ NO
Package insert (PI) submitted in PLR format? **If no**, was a waiver or deferral requested before the application was received or in the submission? **If before**, what is the status of the request? ***If no, request in 74-day letter.*** **Comments**:	☒ YES ☐ NO ☐ YES ☐ NO
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? **Comments**:	☐ YES ☒ NO
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (*send WORD version if available*) **Comments**:	☐ Not Applicable ☐ YES ☒ NO
REMS consulted to OSE/DRISK? **Comments**:	☐ Not Applicable ☐ YES ☒ NO
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP? **Comments**:	☒ Not Applicable ☐ YES ☐ NO

OTC Labeling	
Check all types of labeling submitted. **Comments**:	☒ **Not Applicable** ☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)
Is electronic content of labeling submitted? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.*** **Comments**:	☐ YES ☐ NO
Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP? **Comments**:	☐ YES ☐ NO
Meeting Minutes/SPA Agreements	
End-of Phase 2 meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments**: check with SC	☒ YES Date(s): ☐ NO
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments**: check with SC	☐ YES Date(s): ☒ NO
Any Special Protocol Assessment (SPA) agreements? ***If yes, distribute letter and/or relevant minutes before filing meeting.*** **Comments**: check with SC	☐ YES Date(s): ☒ NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: 11/7/08

NDA/BLA #: 22-145 SE5-004

PROPRIETARY/ESTABLISHED NAMES: Isentress/Raltegravir Potassium

APPLICANT: Merck

BACKGROUND: To expand the indication for raltegravir to include the treatment of HIV treatment-naïve patients based on the 48 week data from Protocol 021. This study is also submitted to fulfill PMC #6.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Amalia Himaya	Y
	CPMS/TL:	Karen Winestock Vicky Tyson-Medlock	Y
Cross-Discipline Team Leader (CDTL)	Kim Struble		Y
Clinical	Reviewer:	Sarah Connelly	Y
	TL:	Kimberly Struble	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
OSE	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	Sung Rhee	Y
	TL:	Jules O'Rear	N

Clinical Pharmacology	Reviewer:	Derek Zhang	N
	TL:	Kellie Reynolds	N
Biostatistics	Reviewer:	Karen Qi	Y
	TL:	Greg Soon	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Ita Yuen	Y
	TL:	Hanan Ghantous	N
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Allan Fenselau	Y
	TL:	De Swapan	N
Facility (*for BLAs/BLA supplements*)	Reviewer:		
	TL:		
Microbiology, sterility (*for NDAs/NDA efficacy supplements*)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Other reviewers			

OTHER ATTENDEES: Debra Birnkrant, Jeff Murray, Kendall Marcus, and Jaewon Hong

505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO

Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☐ NO ☒ To be determined (TBD)
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**: Acceptable	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☒ YES ☐ NO
• Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☐ YES ☒ NO ☐ Not Applicable ☐ YES ☒ NO
• Sterile product? **If yes**, was Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**)	☐ YES ☒ NO ☐ YES ☐ NO
FACILITY (BLAs only)	☒ Not Applicable

Comments:	☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT
Signatory Authority: Amalia C. Himaya **GRMP Timeline Milestones**: Filing Meeting by 11/10/08; Filing Letter issued 11/18/08. PMC/Labeling discussions with sponsor on 6/12/09. **Comments**:

	REGULATORY CONCLUSIONS/DEFICIENCIES
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): ☒ Standard Review ☐ Priority Review

	ACTIONS ITEMS
☐	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
☐	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If BLA or priority review NDA, send 60-day letter.
☒	Send review issues/no review issues by day 74
☐	Other

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amalia Himaya

12/1/2008 02:50:57 PM

CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22 – 145/S004

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-145 SUPPL # 004 HFD # 530

Trade Name Isentress

Generic Name Raltegravir Potassium

Applicant Name Merck

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE5

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 22145 000 (Accelerated approval on treatment-experienced adult subjects)

NDA# 22145 SE7-001 (48-wk data on treatment-experienced adult subjects)

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☒ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

This efficacy supplement (SE5-004) contains Protocol 021, a 48-week study in treatment-naïve subjects.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 69928	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Amalia Himaya
Title: Regulatory Project Manager
Date: June 25, 2009

Name of Office/Division Director signing form: Debra Birnkrant, M.D.
Title: Director, Division of Antiviral Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Debra Birnkrant
7/8/2009 04:24:57 PM
NDA 22-145

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-145 Supplement Number: 004 NDA Supplement Type (e.g. SE5): SE5

Division Name:DAVP PDUFA Goal Date: 7/26/09 Stamp Date: 9/26/2008

Proprietary Name: Isentress

Established/Generic Name: Raltegravir

Dosage Form: Tablets

Applicant/Sponsor: Merck

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) Treatment of HIV infection in treatment-experienced adult patients
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Treatment of HIV infection in treatment-naïve patients

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue

No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); ☐ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☒ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

☒ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for some or all pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☒ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible[#]	Not meaningful therapeutic benefit[*]	Ineffective or unsafe[†]	Formulation failed[Δ]
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or

existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amalia Himaya

6/25/2009 01:59:14 PM

As required by §306(k)(1) of 21 U.S.C. 335a(k)(1), we hereby certify that, in connection with this application, Merck & Co., Inc did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.

R. A. Fromtling

Robert A. Fromtling, Ph.D.
Director
Worldwide Regulatory Affairs

September 25, 2008
Date

CDocuments and SettingshimayaaDesktopRE NDA 22-145; S-004 Reply to #R10.txt
NDA 22-145; S-004 Reply to #R10From: Fromtling, Robert A.
[robert_fromtling@merck.com]
Sent: Friday, June 26, 2009 11:29 AM
To: Himaya, Amalia
Cc: Fromtling, Robert A.
Subject: RE: NDA 22-145; S-004 Reply to #R10

Amalia,

This is acceptable.

Bob

From: Himaya, Amalia [mailto:Amalia.Himaya@fda.hhs.gov]
Sent: Friday, June 26, 2009 11:22 AM
To: Fromtling, Robert A.
Subject: RE: NDA 22-145; S-004 Reply to #R10

Bob, one minor edit in the Highlights section. Addition of (4) in Contraindications, see red font below. Please let me know if you agree. A response to this email is sufficient and no official submission is needed. The enclosed PI label in the action letter will reflect this change.

---------- CONTRAINDICATIONS----------

None (4)

Amalia

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amalia Himaya

6/26/2009 11:58:13 AM

CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

DATE: June 23, 2009

TO: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs

SPONSOR: Merck & Co., Inc.

SUBJECT: NDA 22-145 S-004 Isentress Labeling Comments (Request #R10)

Reference is made to your June 19, 2009 submission to supplement S-004. We agree with the contents of the PI and PPI labels with the exception of the following:

In consultation with FDA's Study Endpoints and Labeling Development (SEALD) team, we propose the following revisions in the PI, under RECENT MAJOR CHANGES of the HIGHLIGHTS section:

1. Please [redacted] (b) (4) replace with "Indication and Usage (1) XX/2009". XX is the month supplement S-004 will be approved.

2. Please replace your [redacted] (b) (4) with "Warnings and Precautions (5.2) – removal XX/2009".

In summary, we propose the RECENT MAJOR CHANGES section be displayed as follows:

Indications And Usage (1)	XX/2009
Dosage And Administration (2)	01/2009
Warnings and Precautions (5.2) – removal	XX/2009

Please provide your response by June 24, 2009. An official submission containing the labels can follow by June 29, 2009. Please feel free to contact me at (301) 796-3391, if you have any questions regarding the contents of this transmission.

{See appended electronic signature page}

Amalia Himaya
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amalia Himaya

6/23/2009 12:59:37 PM

CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-145

Merck & Co., Inc.
Attention: Robert A. Fromtling, Ph.D.
Director, Worldwide Regulatory Affairs
126 E. Lincoln Ave.
P.O. Box 2000, RY33-212
Rahway, New Jersey 07065-0900

Dear Dr. Fromtling:

We refer to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ISENTRESS® (raltegravir potassium) 400 mg tablets.

We have received your submission dated November 13, 2008, reporting on the following postmarketing study commitments, as listed in the October 12, 2007, approval letter:

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

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

We have reviewed your submissions and conclude that the above commitments were fulfilled.

If you have any questions, call Amalia Himaya, Project Manager, at 301-796-3391.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kendall Marcus

6/19/2009 02:32:08 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

DATE: June 15, 2009

TO: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs

SPONSOR: Merck & Co., Inc.

SUBJECT: NDA 22-145 S-004 Isentress Labeling Comments 1 (Request #R9)

Reference is made to your June 12, 2009, submission to supplement S-004. Listed below is our labeling comment on the PI label. This listed comment is not all inclusive as other labeling revisions have been made directly to the PI and PPI labels and will be provided to you via electronic mail. Please review the labels and make note of all the content changes section by section.

- Results from FDA serum lipid-reducing agent use analysis differ from yours. We think subjects on baseline agents were counted twice in your "Through Week 48" analysis if they increased or initiated new agents. Please refer to the attached spreadsheet for FDA listing of subjects on serum lipid-reducing agents at baseline and Week 48, using the CONXCLP dataset limited to C10AA, C10AB, C10AD, C10AX agents in the T_CLASS column and limited to agents initiated prior to Day 378. This analysis results in 6% subjects in each group receiving serum lipid-reducing agents through Week 48.

Please provide your response by June 18, 2009. Please feel free to contact me at (301) 796-3391, if you have any questions regarding the contents of this transmission.

{See appended electronic signature page}

Amalia Himaya
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

23 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amalia Himaya

6/15/2009 10:38:11 PM

CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

DATE: June 2, 2009

TO: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs

SPONSOR: Merck & Co., Inc.

SUBJECT: NDA 22-145 S-004 Isentress Labeling Comments 3 (Request #R8)

Reference is made to your May 8, 2009, and May 15, 2009, submissions to supplement S-004. Listed below are our labeling comments and proposed revisions. Please review the entire label and make note of all the content changes section by section.

PACKAGE INSERT (PI): These listed revisions are not all inclusive as other labeling revisions have been made directly to the label. The PI label will be provided to you via electronic mail.

1. We recognize [redacted] (b) (4) corresponds to the amount of tenofovir disoproxil in a 300 mg tenofovir disoproxil fumarate tablet; however, we believe "tenofovir 300 mg" conveys the more commonly used tenofovir dosage and recommend revising the label accordingly.
2. Section 6.1 **Clinical Trials Experience**, Treatment-Naïve Studies, *Less Common Adverse Reactions* incorporates adverse drug reactions (ADR) occurring "in <2% of subjects receiving ISENTRESS + emtricitabine (+) tenofovir. These events have been included because of their seriousness, increased frequency on ISENTRESS compared with efavirenz or investigator's assessment of potential causal relationship". Please provide your rationale for inclusion of the proposed selected terms in this section. With the exception of abnormal dreams and fatigue, the Division does not agree with the addition of the following proposed terms because they do not satisfy the definition of increased raltegravir frequency or seriousness.

   Abnormal Dreams: The occurrence of abnormal dreams in the common AE and moderate-severe ADR analysis is greater in efavirenz-treated subjects; however, both severe events occurred in the raltegravir group. There are no SAEs or study medication discontinuations due to abnormal dreams.

   Fatigue: Fatigue occurs in approximately twice as many efavirenz-treated subjects as in raltegravir-treated subjects in the common AE and moderate-severe ADR analyses. All severe events occur in the raltegravir group (N=3), including one subject

with an active history of fatigue. There are no fatigue-related SAEs and no raltegravir discontinuations due to fatigue.

AN 23370 On Day 76 the term (b) (4) was assigned to describe *insomnia and vivid dreams* considered related to study medication. Of note, the reported term for this event is "Physiological malfunction arising from mental factors".

AN 23197 On Day 87 the subject experienced (b) (4) considered related to study medication. This AE was associated with *dizziness, headache, memory impairment, anxiety and confusion*.

AN 20026 On Day 268 the subject experienced (b) (4) including *depersonalization, vertigo, memory disorder, irritability and nightmares*.

In addition, because *immune reconstitution syndrome* is listed in the Section 5.1 **Warnings and Precautions**, we do not recommend inclusion in Section (b) (4)

3. In Table 3: Lipid Values, Mean Change from Baseline, Protocol 021 please round the lipid values and percentages to the nearest whole number. In addition, we recommend changing the last sentence to the following: "At baseline, serum lipid-reducing agents were used in 5% subjects in the ISENTRESS group and 3% in the efavirenz group. Through Week 48, serum lipid-reducing agents were used in 6% in the ISENTRESS group and 6% in the efavirenz group."
4. We have discussed the rationale for the (b) (4) and remain opposed to its inclusion in the label. The Division of Drug Marketing, Advertising, and Communications (DDMAC) recommends deletion of the entire paragraph with the rational (b) (4) isted occu (b) (4) in the raltegravir group compared to the efavirenz group when, for example, depression occurs with similar frequency at

Weeks 8 and 48 and drug-related insomnia actually occurs more frequently in the raltegravir group. Furthermore, we do not think raltegravir's (b) (4)

5. As previously noted, several subjects were incorrectly stratified by hepatitis co-infection status. Please remove (b) (4) from Table 8: Baseline Characteristics (b) (4)
6. In Section 14, we do not agree with inclusion of the following sentence: (b) (4)

   We believe the treatment difference and confidence intervals in Table 9: Outcomes by Treatment Group through Week 48 provide adequate comparison information.

PATIENT PACKAGE INSERT (PPI): Listed below are DAVP recommendations in consultation with DDMAC.

7. **What is ISENTRESS?** Statements that ISENTRESS (b) (4) are promotional in nature and may be used in promotional material to misleadingly suggest a guarantee of efficacy, e.g., that treatment with ISENTRESS will (b) (4) Please revise the text, for example "ISENTRESS is an anti-HIV (antiretroviral) medicine used for the treatment of HIV".
8. **How does ISENTRESS work?**
   - Recommend retention of the word "may" due to concern this statement will be used in promotional material to imply a guarantee of efficacy.
   - Recommend deletion of the phrase (b) (4)
9. **What are the possible side effects of ISENTRESS?**
   - *A condition called Immune Reconstitution Syndrome can happen in some patients with advanced HIV infection (AIDS) when combination antiretroviral treatment is started. Signs and symptoms of inflammation from opportunistic infections that a person has or had may occur as the medicines work to* (b) (4) *Call your doctor right away if you notice any signs or symptoms of an infection after starting ISENTRESS with other anti-HIV medicines.*

   The underlined statement is promotional in nature and may be used in promotional material to misleadingly suggest a guarantee of efficacy and/or overstate the efficacy, e.g., that treatment with ISENTRESS wil (b) (4) Please revise the underlined text.

   - *Contact your doctor promptly if you experience unexplained muscle pain, tenderness, or weakness while taking ISENTRESS.*

   Recommend adding "This is because on rare occasions, muscle problems can be serious, including muscle breakdown resulting in kidney damage." This statement is similar to the PPI for Vytorin.

- *Tell your doctor if you have any side effect that bothers you or* [redacted] (b) (4)

This statement minimizes risks associated with ISENTRESS because it implies patients should expect their side effects to [redacted] (b) (4) Please revise this phrase and also make "side effect" plural.

Please provide your response by June 12, 2009. Please feel free to contact me at (301) 796-3391, if you have any questions regarding the contents of this transmission.

{*See appended electronic signature page}*

_____

Amalia Himaya
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

19 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amalia Himaya
6/2/2009 04:29:35 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

Date: May 4, 2009

TO: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs

SPONSOR: Merck & Co., Inc.

SUBJECT: NDA 22-145 S-004 (Request #R7)

Reference is made to our April 23, 2009, correspondence (Request #R5) mentioning our labeling comments on the clinical trials section tables are forthcoming. Listed below are our labeling comments on the clinical trials section tables. These listed revisions are not all inclusive as other labeling revisions have been made directly to **Section 14** of the label. The PLR label will be provided to you via electronic mail. Please review Section 14 of the label and make note of all the content changes since May 1, 2009.

We do not agree with some results in Tables 10, 11, and 13 and have made revisions to these tables in the enclosed label based on the FDA results. For your references, we are also sending the SAS datasets including our results for TLOVR and changed from baseline in HIV-1 RNA at Week 48 (log_{10} copies/mL) via electronic mail. The following factors may have resulted in discrepancies between your and FDA's results from the TLOVR analysis and change from baseline in HIV DNA at Week 48 in log_{10} copies/mL

1. In Protocol 018 and 019, no subjects were supposed to meet the criteria for "never suppressed through Week 48 and on study at Week 48" and "non-responders by Week 48" simultaneously. If a subject was switched to open-label raltegravir before Week 48 and never had HIV RNA suppressed, then the subject should be included in "non-responders by Week 48" only.

2. Similar to Comment 1, in all three studies, there was supposed to be only one reason for each of the subjects discontinued study drug. If a subject discontinued from the study due to multiple reasons, then the subject should be classified into the event occurred first except for death. If a subject died within 30 days after withdrawing from the study, the reason the subject discontinued from the study should be regarded as due to death. If multiple events occurred simultaneously that caused the subject to discontinue from the study drug, then the subject should be included in the category for the most severe event.

3. We used the middle time point between two consecutive scheduled visits as the dividing point for the window of a visit. For example, the visit window for Week 48 should be between Day 309 (Week 44) to Day 378 (Week 54), and the HIV RNA level measured in this time period should be considered as that for Week 48. If there were multiple measurements during the period, then the one closest to the targeted day should be used, such as Day 336 for Week 48.

4. For change from baseline in HIV RNA at Week 48, the following approach was used to impute the missing data. If a subject did not have HIV RNA value at Week 48, but had one at Week 60, then the one at Week 60 was used to impute the missing measurement at Week 48. If HIV RNA at Week 60 was missing as well, then Week 40 RNA level was carried forwards to Week 48. If a subject did not have data at Weeks 40, 48 or 60, then the subject was regarded to have missing data at Week 48 and the change from baseline in HIV RNA at Week 48 was considered as 0.

If possible, please provide your response with the other labeling comments due May 7, 2009. Otherwise, please provide your response no later than May 15, 2009. Please feel free to contact me at (301) 796-3391 if you have any questions regarding the contents of this transmission.

{*see appended electronic signature page*}

_____

Amalia Himaya
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

22 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amalia Himaya
5/4/2009 02:52:44 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

Date: April 30, 2009

TO: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs

SPONSOR: Merck & Co., Inc.

SUBJECT: NDA 22-145 (Original)
NDA 22-145 S-004 (Request #R6)

A. Reference is made to your March 18, 2009 electronic mail correspondence regarding your plan to submit source data in the IMPAACT format for your pediatric program. Please submit your reply to your original application dated April 13, 2007. We have the following comments.

1. Please ensure a data define pdf document will be included to define the "STATUS" column and other variables.
2. The following items are not included or are not obvious from the submitted dataset: verbatim adverse event term, adverse event grades, serious adverse events, discontinuation and/or treatment interruption due to adverse events, drug- relatedness, categorization of AIDS-defining conditions. Please ensure each of these variables are clearly defined and included in submitted safety datasets.
3. Please provide the coding system used to determine the "DIAGSP" terms.

B. Reference is made to your S-004 supplement. **Please submit your reply to this supplement by May 7, 2009** and label this as response to Request #R6. We have the following comment.

> The DISPOS, DEMODATA and SPATSTT datasets include information regarding Protocol 021 subject disposition; however the actual trial discontinuation date/day is not clear. For comparison purposes, please refer to the attachment displaying these terms in one table to illustrate the different values with FDA_TRL_DAYS defined by DISC_DT - RAND_DT. Please explain the differences between "REL_DY" in the DISPOS, "DISC_DT", "TRL_DAYS", "TRT_DAYS" in the DEMODATA, and "VT_DT" in the SPATSTT datasets, respectively, and provide the actual date and day of trial discontinuation to assist completion of our Week 48 Disposition table. Of note, we used Day 378 as the outer cut-off to define Week 48.

Please feel free to contact me at (301) 796-3391 if you have any questions regarding the contents of this transmission.

{*see appended electronic signature page*}

_____

Amalia Himaya
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amalia Himaya
4/30/2009 10:53:53 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

DATE: April 23, 2009

TO: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs

SPONSOR: Merck & Co., Inc.

SUBJECT: NDA 22-145 S-004 Isentress Labeling Comments 1 (Request #R5)

Reference is made to your February 24, 2009, and April 10, 2009, submissions to supplement S-004. Listed below are our labeling comments and proposed revisions. These listed revisions are not all inclusive as other labeling revisions have been made directly to the label. The PLR label will be provided to you via electronic mail. Please review the entire PLR label and make note of all the content changes section by section. Please note our comments on the clinical trials section tables are forthcoming.

1. For future label modifications, please consult other antiretroviral product labels for general safety and statistical formats. In addition, please ensure consistency between sections in your own labels (e.g. treatment-experienced and treatment-naïve populations). If alternative data presentations are proposed, please submit a rationale for the alternative format.

2. We recommend combining treatment-experienced and treatment-naïve adverse reaction information into a single bullet point in the Highlights.

3. We do not agree with the underlined phrase in the following statement: The safety and (b) (4) ISENTRESS have not been established in pediatric patients less than 16 years old. In Protocol 021 subjects were required to be ≥18 years old and in Protocols 018 and 019 only five subjects were less than 18 years old. Therefore, we do not think there is enough data in the clinical trials to support this INDICATIONS AND USAGE modification. In addition, we recommend removing the phrase "less than 16 years of age" from Section 8.4 Use in Specific Populations, *Pediatric Use* and from the PPI.

4. Please change (b) (4) to the generic name throughout the label.

5. In Sections 6 and 14, please place the (b) (4)

6. In Sections 6.1 and Table 5, we do not agree wit [redacted] (b) (4)

7. Please revise Table 3 to be consistent with the treatment-experienced adverse drug reactions (ADR) table. Using the definition of clinical ADRs of moderate to severe intensity occurring in ≥2% of treatment-naïve subjects treated with ISENTRESS and occurring at a higher rate than efavirenz, only insomnia remains.

8. We do not agree with inclusion o [redacted] (b) (4)

9. In Table 5, please remove the [redacted] (b) (4) and revise the table format to be consistent with the REYATAZ label. Please clarify if subjects initiating or increasing serum lipid-reducing agents were censored in the analysis. In each treatment group, the number of subjects on serum lipid-reducing agents at baseline and through Week 48 should be included as a table footnote. In addition, we do not agree with inclusion of the text following Table 5 because Protocol 021 was not powered to detect lipid changes.

10. Please update the PPI to reflect labeling changes.

11. We do not agree with [redacted] (b) (4)
A relatively small number of subjects received the marketed raltegravir dose and the data does not provide additional information to what is reported from the Phase 3 trials.

12. Review of postmarketing reports supports addition of the following terms to Section 6.2: (1) anxiety and paranoia under *Psychiatric Disorders* and (2) angioedema under *Skin and Subcutaneous Tissue Disorders*. In addition, please update the PPI accordingly.

13. We recommend the addition of CYP1A2 and CYP2B6 to the list of enzymes that raltegravir does not induce (Section 7.1), based on our review of your November 13, 2008, submission containing the final study report for in vitro study PK011 in fulfillment of postmarketing commitment 14. Also in Section 7.1, we recommend the addition of methadone to the list of drugs that raltegravir does not affect, based on the results of drug interaction study 030 submitted under IND 69,928 on March 11, 2009.

14. In Table 12, we recognize the removal of those subjects *stratified* as having hepatitis co-infection. Please revise Table 12 to include subjects with *baseline* HBV and/or HCV co-infection.

15. We do not agree with [redacted] (b) (4) as this is not consistent with other antiretroviral drug labels.

16. Please comment when the Protocol 032 and 033 data will be submitted.

Please provide your response by May 7, 2009. Please feel free to contact me at (301) 796-3391, if you have any questions regarding the contents of this transmission.

{See appended electronic signature page}

_____

Amalia Himaya
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

21 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amalia Himaya

4/23/2009 11:07:20 AM

CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

Date: March 13, 2009

TO: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs

SPONSOR: Merck & Co., Inc.

SUBJECT: NDA 22-145 S-001 and S-004 TLOVR Request (Request #R4)

Reference is made to your electronic mail correspondence received on March 11, 2009, regarding the FDA's Information Request dated March 9, 2009, detailing the TLOVR algorithm to use in updating the label.

Merck Proposal: Based on the nature/complexity of this request, we will not be able to perform the necessary programming and validation by March 23 as requested by #R4. After discussion with our programming team, we believe that we can submit a response to this request by 17 April. Please note that this request will have an impact on the recently submitted updated labels for both the 48-week treatment-experienced as well as the 48-week treatment naive submissions. Once these table updates are made by MRL we propose to provide these updates in our response in addition to the specified tables requested in #R4.

FDA Response to Proposal
Please provide the requested information by April 10, 2009. We are scheduled to have our first labeling meeting on April 14, 2009.

Merck Question 1: Is FDA asking MRL to use the protocol definition here for 2c in Table A? Note, this would deviate from section 1 in #R4 regarding the definition of a non-responder. If yes, we note that there will be overlap between 2a and 2c which would not comply with the FDA's request that only one patient be classified into only one of the categories in Table A.

Merck Question 2: If not, please advise. Please confirm whether patients could be counted in both 2a and 2c.

FDA responses to Questions 1 and 2
We still request only one patient be classified into only one of the categories in Table A. If there is any overlap between 2a and 2c in Table A, then 2a takes the priority. Please note that 2c does not apply to Protocol 021.

Merck Question 3: Same applies as in Table B footnote 1: the text also uses >400 copies/mL as a criterion, please confirm whether or not the definition should be based on >50 copies/mL as this would then be consistent with the row labeled "Virologic failure (<50 copies/mL)". Otherwise, please advise.

FDA responses to Question 3

The definition of non-responders by Week 16 should be the same as that in Protocols 018 and 019, which used >400 copies/mL as a criterion. Additionally, in Table B, we decide to put "Never suppressed through Week 48 and on study at Week 48" and "Non-responders by Week 16" together. Please refer to the revised Table B in the appendix for the details. Again, please note that "Non-responders by Week 16" does not apply to Protocol 021.

Merck Question 4: Table deliverables we anticipate from this request are: Label Table 10, 11 and 13; Table A for P018/019 and for P021. Please confirm only Table A, based on virologic failure definition of >50 copies/mL, is needed.

FDA responses to Question 4

Please perform the analyses based on virologic failure definition of both >50 copies/mL and >400 copies/mL for Table A.

Appendix

Table B. Summary of Study Outcomes through Week 48 (randomized and treated)

Outcomes	Study Regimen [2] (N=) n %	Control [2] (N=) n %
Percent of patients with HIV RNA < 50 copies/mL		
Percent of patients with HIV RNA < 400 copies/mL		
Virologic failure (<50 copies/mL)		
Never suppressed through Week 48 or non-responders by Week 16[1]		
Rebound		
Death		
Discontinued study drug		
Clinical AE		
Laboratory AE		
Lack of efficacy		
Loss to follow-up		
Consent withdrawn		
Protocol violation		
Other		

1 The non-responders by Week 16 was defined by the protocol as those who did not achieve > 1.0 log10 HIV-1 RNA reduction and <400 HIV-1 RNA copies/mL by Week 16.
2 Replace with actual regimens. For example, "raltegravir" ,"efavirenz" or "placebo".

Please submit this information to your supplemental application S-004. Please feel free to contact me at (301) 796-3391 if you have any questions regarding the contents of this transmission.

{see appended electronic signature page}

_____

Amalia Himaya
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amalia Himaya

3/13/2009 06:38:29 PM

CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

Date: March 9, 2009

TO: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs

SPONSOR: Merck & Co., Inc.

SUBJECT: NDA 22-145 S-001 and S-004 TLOVR Request (Request #R4)

Based on our review of the data, Tables 10 and 13 in the label for the efficacy outcomes at Week 48 for Protocols 018, 019 and 021 are not based on the TLOVR algorithm. Please use the following TLOVR algorithm (Sections 1 and 2 below) to obtain the efficacy outcomes by Week 48 for HIV RNA level LOQ=400 copies/mL and LOQ=50 copies/mL respectively. Please first summarize the TLOVR results as shown in Table A in Section 3 for each study and then generate the efficacy tables shown in the label based on Table A. Also, please use Table B in Section 4 as the template for the efficacy tables presented in the label. Of note, according to the TLOVR algorithm, each patient should be classified into only one of the categories under the column of outcomes in Table A.

Also, please update the subgroup analysis results for the percentage of subjects with HIV RNA less than 50 copies/mL and the percentage of subjects with HIV RNA less than 400 copies/mL at Week 48 for Studies 018 and 019 displayed in Table 11 in the label based on the results from TLOVR.

Please submit the tables and corresponding datasets.

Section 1. Definitions for a Non-responder (failure)

For each visit, a subject with the following events prior to or at this visit will be considered as a non-responder or failure for that visit (see Section 2) if any of the follow occurs:

a) Death
b) Permanent discontinuation of the study drug or Loss to follow-up
c) Introducing a new drug to the regimen
d) Have not achieved <LOQ that was confirmed later or achieved confirmed <LOQ status but rebounded (i.e., two consecutive ≥LOQ copies/mL (the latter one possibly after the visit of interest) or one ≥LOQ copies/mL for the last available visit).

From the above definitions for a non-responder or failure, a subject who is not a non-responder or failure will be regarded as a responder. In other words, responders are those who had achieved viral load <LOQ that is confirmed later prior to or at the visit of interest, but had not yet lost the virological response defined by the **TLOVR** algorithm below.

Section 2. Time to Loss-of-Virologic-Response (TLOVR) Algorithm

For studies with at least 48 weeks virologic data, one analysis that computes time to virologic failure should follow the algorithm below.

1) For 2) and 3) below, discard all visits with no data. In what follows, a visit means a visit with an observed viral load. Viral load data from all available visits, including off-schedule visits and post Week 48 visits, should be included for the calculation.

2) If a subject had never achieved confirmed HIV RNA levels below the assay limit (on two consecutive visits) before the following events, then this subject will be considered to have failed at time 0:
   a) Death
   b) Permanent discontinuation of the study drug or loss to follow-up
   c) Introduction of a new anti-retroviral drug to the regimen
      With FDA agreement at design stage, exceptions may be made for certain background drug changes where the reason for the change is due to either toxicity or intolerance that can be clearly attributed to the background drug, but not the study drug or its control. Such exceptions should be incorporated into the protocol.
   d) Last available visit.

3) For all subjects who had confirmed HIV RNA levels below an assay limit, i.e., on two consecutive visits below assay limit, the time of failure is the earliest time when a specific event had occurred. Those events are modifications in 4) and are listed below:
   a) Death
   b) Permanent discontinuation of the study drug or loss to follow-up
   c) The event as described in 2c
   d) Confirmed HIV RNA levels above or equal to an assay limit, which are defined as HIV RNA levels from two consecutive visits are greater than or equal to an assay limit or one visit greater than or equal to an assay limit followed by Permanent discontinuation of the study drug or loss to follow-up.

4) If the time of virologic failure defined above is immediately preceded by a single missing scheduled visit or multiple consecutive missing scheduled visits, then the time of virologic failure is replaced by the first time of such missing visits.

   For open-label studies, or studies that blinding is difficult to maintain due to regimen-specific observable events (for example rash, headache, diarrhea, etc.), algorithms that incorporate other ways of handling missing data or treatment changes may be used for additional sensitivity analyses.

   For example, sponsors should perform analyses that explore the sensitivity of the results to potential biases related to such trials. One such analysis should treat all subjects who meet the protocol-defined criteria for treatment changes (for example, protocol defined virological failure, insufficient viral load response, immunologic failure, disease progression, etc.) as failures, while the non protocol-specified treatment changes are treated as failures in the study arm, and as censored at the time of change in the control arm.

Section 3. Summary of study outcomes based on TLOVR

Table A below will be used to assist the reviewing and drafting of the label. It is not a proposal for label.

Table A. Summary of Study Outcomes through Week 48 (randomized and treated)

Outcomes	Study Regimen [3] (N=) n %	Control [3] (N=) n %
1. Responder [1]		
2. Virologic failure		
2a. Never suppressed through Week 48 and on study at Week 48		
2b. Rebound		
2c. Non-responders by Week 16[2]		
3. Discontinued study drug or added new drugs before achieving confirmed suppression due to		
3a. Death		
3b. Clinical AE		
3c. Laboratory AE		
3d. Lack of efficacy		
3e. Loss to follow-up		
3f. Consent withdrawn		
3g. Protocol violation		
3h. Other		
4. Discontinued study drug or added new drugs while suppressed due to		
4a. Death		
4b. Clinical AE		
4c. Laboratory AE		
4d. Lack of efficacy		
4e. Loss to follow-up		
4f. Consent withdrawn		
4g. Protocol violation		
4h. Other		

1 P-value= …
2 The non-responders by Week 16 was defined by the protocol as those who did not achieve > 1.0 log10 HIV-1 RNA reduction and <400 HIV-1 RNA copies/mL by Week 16.
3 Replace with actual regimens. For example, “raltegravir”,“efavirenz” or “placebo”.

Section 4. Summary of Study Outcomes in the Label

Please use Table B as the template to summarize the efficacy results for treatment experienced subjects (i.e. Protocols 018 and 019) and treatment-naïve subjects (i.e., Protocol 021) in the label. Please note that the table can be generated based on Table A above.

Table B. Summary of Study Outcomes through Week 48 (randomized and treated)

Outcomes	Study Regimen [2] (N=) n %	Control [2] (N=) n %
Percent of subjects with HIV RNA < 50 copies/mL		
Percent of subjects with HIV RNA < 400 copies/mL		
Virologic failure (<50 copies/mL)		
Never suppressed through Week 48 and on study at Week 48		
Rebound		
Non-responders by Week 16[1]		
Death		
Discontinued study drug		
Clinical AE		
Laboratory AE		
Lack of efficacy		
Loss to follow-up		
Consent withdrawn		
Protocol violation		
Other		

1 The non-responders by Week 16 was defined by the protocol as those who did not achieve > 1.0 log10 HIV-1 RNA reduction and <400 HIV-1 RNA copies/mL by Week 16.
2 Replace with actual regimens. For example, "raltegravir" ,"efavirenz" or "placebo".

Please submit this information to your supplemental application S-004 and provide your response by March 23, 2009. Please feel free to contact me at (301) 796-3391 if you have any questions regarding the contents of this transmission.

{see appended electronic signature page}

Amalia Himaya
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amalia Himaya
3/9/2009 10:19:06 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

Date: February 19, 2009

TO: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs

SPONSOR: Merck & Co., Inc.

SUBJECT: NDA 22-145 S-004 Information Request (Request #R3)

Please submit the following dataset regarding optimized background therapy received in Studies 018 and 019. Below is an example for illustrative purposes. Please respond by March 4, 2009 and submit this to your supplemental application S-004.

Subject ID	Study number	List each approved ARV in each column and indicate if taken as part of OBT – below is just a partial example for illustrative purposes						
		TDF	ABC	DRV	LPV	ATV	TPV	T20
1223	018	Y	Y	Y	N	N	N	Y
2367	019	Y	N	N	Y	N	N	N

Please feel free to contact me at (301) 796-3391 if you have any questions regarding the contents of this transmission.

{*See appended electronic signature page*}

Amalia Himaya
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amalia Himaya

2/19/2009 12:32:38 PM

CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: OMP/DDMAC

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Amalia Himaya/OAP/DAVP 301-796-3391

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
1/30/09		22-145	SE5-004	9/25/08

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Raltegravir (Isentress)	High	Integrase Inhibitor	5/4/09

NAME OF FIRM: Merck, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☒ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: This supplement expands the indication for raltegravir to include HIV treatment-naïve subjects. Please review the package insert (PI) and patient package insert (PPI) for this supplement. DAVP's first labeling meeting for this supplement is on April 14, 2009 and you will be invited to the meeting. We are proposing DDMAC delay the review of the labels until after this meeting so you can have the most recent label revisions.

Labels submitted in September 25, 2008 are available in EDR: \\CDSESUB1\EVSPROD\NDA022145\0094

SIGNATURE OF REQUESTOR
Amalia C.Himaya

METHOD OF DELIVERY (Check one)
☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amalia Himaya

1/30/2009 01:50:20 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

Date: January 26, 2009

TO: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs

SPONSOR: Merck & Co., Inc.

SUBJECT: NDA 22-145 S-005 Information Request (Request #R2)

Clinical:

1. **Table 13: Patient Baseline Characteristics** in the proposed package insert includes subjects with a history of AIDS. Using the preferred term "acquired immunodeficiency syndrome" in the MEDHIST dataset confirms the numbers in Table 13. However, subjects with preferred terms consistent with CDC Category C AIDS defining conditions are not included. Attached is an excel file with results from our analysis using the MEDHIST dataset. Of note, subject AN 23302 has the REPTTERM "pneumonia recurrent". Please address (1) why these subjects are not included as having a history of AIDS and (2) how the diagnosis of "acquired immunodeficiency syndrome" was applied. If you agree these additional subjects should be included, please update Table 13 accordingly.

PREFTERM	TREATMNT	AN
Histoplasmosis	Efavirenz 600 mg q.h.s.	23237
Histoplasmosis disseminated	Efavirenz 600 mg q.h.s.	23237
Kaposi's sarcoma AIDS related	Efavirenz 600 mg q.h.s.	23211
		23230
		23257
		23336
	MK-0518 400 mg b.i.d.	23236
		24745
Oesophageal candidiasis	Efavirenz 600 mg q.h.s.	23286
		23380
		23450
	MK-0518 400 mg b.i.d.	20100
		23205
		23212
		23507
Pneumocystis jiroveci pneumonia	Efavirenz 600 mg q.h.s.	20046
		20081
		23207
		23339

		23355
		23381
		23415
		23500
	MK-0518 400 mg b.i.d.	23206
		23261
		23345
		23405
		23406
Pneumonia	Efavirenz 600 mg q.h.s.	23302

2. **Table 13's** inclusion of subjects stratified as Hepatitis B or C Positive who are not actually coinfected is misleading. In addition, inclusion of subject AN 23202 as >50,000 copies/mL is also misleading. Therefore, we recommend removal of the "Stratum" categories. Please revise this table to include only subjects with (+)hepatitis B surface antigen and/or (+)hepatitis C PCR. In addition, we recommend inclusion of subject AN 24742 due to (+)HCV antibody and history of hepatitis C. Please ensure this same hepatitis group is the group used in the *Patients Co-Infected with Hepatitis B and/or Hepatitis C Virus* section and update this section accordingly.

3. Please update the proposed label to include drug-related adverse reaction of moderate to severe intensity analyses limited to Week 48 and related to blinded or combination therapy.

Statistical:

For efficacy endpoints of "Subjects with HIV RNA less than 50 copies/mL", "Subjects with HIV RNA less than 400 copies/mL", and "Mean CD4 cell count change from baseline (cells/mm3)" in Table 14: Outcomes by Treatment Group through Week 48:

4. We recommend using the proportion of subjects with HIV RNA less than 50 copies/mL and the proportion of subjects with HIV RNA less than 400 copies/mL at Week 48 based on the TLOVR algorithm. Please also provide the corresponding datasets.

5. For change from baseline in CD4 counts, please use the results based on the following algorithm.

If the subject discontinued from the study or study medication for any reason before Week 48, then the subject was considered having no change from baseline in CD4 at Week 48 (i.e., baseline was carried forward). Otherwise, if the measurement at a visit was missing and the one at the next visit was available, then the one at the next visit was used; and if the one at the next visit was missing as well, then the one at the previous visit was carried forward to Week 48. For example, if a patient did not have CD4 count at Week 48, but had one at Week 60, then the one at Week 60 was used to impute the missing measurement at Week 48. If CD4 count at Week 60 was missing as well, then Week 40 CD4 level was carried forward to Week 48.

Please provide your response by February 2, 2009 and feel free to contact me at (301) 796-3391 if you have any questions regarding the contents of this transmission.

{*See appended electronic signature page}*

Amalia Himaya
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amalia Himaya

1/26/2009 04:37:34 PM

CSO

DSI CONSULT: Request for Clinical Inspections

Date: December 18, 2009

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Anthoine El Hage, Reviewer, GCP1
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: *Sarah Connelly/Medical Officer/HFD-530*
From: *Amalia Himaya, Regulatory Project Manager, HFD-530*

Subject: **Request for Clinical Site Inspections**
Isentress (Raltegravir) Tablet

I. General Information

Application#: Supplement # NDA 22-145/S-004
Applicant/ Applicant contact information:
Merck & Co., Inc.
Contact: Robert A. Fromtling, Ph.D.
Director, Worldwide Regulatory Affairs
126 E. Lincoln Avenue
P.O. Box 2000, RY 33-212
Rahway, NJ 07065-0900
Phone Number: 732 594-4809
Fax: 732 594-5235

Drug Proprietary Name: Isentress
NME or Original BLA (Yes/No): No
Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No): No

Proposed Indication(s): Treatment of HIV-1 infection

PDUFA: 7/26/09
Action Goal Date: 7/24/09
Inspection Summary Goal Date: 6/8/09

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site 0001 Berger, Daniel S. Northstar Medical Ctr 2835 N. Sheffield Ave. Ste 500 Chicago, IL 60657 Phone: 773-296-2400 Email: DSBergerMD@aol.com	021	16	Treatment of HIV-1 infection
Site 0015 Pollard, Richard B. UC Davis Medical Ctr 4150 V St., Ste G500 Sacramento, CA 95817 Phone: 916-734-3711 Fax: 916-734-7766 Email: rbpollard@ucdavis.edu	021	14	Treatment of HIV-1 infection

III. Site Selection/Rationale

Rationale for DSI Audits

NDA 22-145/S-004 proposes expansion of the ISENTRESS indication to treatment-naïve HIV-1 infected adult patients. Study results from a single protocol, Protocol 021, are included to support this expanded indication. The two study sites listed above enrolled the second and third highest number of subjects domestically. In addition, site 0001 had four protocol violations and four premature discontinuations. Site 0015 had five premature discontinuations. Therefore, following consultation with Dr. El Hage, these two sites were selected for DSI audit.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- x Enrollment of large numbers of study subjects
- ____ High treatment responders (specify):
- ____ Significant primary efficacy results pertinent to decision-making
- x There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- ____ Other (specify):

IV. Tables of Specific Data to be Verified (if applicable)

Should you require any additional information, please contact *Amalia Himaya, RPM* at *301-796-3391 or Sarah Connelly, Medical Officer* at 301-796-2085.

Concurrence: (as needed)

Kim Struble eso 12/18/08 Medical Team Leader
Sarah Connelly eso 12/17/08 Medical Reviewer
_____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amalia Himaya

12/18/2008 09:04:45 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-145/S-004

Merck & Co., Inc.
Attention: Robert A. Fromtling, Ph.D.
Director, Worldwide Regulatory Affairs
126 E. Lincoln Avenue
P.O. Box 2000, RY 33-212
Rahway, NJ 07065-0900

Dear Dr. Fromtling:

Please refer to your supplemental new drug application dated September 25, 2008, received September 26, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ISENTRESS™ (raltegravir potassium), 400 mg tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is July 26, 2009.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 12, 2009.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

However, we request that you submit the following information:

1. Please address the following discrepancies:

   a. Subject AN 23202 was stratified as >50,000 copies/mL HIV RNA; however, baseline HIV RNA is <50,000 copies/mL.

   b. [redacted] (b) (4)

   Report for Protocol 021 states that three subjects were incorrectly stratified based on hepatitis status (AN 24749, 24752, 24764). In addition, two subjects had (+) hepatitis C antibody without (+) hepatitis C PCR. [redacted] (b) (4) (b) (4)

2. Please submit a laboratory table that includes the following variables, each as separate columns, for Protocol 021 in SAS transport file format. Also, we request submission of the study day (BASEDAY, MAXDAY, etc) in numerical format and in relation to the first of study medication. The study date (BASEDATE, MAXDATE, etc) will be a character variable. See Attachment 1 as an example in Excel spreadsheet.

   Protocol
   AN
   Parameter
   Unit
   BASEVALUE
   BASEVALUE TOXICITY GRADE
   BASEDAY
   BASEDATE
   MAXVALUE
   MAXVALUE TOXICITY GRADE
   MAXDAY
   MAXDATE
   MINVALUE
   MINVALUE TOXICITY GRADE
   MINDAY
   MINDATE
   LASTVALUE
   LASTVALUE TOXICITY GRADE
   LASTDAY
   LASTDATE
   Treatment Arm
   Age
   Sex
   Race

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Amalia Himaya, Regulatory Project Manager, at (301) 301-796-3391.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1	PROTOCOL	AN	TREATMNT	AGE	RACE	GENDER	TREAT_CD	PARAMTER	UNIT	BASEDATE	BASEDAY	BASEVALC	BASEVALN	LASTDATE
2	21	1	MK-0518					APTT	sec	xx/xx/xxxx	xx	xx	xx	xx/xx/xxxx
3	21	1	MK-0518					CD4						
4	21	1	MK-0518					INR						

	O	P	Q	R	S	T	U	V	W	X
1	LASTDAY	LASTVALC	LASTVALN	MAXDATE	MAXDAY	MAXVALUE	MINDATE	MINDAY	MINVALUE	GRADE
2	xx	xx	xx	xx/xx/xxxx	xx	xx	xx/xx/xxxx	xx	xx	
3										
4										

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Debra Birnkrant
11/18/2008 10:54:37 AM
NDA 22-145

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:	FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Paula Gish, Office of Surveillance and Epidemiology/Division of Adverse Events Analysis II	Amalia Himaya RPM, OAP/DAVP/301-796-3391

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
11/12/08		22-145 SE5-004	AERS database	9/26/08

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Isentress (Raltegravir)	High	Antiretroviral systemic/integrase inhibitor	3/23/09

NAME OF FIRM: Merck & Co., Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☒ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☒ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

As requested by Sarah Connelly, Medical Officer, please review the AERS database for the following adverse events occurring with raltegravir use and provide an analysis of pertinent findings.

(1) Stevens Johnson Syndrome and Hypersensitivity
(2) Hepatitis/Hepatic failure/ (b) (4)
(3) Rhabdomyolysis and elevated Creatine Kinase
(4) Depression
(5) (b) (4)
(6) Suicidal Ideation

SIGNATURE OF REQUESTOR Amalia Himaya, RPM	METHOD OF DELIVERY (Check one) ☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amalia Himaya

11/12/2008 04:10:29 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-145/S-004

PRIOR APPROVAL SUPPLEMENT

Merck & Co., Inc.
Attention: Robert A. Fromtling, Ph.D.
Director, Worldwide Regulatory Affairs
126 E. Lincoln Ave.
P.O. Box 2000, RY33-212
Rahway, New Jersey 07065-0900

Dear Dr. Fromtling:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: ISENTRESS™ (raltegravir potassium) tablets

NDA Number: 22-145

Supplement number: S-004

Date of supplement: September 25, 2008

Date of receipt: September 26, 2008

This supplemental application provides for the following changes:

- To expand the indication for raltegravir to include the treatment of HIV treatment naïve patients based on the 48 week data from Protocol 021

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 25, 2008 in accordance with 21 CFR 314.101(a).

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any question, call Amalia Himaya, Regulatory Project Manager, at (301) 796-3391.

Sincerely,

{See appended electronic signature page}

Karen Winestock
Chief, Project Management Staff
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Karen Winestock

10/14/2008 02:55:19 PM