FDA Antiviral Drugs Advisory Committee Meeting

ISENTRESS™ (raltegravir) 400 mg
For Treatment of HIV
(NDA 22-145)

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Briefing Document (Background Package)

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Merck Research Laboratories
Merck & Co., Inc.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADC	AIDS-defining conditions
ADME	Absorption, distribution, metabolism, and excretion
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APR	Antiretroviral Pregnancy Registry
ART	Anti-retroviral therapy
AST	Aspartate aminotransferase
AZT	Zidovudine
BMI	Body mass index
CI	Confidence interval
CIC_{95}	Cell inhibitory concentration
CNS	Central nervous system
CPK	Creatine phosphokinase
DNA	Deoxyribonucleic acid
EAP	Expanded access program
ECG	Electrocardiogram
EFV	Efavirenz
FBS	Fetal bovine serum
FTC	Emtricitabine
GLP	Good laboratory practices
GMR	Geometric mean ratio
GSS	Genotypic sensitivity score
HAART	Highly active antiretroviral therapy
HIV-1	Human Immunodeficiency Virus-1
IRS	Immune Reconstitution Syndrome
IV	Intravenous
MITT	Modified-intention-to-treat
NC=F	Non-completer = Failure
NDA	New Drug Application
NHS	Normal human serum
NNRTIs	Non-nucleoside reverse transcriptase inhibitors
NRTIs	Nucleoside reverse transcriptase inhibitors
OBT	Optimized background therapy
OF	Observed Failure
OLPVF	Open label post virologic failure
PD	Pharmacodynamic
PDLC	Predefined Limits of Change
P-gp	P-glycoprotein
PIs	Protease inhibitors

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS (CONT.)

Abbreviation	Definition
PIC	Preintegration complex
PK	Pharmacokinetics
PND	Postnatal Day
PNW	Postnatal Week
PSS	Phenotypic sensitivity score
PSURs	Periodic Safety Update Reports
PY	Person-years
Q12 hr	Every 12 hours
RMP	Risk management plan
RNA	Ribonucleic acid
SAEs	Serious adverse experiences
SIRs	Standardized incidence rate ratios
SMC	Safety Monitoring Committee
SUR	Safety Update Report
TFV	Tenofovir
TLOVR	Time-to-loss-of-virologic-responses
UGTs	UDP-glucuronosyltransferases
WAES	Worldwide Adverse Event System

1. Summary

There is a clear unmet medical need for antiretroviral agents with novel mechanisms of action to treat patients infected with Human Immunodeficiency Virus-1 (HIV-1) who have few or no remaining treatment options available to them due to infection with HIV resistant to current antiretroviral drug classes. Raltegravir (also known as MK-0518) is the first agent of a new pharmacological class of antiretroviral agents known as integrase inhibitors. Raltegravir has demonstrated potent activity *in vitro* against HIV-1, including HIV-1 variants that are resistant to currently licensed antiretrovirals.

Phase I studies in healthy subjects suggest that raltegravir is generally well tolerated, has a limited propensity for drug-drug interactions, and has pharmacokinetics that support twice daily dosing without regard to food.

Two (2) Phase II dose ranging studies (Protocol 004 and Protocol 005), in HIV-1-infected treatment naïve and in HIV-1 infected highly treatment experienced individuals, were conducted. The treatment naïve study (Protocol 004) demonstrated comparable potent efficacy of raltegravir as compared to an active comparator (both in combination with tenofovir and lamivudine) at 48 weeks across a range of doses (100, 200, 400, and 600 mg b.i.d.). The treatment experienced study (Protocol 005) demonstrated superior potent efficacy of raltegravir as compared to placebo (both in combination with an optimized background therapy [OBT]) at 48 weeks across a range of doses (200, 400, and 600 mg b.i.d.). All doses were generally well tolerated.

Two (2) Phase III studies (Protocol 018 and Protocol 019), which were identical except for the different geographic locations in which they were conducted, have demonstrated that a 400 mg b.i.d. dose of raltegravir in combination with an OBT was generally well tolerated and leads to suppression of HIV RNA levels to <50 copies/mL in ~ 60% of patients at 16- and 24-weeks of therapy in highly treatment experienced HIV-1 infected patients; similar efficacy was observed in subgroup analyses regardless of gender, race, geographic region, or viral sub-type. Placebo plus OBT led to suppression of HIV RNA levels to <50 copies/mL in ~33% of patients. The difference between the raltegravir and OBT versus the placebo plus OBT groups was highly statistically significant.

In both the Phase II studies resistance to raltegravir was generally associated with one of two primary mutations in the HIV integrase gene at codons 155 or 148, respectively. These resistance patterns were also seen in the Phase III studies. The primary mutations at 155 and 148 were generally observed in the context of one or more secondary mutations. The secondary mutations result in a further decrease in susceptibility to raltegravir, although some of these mutations also appear to act as compensatory mutations for viral replication defects.

An analysis of safety data from Phase I, Phase II, and Phase III suggests that raltegravir is generally well tolerated in healthy subjects, in subjects with advanced liver or kidney disease who are not infected with HIV-1, in HIV-1 infected treatment naïve patients, and in an HIV-1 infected population with advanced disease and multiple co-morbid conditions including hepatitis B and/or C virus infection. Raltegravir does not appear to be associated with adverse lipid abnormalities, changes in body fat distribution, or hyperglycemia.

In the data submitted as part of the original New Drug Application (NDA) based on a cut-off date of 13-Dec-06, the rate of malignant neoplasms in patients receiving raltegravir was numerically higher than that in patients receiving comparator regimens. However, in a subsequent update of the malignant neoplasm analyses performed in the Original Application, now with additional patient follow-up through 09-Jul-2007, this difference was not sustained. A comprehensive discussion regarding malignant neoplasms is included. Though available safety data do not suggest an overall increased risk of malignancy with raltegravir, Phase II and Phase III studies are ongoing and a comprehensive surveillance program is proposed for the post-licensure period.

This briefing document provides an overview of the development of raltegravir, including pre-clinical and clinical data, which support the conclusions that raltegravir, 400 mg b.i.d. dosed in combination with an OBT:

- Fulfills an unmet medical need for a novel anti-retroviral therapy (ART) for patients with multi-drug resistant HIV.
- Has significant antiviral activity against multi-drug resistant HIV-1.
- Has a broad spectrum of activity and no cross-resistance to currently licensed ARTs.
- Has demonstrated rapid, potent, and superior antiretroviral efficacy compared to placebo plus OBT in treatment experienced patients in a comprehensive clinical development program.
- Is both efficacious and generally well tolerated in a diverse group of patients representing different genders, races, geographic regions, viral sub-types, and hepatitis B and/or C virus co-infection status.
- Has a favorable risk/benefit profile.

The proposed prescribing indication is:

- Raltegravir is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy.

Given raltegravir's potential to address a serious unmet medical need, FDA granted a fast track, priority review for the original application on 26-Jun-2007.

2. Introduction

Integrase is 1 of 3 HIV-1 enzymes required for viral replication. Integrase catalyzes the stepwise process that results in the integration of the HIV-1 deoxyribonucleic acid (DNA) into the genome of the host cell (Figure 1). Integration is required for stable maintenance of the viral genome as well as efficient viral gene expression.

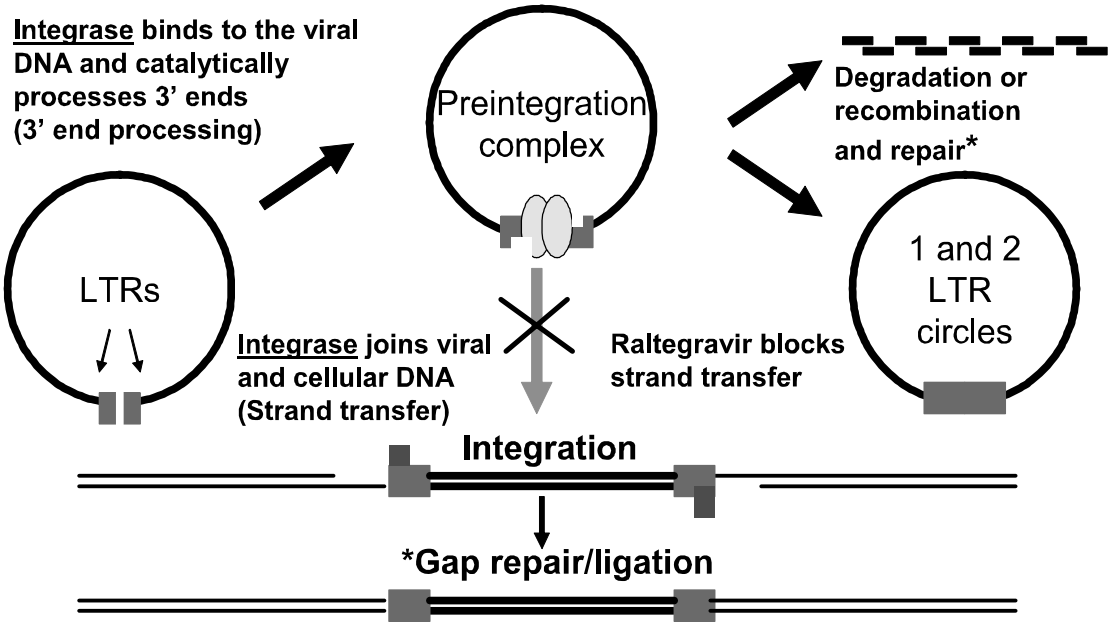
To date, there are no approved drugs targeting the HIV integrase enzyme. A compound targeting HIV integrase would complement currently licensed HIV-1 antiretroviral agents as it would likely show no cross-resistance to agents from other mechanistic classes.

Raltegravir, an HIV integrase inhibitor, was discovered by Merck & Co., Inc. Raltegravir blocks the strand transfer step of integration, thus blocking viral replication. Preclinical data suggested that raltegravir had the promise to be a clinically effective HIV integrase inhibitor with broad activity against circulating variants of HIV-1, including variants with resistance to currently licensed compounds. Laboratory studies demonstrated that HIV-1 viral mutants resistant to raltegravir retained susceptibility to currently licensed agents including efavirenz (EFV), tenofovir (TFV), emtricitabine (FTC), and zidovudine (AZT).

In this briefing document, data are presented that support the proposed indication for the use of raltegravir, 400 mg b.i.d., in treatment experienced HIV-1 infected patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy.

Figure 1

Inhibition of Integrase Strand Transfer



*Cellular functions

3. Microbiology

3.1 Mechanism of Action

Integrase is the only HIV-1 protein known to be required to catalyze each of the specific steps required for integration of the viral DNA into the host cell genome [119; 118], namely assembly with and processing of the HIV-1 DNA followed by strand transfer or joining of the viral and cellular DNAs. Raltegravir inhibits the latter, integrase strand transfer reaction. It has a novel mechanism of action compared with all currently approved antiretroviral agents.

Biochemical studies have shown that raltegravir is highly selective for HIV integrase and suggest the potential for off-target effects is limited. Raltegravir exhibited >1,000-fold selectively for integrase with respect to human DNA polymerases α, β, and γ and showed no significant findings in a screen of 166 assays for cellular enzymes, transporters, and receptors when tested at concentrations of 10 μM or greater.

The mechanism by which raltegravir inhibits HIV-1 replication (see Figure 1) has been studied in cell culture. Normally, after HIV-1 enters a host cell and HIV-1's RNA genome is reverse-transcribed into a linear, double-stranded DNA form, integrase binds to both viral DNA ends and thereby helps to form the "preintegration complex" (PIC). Integrase then cleaves two nucleotides from each 3' DNA end in a step called 3' processing. The PIC migrates into the host cell's nucleus, where integrase binds to the host cell's genomic DNA and then catalyzes the covalent joining, or "strand transfer", of the viral DNA 3' ends to the cell's genomic DNA. The resulting gaps and ragged DNA ends are repaired, probably by host cell enzymes, to yield the fully integrated HIV-1 provirus. Sometimes the HIV-1 DNA fails to become correctly integrated into host cell DNA, and in these cases the HIV-1 DNA is either circularized by host enzymes to form "1-LTR circle" or a "2-LTR circle" or is degraded. In these cases, the viral replication cycle cannot continue because the HIV-1 DNA is shunted into dead-end circular or degraded forms.

Studies using quantitative PCR assays to measure early and late HIV-1 reverse transcriptase products and various unintegrated and integrated forms of HIV-1 DNA support the conclusion that raltegravir inhibits integration. Raltegravir had no significant effect on the appearance of late reverse transcription products when measured at either 6 hours or 48 hours after HIV-1 infection, indicating that raltegravir does not inhibit viral entry or reverse transcription. However, raltegravir significantly inhibited integration of HIV-1 DNA as measured 48 hours post-infection using a quantitative "Alu-LTR" PCR assay, which detects HIV-1 proviruses integrated near the abundant human repetitive DNA sequence Alu [117]. Furthermore, raltegravir promoted a significant increase in the abundance of 2-LTR circular forms of the HIV-1 DNA. 2-LTR circles are known to increase in abundance when integration is prevented due to either genetic ablation [124; 120] or pharmacologic inhibition [120] of integrase. An increase in circular DNA

abundance is therefore considered a surrogate marker for HIV-1 DNA blocked at the point of integration. Taken together, the results of these studies demonstrate that raltegravir does not inhibit viral entry or reverse transcription and support the view that raltegravir's antiviral activity can be directly attributed to inhibiting HIV-1 integrase and preventing integration. Additional evidence for integrase as the physiologic target of raltegravir is provided in Section 3.3, which shows that mutations in integrase acquired either *in vitro* or *in vivo* affect susceptibility to raltegravir.

3.2 Antiviral Activity *in vitro*

Raltegravir was tested for antiviral activity in cell culture against laboratory and primary HIV-1 isolates as well as a laboratory HIV-2 isolate to evaluate its potential for activity across diverse clinical isolated. All antiviral assays were multiple-cycle replication assays. Raltegravir inhibited replication of the laboratory HIV-1 isolate, H9IIIB, in MT4 cells with a 95% cell inhibitory concentration (CIC_{95}) of 18.7 ± 14 nM (n=77) in the presence of 10% fetal bovine serum (FBS). The presence of 50% normal human serum (NHS) reduced the apparent antiviral potency of raltegravir by less than two-fold to 31 ± 20 nM (n=90). However, at the time the clinical development program was ongoing, the pharmacokinetic target was preliminarily determined as a mean raltegravir CIC_{95} derived in 50% NHS of 33 ± 23 nM, and this value is also used in this document.

The 15 primary HIV-1 isolates tested included isolates from six subtypes representing both syncytium-inducing and non-syncytium-inducing isolates. Activity against these isolates in primary human peripheral blood mononuclear cells ranged from 6 to 50 nM (CIC_{95} in 20% FBS). Raltegravir also inhibited replication of HIV-2 in CEMx174 cells (CIC_{95} of 6.3 nM in 10% FBS). Collectively, these studies demonstrate that raltegravir has comparable antiviral activity against diverse HIV-1 isolates and that the addition of 50% NHS only modestly reduces the potency of raltegravir.

Raltegravir, like other antiretroviral agents, is expected to be used in combination with other antiretroviral drugs for treating HIV-1 infection [67]. The potential for interaction between raltegravir and other antiretroviral agents was assessed by evaluating the antiviral activity of raltegravir in combination with each of 18 licensed agents in cell culture. The 18 agents studied included seven NRTIs (nucleoside reverse transcriptase inhibitors: zidovudine, zalcitabine, stavudine, abacavir, tenofovir, didanosine, lamivudine), three NNRTIs (non-nucleoside reverse transcriptase inhibitors: efavirenz, nevirapine, delavirdine), seven PIs (protease inhibitors: indinavir, saquinavir, ritonavir, amprenavir, lopinavir, nelfinavir, atazanavir), and the entry inhibitor enfuvirtide. Depending on concentration, raltegravir was either additive or synergistic with each of these agents. Although this assay was capable of detecting an established antagonistic interaction, such as the known interaction between zidovudine and ribavirin, there was no evidence of antagonistic interactions with raltegravir and any combination examined.

3.3 Resistance *in vitro*

HIV-1 develops resistance to antiretroviral agents through a process of mutation and selection. The potential for HIV-1 to develop resistance to raltegravir was evaluated in cell culture using that laboratory HIV-1 isolate (H9IIIb) in the human T lymphoid H9 cell line. Over the course of several months and increasing concentrations of raltegravir, this selection process produced viral variants that were able to replicate in higher concentrations of raltegravir. Viruses were characterized by amplifying and cloning the integrase gene and determining the nucleotide sequence. These analyses showed that a series of specific amino acid changes occurred over time during culture in increasing raltegravir concentrations. The first change observed was Q148K, which arose during growth in 25 to 50 nM raltegravir and persisted in concentrations up to 500 nM. After passage at 1 μM raltegravir, E138A and G140A were sequentially incorporated and higher concentrations resulted in the acquisition of additional mutations in integrase (e.g., S230R). Thus, the ability of HIV-1 variants to replicate in higher concentrations of raltegravir correlated with the appearance of integrase mutations.

To evaluate the affect of these mutations on raltegravir activity, they were introduced into a wild-type HIV-1 IIIb isolate and the mutant viruses evaluated in a single-cycle HIV-1 infectivity assay. The mutations Q148K, E138A/Q148K, and E138A/G140A/Q148K resulted in average fold-shift in raltegravir IC_{50} of 46-fold, 90-fold, and 508-fold, respectively. These mutations had no effect on sensitivity to reverse transcriptase inhibitors. In addition, all of the mutations resulted in reduced viral replication (infectivity) compared with the wild-type virus. These results demonstrate that integrase mutations which arise during viral growth in the presence of raltegravir confer reduced susceptibility to raltegravir, but these mutations also reduce viral replication.

Viruses containing integrase mutations observed in HIV-1-infected subjects failing treatment regimens including raltegravir were also evaluated (see also Section 7.4). The primary mutations N155H, Q148H, and Q148R each conferred a greater than 10-fold increase in the raltegravir IC_{50}, but did not confer resistance to reverse transcriptase inhibitors. Each of the primary mutations reduced viral replication. In contrast, the mutations E92Q and G140S conferred only 2- to 3-fold resistance to raltegravir, but addition of these mutations to primary mutations at positions 155 or 148 resulted in marked increases in the raltegravir fold-change IC_{50} values. In some cases, the addition of these secondary mutations mitigated the defects in replication observed with primary resistance mutations.

In summary, specific mutations in the HIV-1 integrase gene confer resistance to raltegravir. Single primary mutations (Q148H, Q148R, N155H) can confer 13- to 27-fold resistance but generally result in reduced viral replication. The addition of secondary mutations such as E92Q or G140S augment raltegravir resistance. In some cases, these secondary mutations also improved the replication of viruses with primary resistance mutations.

4. Non-clinical Pharmacology and Toxicology

4.1 Introduction

The pharmacokinetic studies conducted with raltegravir represent a comprehensive evaluation of the absorption, distribution, metabolism, and excretion (ADME) of raltegravir in rats and dogs, the species used for the toxicological evaluation of the compound. The ADME properties of raltegravir have also been studied in humans and interspecies similarities/differences have been addressed. Raltegravir has been evaluated as a substrate and inhibitor of cytochrome P450 enzymes and extensive studies have been conducted to identify the UDP-glucuronosyltransferases (UGTs) responsible for the metabolism of raltegravir. Information from these studies is essential to assess the drug-drug interaction potential of the compound and is useful for interpreting data from clinical studies.

The nonclinical safety pharmacology profile of raltegravir was established using *in vivo* pharmacodynamic animal assays with an emphasis on cardiovascular, respiratory, gastrointestinal, renal, and behavioral functions.

The toxicity profile of raltegravir was assessed in a series of acute toxicity studies in rodents and in subchronic and chronic toxicity studies in rats and dogs of up to 6 and 12 months, respectively. The reproductive and developmental toxicity profile was determined in rats and rabbits. The potential genotoxicity was assessed *in vitro* in bacterial and mammalian cell assays and *in vivo* in the mouse micronucleus assay. Finally, assessment of the carcinogenic potential of raltegravir is ongoing in 2-year rat and mouse carcinogenicity studies conducted at the maximum-tolerated dose in mice and at the maximum feasible dose based on drug formulation in rats.

4.2 Pharmacokinetics

Raltegravir is a low (dog) to intermediate (rat) clearance compound, with a short plasma half-life (≤1.6 hr), and a volume of distribution ranging from ~0.4 to 2 L/kg.

Absorption

After oral dosing, absorption is rapid (T_{max} ≤0.6 hr), nearly complete (≥70%), and bioavailability is high (≥61.6%). The dose-dependence of the pharmacokinetics of raltegravir was also evaluated after single oral dose administration to rats (40 to 240 mg/kg), and dogs (5 to 135 mg/kg). In rats, plasma AUC was nearly linear over the dose range of 40 to 120 mg/kg, but there was no further increase in exposure with increased dose. In dogs, AUC and C_{max} increased proportionally with dose over the dose range of 5 to 45 mg/kg; the increase in either parameter was less than dose-proportional when the dose was increased to 135 mg/kg. Thus, neither absorption nor first-pass extraction was saturable up to doses of 120 and 45 mg/kg in rats and dogs, respectively.

Distribution

Raltegravir shows modest binding (70 to 83%) to plasma proteins in all species examined (mouse, rat, dog, and human). Following oral administration [^{14}C] to rats, radioactivity is distributed rapidly and widely throughout the body and is eliminated within 24 hr. In addition to plasma, the highest concentrations of radioactivity are observed in the gastrointestinal tract and organs of excretion, while the lowest concentration is exhibited by the brain. The drug crosses the rat and rabbit placenta and is excreted extensively in milk of lactating rats.

Metabolism

In preclinical species, raltegravir is cleared primarily by metabolism (glucuronidation), and based on urinary data raltegravir is also eliminated principally by metabolism in humans. The glucuronide derivative of the parent compound is the only metabolite detected in humans and is the major *in vivo* and *in vitro* metabolite in preclinical species. The glucuronidation of raltegravir is catalyzed mainly by UGT1A1 with minor contribution from UGT1A9 and UGT1A3. Therefore, raltegravir may be subject to drug-drug interactions when co-administered with drugs that are known to be UGT1A1 inducers (e.g., rifampin) or inhibitors (e.g., atazanavir, an HIV-protease inhibitor). However, raltegravir is not likely to affect the metabolic clearance of drugs metabolized by UGT1A1 given its low UGT1A1 inhibitory and induction potential. Since raltegravir is neither a substrate nor an inhibitor of cytochrome P450 enzymes and is not an inducer of cytochrome P450 (CYP) 3A4, raltegravir is not expected to exhibit metabolic drug interactions with substrates of cytochromes P450.

Excretion

Recovery of radioactivity in the excreta exceeded 70% following administration of single intravenous (IV) and oral doses of [^{14}C]raltegravir to rats and dogs. The majority of the dose (50% to 74%) was excreted in the feces with the remaining appearing in urine. The high recovery of the dose in feces after IV administration indicates that biliary secretion is the primary mode of elimination of raltegravir-related radioactivity consistent with results observed in bile-duct cannulated rats.

4.3 Safety Pharmacology

Raltegravir was studied in a range of tests to assess its potential for effects on cardiovascular/autonomic or respiratory function in anesthetized dogs and renal or gastric acid secretion functional assays in conscious dogs. Raltegravir was also examined in conscious mice to determine its potential effect on gastrointestinal motility to evaluate behavioral and other central nervous system effects. To assess the potential for QTc prolongation, raltegravir was also tested *in vitro* for activity against the human HERG ion channel.

Overall, there were only 2 significant findings in these studies. Raltegravir caused an increase in gastric motility in mice and a slight increase in body temperature in mice. The safety pharmacology studies thus showed that raltegravir has minimal effects on a diverse range of physiological functions including no effect on cardiovascular parameters.

4.4 Toxicology

Raltegravir is not genotoxic in an *in vivo* assay with mouse micronuclei or in a battery of *in vitro* assays in bacteria and mammalian cells designed to detect mutagenicity, direct DNA damage, or clastogenicity.

Acute oral toxicity studies were conducted with raltegravir in mice, rats and dogs to determine the approximate lethal dose and/or to measure toxicokinetics over a broad dose range following administration of a single dose. Acute toxicity (mortality) was only evident in male mice administered raltegravir orally at 2000 mg/kg. Mortality was not evident in female mice or in males at 1500 mg/kg. In dogs, mortality was not seen following up to 1000 mg/kg of a single oral dose.

In a rat 27-week study, raltegravir caused mortality at 600 mg/kg/day that was associated with body weight loss, urine staining and/or decreased food consumption prior to death. Chronic irritation and inflammation of the nose/nasopharynx were also noted. Observations at 120 mg/kg/day were limited to very slight degeneration of the gastric mucosa which was considered to be related to raltegravir causing local irritation of the stomach mucosa. Therefore the no adverse effect level was 120 mg/kg/day which provides an exposure margin of 1.6-fold above the expected exposure of the 400 mg b.i.d. dose in patients.

Oral dog toxicity studies ranged from single dose to 12 months duration. In the 12-month study, systemic exposure to raltegravir was maximized resulting in a safety margin of approximately 9-fold based on AUC values relative the exposure at the 400 mg b.i.d. clinical dose. There were no significant toxicologic observations at these exposures on the chronic dog study. However, when raltegravir was administered intravenously, mortality was observed following a single high dose (400 mg/kg IV) and was likely due to cardiac arrhythmia secondary to the amount of potassium administered (raltegravir is formulated as a potassium salt) as opposed to a direct effect of the raltegravir molecule. The reported maximum concentration of potassium that should be administered intravenously to animals is 0.125 mEq/kg/hour. Therefore 1.25 mEq of potassium administered over the course of 1 hr is the highest recommended dose that can be safely administered to mildly hypokalemic dogs to avoid heart arrhythmias. In an attempt to define the maximum tolerated dose, at 400 mg/kg IV one dog received approximately 8.8 mEq of potassium as a slow bolus; approximately 7 times the recommended safe level. In a subsequent 1 week intravenous study at lower doses, mortality did not occur at exposures approximately 23-fold greater than the AUC and 71-fold greater than the C_{max} [based on the approximate C_{max} ($C_{0.25h}$)] at the 400-mg b.i.d. clinical dose.

Stomach irritation was observed in rats and not in dogs. To compare relative local exposure of raltegravir to the stomach, an oral dose can be normalized to body surface (mg/m^2) in humans and animals. The recommended human dose of raltegravir is 400 mg b.i.d. which equals 532 mg/m^2 (assuming a 60 kg human). In rats, the highest oral dose administered was 600 mg/kg/day or 3,600 mg/m^2 which is 6.7-fold higher than the human dose. In dogs, the highest oral dose tested in the completed 1-year oral toxicity study was 360 mg/kg/day or 7,200 mg/m^2 which is 13.5-fold higher than the clinical oral dose. There was no evidence of gastrointestinal irritation in dogs from this 1-year study. Stomach irritation was observed in rats at 3600 mg/m^2, but not in dogs at 7200 mg/m^2. One potential explanation for this difference is the unique initial location of the gastric irritation in rats within the "nonglandular" mucosa; an anatomic structure unique to rodents and not present in dogs or in humans. In the 5 week rat oral toxicity study, initial stomach irritation was limited to the nonglandular mucosa, whereas following 6 months of dosing the glandular mucosa was also involved. However, in dogs, receiving twice the dose (mg/m^2) and for twice the duration there was no evidence of stomach irritation. These results suggest that there is minimal risk for gastrointestinal irritation in species, including humans, which lack a nonglandular stomach mucosa.

In reproductive toxicity studies, raltegravir did not affect fertility in either male or female rats at 600 mg/kg/day. In a toxicokinetic study in pregnant and lactating rats, raltegravir was shown to cross the placental barrier with fetal exposure values up to 1.5- to 2.5-fold greater than in maternal plasma mean drug concentrations and was also concentrated in milk about 3-fold compared to plasma. In developmental toxicity studies in rats, a slight increase in the incidence of supernumerary ribs relative to control was found at the top dose of 600 mg/kg/day. There were no external or visceral abnormalities and no other fetal or postnatal developmental effects at this dose. Based on these results, the safety margin at the no observed effect level for developmental toxicity is approximately 3.4-fold the AUC at the 400 mg b.i.d. clinical dose. In rabbits no developmental toxicity was found at the maximum dose of 1000 mg/kg/day, resulting in a safety margin of about 3.7-fold relative the AUC in patients at the 400 mg b.i.d. clinical dose.

The potential toxicity of raltegravir on growth and behavior in juvenile rats, including histomorphology, following oral administration from Postnatal Day (PND) 5 to Postnatal Week (PNW) 8 was determined in a range finding and good laboratory practices (GLP) study. Raltegravir was orally administered to juvenile rats at 50, 200, or 600 mg/kg/day from PND 5 to PNW 8. There was no evidence of toxicity based on antemortem parameters of mortality, physical signs, body weights, developmental signs, hematology, serum biochemistry, ophthalmologic examination, behavioral assessments, and reproductive performance, including embryonic/fetal survival. Histomorphologic results in juvenile rats were similar to the stomach irritation effects seen in adult rats.

Raltegravir is cleared primarily by metabolism (glucuronidation), in both preclinical species and in humans. The glucuronide derivative of the parent compound is the only metabolite detected in humans and is the major *in vivo* and *in vitro* metabolite in preclinical species. In rats and dogs exposure to the glucuronide was 3.3-fold and 3.6-fold, respectively, above the projected exposure in patients receiving 400 mg b.i.d. raltegravir.

4.5 Specific Areas of Interest Addressed in the Nonclinical Safety Program

4.5.1 Hepatotoxicity

Liver toxicity was not observed in dogs receiving raltegravir orally for 1 year at exposures up to 9-fold above the exposure of the 400 mg b.i.d. clinical dose. Similarly in rats, liver toxicity was not observed following 6 months of oral dosing at up to 4.8-fold above the exposure of the 400 mg b.i.d. clinical dose.

However, when raltegravir was administered to dogs in high doses as an IV bolus for 7 days at 100 mg/kg (23-fold greater than the AUC and 71-fold greater than the C_{max} at the 400-mg b.i.d. clinical dose), body weight loss, minimal increases in serum urea nitrogen, increases in alanine aminotransferase (ALT) (up to +1967% compared to concurrent control), alkaline phosphatase (ALP) (up to +374% compared to concurrent control), and cholesterol, and very slight, multifocal tubular dilatation in the cortex of the kidneys was observed. There was no histomorphologic change in the liver to correlate with the increases in ALT or ALP. At the no observed effect level, safety margins were 6.5-fold and 24-fold the AUC and C_{max} , respectively of the 400-mg b.i.d. clinical dose.

In conclusion, there was no evidence of hepatotoxicity following oral dosing of raltegravir to dogs for 1 year or rats for 6 months at 9-fold or 4.8-fold above clinical exposure, respectively. Although intravenous dosing resulted in increases in ALT and alkaline phosphatase in dogs, there were no histomorphologic changes in liver tissue which correlated with these liver enzyme elevations. Further, the high C_{max} (71-fold above clinical $C_{max)}$ associated with liver enzyme elevations is not considered to be clinically relevant.

4.5.2 Carcinogenicity

Carcinogenicity studies in mice and rats are currently ongoing. The in-life phase of these studies is scheduled to be completed by the end of 2007. The study design and dose selection for these studies were reviewed and approved by the FDA Executive Carcinogenicity Assessment Committee. As noted in Section 4.4, raltegravir was negative in all genetic toxicology studies.

In rats, doses of 50, 150, and 300 mg/kg/day in males and 50, 300 and 600 mg/kg/day in females were selected for the carcinogenicity study. The chronic irritation and inflammation of the nose/nasopharynx observed in the 27-week oral toxicity study in rats has also been observed in early death rats on this ongoing 105-week carcinogenicity study. Histomorphologic changes consistent with drug irritation to the nose/nasopharynx

include chronic inflammation and epithelial hyperplasia and metaplasia. Additionally, in the rat, 3 squamous cell carcinomas of the nose/nasopharynx were observed in high dose females and one chondrosarcoma was observed in one mid dose male rat. These neoplasms are considered to represent the expected consequence of chronic irritation and inflammation. Since these neoplasms likely resulted from continuous local deposition of the drug formulation on the nasal mucosa, the relevance of this observation to oral dosing in patients is expected to be minimal. A 26-week toxicokinetic study in rats was conducted in parallel with the ongoing main carcinogenicity study. Results from this study indicate that at 300-600 mg/kg/day in females and 150 to 300 mg/kg/day in males, systemic exposure is approximately 10.3-fold greater (females) or 1.7-fold greater (males) the AUC at the 400-mg b.i.d. clinical dose.

In mice, doses of 50, 250, and 400 mg/kg/day in females and 50, 100 and 250 mg/kg/day in males were selected for the carcinogenicity study. The dose selection was based on a 14 week study where mortality was evident at ≥500 mg/kg/day. Additionally, physical signs, decreases in body weight gains and histomorphologic changes in the stomach and esophagus were seen at 500 mg/kg/day. No neoplasms of the nose or nasopharynx have been observed in the ongoing mouse carcinogenicity study. However histomorphologic changes of chronic irritation and inflammation in the nose and nasopharynx, similar to the rat, have been observed. A 27-week toxicokinetic study in mice was conducted in parallel with the ongoing main carcinogenicity study. Results from this study indicate that at the high dose, 400 mg/kg/day in females and 250 mg/kg/day in males, systemic exposure is approximately 2-fold greater (females) or equal to (males) the AUC at the 400 mg b.i.d. clinical dose.

4.6 Non-clinical Pharmacokinetics and Toxicology Conclusions

Raltegravir is a low (dog) to intermediate (rat) clearance compound, with a short plasma half-life (≤1.6 hr). The glucuronidation of raltegravir is catalyzed mainly by UGT1A1 with minor contribution from UGT1A9 and UGT1A3. Therefore, raltegravir may be subject to drug-drug interactions when co-administered with drugs that are known to be UGT1A1 inducers or inhibitors.

Raltegravir is not genotoxic in a battery of *in vitro* assays in bacteria and mammalian cells or *in vivo* in mice designed to detect mutagenicity, direct DNA damage, or clastogenicity. Raltegravir was well tolerated in chronic toxicology studies in rats and dogs at 1.6-fold and 9-fold above the expected exposure of the 400 mg b.i.d. dose in patients. Therefore, the results of these nonclinical toxicity studies support the registration of raltegravir for the treatment of HIV-1 infection.

5. Clinical Pharmacology

5.1 Clinical Pharmacology Program Overview

Eighteen (18) studies were completed to characterize the safety, tolerability, and pharmacokinetics (PK) of raltegravir. Studies were conducted in healthy subjects (including females, individuals of different races), and in special populations (patients with renal and hepatic insufficiency). Since raltegravir is primarily metabolized by UGT1A1, an additional study is presently ongoing examining the effect of UGT1A1 polymorphisms on raltegravir pharmacokinetics.

Raltegravir was generally well tolerated up to 1600 mg administered as single doses and 800 mg administered every 12 hours (q12 hr) for up to 10 days in healthy subjects. There were no reports of serious clinical or laboratory adverse experiences in the 18 Phase I studies presented. All adverse experiences were generally transient in nature and mild to moderate in intensity. No clinically important abnormalities were noted in routine blood and urine chemistry panels, complete blood count, electrocardiograms, and physical examinations including vital signs. In the thorough QTc study, a single supratherapeutic dose of raltegravir did not prolong the QTc interval; assay sensitivity was verified in this study, as the positive control (moxifloxacin) demonstrated an increase in the placebo-adjusted mean change-from-baseline QTc.

Additional information on the influence of a variety of demographic factors (gender, age, body mass index [BMI], hepatic function, renal function, race, and HIV infection status) were obtained from a composite PK analysis performed using pooled Phase I and Phase II data and from a population PK model-based covariate analysis performed using pooled Phase I and Phase II data (see Section 6.1 for a description of Phase II).

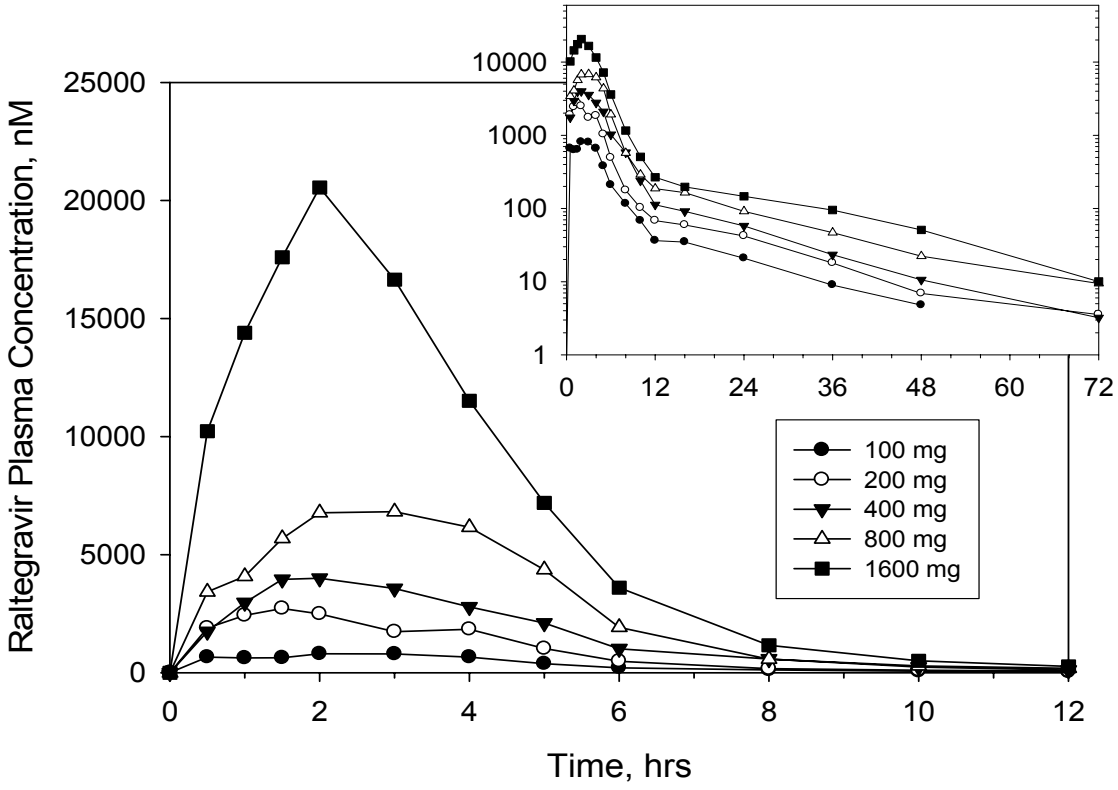
5.2 Pharmacokinetic Profile of Raltegravir

Following fasted oral administration of raltegravir, $AUC_{0-\infty}$ of raltegravir was dose-proportional over the dose range from 100 to 1600 mg, indicating that the plasma clearance and the bioavailability of raltegravir are independent of the dose administered. Plasma C_{max} also increased dose-proportionally over this dose range. Plasma C_{12hr} increased dose-proportionally from 100 to 800 mg, but slightly less than dose-proportionally when assessed over the broader dose range 100 to 1600 mg. The apparent terminal $t_{½}$ of raltegravir is approximately 9 hours with a shorter α-phase half-life (~1 hour) accounting for much of the AUC. Typical concentration-time profiles following single dose administration of raltegravir are shown in Figure 2. This elimination profile coupled with trough concentrations exceeding the pharmacokinetic trough target of 33 nM support the use of a twice-daily dosing regimen for raltegravir. After multiple-dose administration, there was some evidence of higher plasma C_{12hr} values indicating a slight degree of accumulation (20 to 60%). The overall low degree of accumulation resulted in relatively rapid achievement of steady state, demonstrated to be within 2 days.

In patients on 400 mg twice daily monotherapy, raltegravir drug exposures were characterized by a geometric mean AUC_{0-12hr} of 14.3 μM•hr and C_{12hr} of 142 nM.

Figure 2

Arithmetic Mean Raltegravir Plasma Concentration Profiles Following Single-Dose Administration of 100, 200, 400, 800, or 1600 mg to Healthy Male and Female Subjects (N=20; inset: semilog scale)



5.2.1 Absorption

Raltegravir was rapidly absorbed, with a T_{max} of ~3 hours at the dose of 400 mg in the fasted state. A definitive bioavailability study was not conducted; however, ADME results indicate that the absolute bioavailability of raltegravir is at least 32%.

For the final market composition formulation used in all Phase II and Phase III studies, the extent of absorption, as assessed by $AUC_{0-\infty}$, was similar in the fed (high-fat meal) and fasted states, although food appeared to slow the rate and extend the duration of absorption; this resulted in approximately a 34% decrease in C_{max}, an 8.5-fold increase in plasma C_{12hr}, and a 7.3 hr delay in T_{max}. A cross-study comparison of multiple-dose pharmacokinetics suggests that the magnitude of the food effect is diminished following

multiple-dosing and when administered with a standard, rather than high-fat, meal. Food also appears to increase pharmacokinetic variability somewhat over the fasted state and, consequently, a similar lower range of individual C_{12hr} values was observed in the cross-study comparison, suggesting that food does not consistently increase C_{12hr} values. In the Phase II and Phase III development program, raltegravir was dosed without regard to food, and demonstrated comparable potent efficacy in all studies at a range of doses (100-600 mg b.i.d.) that brackets the proposed dose of 400 mg b.i.d. Dose selection is discussed in Section 7.2.2 and was based pharmacokinetic, safety, and efficacy data.

5.2.2 Distribution

Raltegravir is approximately 83% bound to human plasma protein and is minimally distributed into red blood cells (blood-to-plasma partitioning ratio of 0.6). The pharmacokinetics of raltegravir following IV administration were not evaluated and, therefore, the absolute volume of distribution cannot be determined. No data are available regarding human central nervous system (CNS) or brain penetration. Available data in animals suggest a limited penetration of raltegravir to the CNS as tissue-to-plasma radioactivity concentration ratios were 0.016 for brain in the rat tissue distribution studies and a model of brain penetration in wild-type mice with active P-glycoprotein (P-gp) demonstrated brain concentrations below the limit of quantitation. Raltegravir was shown to be a substrate of human P-gp *in vitro*, which may limit CNS penetration in humans as well. Studies in lactating rats determined a milk-to-plasma concentration ratio of ~3, consistent with substantial excretion of raltegravir into milk.

5.2.3 Metabolism and Excretion

Metabolism via glucuronidation is the major pathway of elimination of raltegravir. In humans, raltegravir is metabolized via a single pathway, which results in the formation of the phenolic hydroxyl glucuronide derivative of the parent compound. In a human ADME study, the major circulating entity in plasma was the parent compound (69% of the total drug related material in plasma), while most of the drug related material in urine was accounted for by the glucuronide derivative (72% of the drug related material in urine). In feces, only parent compound was detected, but it is likely that a good fraction of the raltegravir detected in feces is derived from hydrolysis of the glucuronide derivative secreted in bile as observed in preclinical species. Data from *in vitro* studies using human biomaterials indicated that UGT1A1 is the main enzyme responsible for formation of the glucuronide derivative of raltegravir. Therefore, it can be concluded that the major mechanism of clearance of raltegravir in humans is glucuronidation mediated by UGT1A1, with a minor contribution of renal excretion of unchanged parent compound.

The ADME results indicate that renal clearance of unchanged drug is a minor pathway of elimination of raltegravir (9% of total dose). The observed renal clearance values for raltegravir are somewhat higher than the value that would be anticipated based on filtration alone, implying that raltegravir may be actively excreted into urine. Based on the low percent of dose excreted unchanged into urine, however, renal clearance overall and any secretory component to renal clearance plays a minor role in overall elimination of raltegravir. In situations with codosing of drugs that may inhibit renal excretion, clinically meaningful elevated levels of raltegravir are not expected.

The pharmacokinetics of raltegravir following IV administration were not evaluated in this program and, therefore, the total plasma clearance was not determined. Raltegravir has a moderate clearance in preclinical species.

In an ongoing clinical trial, there is no evidence that UGT1A1 polymorphism alters raltegravir pharmacokinetics based on limited data. In a comparison of 7 subjects with *28/*28 genotype to 4 subjects with wild-type genotype, the geometric mean ratio (GMR) (90% confidence interval [CI]) of AUC was 0.94 (0.36, 2.49).

5.3 Comparability Bounds Defining a Clinically Significant Change in Raltegravir Pharmacokinetics

Section 10.1 contains a detailed discussion regarding the rationale for comparability bounds that help to define clinical relevance for drug-drug interactions and for dosing recommendations in special populations. These bounds were based on the safety and efficacy of the combined clinical experience in this application. Only the conclusions are outlined here, to help in understanding the relevance of the Phase I drug-drug interaction studies presented below.

Effects up to a 2-fold increase in exposure (AUC) and less than a 60% decrease (equivalent to GMR of 0.4) in trough concentration (C_{12hr}) were considered to be not clinically relevant based on available clinical experience from Phase I and Phase II studies with regard to safety and efficacy (see Section 10.1).

5.4 Effect of Demographic Factors on Raltegravir Pharmacokinetics

Effects of intrinsic and extrinsic demographic factors on the pharmacokinetics of raltegravir were evaluated. Results from the analyses indicate that the demographic factors of gender, age (adults ≤65 years), body mass index, hepatic function (moderate), renal function (severe), race, and HIV infection status do not have clinically meaningful effects on the pharmacokinetics of raltegravir, and no dose adjustment is warranted for these factors.

5.5 Assessment of Drug-Drug Interactions

5.5.1 Effect of Raltegravir on Coadministered Drugs

Raltegravir has a low propensity to meaningfully affect the pharmacokinetics of coadministered drugs. *In vitro* results indicated that raltegravir is generally not expected to alter the pharmacokinetics of coadministered drugs. At concentrations up to 100 μM, raltegravir is not an inhibitor of the major CYP450 isozymes, several major UGTs, or P-gp. Additionally, raltegravir was not found to be a time-dependent inhibitor of CYP3A4 nor an inducer of CYP3A4.

Raltegravir was evaluated in a midazolam interaction study and was shown to be neither an inducer nor inhibitor of this sensitive CYP3A4 probe substrate corroborating the *in vitro* results (midazolam $AUC_{0-\infty}$ GMR [raltegravir and midazolam/midazolam] (90% CI) = 0.92 (0.82, 1.03)). Based on these data, it is anticipated that raltegravir may be dosed with other agents which are CYP3A4 substrates with no potential for raltegravir to affect the pharmacokinetics of the coadministered drug.

Tenofovir is an antiretroviral agent eliminated primarily by a combination of glomerular filtration and active tubular excretion. A drug-drug interaction study was conducted with tenofovir and raltegravir demonstrating that raltegravir had no substantial effect on tenofovir pharmacokinetics. Multiple-dose coadministration of tenofovir and raltegravir led to a slight decrease in peak serum concentrations of tenofovir (tenofovir C_{max} GMR [raltegravir and tenofovir/ tenofovir] (90% CI) = 0.77 (0.69, 0.85)), with less of an effect on tenofovir AUC (tenofovir AUC_{0-24hr} GMR (90% CI) = 0.90 (0.82, 0.99)) and no effect on $C_{24\ hr}$ (tenofovir C_{24hr} GMR (90% CI) = 0.87 (0.74, 1.02)). The effect of raltegravir on tenofovir is similar to the reported effect of rifampin on tenofovir. No dose adjustment is recommended for tenofovir in the presence of rifampin, implying that the effect of raltegravir is unlikely to be of clinical importance.

The effect of raltegravir on the pharmacokinetics of lamivudine was assessed in a Phase II study by comparing lamivudine PK data from coadministration with raltegravir and tenofovir to that obtained from coadministration with efavirenz and tenofovir. There appeared to be no meaningful differences in the lamivudine pharmacokinetics. Lamivudine is predominantly renally eliminated via active organic cationic secretion.

5.5.2 Effect of Coadministered Drugs on Raltegravir

Raltegravir has a low propensity for clinically meaningful drug-drug interactions as a victim. Raltegravir is eliminated primarily by metabolism via UGT1A1. Studies were conducted evaluating the effect of inducers and inhibitors of drug metabolizing enzymes (including UGT1A1) on raltegravir pharmacokinetics and results are summarized in Table 1. The selection of compounds in these investigations was based on their respective drug interaction profiles. The overall objective was to bracket the most potent inhibitors and inducers potentially causing respective increases and decreases in

raltegravir plasma concentrations. Atazanavir is a known inhibitor of UGT1A1, the primary pathway of clearance of raltegravir, and was selected to assess the greatest potential for increases in raltegravir pharmacokinetics. A number of agents are relatively potent inducers of a broad range of drug-metabolizing enzymes. Rifampin was selected as a representative of the strongest inducers to characterize the greatest potential for decreases in raltegravir pharmacokinetics. Other inducers investigated included ritonavir, efavirenz, tipranavir, and etravirine. Tenofovir was also investigated; although tenofovir has not been characterized *in vivo* as an inducer or inhibitor it has been shown to significantly affect the pharmacokinetics of other antiretroviral agents through mechanisms that are not entirely clear.

Raltegravir is eliminated primarily by metabolism with minor elimination via renal excretion. Therefore, drugs that inhibit renal secretion, including agents that inhibit the transporter P-gp, are unlikely to cause a clinically meaningful change in the pharmacokinetics of raltegravir. Ritonavir (an inhibitor of P-gp as well as an inducer and inhibitor of several drug metabolizing enzymes) had no significant effect on the pharmacokinetics of raltegravir (see additional discussion regarding ritonavir in this section below).

Table 1

Summary of Raltegravir Drug Interaction Data – Effect on Raltegravir When Coadministered With Other Agents

Coadministered Drug	**Study Design**	**C_{12hr} GMR (90% CI)**	**AUC GMR (90% CI)**	**C_{max} GMR (90% CI)**
Atazanavir	SD/MD	1.95 (1.30, 2.92)	1.72 (1.47, 2.02)	1.53 (1.11, 2.12)
Atazanavir and Ritonavir	MD/MD	1.41 (0.90, 2.20)	1.29 (1.02, 1.64)	NA
Atazanavir and Ritonavir (Phase II) †	MD/MD	1.77 (1.39, 2.25)	1.41 (1.12, 1.78)	1.24 (0.87, 1.77)
Ritonavir	SD/MD	0.99 (0.70, 1.40)	0.84 (0.70, 1.01)	0.76 (0.55, 1.04)
Efavirenz	SD/MD	0.79 (0.49, 1.28)	0.64 (0.52, 0.80)	0.64 (0.41, 0.98)
Rifampin	SD/MD	0.39 (0.30, 0.51)	0.60 (0.39, 0.91)	0.62 (0.37, 1.04)
Tipranavir and Ritonavir	MD/MD	0.45 (0.31, 0.66)	0.76 (0.49, 1.19)	0.82 (0.46, 1.46)
Tipranavir and Ritonavir (Phase III) †	MD/MD	0.49 (0.37, 0.64)	0.65 (0.58, 0.73)	NA
Etravirine	MD/MD	0.66 (0.34, 1.26)	0.90 (0.68, 1.18)	0.89 (0.68, 1.15)
Tenofovir	MD/MD	1.03 (0.73, 1.45)	1.49 (1.15, 1.94)	1.64 (1.16, 2.32)
Tenofovir (Phase II) †	MD/MD	1.42 (0.89, 2.28)	1.41 (1.11, 1.79)	1.33 (0.96, 1.85)

Geometric Mean Ratio (GMR; coadministration/administration alone) for single-dose $AUC_{0-\infty}$ or multiple-dose $AUC_{0-\tau}$ and C_{12hr} of raltegravir on the day of coadministration.

SD/MD=Single dose administration of raltegravir and multiple dose administration of the other agent; MD/MD=Multiple dose administration of raltegravir and the other agent; NA=Not available.

† Data obtained from Phase II or III population PK analyses. For a description of Phase II and III studies, see Section 6.1.

Both atazanavir alone and in combination with ritonavir were investigated in Phase I. Additional data on this interaction was also obtained from the Phase II population PK data. As anticipated, raltegravir plasma levels were increased with coadministration, consistent with inhibition of UGT1A1. The increases, however, were on the whole modest (30 to 70% increases in AUC; Table 1) and not considered clinically meaningful, because the upper bounds of the 90% CIs for AUC (2.02, 1.78, and 1.64, respectively) were similar to or less than the defined upper bound of clinical significance of 2.0 (See Section 10.1). Of note, concomitant use of raltegravir and atazanavir was well tolerated in the Phase II and Phase III studies. Based on these data, atazanavir may be coadministered with raltegravir without adjustment in the dose of raltegravir.

The effect of tenofovir on raltegravir pharmacokinetics was evaluated in a Phase I interaction study and in a Phase II study. The results from both studies are consistent with a modest effect of tenofovir on raltegravir (~40 to 50% increase in AUC) that is similar in magnitude to the atazanavir effect. The mechanism of this interaction is unknown. This effect is not clinically significant, because the upper bounds of the 90% CIs for AUC (1.94 and 1.79, respectively) were less than the defined upper bound of clinical significance of 2.0 (See Section 10.1). The effect of tenofovir on C_{12hr} was somewhat inconsistent in the two studies, with no effect in the Phase I study and a modest increase in the Phase II study, but the effect in either study would not be judged clinically meaningful. Of note, concomitant use of raltegravir and tenofovir was well tolerated in the Phase II and III studies. Based on these data, tenofovir disoproxil fumarate may be coadministered with raltegravir without dose adjustment.

Ritonavir (100 mg twice-daily) had no effect on the pharmacokinetics of raltegravir, despite the potential for induction of UGT1A1 by ritonavir. Due to the multiple effects of ritonavir on enzymes and transporters, a balance of competing effects of induction and inhibition cannot be ruled out. Based on these data, ritonavir may be coadministered with raltegravir without dose adjustment.

Efavirenz and etravirine had a modest influence on the pharmacokinetic profile of raltegravir. There is evidence of a modest reduction in C_{12hr} (21% and 34%, mean decrease, respectively), which is probably due to slight induction of UGT1A1; however, the point estimates and 90% CIs for these effects indicate that the magnitude of these effects are small and not likely to be clinically meaningful. Although the lower bound of the CI (0.34) for etravirine was less than 0.4 with a wide 90% CI, the lack of effect on the other raltegravir exposure parameters suggests that etravirine has only a slight effect on raltegravir pharmacokinetics that is unlikely to be clinically meaningful. Based on these data, efavirenz and etravirine may be coadministered with raltegravir without dose adjustment

Based on data from a Phase I interaction study and an analysis of Phase III population PK data, ritonavir–boosted tipranavir decreased plasma levels of raltegravir. The interaction is consistent with a modest inductive effect of tipranavir on the metabolism of raltegravir, because, as described above, ritonavir alone had little effect on raltegravir pharmacokinetics. The raltegravir C_{12hr} value was most impacted, with a mean decrease of approximately 51 to 55%. Smaller mean decreases were observed for $AUC_{0\text{-}12hr}$ (24 to 35 %) and C_{max} (18%). Based on pharmacokinetic data alone, it is unclear if the effect of tipranavir on raltegravir is clinically significant; the point estimate for the effect on raltegravir C_{12hr} in both analyses is close to the 60% reduction that is considered of potential significance. However, there are considerable clinical efficacy data available from the Phase III program which support that this interaction is not clinically significance (Section 7.3.5 and Section 10.1). Based on these data, tipranavir with low-dose ritonavir may be coadministered with raltegravir without dose adjustment. See Section 10.1 for additional discussion.

Rifampin, which is an overall broad potent inducer of drug metabolizing enzymes, decreased raltegravir C_{12hr} by an average of 61%. Mean $AUC_{0\text{-}\infty}$ and C_{max} values decreased by 40% and 38%, respectively. The observed interaction is consistent with a modest effect of even a very potent inducer on the metabolism of raltegravir. These alterations in pharmacokinetics with coadministered rifampin may be clinically significant, because the true decrease in raltegravir C_{12hr} is likely greater than a 60% reduction (both the point estimate of the GMR and the lower bound of the 90% CI for C_{12hr} fell below 0.4). In contrast to tipranavir, there is no clinical experience from the Phase III program with coadministration of rifampin and raltegravir. Since this appears to be a slightly greater decrease in exposure than with tripranavir, and no clinical experience is available from the Phase III program, it is conservative to suggest a dose adjustment. Based on these data, rifampin may be used with raltegravir, but a doubling of the raltegravir dose should be considered when coadministered with rifampin. To confirm this recommendation, a study is currently being conducted comparing the pharmacokinetics of 400-mg raltegravir dosed alone and 800-mg raltegravir dosed in combination with rifampin. The potential for interactions with phenytoin and phenobarbital was not evaluated in the clinical program for raltegravir; however, both drugs are strong inducers with inductive potential similar to rifampin. On the basis of the results with rifampin, a doubling of the raltegravir dose should be considered when coadministered with either phenytoin or phenobarbital.

Other drugs in the inducer class have less potent inductive activity than rifampin, and the evidence from studies such as the efavirenz interaction study support that no dose adjustment is needed when these drugs are used with raltegravir. On this basis, no dose adjustment is recommended for coadministration with nevirapine, rifabutin, glucocorticoids, St. John's Wort, and pioglitazone.

5.6 Raltegravir Population Pharmacokinetic and Pharmacokinetic/ Pharmacodynamic (PK/PD) Analyses

To define the pharmacokinetics of raltegravir in HIV-1 infected patients, full pharmacokinetic profiles over a steady state dosing interval were collected in a subset of patients enrolled in the Phase II treatment naïve study (Protocol 004), in both the 10-day monotherapy treatment in Part I and the combination therapy treatment in Part II. In addition, sparse sampling for population PK analyses was conducted in all patients in the Phase II and III studies. The geometric mean observed C_{12hr} was defined as the primary population PK exposure estimate. Several PK/PD analyses were conducted using these data to explore potential relationships between raltegravir PK parameters and treatment outcomes.

An analysis of the PK/PD relationship with early viral response was conducted using data from the Phase II treatment naïve study (Protocol 004) during the 10-day monotherapy treatment in Part I. Limited data suggested a possible association between the short-term antiretroviral activity of raltegravir (change from baseline in HIV RNA at Day 10 and slope of HIV RNA decrease from Day 2 to 8) and the corresponding C_{12hr} value on Day 10 (nominal p-values <0.05 for Pearson's and Spearman correlations), but not $AUC_{0\text{-}12hr}$ or C_{max}. This suggests that trough concentration may be the most sensitive PK parameter for early viral response, which would be similar to several other HIV therapies in other classes where an association of response with trough concentration has been noted. It is important to note, however, all doses and trough concentrations of raltegravir were associated with potent Day 10 antiretroviral effect. In particular, there were 3 patients with trough concentrations below the *in vitro* CIC_{95}; all of these patients achieved either HIV RNA <400 copies/mL or a >2 $\log_{10}$ decline in HIV RNA by Day 10.

The potential association of raltegravir pharmacokinetics with longer-term viral response measures was also investigated. The longer-term antiretroviral efficacy response measures used in these assessments included: HIV RNA <400 copies/mL; HIV RNA <50 copies/mL; occurrence of virologic failure; and development of integrase mutations at amino acid 148 and/or 155. In separate analyses of data from the Phase II studies in treatment experienced or treatment naïve patients, no statistically significant associations were obtained for any efficacy response compared with any PK parameter, suggesting no meaningful associations between raltegravir pharmacokinetics and measures of antiretroviral response in treatment-naïve or treatment-experienced patients over the range of pharmacokinetic values obtained in these dose-ranging studies. In a pooled analysis of data in treatment experienced patients from the Phase II and III studies, there was no evidence of a meaningful PK/PD association for any efficacy response compared with the observed C_{12hr} parameters.

Given the high proportion of favorable outcomes achieved with raltegravir therapy in the Phase II and Phase III studies, the lack of clinically meaningful PK/PD associations with measures of longer-term antiretroviral response suggest that the range of concentrations obtained in the Phase II and Phase III studies falls near the top of the concentration-response curve, where treatment response has, at most, only a modest concentration-dependency. The available data do not suggest any thresholds for C_{12hr} or other PK parameter values that are known to be associated with reduced long term efficacy and it supports that raltegravir concentrations throughout the range of clinical experience from Phase II and Phase III studies are likely associated with a similar high-level of efficacy.

5.7 Clinical Pharmacology Conclusions

- Raltegravir C_{trough}, after administration of 400 mg orally, twice daily, exceeds the *in vitro* CIC_{95}.
- Raltegravir has a low propensity for drug-drug interactions -- as a victim or as a perpetrator.
- Coadministration of raltegravir with drugs that are known to be potent UGT1A1 inhibitors (e.g., atazanavir) may increase raltegravir plasma levels; however, the degree of increase is modest and combination therapy with these inhibitors was well tolerated in the clinical studies such that no dose adjustment is required.
- A dose increase of raltegravir to 800 mg twice daily should be considered when coadministered with rifampin, phenytoin, or phenobarbital.
- Gender, age, BMI, hepatic function, renal function, race, and HIV infection status do not have clinically meaningful effects on the pharmacokinetics of raltegravir. No dose adjustment is warranted on the basis of gender, age, BMI, hepatic function, renal function, race, and HIV infection status.
- In the fed and fasted states, total exposure to raltegravir is similar.

6. Overview of Raltegravir Clinical Development

6.1 Overview of Phase II/III

Raltegravir has been studied in HIV-1 infected individuals during the course of 2 Phase II clinical trials and 2 Phase III clinical trials. In all, a total of 755 patients have received raltegravir during the double blind portions of the Phase II and III studies, including 160 treatment naïve patients and 595 treatment experienced patients.[1]

An overview of the clinical development program is provided below:

1. **Demonstration of Proof of *in vivo* HIV-1 Antiretroviral Activity** (Protocol 004 Part 1): This portion of the program was designed to show that raltegravir was safe and had antiviral effect as measured by decreases in HIV ribonucleic acid (RNA) when given to HIV-infected patients as monotherapy for 10 days. This study provided evidence of the short-term antiretroviral efficacy as monotherapy and supported moving forward into larger trials, using combination therapy.
2. **Dose Finding (Protocol 004 Part II and Protocol 005):** These 2 Phase II studies were conducted in treatment-naïve (Protocol 004) and treatment-experienced (Protocol 005) patients and were designed to evaluate the longer-term safety, tolerability and efficacy of several doses of raltegravir used as part of initial or salvage antiretroviral therapy. These studies demonstrated similar efficacy and safety across the range of doses tested and provide the basis for choosing the 400 mg b.i.d. dose of raltegravir for evaluation in the Phase III trials (discussed in Section 7.2.2). Because Protocols 004 and 005 were initiated prior to the Phase III trials, they also provide longer term efficacy and tolerability data than the Phase III studies.
3. **Demonstration of Efficacy (Protocols 018 and 019):** These 2 identical Phase III trials were designed to evaluate the 400 mg b.i.d. dose of raltegravir in treatment-experienced patients and demonstrated safety, tolerability, and superior efficacy in patients with previous antiretroviral experience and advanced HIV infection.

Table 2 provides a listing of the populations, key purposes, and major findings of each study. In addition to the listings in Table 2, there is an ongoing multi-center, double-blind, randomized, active-controlled study (Protocol 021) to evaluate the safety and antiretroviral activity of raltegravir versus efavirenz in treatment naïve HIV-infected patients, each in combination with tenofovir and emtricitabine, and monitored used of raltegravir through expanded access programs. Two identical studies, Protocols 032 and 033, started after the NDA; these protocols will evaluate the safety and antiretroviral activity of raltegravir versus lopinavir/ritonavir in HIV-infected patients switched from a stable lopinavir/ritonavir-based regimen.

[1] In addition, 3 treatment-naïve patients received raltegravir only in the monotherapy portion of Protocol 004 and did not continue on to the combination portion. These 3 patients are included in the analyses of raltegravir mono-therapy, but do not appear in other efficacy analyses.

Raltegravir is also being made available pre-licensure through Protocol 023, an Expanded Access Program (EAP), and in some countries, through alternative means of pre-licensure access. Only safety data is being collected in the expanded access environment.

Table 2

Overview of the Phase II and Phase III Clinical Trials

Phase	Protocol Number	Dose(s) of Raltegravir Studied	Number of Patients Receiving Raltegravir†	Population	Key Purpose	Major Findings Regarding Raltegravir
Phase II	004	100 mg b.i.d.	39‡	Treatment-Naïve	Part 1: Dose Finding and Proof of Concept (Monotherapy) Part 2: Dose Finding In the Setting of Combination Therapy	• Comparable Efficacy Across All Doses • Efficacy Comparable to Standard of Care • Generally well tolerated at all doses as monotherapy for 10 days • Generally well tolerated at all doses as compared to efavirenz when both are given in combination with tenofovir and lamivudine.
		200 mg b.i.d.	40‡			
		400 mg b.i.d.	41‡			
		600 mg b.i.d.	40‡			
	005	200 mg b.i.d.	43	Treatment-Experienced	Dose Finding In the Setting of Combination Therapy	• Comparable Efficacy Across All Doses • Efficacy Superior to Placebo • Generally well tolerated at all doses as compared to placebo, both given in combination with OBT across all doses.
		400 mg b.i.d.	45			
		600 mg b.i.d.	45			
Phase III	018	400 mg b.i.d.	232	Treatment-Experienced	Demonstration of Efficacy	• Efficacy Superior to Placebo • Generally well tolerated as compared to placebo, both given in combination with OBT
	019	400 mg b.i.d.	230	Treatment-Experienced	Demonstration of Efficacy	• Efficacy Superior to Placebo • Generally well tolerated as compared to placebo, both given in combination with OBT

† Includes only patients who received at least one dose of raltegravir.
‡ Numbers are from Part II and include both Part I and Part II patients.
OBT = Optimized background therapy.

Pediatric Development:

Merck & Co., Inc. plans to conduct 2 studies in pediatrics, the first in HIV-infected children, and the second in neonates born to HIV-infected mothers. Merck & Co., Inc. has initiated an open-label pediatric study of raltegravir for PK, safety and efficacy in collaboration with IMPAACT (formerly the Pediatric AIDS Clinical Trials Group), IMPAACT P1066, which as currently written includes patients from 2 – 18 years of age. This study will soon be amended to include a pediatric chewable formulation to allow dosing in younger HIV infected children. A subsequent amendment is anticipated to include HIV infected patients as young as 1 month of age once an appropriate formulation for suspension is available and data in older children are supportive. Once PK and safety data in HIV infected young infants are available, the second pediatric study of PK and safety in neonates born to HIV infected mothers will be initiated.

6.2 Methods

6.2.1 Individual Study Designs

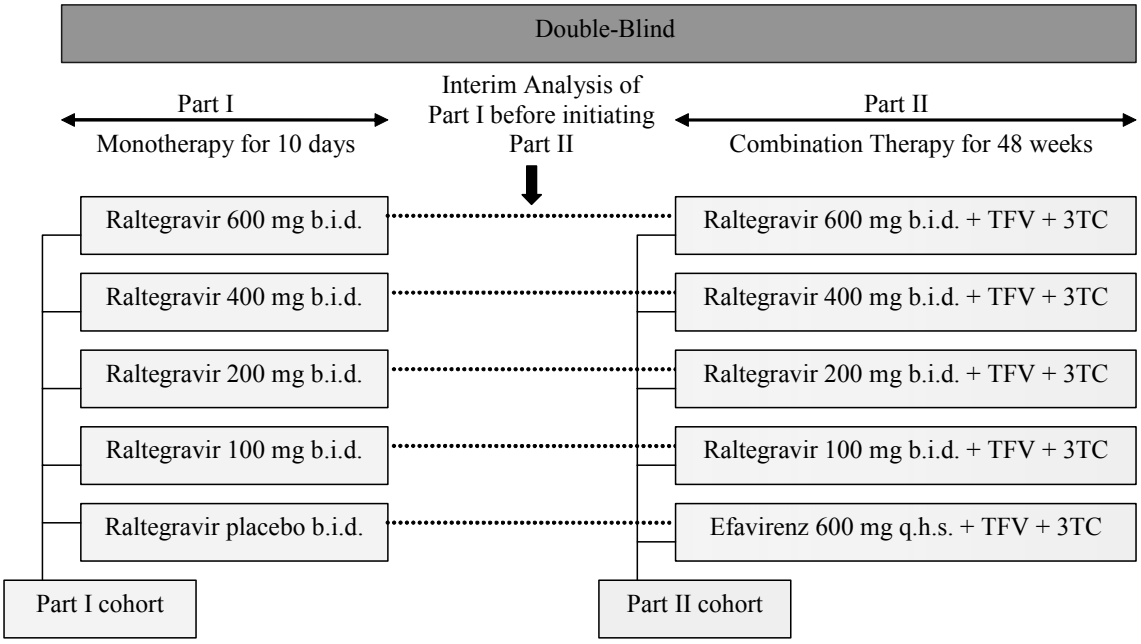
In all Phase II and Phase III studies, raltegravir was dosed without regard to food.

Dose Ranging in Treatment Naïve Patients: Protocol 004

Protocol 004 was a multi-center, double-blind (with in-house blinding) randomized dose-ranging, controlled study with 2 parts (Figure 3): Part I compared raltegravir monotherapy at doses ranging from 100 to 600 mg b.i.d. with placebo for 10 days. Part II compared the same doses of raltegravir with a standard-of-care comparator, EFV 600 mg at bedtime, both in combination with TFV and 3TC.

Figure 3

Protocol 004 Study Design



Dose Ranging in Treatment Experienced Patients: Protocol 005

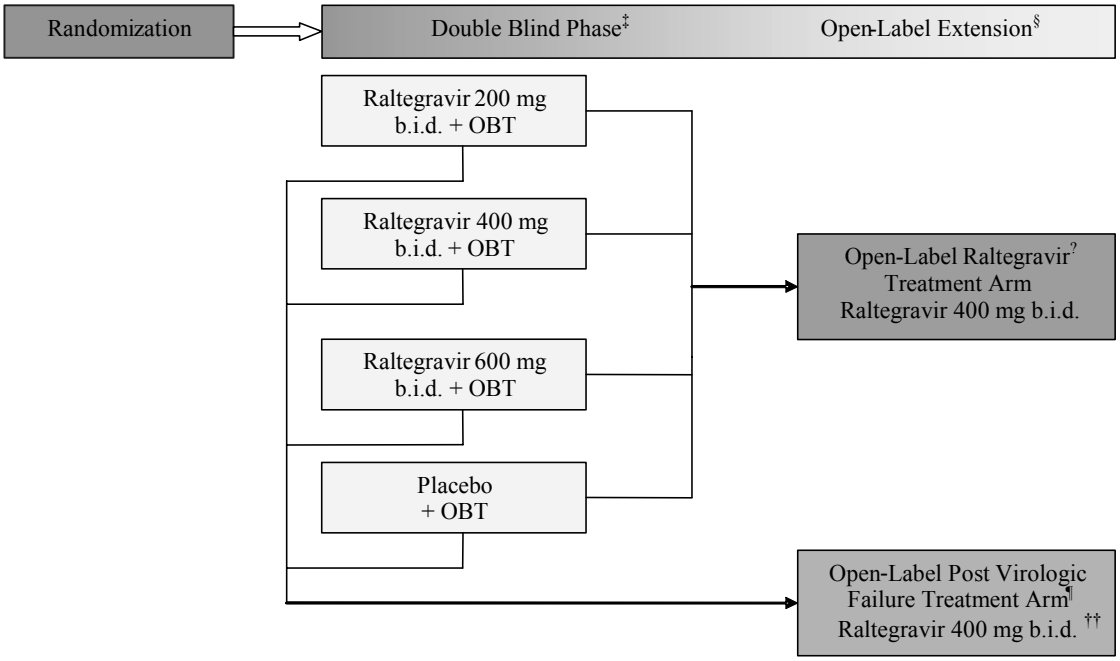
Protocol 005 was a multi-center, double-blind (with in-house blinding) randomized dose-ranging, controlled study which evaluated 3 doses of raltegravir (200, 400, and 600 mg b.i.d.) in combination with an OBT versus placebo in combination with OBT for at least 24 weeks in HIV-1 infected patients with CD4 cell count >50 cells/mm^3 who had failed therapy as documented by HIV RNA >5,000 copies/mL while on stable therapy and documented resistance to at least 1 drug in each of 3 classes of oral ARTs (NRTI, NNRTI, and PI) (Figure 4). Tipranavir and darunavir were investigational at the time of protocol initiation and were not allowed in the OBT. Because preliminary PK data suggested that co-administration of raltegravir with atazanavir increased overall exposure to raltegravir, 2 substudies were conducted in Protocol 005: Substudy A for patients who did not receive atazanavir in their OBT and Substudy B for patients who received atazanavir in their OBT. Testing for homogeneity of treatment effect suggested no statistically or clinically significant difference between Substudy A and Substudy B for each of the 3 doses of raltegravir tested versus placebo, thus permitting the combination of data from both substudies. After the Phase III dose of 400 mg b.i.d. was selected, Protocol 005 was amended to allow all patients (including the placebo group) who had

completed at least 24 weeks of therapy in the double-blind, dose-ranging phase to receive the Phase III dose in an open-label extension (Figure 4); patients were not unblinded as to their originally randomized arm and changes in OBT were not permitted. All patients ultimately switched to the open-label extension, with the majority switching between Week 24 and 48.

In addition to the open-label extension described above, an open label post virologic failure arm (OLPVF) allowed for patients who had completed at least 16 weeks of therapy and were found to meet study criteria for virologic failure (a confirmed decrease from baseline plasma HIV RNA <1.0 $\log_{10}$ and HIV RNA >400 copies/mL) or virologic relapse (HIV RNA >400 copies/mL on two consecutive measurements at least one week apart after initial response with HIV RNA <400 copies/mL or >1.0 $\log_{10}$ increase in HIV RNA above nadir level on 2 consecutive measurements at least one week apart) to receive raltegravir. Patients who switched to OLPVF before the open label amendment received raltegravir 600 mg b.i.d.; after the open-label amendment, all patients in the OLPVF arm received the Phase III dose of 400 mg b.i.d.

Figure 4

Protocol 005 Overall Study Design†



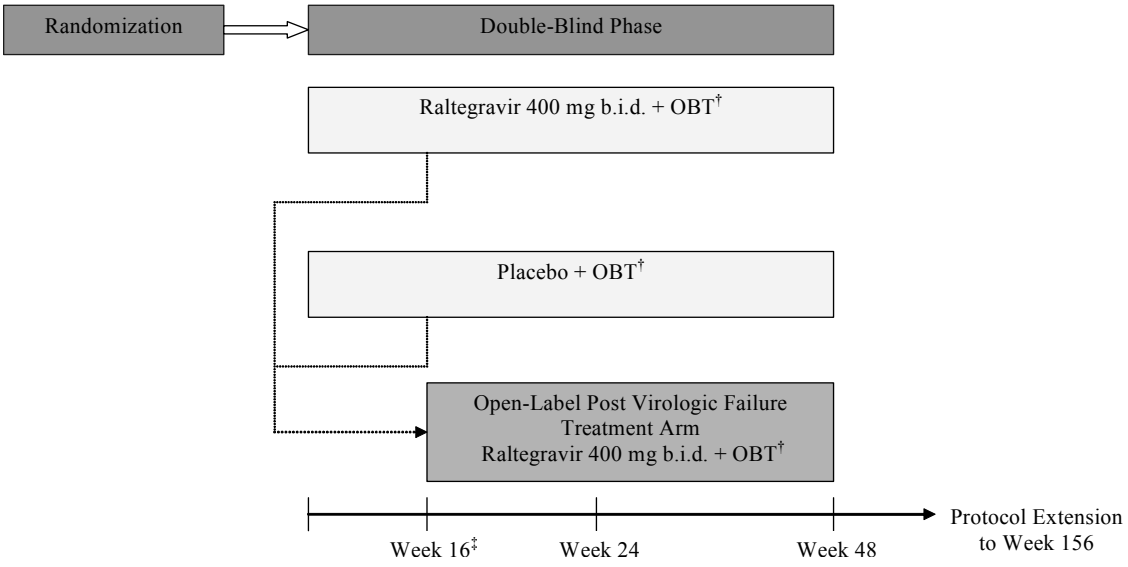
† Two sub-studies, A and B, without and with atazanavir respectively, were included in Protocol 005.
‡ Double blind up to Week 24.
§ Total study duration (double-blind plus open-label) 3 years.
‖ After at least 24 weeks of therapy.
¶ After at least 16 weeks of therapy.
†† Prior to open label amendment, patients in OLPVF treatment arm received raltegravir 400 mg b.i.d.

Pivotal Phase III Trials: Protocols 018 and 019

Protocols 018 and 019 (Figure 5) were identical, multi-center, double-blind (with in-house blinding), randomized, placebo-controlled studies in HIV-1 infected patients who had failed therapy as documented by HIV RNA >1,000 copies/mL (no CD4 cell count minimum) while on stable therapy and documented resistance to at least 1 drug in each of 3 classes of oral ARTs (NRTI, NNRTI, and PI). Protocol 018 was conducted at study sites in Europe, Asia/Pacific, and South America. Protocol 019 was conducted at study sites in North and South America. The studies evaluated the safety, tolerability, pharmacokinetics, and efficacy of raltegravir 400 mg b.i.d. compared with placebo, each in combination with an investigator-selected OBT. Two (2) to 1 randomization (raltegravir:placebo) was employed. Like Protocol 005, Protocols 018 and 019 included an OLPVF arm, for which patients who completed at least 16 weeks of therapy became eligible if experiencing virologic failure.

Figure 5

Protocols 018 and 019 Study Design



† Optimized background therapy
‡ Primary analysis time point

Procedure for Selecting and Changing Optimized Background Therapy

Consistent with treatment guidelines, the optimization of background therapy was encouraged in the studies in treatment experienced patients. Both genotypic and phenotypic resistance testing were performed at screening. In Protocols 018 and 019, but not in Protocol 005, the use of recently validated investigational drugs, tipranavir and darunavir, was allowed. To accurately assess the efficacy of raltegravir, change of OBT was not permitted except for toxicity management or after patients had confirmed virologic failure.

6.2.2 Endpoints

HIV RNA and CD4 cell counts are well accepted surrogate markers for efficacy in clinical trials of HIV therapeutics [29; 395; 427]. Over the past several years, the treatment of heavily treatment-experienced patients has evolved, impacting the choice of primary study endpoints in clinical trials. For example, enfuvirtide in 2003 demonstrated superiority of efficacy by using the change of HIV RNA from baseline as primary endpoint [7; 8]. However, with subsequent availability of more potent PIs, the primary efficacy measurements have changed to include proportion of patients with at least 1 $\log_{10}$ copies/mL decrease or with HIV RNA <400 copies/mL [248; 425]. Recently, treatment guidelines have recommended proportion of patients with HIV RNA <50 copies/mL as the ultimate goal [67; 310]. This evolution is reflected in the raltegravir development program; Protocol 005 (designed at end of 2004) utilized change of HIV RNA from baseline as the primary efficacy endpoint, while Protocols 018 and 019 (designed at end of 2005) utilized the proportion of patients with HIV RNA <400 copies/mL. In considering the integrated efficacy data for treatment-experienced patients, the more stringent virologic endpoints of HIV RNA <400 and <50 copies/mL have been used. Time-to-loss-of-virologic-responses (TLOVR), which is the time between randomization and the first rebounding HIV RNA value >400 copies/mL (with non-responders who did not achieve HIV RNA <400 copies/mL assigned a time of zero), was used to assess the durability of antiretroviral effect. The Phase III studies were not powered to evaluate clinical endpoints (e.g., progression to AIDS-defining conditions [ADC] and/or death).

The primary time point was Week 16 in Phase III and Week 24 in Phase II. The Week 16 time point was chosen for Phase III because review of preliminary analyses of the ongoing Phase II studies indicated that regimens containing raltegravir appeared to be highly potent and generally well tolerated with 2 observations of particular interest: (1) in treatment-naïve patients the raltegravir regimens achieved an HIV viral load <50 copies/mL more quickly than the efavirenz group with the efficacy results seen at Week 16 sustained through Week 24; and (2) in a treatment-experienced population comparable to the Phase III studies, raltegravir in combination with OBT demonstrated superior, potent antiretroviral efficacy as compared to placebo with OBT with the efficacy results seen at Week 16 sustained through Week 24.

It is important to note that the analyses in the Phase III studies submitted as part of the original application were undertaken using a visit cut-off date of 13-Dec-06. As of this date, Week 16 efficacy data from all enrolled patients (100%) and Week 24 data from approximately 60% of enrolled patients were available, as not all enrolled patients had reached Week 24 of the study by that time. Week 24 efficacy data from 100% of enrolled patients became available as of 16-Feb-07, allowing sufficient time for submission and preparation of the information for the advisory committee. Per prior agreement with the FDA, efficacy analyses performed as part of the original application have been repeated using the cumulative updated data and included in this document. The updated data were consistent with the data used in the original application, and support the original conclusions. Where presented, notation has been made that these data have not yet been reviewed by the FDA.

6.2.3 Statistical Methodology

Definitions of Study Populations

The primary analysis population used to assess efficacy was the modified-intention-to-treat (MITT) population for all studies in the Phase II and Phase III clinical development program. In the MITT approach, patients were included in the treatment group to which they were randomized, regardless of their adherence to the entry criteria, regardless of the treatment they actually received, and regardless of deviation from the protocol, provided they received at least one dose of study therapy. Patients who were randomized but never dosed are not included in the efficacy analyses.

Statistical Methods

For showing proportion of patients with HIV RNA <400 copies/mL and <50 copies/mL over time, results from the Non-completer = Failure (NC=F) analysis are presented. In the NC=F approach, patients who prematurely discontinued assigned treatment regardless of reason were considered as failures thereafter (failure carried forward). For example, all patients who experienced virologic failure and transferred to an OLPVF arm were considered as failures thereafter, regardless of the response to open label therapy. Intermittent missing values due to a missed or skipped visit or due to an inadequate sample were excluded from the NC=F approach if the missing value was immediately flanked by 2 successes.

For efficacy by prognostic factors and by subpopulations, and the association analysis of resistance-associated mutations versus potential prognostic factors, the Observed Failure (OF) analyses, which consider the pure antiretroviral effect of the treatment, was used. In the OF approach, patients who prematurely discontinued assigned treatment due to lack of efficacy were considered as failures thereafter (failure carried forward), while patients who prematurely discontinued assigned treatment, for reasons other than lack of efficacy, were excluded from the analyses. The OF approach was also used for change from baseline in HIV RNA and CD4 cell counts (baseline value carried forward for discontinuations due to lack of efficacy).

Logistic Regression Model for Hypothesis Testing

Logistic regression models adjusted for prognostic factors were also applied to compare raltegravir 400 mg b.i.d. with placebo in virologic responses at Weeks 16 and 24. The following covariates were used: baseline plasma HIV RNA, enfuvirtide use in OBT in enfuvirtide-naïve patients (Yes/No), active PI in OBT determined by phenotypic resistance test (Yes/No), darunavir use in the OBT in darunavir-naïve patients (Yes/No), and treatment group. A similar logistic regression model was used when performing pre-planned testing for homogeneity of treatment effect to assess the combinability of Protocol 005 Sub-study A and B, and Protocols 018 and 019.

Regression Model for the Estimation of Change From Baseline

In the Treatment Outcome tables (Table 5, Appendix 8, Appendix 9, Appendix 10, Appendix 11, Appendix 19, Appendix 20, and Appendix 21), mean differences (95% confidence interval [CI]) for change from baseline in log10 plasma HIV RNA and p-value were calculated using a parametric regression model (normal assumption), which can handle censored observation and was adjusted for the same covariates as described in the previous logistic regression model. For change from baseline in CD4 cell counts, a mixed-effects model (with patients as random effects) adjusted for baseline CD4 cell counts, visit, stratum, and treatment was applied.

Calculating GSS and PSS

The contribution of the OBT to therapy was assessed by the genotypic sensitivity score (GSS) and the phenotypic sensitivity score (PSS). These scores were generated using the results from the genotypic and phenotypic resistance assay of the patients' HIV at screening; the Phenosense GT™ assay (Monogram Biosciences) was utilized for Phase II and Phase III studies. The baseline GSS and PSS were defined as the total ARTs in the OBT to which the patient's viral isolate showed genotypic and phenotypic sensitivity, respectively. Because there is no widely agreed upon clinical cutoff, enfuvirtide use in enfuvirtide-naïve patients was counted as an active drug and added (+1) to the GSS and PSS. Because the resistance testing for darunavir was not available at the time of Phase III initiation, darunavir use in darunavir-naïve patients was counted as an active drug and added (+1) to the GSS and PSS. This convention may not provide a perfect estimate of the contribution of darunavir to the OBT. For instance, in darunavir-naïve patients receiving darunavir, the antiviral activity of darunavir may be less than its activity in a protease inhibitor naïve patient, as darunavir displays cross resistance with other protease inhibitors.

Duration of Follow-up: Time at Risk

When adjusting data for imbalance for duration of follow-up (also called time at risk) for raltegravir versus placebo, statistical analysis was performed based upon the pooled data (all doses) from Protocols 004, 005, 018, and 019 for the double-blind and/or open label/OLPVF portions of the study.

For each patient, only the first confirmed event was considered in the time-to-event analyses. For example, if a patient had multiple events of a given condition, either recurrences or events of different types, the first event would be included in the analyses but not the second event. Both events, however, are included in counts tables.

Time at risk for patients with a certain event was defined as the duration from the randomization date to the first event date; for patients without an event, time at risk was defined as the duration from the date of first dose to the date of the last recorded dose of study therapy. Most patients were still receiving drug at the time of the analyses as the studies are ongoing. Patients who discontinued study therapy but continued to be followed were censored at 14 days after study therapy discontinuation. It is important to note that time at risk will be slightly different depending on the endpoint being examined. For example, mortality generally gives the longest time at risk as no other events can occur after the event of mortality. These differences are generally small.

It is important to distinguish duration of treatment (i.e. exposure) from duration of follow-up (i.e. time at risk). Exposure, discussed briefly in Section 9 with respect to the Risk Management Plan, is defined as the time between first dose of study drug and the last dose recorded in the database minus days off study drug.

7. Efficacy

7.1 Overview

The pivotal (Protocols 018 and 019) and supportive (Protocols 004 and 005) studies provide evidence of the clinical efficacy of raltegravir used in combination with other ARTs in the treatment of HIV-infected patients. In this section, results of each of the individual studies are presented first (Section 7.2). The rationale for Phase III dose selection is explained (Section 7.2.2).

The Phase III studies, Protocol 018 and 019, were identical in terms of design. After pre-planned testing confirmed the homogeneity of treatment effects, the data from these 2 studies were combined. The combined data from Protocols 018 and 019 comprise the bulk of the evidence supporting the proposed indication (Section 7.3).

The following provides an overview of the efficacy evidence from each of the individual studies as well as the combined data set from Protocols 018 and 019.

- In **Protocol 004** (treatment-naïve), raltegravir demonstrated similar potent efficacy across the range of doses 100-600 mg b.i.d. in combination with tenofovir and lamivudine. This efficacy was similar to that seen in a standard of care comparator arm, efavirenz 600 mg q.h.s in combination with tenofovir and lamivudine. The treatment effect was sustained through Week 48, and interestingly, patients receiving raltegravir experienced faster declines in HIV RNA levels than patients receiving efavirenz.

- In **Protocol 005** (treatment-experienced), raltegravir demonstrated similar potent efficacy across the range doses of 200-600 mg b.i.d. in combination with OBT. This efficacy is superior to that seen in patients receiving placebo in combination with OBT and is sustained through at least 24 weeks of double blind therapy. Analysis of the data from the open label portions of Protocol 005 suggest sustained efficacy at week 48 and week 72.
- Data from **Protocol 004 and Protocol 005** provide the basis for the selection of the 400 mg b.i.d. dose of raltegravir carried forward into Phase III.
- The individual Phase III studies, **Protocols 018 and 019** (treatment-experienced), each confirmed the superiority of raltegravir 400 mg b.i.d. in combination with OBT as compared to placebo, through at least Week 16 (100% of patients enrolled), with confirmatory data available for the ~60% of patients who had reached Week 24 as of 13-Dec-06, the cut-off used for the original application. After the original application, Week 24 data for all patients was available, and was supplied to the FDA. With the agreement with the FDA, Week 24 data for all patients are also provided in this document, though these data were not reviewed by the FDA as part of the original application.
- The **Protocol 018 and 019 combined data** confirmed the superior antiretroviral effect of raltegravir 400 mg b.i.d. plus OBT versus placebo plus OBT. Sub-group analyses suggest that potent efficacy is seen in patients with: high HIV RNA levels; low CD4 cell counts; and high levels of resistance to currently licensed ARTs. Potent efficacy was seen in a diverse patient population regardless of hepatitis B and/or C virus co-infection, gender, race geographic region, or viral sub-type.

7.2 Efficacy in Individual Studies (Protocols 004, 005, 018, and 019)

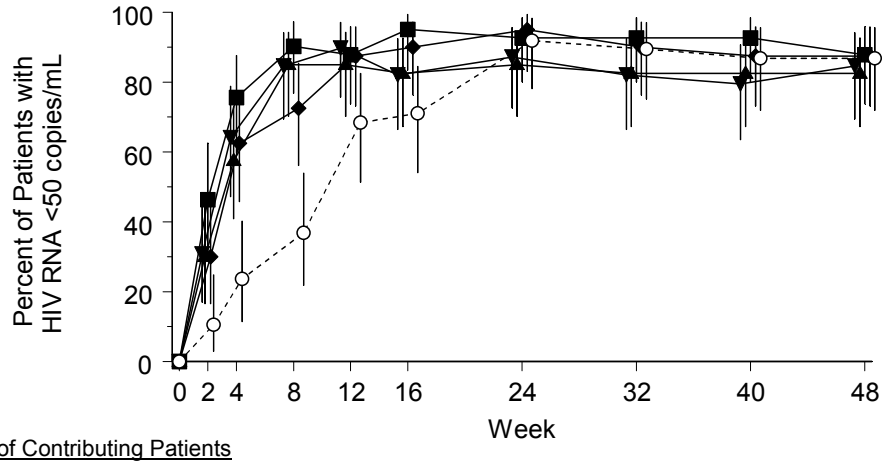
7.2.1 Efficacy in Phase II Dose Ranging Studies (Protocols 004 and 005)

The Phase II dose-ranging studies support the dosing recommendation of raltegravir at 400 mg b.i.d. without regard to food, and in combination with other licensed ARTs.

In ***treatment-naïve patients*** (raltegravir doses of 100, 200, 400, and 600 mg), 85 to 95% achieved HIV RNA <50 copies/mL at Week 24, which was sustained through at least Week 48 (Figure 6). Immunological benefits as measured by increases in CD4 cell counts were also demonstrated at all doses studied. At Week 48, in the raltegravir groups, CD4 cell counts increased by 271-336 cells/mm^3, and in the efavirenz comparator arm, CD4 cell counts increased by 274 cells/mm^3. The antiretroviral effects demonstrated for raltegravir were comparable to those demonstrated by the efavirenz-based regimen, one of the current standards of care for treatment-naïve patients. Interestingly, the raltegravir regimens resulted in a more rapid reduction in viral load than the efavirenz-based regimen.

Figure 6

Percent (95% CI) of Patients Achieving Plasma HIV RNA <50 Copies/mL
Over Time by Treatment Group—Protocol 004†
(Non-Completer=Failure Approach)



Number of Contributing Patients

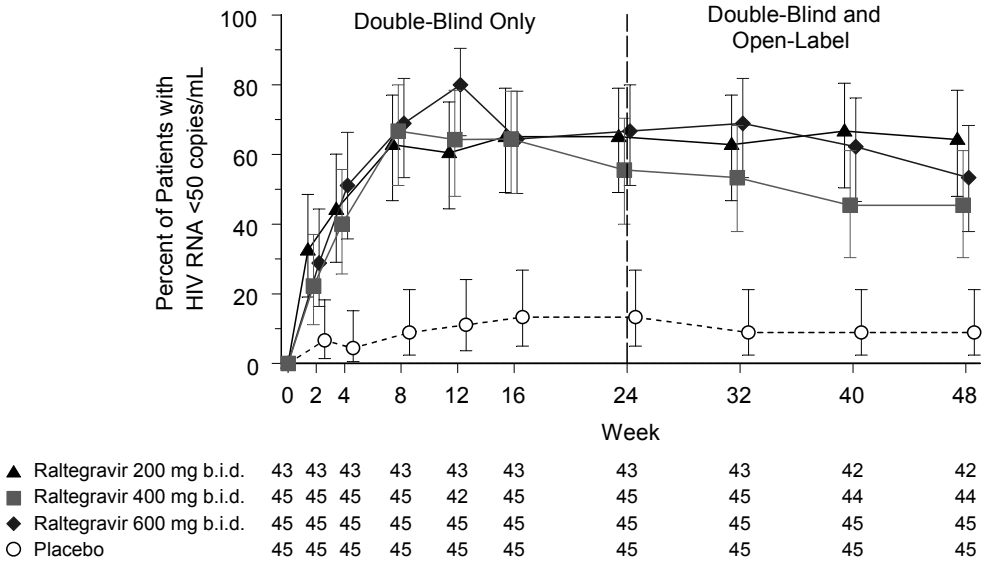
Raltegravir 100 mg b.i.d.	39	39	39	39	39	39	39	39	39	39
Raltegravir 200 mg b.i.d.	40	40	40	40	40	40	40	40	40	40
Raltegravir 400 mg b.i.d.	41	41	41	41	41	41	41	41	41	41
Raltegravir 600 mg b.i.d.	40	40	40	40	40	40	40	40	40	40
Efavirenz 600 mg q.d.	38	38	38	38	38	38	37	38	38	38

† Cohorts I and II Combined; Combination Therapy Phase

In ***treatment-experienced patients*** (Figure 7), 56% to 67% achieved HIV RNA <50 copies/mL at Week 24, the end of the double blind portion; this was sustained through at least Week 48. In the placebo arm, 13% achieved HIV RNA <50 copies/mL. Immunological benefits, as measured by increases in CD4 cell counts during the double blind portion, were also demonstrated at all doses studied. In the raltegravir arms, mean CD4 cell counts increased by 64-100 cells/mm^3, and in the placebo comparator arm, mean CD4 cell counts increased by 17 cells/mm^3. These results were also sustained through at least Week 48. The antiretroviral effect demonstrated for raltegravir was superior to that seen in the placebo group. Protocol 005 provides a stringent test of efficacy, because patients had extensive prior experience and limited treatment options (e.g., 71 of raltegravir-treated patients had GSS=0; 90% of patients had no active PI in the OBT; 26% of patients had prior enfuvirtide exposure). Appendix 1 presents the percentages of patients achieving HIV RNA <400 copies/mL over the same time period.

Figure 7

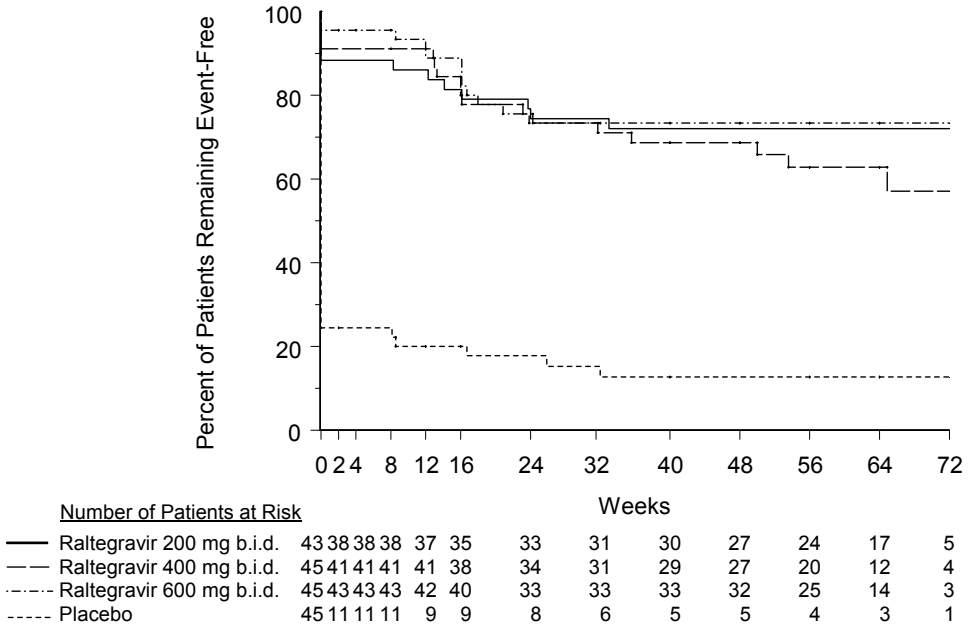
Percent (95% CI) of Patients With HIV RNA <50 Copies/mL Over Time
by Originally Randomized Treatment Group—Protocol 005
(Substudies A and B Combined; Entire Study Period)
(Non-Completer = Failure Approach)



In Protocol 005, the durability of antiretroviral activity was also assessed using Time to Loss of Virological Response (TLOVR) (Figure 8). This analysis includes all data for patients randomized to raltegravir, and encompasses the 24-week double-blind portion of the study, the period between Week 24 and Week 48 representing a mix of double-blind data and open-label extension data, and the period beyond Week 48 during which all patients remaining in study were receiving raltegravir 400 mg b.i.d. Only 3 patients on raltegravir lost virologic response after Week 48, noting that the number of patients with data beyond Week 56 is small (n=13).

Figure 8

Time to Loss of Virological Response – Kaplan-Meier Approach
Protocol 005 All Doses (Substudies A and B Combined; Entire Study Period)



7.2.2 Dose Selection for Phase III

The Phase I development program evaluated raltegravir doses up to 1600 mg administered as single doses and up to 800 mg b.i.d. in healthy volunteers. The Phase II development program evaluated raltegravir doses of 100 to 600 mg b.i.d. in treatment-naïve patients (Protocol 004) and 200 to 600 mg b.i.d. in treatment-experienced patients (Protocol 005). In selecting the dose for the Phase III trials, consideration was given to pharmacokinetic, efficacy and safety data from Phase I and Phase II trials.

Previous experience with antiretroviral therapy suggests that the ratio of trough (C_{12hr})/CIC_{95} is one important predictor of HIV RNA suppression *in vivo*. Treatment experienced patients, in particular, may require a high ratio in order to achieve optimal suppression. Intensive pharmacokinetic sampling performed in the 10 day monotherapy portion of the treatment-naïve study, Protocol 004, confirmed that at 100 mg b.i.d., raltegravir C_{12hr} concentrations (C_{12hr}=42.6 nM [90% CI 24.2,75.0]) potentially overlap with the mean *in vitro* CIC_{95} (33±23 nM), while the 200 mg b.i.d. dose provided only modest margins (C_{12hr}=112.4 nM [90% CI 78.4,161.1]). The 400 mg b.i.d. dose was

potentially more robust (C_{12hr}=141.7 nM [90% CI 87.6, 229.1]). Subsequently, sparse sampling data from the Phase III trials at the 400 mg b.i.d. dose (treatment experienced patients on combination therapy) confirmed robust margins (observed geometric mean C_{12hr}=271.5 nM [90% CI 240.7, 306.2]).

As presented in Section 7.2, there was no differentiation of doses based on efficacy in either Protocol 004 or Protocol 005 through 48 weeks of observation. All doses studied demonstrated potent and sustained efficacy. Extensive population pharmacokinetic/pharmacodynamic analyses in the combination therapy portion of Protocols 004 and in Protocol 005 did not identify a relationship between raltegravir pharmacokinetics and treatment outcomes (see Section 5.6), suggesting that the raltegravir doses studied in these combination regimens were likely on the top plateau of the dose response curve.

As will be presented in Section 8, careful review of safety data revealed no dose-limiting or dose-related toxicities in either Protocol 004 or Protocol 005, including patients receiving 600 mg b.i.d. of raltegravir in combination with atazanavir and tenofovir, which represents the highest exposures to raltegravir in the clinical program.

Phase III studies were planned to include highly treatment experienced patients requiring multiple concomitant medications (including combination antiretrovirals) to manage their overall disease. Drug interaction studies had demonstrated that certain medications could modestly increase or decrease the serum levels of raltegravir through inhibition or induction of UGT1A1 (see Section 5). Given the absence of dose related differences in efficacy or safety in Phase II, the ability to achieve reasonable pharmacokinetic margins in relation to the mean in vitro CIC_{95}, and the potential risks associated with underdosing in HIV therapy (inadequate suppression of HIV RNA and subsequent selection for resistant viral variants), the 400 mg b.i.d. dose of raltegravir was selected for Phase III. This dose provided the best margin of safety and efficacy in the setting of combination therapy.

7.2.3 Efficacy in Phase III (Protocol 018 and Protocol 019)

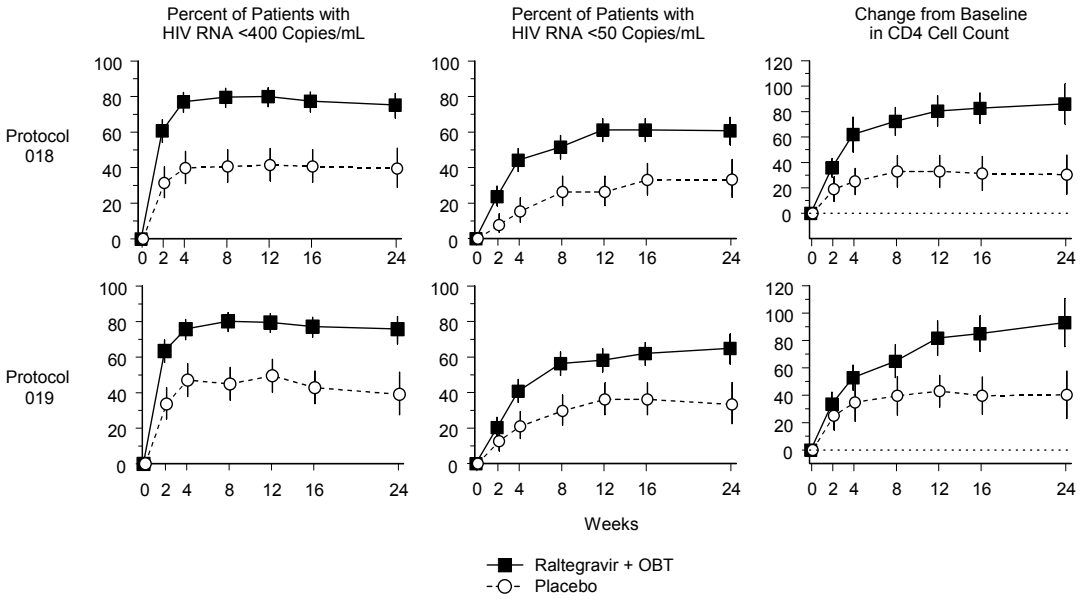
Brief results for the individual studies, Protocols 018 and Protocol 019 are presented here. A detailed discussion of the combined Protocols 018 and 019 dataset is presented in Section 7.3. For completeness, Appendices 1-10 contain details regarding the individual studies, and these appendices will be referenced in the detailed discussion in Section 7.3.

Figure 9 displays the percent of patients achieving HIV RNA <400 copies/mL, HIV RNA <50 copies/mL and the change from baseline CD4 cell count for Protocol 018 and for Protocol 019 individually. Approximately 75% of patients in both studies achieved HIV RNA <400 copies/mL and approximately 60% of patients in both studies achieved HIV RNA<50 copies/mL by Week 16 and this was maintained through Week 24, in the NC=F analyses. At Week 16, which is the primary time point for efficacy analysis, raltegravir was found to be superior to placebo ($p<0.001$) in both studies.

Immunologic benefit, as measured by significantly larger increases in CD4 cell count (cells/mm^3) in the raltegravir 400 mg b.i.d. group as compared to the placebo group (OF analysis; $p<0.001$) was also observed in both studies.

Figure 9

Percent (95% CI) of Patients Achieving Plasma HIV RNA <400 and <50 Copies/mL and Change from Baseline CD4 Cell Count Over Time by Treatment Group (Protocol 018 and Protocol 019)[†]



[†] Non-Completer=Failure Approach (NC=F) for HIV RNA <400 copies/mL and HIV RNA <50 copies/mL. For CD4 cell count: Observed Failure (OF) with baseline value carried for virologic failures. These figures are based on complete data for Week 16 and partial data for Week 24. For Week 16 n=230/118 raltegravir/placebo for Protocol 018 and n=229/119 raltegravir/placebo for Protocol 019. For Week 24 n=158/81 raltegravir/placebo for Protocol 018 and n=128/69 raltegravir/placebo for Protocol 019.

7.3 Efficacy in Protocols 018 and 019 Combined

7.3.1 Patient Demographics: Overview and Relevance of the Patient Population

Figure 10 displays the accounting of all screened patients in Protocols 018 and 019 combined. Of the 1012 patients screened 309 did not meet one or more entry criteria. Most of the screening failures were due either to an HIV RNA level below the study cutoff of 1000 copies/mL, or to a lack of documented resistance to at least 1 agent in each of the 3 classes NRTI, NNRTI, and PI. Of the 703 patients randomized, 699 received at least one dose of study medication. A high proportion of patients randomized to the raltegravir arm (413/462; 89%) remained in the double blind phase through the frozen file. A substantially lower proportion of patients randomized to the placebo arm (145/237; 61%) remained in the double blind portion of the study as 85 patients entered the OLPVF in order to receive raltegravir and 7 discontinued the study. Appendix 2 and Appendix 3 provide the patient accounting for Protocol 018 and Protocol 019 individually.

Figure 10

Summary of Patients Contributing to the Summary of Clinical Efficacy (Protocols 018 and Protocol 019 Combined)

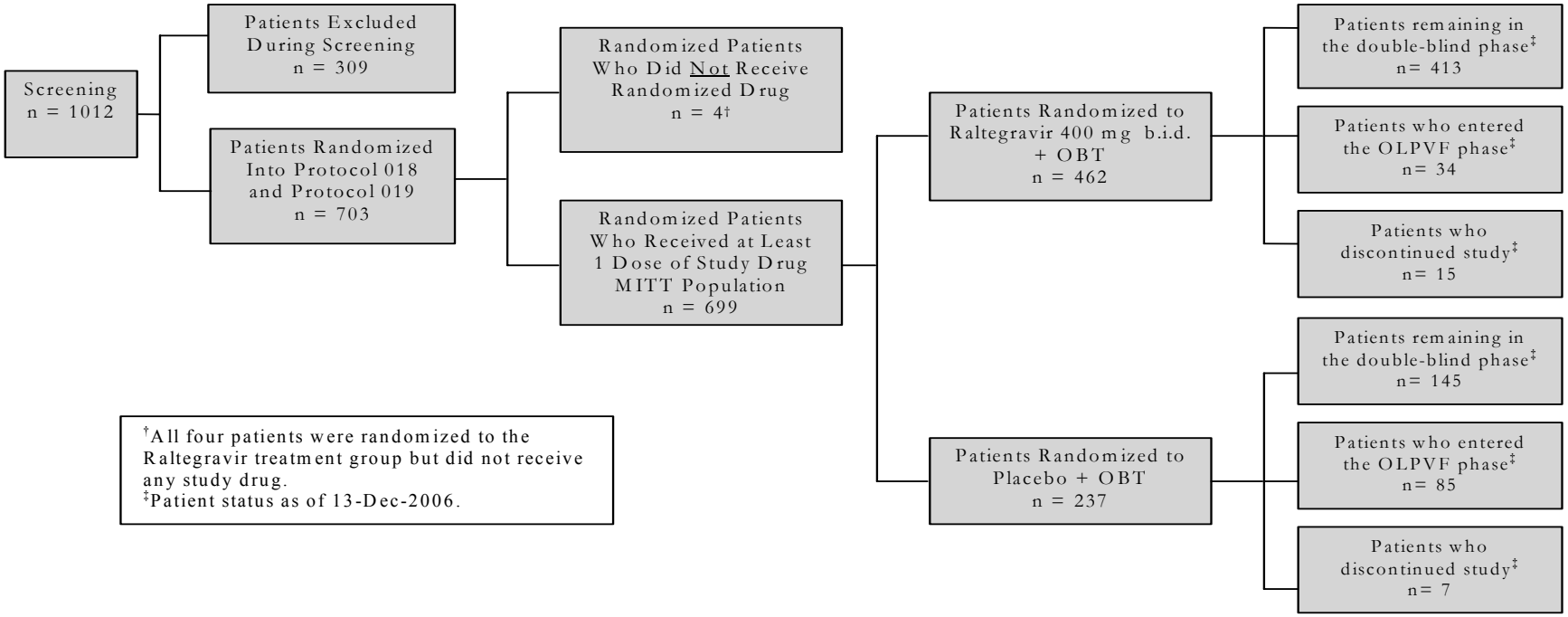


Table 3 and Table 4 present important characteristics of the treatment experienced populations in Protocols 018 and 019 combined. All patients had advanced HIV disease and extensive prior ART experience. The median baseline CD4 cell counts for the raltegravir group and placebo group were 119 cells/mm^3 and 123 cells/mm^3, respectively, with approximately 32% of patients in both groups having CD4 cell counts of ≤50 cells/mm^3 at baseline. Tables presenting this data for Protocols 018 and 019 individually can be found in Appendix 4, Appendix 5, Appendix 6, and Appendix 7. Overall, the baseline data were homogenous for the two studies, and thus combinable.

In order for the results of the Phase III studies to be most informative for the likely patient population in clinical practice, the studies allowed: the inclusion of patients regardless of CD4 cell counts; patients with hepatitis B and/or C virus co-infection; and patients with abnormal baseline laboratory values (e.g., ALT/AST up to 5 times the upper limit of normal). Overall, there was a broad representation of gender, race, international geographic region, and viral subtype. Furthermore, the studies allowed patients in the Phase III studies to utilize certain investigational agents, darunavir and tipranavir, in the OBT subject to local regulatory agencies' approval, in order to maximize the chance that the patient would receive an effective regimen.

As a consequence, patients in the Phase III studies generally had a greater number of active agents in OBTs than those in the Phase II treatment experienced study. In Protocol 005, 71% (32/45) of patients receiving raltegravir 400 mg b.i.d. and 51% (23/45) receiving placebo had GSS of 0. In contrast, in Protocols 018 and 019 combined, 25% (115/462) of patients receiving raltegravir 400 mg b.i.d. and 27% (65/237) of patients receiving placebo had a GSS of 0.

Table 3

Patient Baseline Characteristics by Treatment Group
(Protocols 018 and 019 Combined)

	Protocols 018 and 019	
	Raltegravir 400 mg b.i.d. (N = 462)	Placebo (N = 237)
Gender n (%)		
Male	405 (87.7)	210 (88.6)
Female	57 (12.3)	27 (11.4)
Race n (%)		
White	301 (65.2)	173 (73.0)
Black	66 (14.3)	26 (11.0)
Asian	16 (3.5)	6 (2.5)
Hispanic	53 (11.5)	19 (8.0)
Native American	1 (0.2)	0 (0.0)
Others	25 (5.4)	13 (5.5)
Region n (%)		
North America	192 (41.6)	99 (41.8)
Central/South America	61 (13.2)	31 (13.1)
Asia Pacific	38 (8.2)	20 (8.4)
Europe	171 (37.0)	87 (36.7)
Age (years)		
16-64	455 (98.5)	235 (99.2)
≥65	7 (1.5)	2 (0.8)
Mean (SD)	45.7 (8.6)	45.1 (8.1)
Median (min, max)	45.0 (16 to 74)	45.0 (17 to 70)

Table 3 (Cont.)

Patient Baseline Characteristics by Treatment Group
(Protocols 018 and 019 Combined)

	Protocols 018 and 019	
	Raltegravir 400 mg b.i.d. (N = 462)	Placebo (N = 237)
CD4 Cell Count (cells/mm^3)		
Mean (SD)	151.4 (141.2)	158.0 (150.4)
Median (min, max)	119.0 (1 to 792)	123.0 (0 to 759)
Plasma HIV RNA (log_{10} copies/mL)		
Mean (SD)	4.6 (0.8)	4.6 (0.8)
Median (min, max)	4.8 (2 to 6)	4.7 (2 to 6)
Plasma HIV RNA (copies/mL)		
Geometric Mean	44252.2	39033.6
Median (min, max)	59650.0 (200 to 750000)	45200.0 (200 to 750000)
History of AIDS n (%)		
Yes	426 (92.2)	216 (91.1)
Prior Use of ART Median (1st quartile to 3rd quartile)		
Year of ART Use	10.1 (7.4 to 12.1)	10.2 (7.9 to 12.4)
Number of ART	12.0 (9 to 15)	12.0 (9 to 14)
NRTI	6.0 (0 to 11)	6.0 (0 to 11)
NNRTI	1.0 (0 to 3)	1.0 (0 to 3)
PI	5.0 (0 to 9)	5.0 (0 to 9)
Hepatitis Co-infection† n (%)		
No Hepatitis B or C	385 (83.3)	201 (84.8)
Hepatitis B and/or C	77 (16.7)	36 (15.2)
Hepatitis B only	36 (7.8)	7 (3.0)
Hepatitis C only	37 (8.0)	27 (11.4)
Hepatitis B and C	4 (0.9)	2 (0.8)
Stratum n (%)		
Enfuvirtide in OBT	175 (37.9)	89 (37.6)
Resistant to ≥ 2 PI	447 (96.8)	226 (95.4)
Viral Subtype n (%)		
Clade B	415 (89.8)	217 (91.6)
non-Clade B	40 (8.7)	16 (6.8)
Missing	7 (1.5)	4 (1.7)

† Hepatitis B surface antigen positive or hepatitis C antibody positive.
Note: Raltegravir and Placebo were administered with Optimized Background Therapy (OBT).
N = Number of patients in each treatment group.
n (%) = Number (percent) of patients in each subcategory.

Table 4

Summary of Potential Prognostic Factors and Active Antiretroviral Therapies (ARTs) in OBT (Protocols 018 and 019 Combined)

Baseline Characteristic	Protocols 018 and 019	
	Raltegravir 400 mg b.i.d. (N = 462) n (%)	Placebo (N = 237) n (%)
Baseline Plasma HIV RNA (copies/mL)		
≤ 50,000	217 (47.0)	125 (52.7)
> 50,000	245 (53.0)	112 (47.3)
≤ 100,000	298 (64.5)	159 (67.1)
> 100,000	164 (35.5)	78 (32.9)
Baseline CD4 Cell Counts (cells/mm^3)		
≤ 50	146 (31.6)	78 (32.9)
> 50 and ≤ 200	173 (37.4)	85 (35.9)
> 200	142 (30.7)	74 (31.2)
Missing	1 (0.2)	0 (0.0)
Number of ARTs in OBT		
Median (min, max)	4.0 (1 to 7)	4.0 (2 to 7)
Enfuvirtide Use in OBT		
No	287 (62.1)	148 (62.4)
Yes in enfuvirtide-experienced patients	83 (18.0)	41 (17.3)
Yes in enfuvirtide-naïve patients	92 (19.9)	48 (20.3)
Darunavir Use in OBT		
No	278 (60.2)	138 (58.2)
Yes in darunavir-experienced patients	18 (3.9)	9 (3.8)
Yes in darunavir-naïve patients	166 (35.9)	90 (38.0)
Tipranavir Use in OBT		
No	364 (78.8)	193 (81.4)
Yes in tipranavir Resistant Patients (Phenotypic Test)	41 (8.9)	19 (8.0)
Yes in tipranavir Sensitive Patients (Phenotypic Test)	53 (11.5)	25 (10.5)
Yes in tipranavir Resistant Patients (Genotypic Test)	44 (9.5)	22 (9.3)
Yes in tipranavir Sensitive Patients (Genotypic Test)	53 (11.5)	22 (9.3)
Number of Active PI in OBT by Phenotypic Resistance Test[†]		
0	166 (35.9)	97 (40.9)
1 or more	278 (60.2)	137 (57.8)
Missing	18 (3.9)	3 (1.3)

Table 4 (Cont.)

Summary of Potential Prognostic Factors and Active Antiretroviral Therapies (ARTs) in OBT (Protocols 018 and 019 Combined)

Baseline Characteristic	Protocols 018 and 019	
	Raltegravir 400 mg b.i.d. (N = 462) n (%)	Placebo (N = 237) n (%)
Phenotypic Sensitivity Score (PSS)‡		
0	67 (14.5)	44 (18.6)
1	145 (31.4)	71 (30.0)
2	142 (30.7)	66 (27.8)
3 or more	85 (18.4)	48 (20.3)
Missing	23 (5.0)	8 (3.4)
Genotypic Sensitivity Score (GSS) ‡		
0	115 (24.9)	65 (27.4)
1	178 (38.5)	96 (40.5)
2	111 (24.0)	49 (20.7)
3 or more	51 (11.0)	23 (9.7)
Missing	7 (1.5)	4 (1.7)

† Darunavir use in OBT in darunavir naïve patients 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 patient's viral isolate showed phenotypic sensitivity and genotypic sensitivity, respectively, based upon phenotypic and genotypic resistance tests. Enfuvirtide use in OBT in enfuvirtide-naïve patients was counted as one active drug in OBT and added to the GSS and PSS. Darunavir use in OBT in darunavir-naïve patients was counted as one active drug in OBT and added to the PSS and GSS.

Note: Missing refers to patients whose baseline genotypic and/or phenotypic test results are not available, or whose baseline CD4 cell count is not available.

Note: Raltegravir and Placebo were administered with Optimized Background Therapy (OBT).

N = Number of patients in each treatment group.

n (%) = Number (percent) of patients in each subcategory.

7.3.2 Efficacy in Protocols 018 and 019 Combined

Protocols 018 and 019 combined, demonstrated the consistently superior efficacy of raltegravir 400 mg b.i.d. plus OBT over placebo plus OBT at Week 16 (Table 5). Data from the 62% of patients who had reached Week 24 were consistent with the Week 16 data (Table 5). In Protocols 018 and 019 combined, the primary efficacy endpoint (percent of patients achieving HIV RNA <400 copies/mL) and all secondary endpoints demonstrated superiority of raltegravir 400 mg b.i.d. over placebo ($p<0.001$ by logistic regression model). Data for the individual studies can be found in Appendix 8, Appendix 9, Appendix 10, and Appendix 11 and show similar results.

The percentages of patients achieving HIV RNA <400 copies/mL, <50 copies/mL, and the change from baseline in CD4 cell count over time are displayed graphically in Figure 11. It is of note that in Protocols 018 and 019, the percentages of patients receiving placebo who had a virologic response was higher than that observed in Protocol 005 (Figure 7). This is most likely related to the permitted use of investigational ARTs in OBT in the Phase III studies, but not in Protocol 005.

TLOVR analysis from Protocols 018 and 019 combined, demonstrate that failures beyond Week 16 were uncommon based on available data up to Week 32 (Figure 12).

Table 5

Treatment Outcome at Week 16 and Week 24 (All Randomized and Treated Patients)
(Protocols 018 and 019 Combined)

	Protocols 018 and 019 Combined			
	Week 16		Week 24[§]	
Outcome	Raltegravir (N=462) n (%)	Placebo (N=237) n (%)	Raltegravir (N=286) n (%)	Placebo (N=150) n (%)
Patients with HIV RNA < 400 copies/mL	355 (76.8)	99 (41.8)	216 (75.5)	59 (39.3)
Patients with HIV RNA < 50 copies/mL	283 (61.3)	82 (34.6)	179 (62.6)	50 (33.3)
Patients with > 1 Log_{10} drop in HIV RNA or HIV RNA < 400 copies/mL	387 (83.8)	109 (46.0)	231 (80.8)	65 (43.3)
Mean HIV RNA change from baseline (Log_{10} copies/mL)	-1.88	-0.92	-1.85	-0.84
Mean CD4 cell count change from baseline (cells/mm^3)	83.9	35.6	89.2	35.0
Virologic Failure (confirmed) [†]	70 (15.2)	120 (50.6)	74 (16.0)	121 (51.1)
Non responder [†]	13 (2.8)	78 (32.9)	13 (2.8)	78 (32.9)
Rebound [†]	57 (12.3)	42 (17.7)	61 (13.2)	43 (18.1)
Death	6 (1.3)	3 (1.3)	6 (1.3)	3 (1.3)
Adjudicated AIDS-Defining Conditions (ADC)	11 (2.4)	5 (2.1)	14 (3.0)	6 (2.5)
Discontinuation due to clinical adverse events	7 (1.5)	5 (2.1)	8 (1.7)	5 (2.1)
Discontinuation due to laboratory adverse events	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)
Discontinuation due to other reasons [‡]	6 (1.3)	1 (0.4)	6 (1.3)	1 (0.4)

[†] Virologic failure: defined as non-responders who did not achieve >1.0 log_{10} HIV RNA reduction or <400 HIV RNA copies/mL by Week 16, or viral rebound, which was defined as: (a) HIV RNA >400 copies/mL (on 2 consecutive measurements at least 1 week apart) after initial response with HIV RNA <400 copies/mL, or (b) >1.0 log_{10} increase in HIV RNA above nadir level (on 2 consecutive measurements at least 1 week apart).

[‡] Includes loss to follow-up, patient withdrew consent, noncompliance, protocol violation and other reasons.

[§] Based on ~60% of enrolled patients who had reached Week 24.

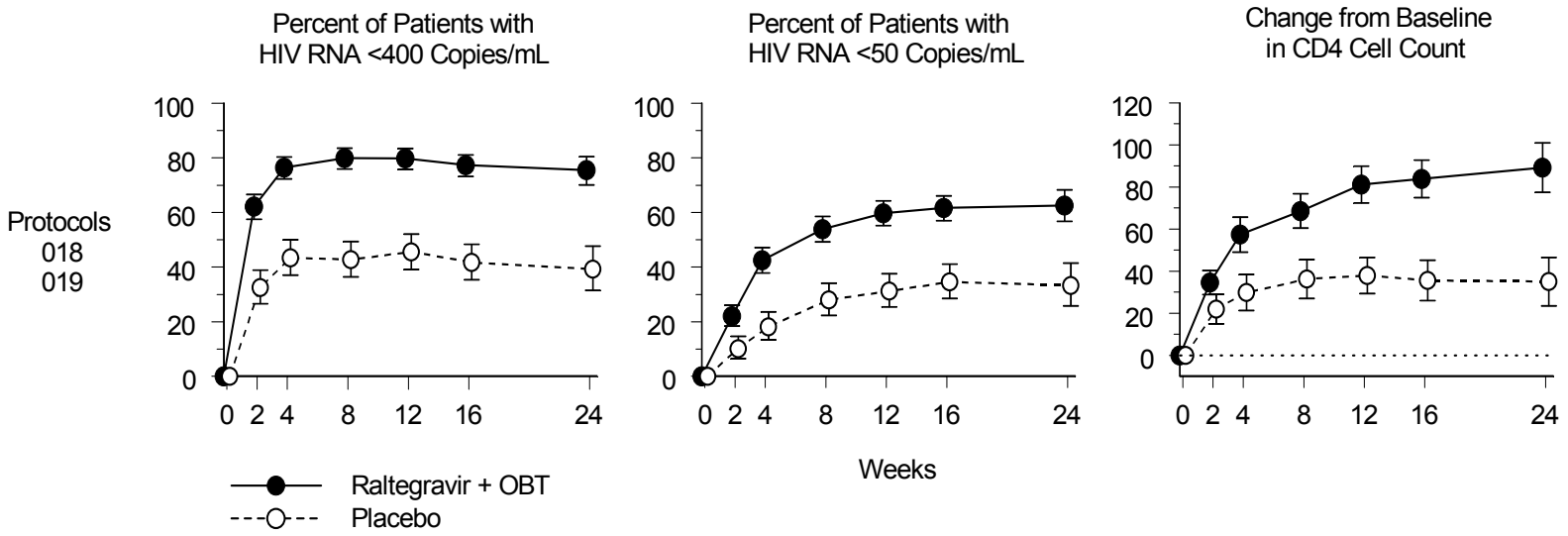
Note: Raltegravir and Placebo were administered with Optimized Background Therapy (OBT).

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

N/A = Not applicable

Figure 11

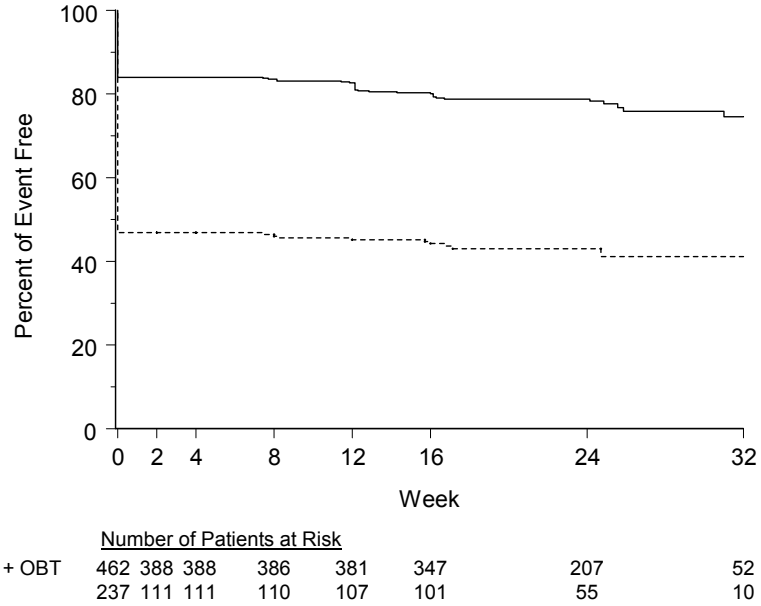
Percent (95% CI) of Patients Achieving HIV RNA <400 Copies/mL, HIV RNA <50 Copies/mL, and Mean (95% CI) Change From Baseline CD4 Cell Count (cells/mm^3) by Treatment Group
Protocols 018 and 019 Combined[†]



[†] For HIV RNA <400 copies/mL and <50 copies/mL: Non-Completer = Failure approach.
For CD4: Baseline carried forward for virologic failures.
All patients had reached Week 16. Approximately 60% of patients had reached Week 24.

Figure 12

Time to Loss of Virologic Response—Protocols 018 and 019 Combined (Double-Blind Period)†



† Patients who never responded were assigned virologic failure at Time=0.

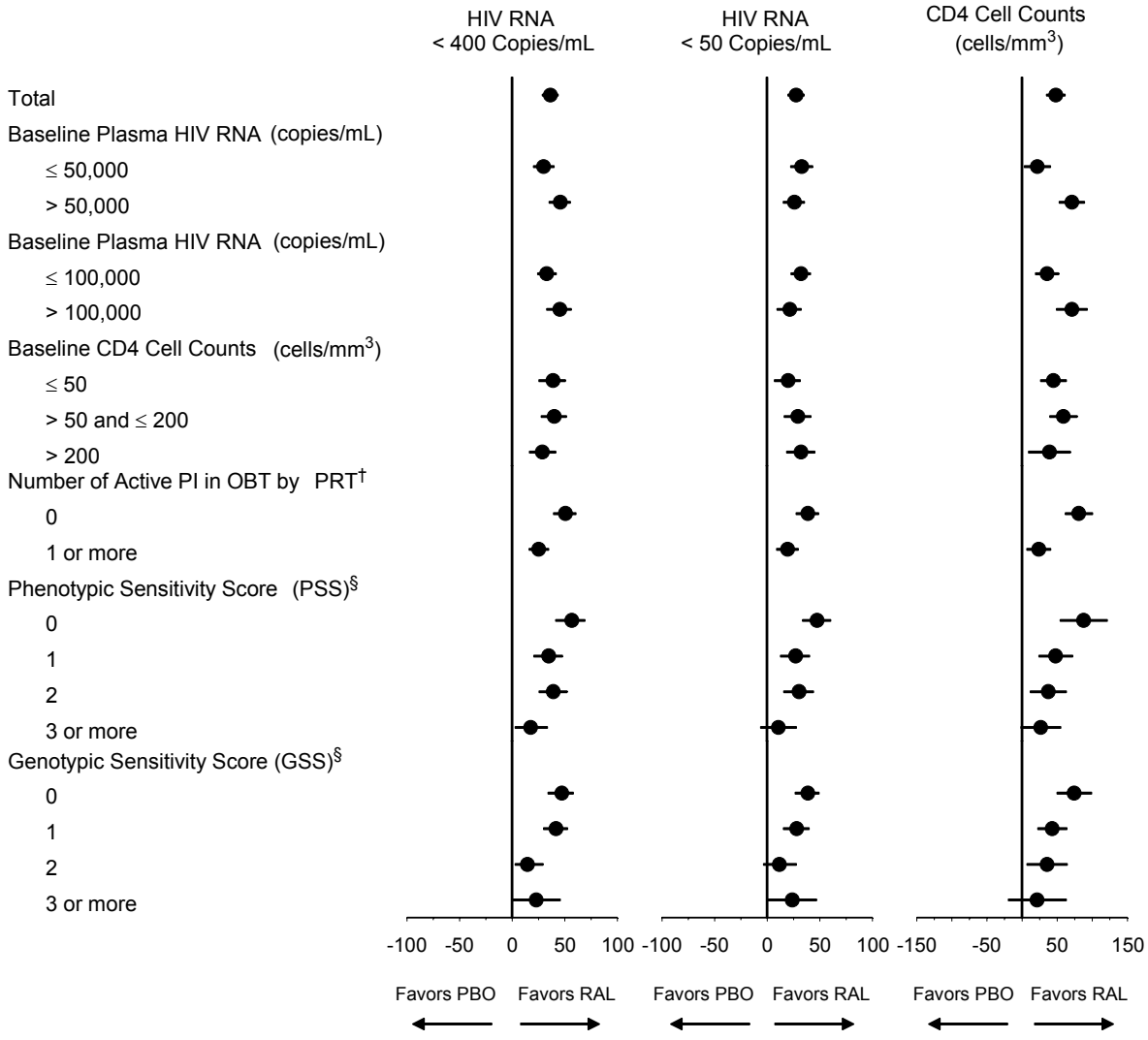
7.3.3 Efficacy by Prognostic Factors

Subgroup analyses using combined data from Protocols 018 and 019 evaluated efficacy of raltegravir by baseline prognostic factors including baseline HIV RNA, baseline CD4 cell count, active PI in OBT, and PSS and GSS of OBT (Proportion of patients by treatment group presented in Appendix 12 and differences between treatment groups shown in Figure 13). Taking into consideration that within each subgroup analysis there may be an imbalance in other prognostic factors between the raltegravir group versus the placebo group and that the studies were not powered to show statistically significant effects within the subgroups, these analyses confirmed the consistent efficacy of raltegravir in combination with OBT. Specifically, raltegravir demonstrated potent efficacy as compared to placebo across all of these baseline prognostic factors.

Raltegravir demonstrated potent efficacy as compared to placebo in patients with GSS and/or PSS of 0, generally regarded as the hardest to treat patients. As expected, a higher response rate was observed in patients with greater GSS/PSS (e.g., GSS/PSS ≥2) in the control group. None the less, raltegravir demonstrated potent efficacy as compared to placebo when used in combination with these relatively active OBTs.

Figure 13

Difference in Percentages of Patients With HIV RNA <400 Copies/mL, HIV RNA <50 Copies/mL, and Difference in Means of Change From Baseline CD4 Cell Count (cells/mm^3) Between the Raltegravir 400 mg b.i.d. Group and the Placebo Group (Raltegravir minus Placebo) at Week 16 by Prognostic Factors─Protocols 018 and Protocol 019 Combined (Observed Failure Approach)



† PRT=Phenotypic Resistance Test. Darunavir use in OBT in darunavir-naïve patients 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 patient's viral isolate showed phenotypic sensitivity and genotypic sensitivity, respectively, based upon phenotypic and genotypic resistance tests. Enfuvirtide use in OBT in enfuvirtide-naïve patients was counted as one active drug in OBT and added to the PSS and GSS. Darunavir use in OBT in darunavir-naïve patients was counted as one active drug in OBT and added to the PSS and GSS.

Lines to the right of the 0% difference mark favor raltegravir (RAL), while lines to the left, favor placebo (PBO).

7.3.4 Efficacy by Darunavir, Enfuvirtide, and Darunavir Plus Enfuvirtide

Additional analyses to evaluate the effect of more recently available ART used in OBT were performed. The efficacy analysis by darunavir, enfuvirtide, and darunavir plus enfuvirtide use in OBT demonstrated that raltegravir had potent efficacy as compared to placebo across all subgroups (see Table 6 and Figure 14). In fact, when patients in the raltegravir group had first use of both darunavir and enfuvirtide, 98% achieved HIV RNA <400 copies/mL at Week 16. These data suggest that while raltegravir demonstrates potent efficacy in patients with few or no fully active agents for use in OBT, best overall treatment responses may be seen when raltegravir is used in combination with 1 or 2 newer active antiretrovirals such as enfuvirtide and/or darunavir.

Table 6

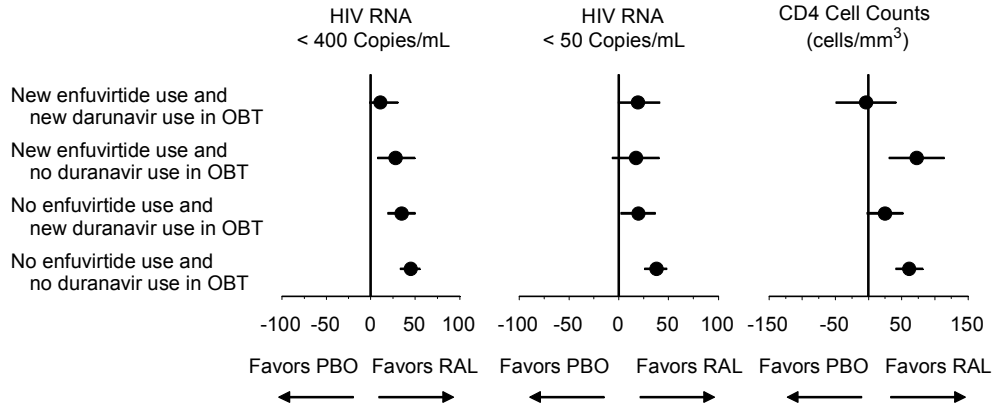
Proportion of Patients With Plasma HIV RNA <400 Copies/mL at Week 16 by First Use of Enfuvirtide and Darunavir
Protocols 018 and 019 Combined
(Observed Failure Approach)

First Use of OBT Factor	Response				Difference in Percent Response
	Raltegravir (Group A)		Placebo (Group B)		
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Naive enfuvirtide use and naive darunavir use †	43/44	97.7 (88.0, 99.9)	20/23	87.0 (66.4, 97.2)	10.8 (-1.4, 30.3)
Naive enfuvirtide use and no darunavir use ‡	38/42	90.5 (77.4, 97.3)	15/24	62.5 (40.6, 81.2)	28.0 (7.7, 49.4)
No enfuvirtide use and naive darunavir use §	72/80	90.0 (81.2, 95.6)	26/47	55.3 (40.1, 69.8)	34.7 (19.2, 50.0)
No enfuvirtide use and no darunavir use ‖	141/191	73.8 (67.0, 79.9)	26/90	28.9 (19.8, 39.4)	44.9 (33.0, 55.4)

† Patients received both enfuvirtide and darunavir for the first time in Protocol 018/019. Patients who received either enfuvirtide or darunavir prior to enrollment in Protocol 018/019 were excluded.
‡ Patients received enfuvirtide for the first time in Protocol 018/019. Patients who received enfuvirtide prior to enrollment in Protocol 018/019 were excluded.
§ Patients received darunavir for the first time in Protocol 018/019. Patients who received darunavir prior to enrollment in Protocol 018/019 were excluded.
‖ Patients may or may not have received either darunavir or enfuvirtide prior to enrollment in Protocol 018/019.
Note: Raltegravir and Placebo were administered with Optimized Background Therapy (OBT).
N = Number of patients in each treatment group.
n = Number of patients in each subcategory.
CI = confidence interval

Figure 14

Difference in Percentages of Patients With HIV RNA <400 Copies/mL, HIV RNA <50 Copies/mL, and Difference in Means of Change From Baseline CD4 Cell Count (cells/mm^3) Between the Raltegravir 400 mg b.i.d. Group and the Placebo Group (Raltegravir Minus Placebo) at Week 16 by First Use of Enfuvirtide and Darunavir─Protocols 018 and 019 Combined
(Observed Failure Approach)



For each of the above three plots, right side of the vertical line at 0 difference favors raltegravir (RAL) and the left side of the line favors placebo (PBO).
New = naïve

7.3.5 Efficacy by Tipranavir Use

In light of the potential inductive effect of tipranavir on the pharmacokinetics of raltegravir, analysis of tipranavir use in the Phase III studies was undertaken (See Table 7 and Figure 15). Raltegravir demonstrated potent efficacy as compared to placebo regardless of whether or not tipranavir was used as part of OBT. In patients with genotypically tipranavir sensitive HIV, 86% of patients receiving raltegravir achieved HIV RNA<400 copies/mL as compared to 48% of patients receiving placebo. The evaluation of raltegravir in patients utilizing tipranavir in the setting of tipranavir-resistant HIV represents a strict test of the impact of the pharmacokinetic interaction between tipranavir and raltegravir because in these patients tipranavir would not be predicted to be adding substantive antiretroviral efficacy into the regimen and would modestly reduce raltegravir levels; 56% of genotypically tipranavir resistant patients on raltegravir versus 26% on placebo achieved HIV RNA <400 copies/mL. The response rates were lower in both groups as one would anticipate because tipranavir was not active in the regimen and no other protease inhibitor would likely be used in a tipranavir-

containing OBT. Despite this, the magnitude of the treatment effect versus placebo was preserved in the raltegravir group. Overall, these data support that the impact of tipranavir on raltegravir PK is unlikely to be clinically significant in the setting of combination therapy.

Table 7

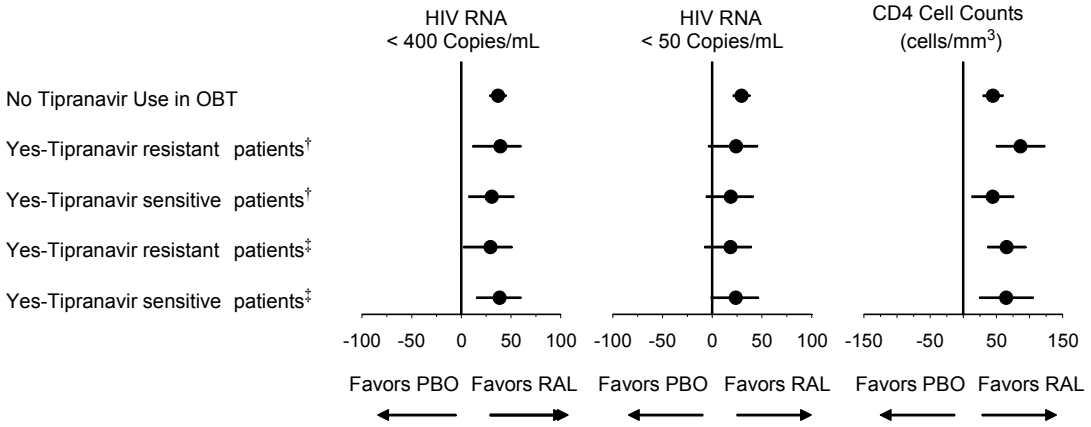
Proportion of Patients With Plasma HIV RNA <400 Copies/mL at Week 16 by Tipranavir Use
Protocols 018 and 019 Combined
(Observed Failure Approach)

	Response				Difference in Percent Response
	Raltegravir 400 mg b.i.d. (Group A)		Placebo (Group B)		
Prognostic Factor	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
Total	355/447	79.4 (75.4, 83.1)	99/230	43.0 (36.6, 49.7)	36.4 (28.8, 43.6)
Tipranavir Use in OBT					
No	286/352	81.3 (76.8, 85.2)	84/190	44.2 (37.0, 51.6)	37.0 (28.8, 45.0)
Yes in Tipranavir Resistant Patients (Phenotypic Test)	24/39	61.5 (44.6, 76.6)	4/18	22.2 (6.4, 47.6)	39.3 (11.5, 60.0)
Yes in Tipranavir Sensitive Patients (Phenotypic Test)	42/52	80.8 (67.5, 90.4)	11/22	50.0 (28.2, 71.8)	30.8 (7.7, 52.7)
Yes in Tipranavir Resistant Patients (Genotypic Test)	24/43	55.8 (39.9, 70.9)	5/19	26.3 (9.1, 51.2)	29.5 (2.4, 50.9)
Yes in Tipranavir Sensitive Patients (Genotypic Test)	44/51	86.3 (73.7, 94.3)	10/21	47.6 (25.7, 70.2)	38.7 (15.5, 60.0)

Note: Raltegravir and Placebo were administered with Optimized Background Therapy (OBT).
N = Number of patients in each treatment group.
n = Number of patients in each subcategory.
CI = confidence interval

Figure 15

Difference in Percentages of Patients With HIV RNA <400 Copies/mL, HIV RNA <50 Copies/mL, and Difference in Means of Change From Baseline CD4 Cell Count (cells/mm^3) Between the Raltegravir 400 mg b.i.d. Group and the Placebo Group (Raltegravir Minus Placebo) at Week 16 by Tipranavir Use in OBT—Protocols 018 and Protocol 019 Combined (Observed Failure Approach)



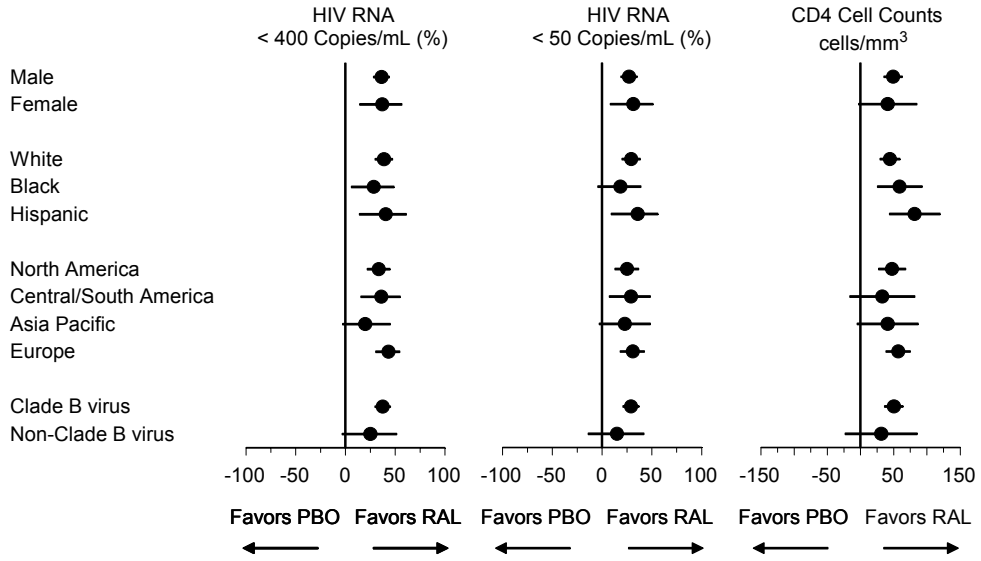
† Based on phenotypic test
‡ Based on genotypic test
For each of the above three plots, right side of the vertical line at 0 difference favors raltegravir (RAL) and the left side of the line favors placebo (PBO).

7.3.6 Efficacy in Special Populations

Efficacy analyses by gender, race, viral subtype (B versus non-B clade), and geographic region demonstrated potent efficacy of raltegravir as compared to placebo and this efficacy did not appear different in any of the subgroups analyzed (Figure 16). Given the limited number of patients 65 years or older studied (N=9), assessment of efficacy of raltegravir in this patient population could not be made. There were no data in the pediatric patient population (age <16) and no data in pregnant HIV-infected women. Appendix 13, Appendix 14, and Appendix 15 contain the supporting data.

Figure 16

Difference in Percentages of Patients with HIV RNA <400 copies/mL, HIV RNA <50 copies/mL, and Differences in Means of Change from Baseline CD4 Cell Count (cells/mm^3) between the Raltegravir 400 mg b.i.d. Group and the Placebo Group (Raltegravir Minus Placebo) at Week 16─Protocols 018 and 019 Combined



For each of the above three plots, right side of the vertical line at 0 difference favors raltegravir (RAL) and the left side of the line favors placebo (PBO).

7.3.7 Conclusions Regarding the Clinical Efficacy of Raltegravir

1. In HIV-infected, treatment-experienced patients failing antiretroviral therapy with triple-class resistant HIV, raltegravir at 400 mg b.i.d. in combination with an optimized background therapy (OBT):

   - Has superior antiretroviral and immunological efficacy compared with placebo in combination with OBT at Week 16.
   - Has antiretroviral and immunological efficacy at Week 24 that is comparable to that at Week 16 based on Week 24 data from 90 patients from Protocol 005, and Week 24 data from 436 patients from Protocols 018 and 019 combined.
   - Has efficacy in patients whose baseline factors predict poor response to therapy, and in patients with few or no available active antiretroviral agents for use in OBT.

- Has efficacy in patients receiving newer active antiretrovirals as part of OBT, including darunavir and enfuvirtide.
- Has sustained efficacy in patients followed to Week 32 and to Week 72 based on available time to loss of virologic response data from Protocols 018 and 019 combined, and Protocol 005, respectively.
- Is efficacious when dosed without regard to food, and when used in combination with drugs that are known to modestly alter raltegravir levels.

2. In HIV-infected, treatment-naïve patients, raltegravir at 400 mg b.i.d., in combination with tenofovir and lamivudine demonstrates potent antiretroviral activity at Week 48 that is comparable to that demonstrated in patients taking efavirenz at 600 mg q.h.s, in combination with tenofovir and lamivudine. Patients receiving raltegravir achieved HIV RNA <50 copies/mL faster than patients receiving efavirenz.

7.3.7.1 Efficacy Update: Week 24 Analysis

The data in this section have been submitted to the Food and Drug Administration (FDA), and are included in this document with their agreement. However, this data have not been reviewed by the FDA.

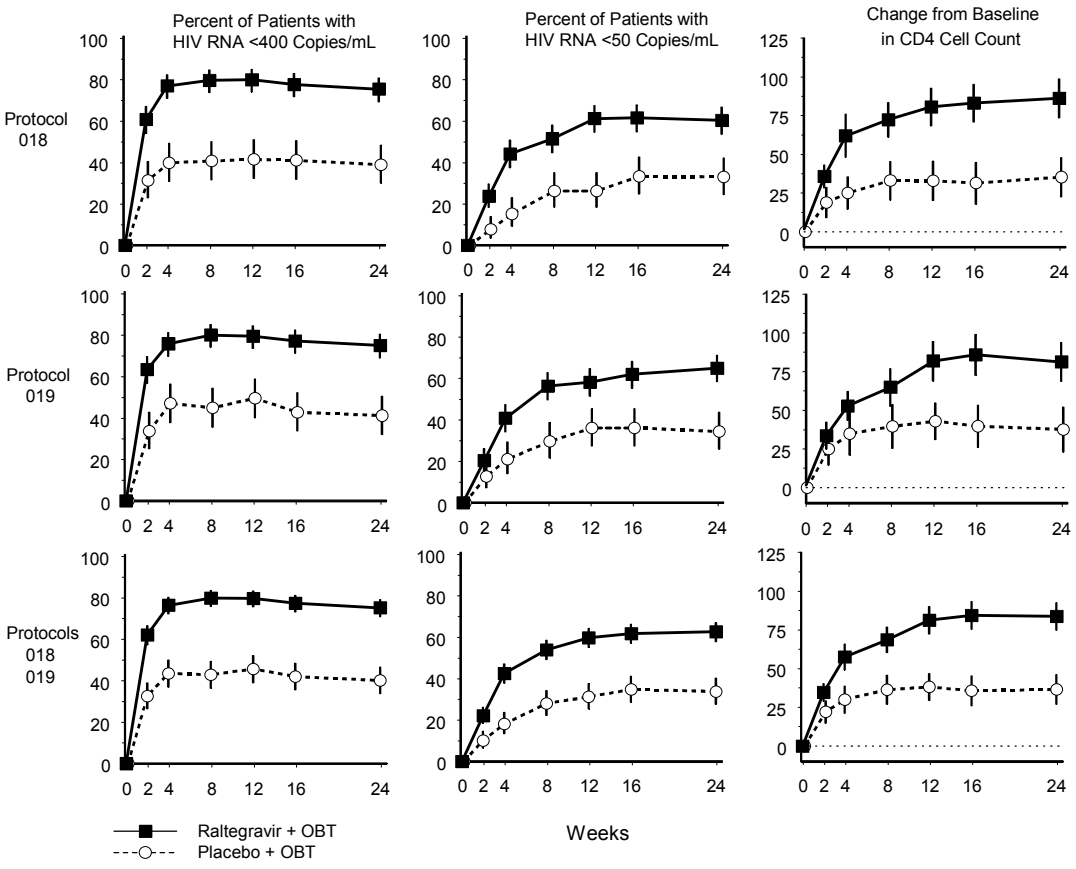
For Protocol 018 and Protocol 019, the Week 24 efficacy data submitted in the original application (data through 13-Dec-2007) represented data on ~60% of patients enrolled, as not all patients had reached the Week 24 visit of the study by that time. Week 24 data from all (100%) patients became available as of 16-Feb-07. As per agreement with the FDA, analyses from the original application have been repeated using the cumulative updated data for all patients at Week 24, and are included here.

Appendix 16, Appendix 17, and Appendix 18 display the patient accounting for Protocol 018, Protocol 019, and Protocol 018 and 019 combined, respectively. In the combined data set, 54/466 (11%) of patients in the raltegravir arm and 104/237 (44%) of patients receiving placebo experienced virologic failure and transferred to the OLPVF through Week 24 of these studies. It is important to note that all patients transferring to the OLPVF were carried forward as failures in the analyses.

Figure 17 displays the percent of patients achieving HIV RNA <400 copies/mL, HIV RNA <50 copies/mL and the change from baseline CD4 cell count for each of the individual studies and for the combined dataset, over time. Appendix 19, Appendix 20, and Appendix 21 present all pre-specified treatment outcomes for Protocol 018, Protocol 019, and Protocol 018 and 019 combined, respectively. The efficacy at Week 24 based on all patients (100%) is very similar to that shown previously based on ~60% of patients and is consistent with the relevant efficacy conclusions in Section 7.5.

Figure 17

Percent (95% CI) of Patients Achieving Plasma HIV RNA <400 and <50 Copies/mL and Change from Baseline CD4 Cell Count Over Time by Treatment Group (Protocols 018 and 019 Individually and Combined)- Updated Analysis of Week 24 Data with all Patients)†
These data have not yet been reviewed by the FDA



† Non-Completer=Failure Approach.
Based on complete data for Week 16 and complete data for Week 24.

7.4 Resistance

7.4.1 Principles of Antiviral Drug Resistance in HIV-1 Therapy

Patients whose HIV RNA levels are suppressed to <50 copies/mL are at low risk of virologic rebound secondary to antiretroviral resistance. Despite treatment with the best available antiretroviral regimens, however, a loss of virologic control inevitably occurs in a significant percentage of patients. The viruses that rebound despite antiretroviral therapy usually display specific mutations that confer drug resistance.

In clinical studies of the 1990's where antiretroviral drugs were given as monotherapy for extended time periods, most patients experienced rapid virologic failure due to the emergence of drug-resistant HIV-1 variants. Because HIV-1 replication is driven by an error-prone polymerase (reverse transcriptase), clinical HIV-1 isolates normally display extensive genetic heterogeneity and have high potential for rapid evolution. The failure of antiviral drugs to completely suppress viral replication allows for continued viral evolution, and, ultimately, for the selection of variants able to replicate better in the presence of the drug. Investigators later found that using potent antiretroviral drugs in combination, now the standard of care, promotes more durable virologic control by minimizing ongoing replication and thereby reducing the chance for resistant viruses to evolve.

Collectively, these earlier clinical studies teach that the likelihood of resistant viruses emerging during therapy increases as the effectiveness of the therapy decreases, and that maximally effective therapy requires a combination of potent antiviral drugs. For any new antiviral drug, maximum efficacy is expected when the drug is administered with other potent antiretroviral agents to which patient viruses are sensitive. In contrast, administration of a new drug in combination with other drugs to which patient viruses are already resistant increases the chance that resistance will develop to the new drug, resulting in virologic failure.

7.4.2 Overall Summary of Raltegravir Resistance

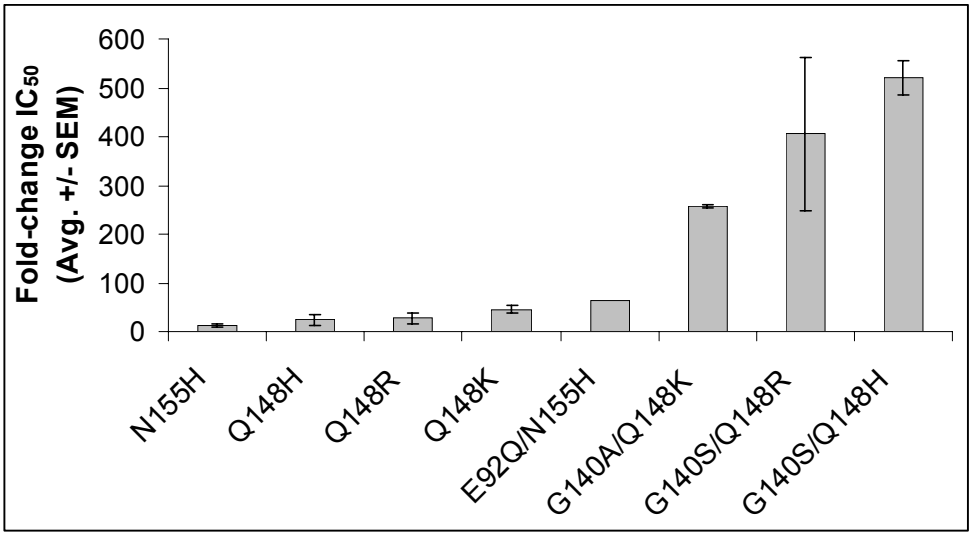
In the three clinical studies of raltegravir in highly treatment-experienced patients (Protocols 005, 018, and 019), virologic failure occurred in the minority of patients receiving a regimen containing raltegravir, and was less common in patients who had one or more additional active drugs in their regimen (i.e., patients with GSS>0 or PSS>0). Virologic failure was even less frequent in Protocol 004, where patients who had not previously been treated with antiviral drugs received raltegravir in combination with tenofovir and lamivudine, all drugs to which the patient viruses were sensitive.

As described above, when viral rebound or non-response is observed during therapy, it is likely that the predominant circulating virus populations are drug resistant. In raltegravir-treated patients displaying viral rebound or non-response, the emergence of raltegravir resistant viruses was monitored by isolating plasma viral RNA, determining the amino acid sequences encoded by the integrase gene via population sequencing, and comparing the sequence at virologic failure with the sequence at baseline for the same patient.

In most instances, viruses isolated from patients experiencing virologic failure during raltegravir therapy displayed mutations that confer raltegravir resistance. Virologic failure was generally associated with at least two mutations in the integrase gene in which one of the mutations present included a change at either amino acid 148 (Q changed to H, K, or R) or amino acid 155 (N changed to H). When introduced into HIV-1 by site-directed mutagenesis, these mutations at 155 or 148 were observed to confer decreased susceptibility to raltegravir (Figure 18), but these mutations also decreased viral replication capacity in cell culture.

Figure 18

Integrase Mutations Associated With Raltegravir Virologic Failure Confer Raltegravir Resistance



The indicated mutations were introduced into wild-type HIV by site-directed mutagenesis, and the mutant viruses were tested for sensitivity to raltegravir in a single-cycle HIV-1 infection assay. Fold-change IC_{50} is defined as the IC_{50} of the mutant virus divided with the IC_{50} of the wild-type virus. Fold-change IC_{50} values are shown as mean ± SEM (standard error of the mean) for multiple independent experiments except for E92Q/N155H, which was the result of a single experiment.

In addition to the primary integrase mutations at amino acid 148 or 155, viruses from many patients displayed secondary changes including L74M, E92Q, T97A, F121N, E138A/K, G140A/S, Y143H/C/R, G163K/R, S230R, and D232N. Among these, we have examined the effect of mutations at residues L74, E92, T97, F121, E138, and G140 in detail. By themselves, each of these changes had only a minimal impact on raltegravir susceptibility, but when combined with a primary mutation these mutations further decreased susceptibility to raltegravir. Figure 18 shows examples of adding E92Q to

N155H, and of adding G140A or G140 S to mutations at Q148. In some cases, addition of secondary mutations also resulted in increased viral replication capacity, however the replication capacities of these multiply-mutated viruses were generally decreased to that of the wild-type virus.

Although examples of virologic failures were observed in which integrase displayed other mutations in the absence of a mutation at 148 or 155, the viruses of most virologic failures did contain a change in one of these two integrase residues. In addition, the majority of viruses contained two or more mutations in the integrase coding region.

7.4.3 Protocol 004 – Treatment-Naïve Patients (Combination Therapy Phase)

Five patients in the raltegravir treatment groups experienced virologic failure. Of these, mutations in the integrase region were observed in virus isolated from 2 subjects (1 with N155H, V151I, G163R/G, D232D/N; 1 with N155H). Both also had reverse transcriptase (RT) mutations and phenotypic resistance documented to TFV and 3TC (1 patient) or 3TC alone (1 patient). The virus from the remaining 3 patients had no integrase mutations, but 2 had RT mutations and phenotypic resistance to 3TC. One patient had virus that was genotypically fully sensitive at failure.

7.4.4 Protocols 005, 018, and 019 – Treatment-Experienced Patients

Out of the patients treated with raltegravir in Protocol 005, virologic failure was observed in 38 patients. Integrase sequences were obtained at baseline and a point near virologic failure for all 38 of the virologic failures, and resistance-related integrase mutations were observed in 35 of these patients (Table 8). Most of the HIV from these patients showed a mutation at either amino acid 155 (14 patients) or amino acid 148 (20). Two or more integrase mutations were observed in the majority of subjects. Thus, virologic failure in Protocol 005 was usually associated with mutations understood to confer raltegravir resistance.

Table 8

Integrase Mutation Patterns Observed in Raltegravir Failures
Protocol 005

N155H Pathway (N = 14)	Q148 Pathway (N = 20)	Other Pathways (N = 1)
N155H (n = 2) N155H, L74L/M (n = 1) N155H, E92Q (n = 1) N155H, T97A (n = 3) N155H, Y143H (n = 1) N155H, G163K (n = 1) N155H, E92Q, T97A (n = 1) N155H, V151I (n = 1) N155H, G163G/R (n = 2) N155H, D232N (n = 1)	Q148H, G140S (N=13) Q148R (n = 1) Q148R, G140S (n = 2) Q148K, E138K (n = 1) Q148R, E138E/K (n = 1) Q148R, L74L/M, E138A (n = 1) Q148H/R, G140S (n = 1)	Y143R (n = 1)
Results represent analysis based on genotyping baseline and failure isolates from 38 patients failing raltegravir-containing regimen in Protocol 005. Mutations listed represent changes observed in isolates at virologic failure that were not observed in the corresponding baseline isolates, and are limited to changes known or suspected to contribute to raltegravir resistance. Among the 38 patients genotyped, 35 patients displayed integrase changes and 3 displayed no consistent changes from baseline. Each mutation pattern observed is listed only once; the number in parenthesis (n) equals the number of patients displaying each specific mutation pattern.		

Out of the patients treated with raltegravir in Protocols 018 and 019 combined, only viruses isolated from 39 patients identified as virologic failures before the integrase genotyping cutoff date of 15-Nov-2006 have been analyzed. Among these 39 patients, 28 displayed integrase mutations known or suspected to contribute to raltegravir resistance, and the mutation patterns observed in viruses isolated from these patients are shown in Table 9. As in Protocol 005, the majority of patients experiencing virologic failure displayed a mutation at either amino acid 155 or 148, and most displayed two or more mutations in integrase.

Table 9

Partial Analysis of Integrase Mutation Patterns Observed in Raltegravir Failures
Protocols 018 and 019 Combined

N155H Pathway (n = 14)	Q148 Pathway (n = 6)	Q148 + N155H (n = 3)	Other pathways (n = 5)
N155H (3) N155N/H (3) N155H, E92E/Q (1) N155H, E92Q (1) N155N/H, E92E/Q (1) N155N/H, T97A/T (1) N155H, G163R/G (1) N155H, V151I (1) N155N/H, L74M/L, E92Q (1) N155H, E92E/Q, V151V/I (1)	Q148K/Q/R (1) Q148H, G140G/S (1) Q148H, G140S (1) Q148Q/H/R, G140S/G (1) Q148Q/R, G140G/A (1) Q148R, G140G/S (1)	Q148Q/R, N155N/H, E138K/E (1) Q148Q/R, N155N/H, V151V/I (1) Q148K/Q, N155N/H, E92Q/E, E138E/K,V151I (1)	L74M, E92Q (1) E92E/Q, T97T/A, Y143Y/C (1) T97A, Y143R/C, S230S/R (1) L74I, E92E/Q, T97A, Y143H/R/Y/C (1) L74M/L, Y143Y/C, G163R/G, I203M, S230R (1)
Results represent partial analysis based on genotyping baseline and failure isolates from 39 patients failing a raltegravir-containing regimen in Protocols 018 and 019 combined. Among the 39 patients genotyped, 28 patients displayed integrase changes. Mutations listed represent changes observed in isolates at virologic failure that were not observed in the corresponding baseline isolates, and are limited to changes known or suspected to contribute to raltegravir resistance. The number in parentheses represents the number of patients in which each pattern was observed.			

7.4.5 Prognostic Factors for Emergence of Raltegravir Resistance

An exploratory analysis of putative prognostic factors associated with the emergence of integrase mutations was performed for Protocol 005 and for Protocols 018 and 019 combined, and results are shown below. Overall, the factors increasing the likelihood of developing raltegravir resistance were consistent with the factors increasing the likelihood of virologic failure. These findings are in agreement with the observation that raltegravir resistance was observed in the majority of raltegravir virologic failures.

The exploratory analysis for Protocol 005 showed that factors decreasing the likelihood of developing mutation at either amino acid 148 or 155 (i.e. with a Hazard Ratio<1) included lower viral load (≤50,000 versus >50,000; ≤100,000 versus >100,000 copies/mL); new use of enfuvirtide in OBT; and PSS>0. Similar patterns were observed for mutation at either amino acid position, mutation at 155, or mutation at 148. The same exploratory analysis for Protocols 018 and 019 combined showed that factors decreasing the likelihood of developing mutation at either amino acid 148 or 155 included lower viral load (≤50,000 versus >50,000; ≤100,000 versus >100,000 copies/mL); new use of darunavir in OBT; PSS>0; and GSS>0. A factor increasing the likelihood of developing a mutation at either amino acid 148 or 155 was lower CD4 count (≤50 versus >200). Similar patterns were observed for mutation at either position, mutation at amino acid 155, or mutation at amino acid 148.

No association between dose and/or drug concentration and resistance was noted.

Discussion of Prognostic Factors: Viral variants resistant to raltegravir were more likely to emerge in patients who began therapy with higher viral loads or in patients who received raltegravir in combination with drugs that were not fully active against their viruses (i.e., PSS=0 or GSS=0). On the other hand, clinical resistance to raltegravir was less likely to emerge in patients taking raltegravir in combination with other potent antiviral drugs to which their viruses were sensitive, such as darunavir (Protocols 018 and 019) or tenofovir plus lamivudine (Protocol 004). These findings are consistent with first principles of antiviral drug resistance, and support the hypothesis that evolution of resistance can be reduced by giving raltegravir in combination with other potent active agents so as to maximally suppress viral replication in as short a time as possible.

7.4.6 Resistance Conclusions

The genotyping data obtained from integrase sequences of patients in clinical trials experiencing virologic failure while taking raltegravir can best be interpreted by considering this information along with the non-clinical (*in vitro*) data on raltegravir resistance. Taken together, the non-clinical and clinical resistance results show the following:

- In the majority of patients experiencing virologic failure while receiving a raltegravir-containing regimen, viruses isolated after virologic failure displayed integrase mutations that confer resistance to raltegravir.
- The majority of viruses isolated from raltegravir failures displayed a mutation at either amino acid residue 148 or 155 (N155H, Q148H, Q148K, or Q148R) in the integrase gene. These mutations confer decreased susceptibility to raltegravir (13- to 46-fold) in a single-cycle HIV infection assay, and also reduce viral replication capacity.
- In the majority of raltegravir virologic failures, one or more secondary mutations (e.g., L74M, E92Q, T97A, E138K, G140S) was also present. When combined with a primary mutation at 148 or 155, these additional mutations confer a substantial further decrease in raltegravir susceptibility (64- to 521-fold), and sometimes also mitigate the replication capacity defects associated with primary resistance mutations.
- The observation that most viruses isolated from raltegravir virologic failures display $\geq$2 integrase mutations suggests that, *in vivo*, single mutations appear inadequate to confer complete resistance to raltegravir.
- In clinical trials, no association between dose and/or drug concentration and resistance was noted.
- Raltegravir should always be used in combination with other potent active agents to minimize the likelihood of developing raltegravir resistance and thereby maximize its clinical benefits.

8. Safety

8.1 Safety in Phase I

Eighteen (18) Phase I studies in which a total of 315 subjects received raltegravir were completed and included in the safety analysis. Raltegravir was given as single and multiple doses alone or in combination with one or more of the following drugs: ritonavir, efavirenz, atazanavir, tenofovir, rifampin, midazolam, or tipranavir. Most participants were healthy subjects except in a hepatic insufficiency study and a renal insufficiency study in which half of the participants had moderate hepatic insufficiency (a score of 7 to 9 on the Child-Pugh scale) or severe renal insufficiency (24-hr creatinine clearance <30 mL/min/1.73 m^2).

Raltegravir was generally well tolerated in male and female subjects and/or patients with hepatic or renal insufficiency. No serious clinical or laboratory adverse experiences were reported in the 18 completed Phase I clinical trials presented. All adverse experiences reported were transient in nature and rated mild to moderate in intensity. There were no consistent treatment-related changes in laboratory, vital signs, or electrocardiogram (ECG) safety parameters when raltegravir was given alone or in combination with other therapies in comparison to placebo. No evidence of clinically significant prolongation of QT_c was found.

There were no deaths in the Phase I studies.

8.2 Safety in HIV Infected Patients

8.2.1 Study Population and Extent of Exposure

The evaluation of safety of raltegravir in HIV-infected patients includes data from the Phase II and Phase III studies described in Section 6.3. This evaluation includes data from 878[2] patients who were treated with raltegravir (at least one dose) for up to 78 weeks (with most receiving raltegravir for at least 16 weeks) in combination regimens. These 878 patients included the 758 patients who received raltegravir by initial randomization, 114 patients from the placebo arms of Protocol 005, Protocol 018, and Protocol 019 who switched to OLPVF, and 6 patients from the Protocol 005 placebo group who received raltegravir in the open-label extension phase per amendment. In addition, ongoing studies contribute safety data through serious adverse experience reports.

[2] This includes 3 patients from the monotherapy portion of Protocol 004 who did not continue on in the combination therapy portion

The design of the clinical studies resulted in imbalance of the numbers of patients treated with raltegravir versus comparator and **the duration of follow-up (or time at risk)** for raltegravir versus control. Depending on the specific analysis, the magnitude of the imbalance between raltegravir and control arms varied:

- **Protocols 005, 018, and 019 double-blind portions (the integrated safety data analysis):** The raltegravir 400 mg b.i.d. arms collectively (N=507) were compared to the placebo containing comparator arms (N=282). The duration of follow-up was ~261 patient-years for raltegravir versus ~127 patient-years for comparator. This grouping constitutes the main population used in the safety analyses as it provides comparative data regarding the proposed dose of raltegravir in treatment experienced patients.
- **Protocols 004, 005, 018, and 019 double-blind portions (all doses):** The duration of follow-up for the raltegravir containing arms (N=748) increases to 508 patient-years and for control arms (N=323) the duration of follow-up increases to 169 patient-years.
- **Protocols 004, 005, 018, and 019 double blind, open-label (OL), and open-label post-virologic failure (OLPVF) arms:** The duration of follow-up for raltegravir containing arms (N=878) increases to 619 patient-years while the duration of follow-up for control arms (N=323) remains at 169 patient-years (as patients in the OL and OLPVF arms all received raltegravir).

Unless specifically indicated, however, the frequencies (%) presented for adverse experiences in subsequent sections are not adjusted for different durations of follow-up.

The focus of this document is on the double-blind populations outlined above. These populations provide the best controlled comparisons for safety.

Overall, raltegravir was generally well tolerated in terms of overall adverse events and drug related adverse events. In the treatment experienced studies, drug related was defined as possibly, probably, or definitely related to raltegravir, alone or in combination with OBT, or to OBT alone.

In the data submitted as part of the original New Drug Application (NDA) based on a cut-off date of 13-Dec-06, the rate of malignant neoplasms in patients receiving raltegravir was numerically higher than that in patients receiving comparator regimens. However, in a subsequent repeat of the analyses in the Original Application with increased patient follow-up through 09-Jul-2007, this difference was not sustained. A comprehensive discussion regarding malignant neoplasms is included below (See Section 8.2.5).

8.2.2 Safety in Phase II Studies (Protocols 004 and 005)

Protocol 004 - Part I Monotherapy

Protocol 004 included a 10-day monotherapy phase of raltegravir at 4 doses versus placebo, and there were no serious adverse experiences or discontinuations due to adverse experiences. There were no dose-related toxicities. Three (3) patients from Part I did not continue on to Part II. These patients are included in subsequent safety analyses involving Protocol 004.

Protocol 004 - Part II Combination Therapy

Protocol 004 Part II evaluated the tolerability of raltegravir as compared to a standard of care comparator (efavirenz) each in combination with tenofovir and lamivudine. Because the concomitant antiretrovirals in Protocol 004 were the same for all patients in all arms of the study (as opposed to individualized for each patient as in the treatment experienced studies), Protocol 004 data presents an important part of the safety assessment. In particular, the effect of raltegravir on lipid parameters is best evaluated in Protocol 004.

Clinical adverse experiences were reported by 171 of the 198 patients (86.4%) in this study. There were no discontinuations due to adverse experiences. All groups showed similar clinical adverse experience profiles. There was no evidence of dose-related toxicity. Thirteen (13) patients reported post-randomization serious clinical adverse experiences, none of which was determined by the investigators to be drug related.

The most frequently reported (incidence >10%) clinical adverse experiences reported by patients in the raltegravir groups (all doses combined) were: diarrhea (18.8%), nausea (18.1%), upper respiratory infection (16.9%), headache (16.3%), dizziness (11.9%), nasopharyngitis (10.6%), and insomnia (10.6%). There was no apparent association between the frequency of clinical adverse experiences and increasing raltegravir dose. The most frequently reported (incidence >10%) clinical adverse experiences in the efavirenz group were: dizziness (34.2%), headache (31.6%), diarrhea (21.1%), abnormal dreams (21.1%), upper respiratory infection (18.4%), nausea (15.8%), vomiting (15.8%), nasopharyngitis (13.2%), insomnia (10.5%), herpes zoster (10.5%), and nightmare (10.5%).

Clinical adverse experiences considered to be drug-related by the investigator (referred to as drug-related adverse experiences) were reported by 103 of 198 patients (52%). The most frequently reported (incidence >10%) drug-related clinical adverse experience in the raltegravir treatment groups (all doses combined) was nausea (11.3%). There was no apparent association between the frequency of drug-related clinical adverse experiences and increasing raltegravir dose. The most frequently reported (incidence >10%) drug-related clinical adverse experiences in the efavirenz group were: diarrhea (10.5%), nausea (13.2%), dizziness (28.9%), headache (23.7%), insomnia (10.5%), nightmare (10.5%), and abnormal dreams (18.4%).

Laboratory adverse experiences were reported in 39 of 198 patients, and the most frequently (incidence >10%) reported laboratory adverse experience was aspartate aminotransferase increased, reported in 10.5% of the patients in the efavirenz group versus 5.6 % of the patients in the raltegravir (all doses combined) group. The most frequently reported drug-related laboratory adverse experiences were alanine aminotransferase increased and aspartate aminotransferase increased, both of which were reported in 3.8% of patients in the raltegravir treatment groups (all doses combined) and 5.3% of patients in the efavirenz group. All groups showed similar laboratory adverse experience profiles. There was no apparent association between the frequency of laboratory adverse experiences, including those determined by the investigator to be drug-related, and increasing raltegravir dose.

Raltegravir 400 mg b.i.d. in combination with TFV and 3TC does not increase fasting serum cholesterol, LDL- cholesterol, or triglyceride levels based upon post hoc analysis of serum lipids (Table 10). Results for other doses (100, 200, 600 mg, all b.i.d.) were similar.

Table 10

Protocol 004 Lipid Values, Percent (%) Change from Baseline

Laboratory Parameters	Week 24		Week 48	
	Raltegravir 400 mg, b.i.d.	Efavirenz 600 mg, q.d.	Raltegravir 400 mg, b.i.d.	Efavirenz 600 mg, q.d.
Total Cholesterol	-2.2	11.5	1.4	13.4
LDL	0.4	6.5	4.2	3.1
HDL	7.2	15.3	14.3	30.0
Triglycerides	2.0	39.6	2.7	45.2
Raltegravir and efavirenz were administered with tenofovir and lamivudine.				

Safety in Protocol 005-Double Blind Phase

One-hundred fifty two (152) of the 178 patients (85.4%) reported a clinical adverse experience. There were 3 discontinuations due to adverse experiences (2 patients in the raltegravir groups combined and 1 patient in the placebo group). All groups showed similar clinical adverse experience profiles. There was no evidence of dose-related toxicity. In particular, there was no evidence of additional toxicity emerging even for patients receiving 600 mg b.i.d. of raltegravir with atazanavir and/or tenofovir in Substudy B, which represents the highest plasma concentrations of raltegravir. As the adverse experience profiles were similar in Substudy A (OBT without atazanavir) and Substudy B (OBT containing atazanavir), adverse experiences are reported for the 2 substudies combined.

Seventeen (17) of the 178 randomized patients experienced a serious clinical adverse experience, 14 (10.5%) in the raltegravir arms combined, and 3 (6.7%) in the placebo arm. Serious clinical adverse experiences considered to be related to study drug were reported in 2 (1.5%) patients in the raltegravir arm and 2 (4.4%) patients in the placebo arm.

The most frequently (incidence >10%) reported clinical adverse experiences in the raltegravir groups (all doses combined) were diarrhea (13.5%) and nausea (12.8%). There was no apparent association between the frequency of adverse experiences and increasing raltegravir dose. The most frequently (incidence >10%) reported clinical adverse experiences for the placebo control group were: nausea (20%), diarrhea (17.8%), bronchitis (11.1%), and headache (11.1%). The frequency of specific clinical adverse experiences was comparable between the raltegravir groups and the placebo control group.

Drug-related clinical adverse experiences were reported by 85 of 178 patients (47.8%). The most frequently (incidence >5%) reported clinical adverse experiences that were considered drug related in the raltegravir group were nausea (8.5%), and injection site reaction (6.0%). In the placebo control group, the most frequently reported drug related clinical adverse experiences were diarrhea (15.6%) and nausea (11.1%). There was no apparent association between the frequency of drug-related clinical adverse experiences and increasing raltegravir dose.

Laboratory experiences reported with an incidence >5% were blood bilirubin increased (8.3%) and creatine phosphokinase increased (7.5%) in the raltegravir groups (all doses combined). In comparison, in the placebo control group, 4.4% experienced blood bilirubin increased and 0% experienced increased creatine phosphokinase. There were no laboratory adverse experiences with an incidence >5% in the placebo control group. The increased blood bilirubin was most likely due to atazanavir sulfate, which is known to be associated with hyperbilirubinemia secondary to inhibition of UGT1A1. Only 1 of the

patients for whom increased blood bilirubin was reported was not receiving atazanavir. This patient was, however, receiving indinavir, also known to inhibit UGT1A1. Creatine phosphokinase elevations were considered by the investigator to be related to strenuous physical activity in most cases (7/10).

Overall, there was no evidence to suggest any clinically important differences in the frequency of drug-related laboratory adverse experiences in the raltegravir groups compared with that of the placebo control group. There was also no apparent association between the frequency of laboratory adverse experiences, including those assessed by the investigator as drug-related, and increasing raltegravir dose.

8.2.3 Safety in Treatment-Experienced HIV Patients Randomized to the 400 mg Dose (Protocols 005, 018, and 019 Double Blind Portion)

Raltegravir 400 mg b.i.d. was the dose evaluated in Phase III, and is the recommended clinical dose. Integrated adverse experience data from patients in Protocols 005, 018, and 019, receiving the 400 mg b.i.d. dose, are discussed in this Section.

8.2.3.1 Clinical Adverse Experiences in Treatment-Experienced HIV Patients (Protocols 005, 018, and 019)

Table 11 presents a summary of the clinical adverse experiences in the treatment experienced 400 mg b.i.d. double blind cohort. Adverse experiences were balanced between the raltegravir arms and the placebo arms. Serious adverse experiences occurred in approximately 10.7% of patients receiving raltegravir and 12.8% receiving placebo. Discontinuations and/or deaths due to adverse experiences were uncommon in both arms.

The most common clinical adverse experiences (incidence ≥3% in one or more treatment groups), during the double-blind phase by system organ class are presented in Table 12. In general, the adverse experience profiles of raltegravir and placebo were similar. Injection site reactions are included for completeness, but are related to enfuvirtide, the only injectable antiretroviral used.

Table 11

Summary of Clinical Adverse Experience
(Treatment-Experienced Raltegravir 400 mg b.i.d. Double-Blind Cohort)
(Protocols 005, 018, and 019)

	Raltegravir 400 mg b.i.d. (N=507)		Placebo (N=282)		Difference From Placebo[†]	
	N	(%)	n	(%)	% (95% CI)	p-Value
Number (%) of patients:						
With one or more adverse experiences	411	(81.1)	238	(84.4)	-3.33 (-8.6, 2.3)	0.285
With no adverse experience	96	(18.9)	44	(15.6)	3.33 (-2.3, 8.6)	0.285
With drug-related[‡] adverse experiences	242	(47.7)	146	(51.8)	-4.04 (-11.3, 3.2)	0.298
With serious adverse experiences	54	(10.7)	36	(12.8)	-2.12 (-7.1, 2.4)	0.414
With serious drug-related adverse experiences	8	(1.6)	5	(1.8)	-0.20 (-2.6, 1.6)	1.000
Who died	6	(1.2)	3	(1.1)	0.12 (-2.0, 1.7)	1.000
Discontinued due to adverse experiences	8	(1.6)	4	(1.4)	0.16 (-2.1, 1.9)	nps[§]
Discontinued due to drug-related adverse experiences	4	(0.8)	2	(0.7)	0.08 (-1.8, 1.4)	nps[§]
Discontinued due to serious adverse experiences	6	(1.2)	2	(0.7)	0.47 (-1.5, 2.0)	nps[§]
Discontinued due to serious drug-related adverse experiences	2	(0.4)	1	(0.4)	0.04 (-1.6, 1.1)	nps[§]

[†] Tests of significance were performed on the percentage of patients with at least one adverse experience in the category. The 95% CIs were calculated using Miettinen and Nurminen's method. p-Values were generated using the Fisher exact test.

[‡] Determined by the investigator to be possibly, probably, or definitely drug-related.

[§] nps=not pre-specified for statistical analysis.

Note: Raltegravir and Placebo were administered with Optimized Background Therapy (OBT).

Table 12

Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence ≥3% in One or More Treatment Groups) by System Organ Class - Treatment-Experienced Raltegravir 400 mg b.i.d. Double-Blind Cohort (Protocols 005, 018, and 019)

	Raltegravir 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Patients With One Or More Adverse Experiences	411	(81.1)	238	(84.4)	649	(82.3)
Patients With No Adverse Experience	96	(18.9)	44	(15.6)	140	(17.7)
Blood And Lymphatic System Disorders	31	(6.1)	19	(6.7)	50	(6.3)
Lymphadenopathy	15	(3.0)	8	(2.8)	23	(2.9)
Eye Disorders	14	(2.8)	12	(4.3)	26	(3.3)
Gastrointestinal Disorders	191	(37.7)	122	(43.3)	313	(39.7)
Abdominal Pain	23	(4.5)	10	(3.5)	33	(4.2)
Abdominal Pain Upper	11	(2.2)	10	(3.5)	21	(2.7)
Diarrhoea	79	(15.6)	54	(19.1)	133	(16.9)
Flatulence	13	(2.6)	9	(3.2)	22	(2.8)
Nausea	48	(9.5)	37	(13.1)	85	(10.8)
Vomiting	34	(6.7)	21	(7.4)	55	(7.0)
General Disorders And Administration Site Conditions	150	(29.6)	80	(28.4)	230	(29.2)
Asthenia	14	(2.8)	11	(3.9)	25	(3.2)
Fatigue	36	(7.1)	11	(3.9)	47	(6.0)
Injection Site Reaction[†]	47	(9.3)	27	(9.6)	74	(9.4)
Pyrexia	22	(4.3)	27	(9.6)	49	(6.2)
Infections And Infestations	205	(40.4)	122	(43.3)	327	(41.4)
Bronchitis	10	(2.0)	9	(3.2)	19	(2.4)
Herpes Simplex	17	(3.4)	12	(4.3)	29	(3.7)
Herpes Zoster	17	(3.4)	2	(0.7)	19	(2.4)

Table 12 (Cont.)

Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence ≥3% in One or More Treatment Groups) by System Organ Class - Treatment-Experienced Raltegravir 400 mg b.i.d. Double-Blind Cohort (Protocols 005, 018, and 019)

	Raltegravir 400 mg b.i.d. (N = 507)		Placebo (N = 282)		Total (N = 789)	
	n	(%)	n	(%)	n	(%)
Infections And Infestations	205	(40.4)	122	(43.3)	327	(41.4)
Nasopharyngitis	25	(4.9)	10	(3.5)	35	(4.4)
Oral Candidiasis	7	(1.4)	13	(4.6)	20	(2.5)
Sinusitis	15	(3.0)	7	(2.5)	22	(2.8)
Upper Respiratory Tract Infection	21	(4.1)	13	(4.6)	34	(4.3)
Injury, Poisoning And Procedural Complications	25	(4.9)	9	(3.2)	34	(4.3)
Investigations	12	(2.4)	15	(5.3)	27	(3.4)
Metabolism And Nutrition Disorders	43	(8.5)	21	(7.4)	64	(8.1)
Musculoskeletal And Connective Tissue Disorders	65	(12.8)	34	(12.1)	99	(12.5)
Pain In Extremity	15	(3.0)	4	(1.4)	19	(2.4)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	23	(4.5)	10	(3.5)	33	(4.2)
Nervous System Disorders	99	(19.5)	63	(22.3)	162	(20.5)
Dizziness	19	(3.7)	6	(2.1)	25	(3.2)
Headache	44	(8.7)	33	(11.7)	77	(9.8)
Psychiatric Disorders	45	(8.9)	30	(10.6)	75	(9.5)
Insomnia	17	(3.4)	10	(3.5)	27	(3.4)
Renal And Urinary Disorders	17	(3.4)	10	(3.5)	27	(3.4)
Reproductive System And Breast Disorders	17	(3.4)	5	(1.8)	22	(2.8)
Respiratory, Thoracic And Mediastinal Disorders	56	(11.0)	34	(12.1)	90	(11.4)
Cough	21	(4.1)	9	(3.2)	30	(3.8)
Pharyngolaryngeal Pain	8	(1.6)	10	(3.5)	18	(2.3)
Skin And Subcutaneous Tissue Disorders	112	(22.1)	57	(20.2)	169	(21.4)
Rash	23	(4.5)	8	(2.8)	31	(3.9)
Vascular Disorders	23	(4.5)	9	(3.2)	32	(4.1)

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

This table was run using a "percent incidence". This means that a row will appear on this report only if one of the columns is greater than or equal to that percentage, after rounding.

The number and percent of patients in this cohort with specific *drug-related* clinical adverse experiences considered related to raltegravir alone or in combination with OBT; or to OBT alone; or to both (incidence ≥2% in one or more treatment groups), by system organ class are presented in Table 13. The number of drug-related clinical adverse experiences was low and generally balanced between the treatment groups. Diarrhea, nausea, and headache were the most commonly reported drug-related clinical adverse experiences.

Table 13

Number (%) of Patients With Specific Drug-Related Clinical Adverse Experiences (Incidence ≥2% in One or More Treatment Groups) by System Organ Class - Treatment-Experienced Raltegravir 400 mg b.i.d. Double-Blind Cohort (Protocols 005, 018, and 019)

	Raltegravir 400 mg b.i.d. (N = 507)		Placebo (N = 282)	
	n	(%)	n	(%)
Patients With One Or More Adverse Experiences	242	(47.7)	146	(51.8)
Patients With No Adverse Experience	265	(52.3)	136	(48.2)
Blood And Lymphatic System Disorders	5	(1.0)	8	(2.8)
Gastrointestinal Disorders	109	(21.5)	65	(23.0)
Abdominal Distension	10	(2.0)	6	(2.1)
Abdominal Pain	14	(2.8)	6	(2.1)
Diarrhoea	44	(8.7)	31	(11.0)
Flatulence	11	(2.2)	5	(1.8)
Nausea	32	(6.3)	23	(8.2)
Vomiting	13	(2.6)	13	(4.6)
General Disorders And Administration Site Conditions	98	(19.3)	48	(17.0)
Fatigue	14	(2.8)	4	(1.4)
Injection Site Reaction	44	(8.7)	27	(9.6)
Pyrexia	5	(1.0)	6	(2.1)
Infections And Infestations	11	(2.2)	2	(0.7)
Metabolism And Nutrition Disorders	21	(4.1)	11	(3.9)
Musculoskeletal And Connective Tissue Disorders	14	(2.8)	4	(1.4)
Nervous System Disorders	49	(9.7)	31	(11.0)
Headache	24	(4.7)	16	(5.7)
Psychiatric Disorders	16	(3.2)	12	(4.3)
Skin And Subcutaneous Tissue Disorders	40	(7.9)	27	(9.6)

The most frequently reported (incidence ≥2% in one treatment group) overall drug-related clinical adverse experiences of moderate or severe intensity were:

- Diarrhea: in 3.7% (19/507) of patients in the raltegravir group compared to 3.5% (10/282) of patients in the placebo group.
- Nausea: in 2.2% (11/507) of patients in the raltegravir group compared to 3.2% (9/282) of patients in the placebo group.
- Injection-site reaction related to enfuvirtide use: in 2.4% (12/507) of patients in the raltegravir group compared to 2.8% (8/282) of patients in the placebo group.
- Headache: in 2.2% (11/507) of patients in the raltegravir group compared to 1.4% (4/282) of patients in the placebo group.

Moderate and severe drug related adverse events were well balanced between treatment groups.

8.2.3.2 Evaluation of Laboratory Parameters in Treatment-Experienced HIV Patients (Protocols 005, 018, and 019) Double-Blind Cohort - Double-Blind Phase

Laboratory parameters were evaluated by investigator-reported laboratory adverse experiences (below) and by predefined limits of change analysis of laboratory values (below).

Laboratory adverse experiences (Table 14) were reported for 99 of the 507 patients (19.5%) in the raltegravir 400 mg b.i.d. double-blind cohort, as compared to 51 of the 282 patients (18.1%) receiving placebo. There were 2 serious laboratory adverse experiences and 1 discontinuation due to a laboratory adverse experience in the raltegravir group, compared with none in these categories for the placebo group. One of these serious laboratory adverse experiences included increased AST (69 U/L, normal range = 0-50) and increased ALT (191 U/L, normal range = 0-50). This patient continued on raltegravir plus OBT and subsequent laboratory values revealed that ALT and AST had returned to normal. The other patient with a serious laboratory adverse event experienced decreased neutrophil count. One patient discontinued the study due to a non-serious adverse experience of increased AST (411 U/L, NR = 17-59) and increased ALT (520 U/L, NR = 11-66). This patient had no subsequent laboratory values.

There were no serious, drug-related laboratory adverse experiences or deaths due to laboratory adverse experiences in either group. The proportions of laboratory adverse experiences were comparable between the raltegravir 400 mg b.i.d. group and the placebo group.

Table 14

Summary of Laboratory Adverse Experience
(Treatment-Experienced Raltegravir 400 mg b.i.d. Double-Blind Cohort)
(Protocols 005, 018, 019)

	Raltegravir 400 mg b.i.d. (N=507)		Placebo (N=282)		Difference From Placebo[†]	
	n	(%)[‡]	n	(%)[‡]	% (95% CI)	p-Value
Number (%) of patients:						
With one or more adverse experiences	99	(19.5)	51	(18.1)	1.44 (-4.4, 7.0)	0.637
With no adverse experience	408	(80.5)	231	(81.9)	-1.44 (-7.0, 4.4)	0.637
With drug-related[§] adverse experiences	58	(11.4)	32	(11.3)	0.09 (-4.8, 4.6)	1.000
With serious adverse experiences	2	(0.4)	0	(0.0)	0.39 (-1.0, 1.4)	0.540
With serious drug-related adverse experiences	0	(0.0)	0	(0.0)	0.00 (-1.4, 0.8)	N/A
Who died	0	(0.0)	0	(0.0)	0.00 (-1.4, 0.8)	N/A
Discontinued due to adverse experiences	1	(0.2)	0	(0.0)	0.20 (-1.2, 1.1)	nps[‖]
Discontinued due to drug-related adverse experiences	0	(0.0)	0	(0.0)	0.00 (-1.4, 0.8)	nps[‖]
Discontinued due to serious adverse experiences	0	(0.0)	0	(0.0)	0.00 (-1.4, 0.8)	nps[‖]
Discontinued due to serious drug-related adverse experiences	0	(0.0)	0	(0.0)	0.00 (-1.4, 0.8)	nps[‖]

[†] Tests of significance were performed on the percentage of patients with at least one adverse experience in the category. The 95% CIs were calculated using Miettinen and Nurminen's method. p-Values were generated using the Fisher exact test.

[‡] The percent = Number of patients within the laboratory adverse experience category / number of patients with one or more laboratory adverse experience.

[§] Determined by the investigator to be possibly, probably, or definitely drug-related.

[‖] nps=not pre-specified for statistical analysis.

Note: Raltegravir and Placebo were administered with Optimized Background Therapy (OBT).

Of the tests performed in routine monitoring, the most frequently reported (≥3% in at least one treatment group regardless of drug relationship) laboratory adverse experiences were:

- Alanine aminotransferase (ALT) increased: 4.5% (23/507) in the raltegravir group compared with 2.1% (6/282) in the placebo group.
- Aspartate aminotransferase (AST) increased: 4.3% (22/507) in the raltegravir group compared with 2.5% (7/282) in the placebo group.
- Blood triglycerides increased: 3.6% (18/507) in the raltegravir group compared with 3.2% (9/279) in the placebo group.
- Creatine phosphokinase (CPK) increased: 3.2% (16/507) in the in the raltegravir group compared with 0.7% (2/282) in the placebo group.

The number and percent of patients in this cohort with specific *drug-related* (defined as related to raltegravir and/or OBT) laboratory adverse experiences (incidence ≥2% in one or more treatment groups), by laboratory test category are presented in Table 15. Overall, the number of drug-related laboratory adverse experiences was low and generally balanced between the treatment groups.

Table 15

Number (%) of Patients With Specific Drug-Related (Overall) Laboratory Adverse Experiences (Incidence ≥2% in One or More Treatment Groups) by Laboratory Test Category - Treatment-Experienced Raltegravir 400 mg b.i.d. Double-Blind Cohort (Protocols 005, 018, and 019)

	Raltegravir 400 mg b.i.d. (N=507)		Placebo (N=282)		Total (N=789)	
	n/m	(%)	n/m	(%)	n/m	(%)
Patients with one or more drug-related adverse experiences	58/507	(11.4)	32/282	(11.3)	90/789	(11.4)
Patients with no drug-related adverse experiences	449/507	(88.6)	250/282	(88.7)	699/789	(88.6)
Blood Chemistry Test	**53/507**	**(10.5)**	**25/282**	**(8.9)**	**78/789**	**(9.9)**
Alanine aminotransferase increased	16/507	(3.2)	2/282	(0.7)	18/789	(2.3)
Aspartate aminotransferase increased	13/507	(2.6)	3/282	(1.1)	16/789	(2.0)
Blood creatinine increased	7/507	(1.4)	6/282	(2.1)	13/789	(1.6)
Blood lactic acid increased	1/7	(14.3)	0/1	(0.0)	1/8	(12.5)
Blood pancreatic amylase increased	1/58	(1.7)	1/27	(3.7)	2/85	(2.4)
Blood triglycerides increased	13/507	(2.6)	3/279	(1.1)	16/786	(2.0)
Hematology Laboratory Test	**5/507**	**(1.0)**	**7/282**	**(2.5)**	**12/789**	**(1.5)**
Neutrophil count decreased	0/14	(0.0)	1/8	(12.5)	1/22	(4.5)

Although a patient may have had two or more drug-related laboratory adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.
This table was run using a "percent incidence". This means that a row will appear on this report only if one of the columns is greater than or equal to that percentage, after rounding.
Note: Raltegravir and Placebo were administered with Optimized Background Therapy (OBT).
Adverse experience terms are from MedDRA Version 9.1.
n/m = Number of patients with laboratory adverse experiences / number of patients for whom the laboratory test was recorded postbaseline.

Predefined Limits of Change (PDLC)

Patients were monitored through a protocol specified schedule of routine laboratory evaluations. Investigators had the option of additional laboratory monitoring when clinically indicated. Predefined limits of change were derived using DAIDS toxicity criteria for the tests of interest, or based on the fold-change from baseline.

There were no clinically meaningful differences between the raltegravir and placebo treatment groups for any of the comparisons (Appendix 22). The rates of PDLC abnormalities were generally balanced between treatment groups.

Discussion of other Potential Safety Concerns

Summary of Aminotransferase (ALT/AST) Elevations

As discussed above, in the treatment-experienced raltegravir 400 mg b.i.d. cohort, laboratory adverse experiences of increased serum ALT and increased serum AST were reported in 4.5% (23/507) and 4.3% (22/507) of patients, respectively, in the raltegravir group compared with 2.1% (6/282) and 2.5% (7/282) of patients, respectively, in the placebo group. In this cohort, overall drug-related laboratory adverse experiences of increased ALT and increased AST were reported in 3.2% (16/507) and 2.6% (13/507), respectively, of patients in the raltegravir group compared with 0.7% (2/282) and 1.1% (3/282), respectively, of patients in the placebo group. In terms of the predefined limits of change for the treatment-experienced raltegravir 400 mg b.i.d. cohort, serum ALT and AST increases were generally similar in the raltegravir group compared with the placebo group (Appendix 22).

Of note, the percentages of patients experiencing AST and/or ALT elevations were low in this treatment experienced population on combination therapy. In addition, these AST and/or ALT elevations generally did not limit study therapy in either the raltegravir group or the placebo group. Furthermore, the aminotransferase elevations were usually transient, resolved with or without interruption of therapy, and did not recur when therapy was re-introduced.

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

Overall, raltegravir was generally well tolerated in patients with hepatitis B and/or C coinfection.

In general, patients with hepatitis B and/or C virus co-infection had similar clinical and laboratory adverse experience profiles in both treatment groups as the complement population (patients without hepatitis B and/or C), including for rates of overall adverse experiences, drug-related adverse experiences, and serious adverse experiences. Discontinuations due to adverse experiences were infrequent in all groups. Specifically, hepatobiliary disorders such as hepatitis and jaundice were seen with low and similar frequencies in the 2 populations and in both treatment groups. Additionally, the remainder of the clinical adverse experience profile was similar in the 2 populations and for both treatment groups.

Laboratory adverse experiences were also generally similar in both populations and in the 2 treatment groups. Specifically, adverse experiences of increased ALT and AST were marginally higher in both treatment groups for patients with hepatitis B and/or C virus co-infection compared with the hepatitis uninfected (complement) groups but similar in both treatment groups: in patients with hepatitis B and/or C co-infection, adverse experiences of increased ALT and AST were 5.1% and 7.7%, respectively, for the raltegravir group and 5.1% and 5.1%, respectively, for the placebo group. .

With respect to predefined limits of change for ALT and AST, there appeared to be somewhat higher rates of Grade 1 or higher elevations for the population with hepatitis B and/or C virus coinfection, as compared to the complement group, but the raltegravir and placebo treatment groups were again comparable. Grades 3 and 4 abnormalities were uncommon in both populations and similar in both treatment groups.

Summary of Elevations in Creatine Phosphokinase (CPK)

In the treatment-experienced raltegravir 400 mg b.i.d. cohort, laboratory adverse experiences of increased CPK were reported in 3.2% (16/507) of patients in the raltegravir group compared with 0.7% (2/282) of patients in the placebo group. In this cohort, overall drug-related laboratory adverse experiences of increased CPK were reported in 0.8% (4/507) of patients in the raltegravir group compared with 0.7% (2/282) of patients in the placebo group. There were no serious adverse experiences of increased CPK and no patients discontinued therapy due to increased CPK. Many of these elevations were isolated increases that returned to normal with time and elevations for several patients were noted by the investigators to be related to physical exercise.

For the Phase III studies, CPK increases were also evaluated for associated clinical adverse experiences. In Protocol 018, no patients with laboratory adverse experiences of increased CPK had associated clinical adverse experiences (e.g., myopathy or rhabdomyolysis). In Protocol 019, one patient in the raltegravir group (AN 15079) had elevated CPK reported as a laboratory adverse experience temporally associated with a clinical adverse experience of myositis, which was considered by the investigator to be due to ritonavir in OBT. The ritonavir dosage was reduced while raltegravir was continued, and the next CPK result (performed 13 days later) had returned to baseline. Another Protocol 019 patient, AN 16272 in the raltegravir group, had elevated (Grade 3) CPK results temporally associated with a clinical adverse experience myalgia. The myalgia was not considered by the investigator to be drug-related and the patients continued on study therapy.

In summary, the occurrence of CPK elevations, while slightly more common in the raltegravir group than in the placebo group, were generally transient, were not associated with clinically significant adverse experiences, and did not limit therapy. In at least some cases, the CPK elevations observed appeared to be due to increased physical exercise.

8.2.3.3 Open-Label Post Virologic Failure (OLPVF) Phase in Phase II and Phase III Studies

One hundred and seventy seven (177) patients, 114 from placebo groups and 63 from raltegravir groups, from Protocols 005, 018, and 019 had entered an OLPVF phase as of 13-Dec-07, In general, adverse experiences in the OLPVF phase were similar to those seen in the double-blind portions of the study.

8.2.4 Reports of Death or Other Serious Adverse Experiences in HIV Patients (Protocols 004, 005, 018, and 019)

There were no clinical adverse experiences resulting in death in Protocol 004. There were 3 patients with adverse experiences resulting in death in Protocol 005; 2 occurred during the double-blind phase of the study and 1 occurred during the open-label phase of the study. None of these fatal adverse experiences were determined by the investigator to be drug-related. There were no laboratory adverse experiences resulting in death in either Protocol 004 or Protocol 005.

The fatal clinical adverse experiences from Protocol 005 included laceration/suicide (raltegravir 200 mg b.i.d. group), sepsis, bradycardia, cardio-respiratory arrest, shock (raltegravir 600 mg b.i.d. group), and acute myocardial infarction (Open-label raltegravir 400 mg b.i.d. group).

There were 9 patients with clinical adverse experiences that resulted in death in Protocols 018 and 019. Six (6) of these patients are from the raltegravir group (1.2%) and 3 are from the placebo group (1.1%). The fatal clinical adverse experiences for the raltegravir group included bronchopneumonia/rectal haemorrhage/septic shock (Protocol 018), cryptococcal meningitis (Protocol 018), mycobacterial infection/lymphoma/multi-organ failure/shock (Protocol 018), bronchopulmonary aspergillosis/pulmonary tuberculosis (Protocol 019), lymphoma (Protocol 019), and malignant hepatic neoplasm (Protocol 019). In the placebo group, the fatal clinical adverse experiences included pneumonia (Protocol 018), worsening end-stage AIDS (Protocol 018), and urosepsis (Protocol 018).

In general, the fatal adverse experiences were related to severe bacterial or other opportunistic infection and/or malignancy. These events are not unexpected in a highly immunodeficient population with advanced HIV infection. The relative onset date of the fatal adverse experience ranged from 5 to 119 days for those patients in the treatment phase of the study. None of these fatal clinical adverse experiences were determined by the investigator to be drug-related. There were no laboratory adverse experiences resulting in death in the treatment-experienced raltegravir 400 mg b.i.d. double-blind cohort.

Analysis of all-cause mortality was performed using data for Protocols 004, 005, 018, and 019 (all doses), for the double-blind portion of the studies, and adjusted for duration of follow-up. The patient-year adjusted incidence rates for all-cause mortality were 1.568 and 1.771 per 100 patient-years for the raltegravir and comparator arms, respectively, resulting in a relative risk of 0.885 with a 95% confidence interval of (0.212, 5.180) [3].

[3] Only events from the double blind portion were included in the analysis of mortality rates.

Serious Adverse Experiences (Non-Fatal) Related to Raltegravir 400 mg b.i.d. (P005, 018, and 019)

Serious adverse experiences were reported for 90 patients (54 in the raltegravir group and 36 in the placebo group). Of these, 13 were considered drug related (8 in the raltegravir group and 5 in the placebo group). The serious drug related adverse experiences reported for the 8 patients receiving raltegravir included: toxic nephropathy; myocardial infarction; hypersensitivity (2 patients); hepatitis; gastritis; anemia/neutropenia; renal failure. Only two of these patients did not recover (hepatitis and renal failure). For the patients receiving placebo, the serious drug related adverse experiences were: lacunar infarction; lipoatrophy; hyperglycemia; nephrolithiasis and pancreatitis (in one patient); neutropenia.

8.2.5 Malignancy

Overview

In the original application (data through 13-Dec-2006), in the double blind portions of the studies (Protocols 004, 005, 018, and 019), there were 10 patients (1.3%) on raltegravir and 1 patient (0.3%) on a comparator arm diagnosed with malignancies on study treatment. The patient-year adjusted rates of malignancies per 100 patient-years in the double blind portions of these studies were 1.970 in the raltegravir arms and 0.592 in the comparator groups. The apparent imbalance prompted a systematic review of malignancies overall in the safety database. The review examined all available data including double-blind and open label data from the ongoing Phase II and Phase III studies and from the Expanded Access Program.

The focus in this document is the malignancy data from the original application from the double-blind, and double-blind plus open-label portions of Protocols 004, 005, 018, and 019. Additionally, the analyses performed in the original application have been updated using cumulative data accrued during ongoing follow-up from these same studies and same patients as of 09-Jul-2007. Timing for this update was discussed with the FDA and was chosen to allow sufficient time for preparation of the updated information for the advisory committee. Per agreement with the FDA, the updated data have also been presented in this section and have been submitted to the FDA. Because these updated data were provided during review of the application the FDA has not yet reviewed these data.

In the updated cumulative dataset there were a total of 19 patients (2.5%) on raltegravir and 5 patients (1.5%) on a comparator arm diagnosed with malignancies on study treatment. The updated patient-year adjusted rates of malignancies per 100 patient-years were 2.32 in the raltegravir arms and 1.92 in the comparator groups. The apparent imbalance with respect to malignancies in the initial application appears to have not been sustained with additional follow-up. However, the sponsor plans to continue to evaluate and monitor malignancies closely; these plans are discussed in more detail in Section 9 (Risk Management Plan) of this document.

The rates and types of malignancies observed both at the time of the data cutoff for the original application as well as for the 09-Jul-2007 update are presented in more detail below. In reviewing the malignancy data, it is important to note that HIV is a risk factor for malignancy, especially in the treatment experienced patients in this application. For context, a review of the baseline medical history of the patients in the raltegravir clinical development program revealed that in patients enrolled in Protocols 004, 005, 018, and 019, 17.4% of patients in raltegravir arms and 16.4% of patients in comparator arms had been diagnosed with malignancies or pre-malignant conditions prior to enrollment. Thus the appearance of malignancies was not unexpected in the post-enrollment period.

Double Blinded Analyses of Protocols 004, 005, 018, and 019 Included in the Original Application

As mentioned previously, in the double blind portions of Protocols 004, 005, 018, and 019, there were 10 patients (1.3%) with malignancies occurring post-randomization in participants on raltegravir and 1 patient (0.3%) with a malignancy occurring in participants on a comparator arm. The time at risk (duration of follow-up), however, for patients receiving raltegravir is not balanced compared to comparator arms because of study design. The time at risk for the raltegravir arms as of the original application for Protocols 004, 005, 018, and 019 was 508 patient-years. For the comparator arms, the time at risk was 169 patient-years.

The patient-year adjusted rates of malignancies per 100 patient-years in the double blind portions of the studies were 1.970 in the raltegravir arms and 0.592 in the comparator groups. This constitutes a Relative Risk of 3.328 (95% confidence interval 0.47, 144.45).

Table 16 lists the types of malignancies seen in the double blind phase of the studies. The kinds of malignancies seen approximate the kinds of malignancies expected in heavily treatment experienced HIV patients. Patient-year adjusted rates for individual malignancy types are presented in Appendix 23.

The timing of malignancies in relationship to the initiation of ART provides information regarding malignancy in the double-bind cohort. Most (9/10) malignancies occurring in patients on raltegravir were detected within a short period after enrollment (3 months), and several showed advanced disease state at the time of diagnosis, suggesting that the malignancies were likely present, but not detected at the time of enrollment. Three (3) of 10 malignancies occurring in patients on raltegravir were recurrences of previously diagnosed malignancies (1 case of recurrent squamous cell carcinoma of the ear, 1 case of recurrent Kaposi's sarcoma, and 1 case of recurrent lymphoma), suggesting either an ongoing but undetected malignant process, or a predisposition to malignancy unrelated to study medications

Table 16
Summary of Malignancy – Double Blind Data
Phase II and III Studies
Original Application

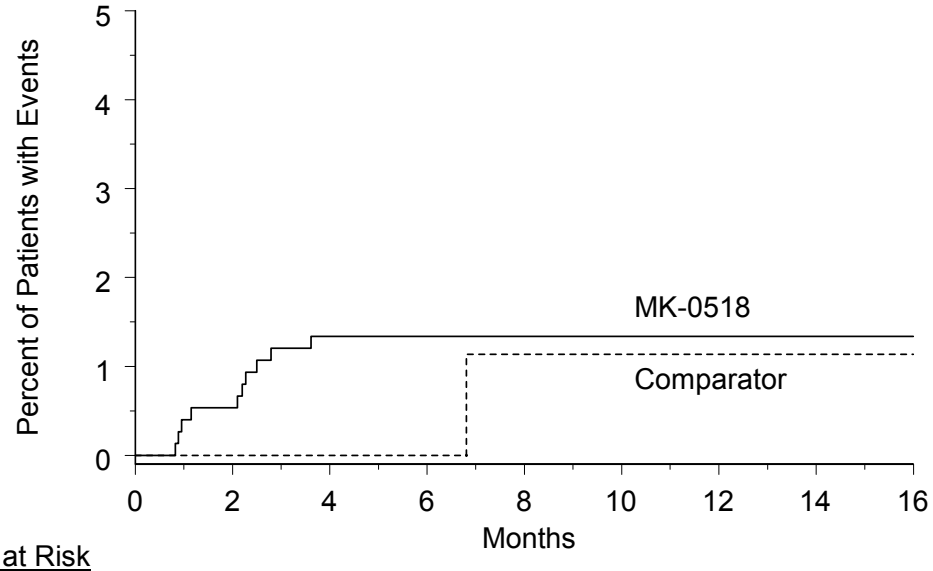
	Raltegravir			Comparator Group		
	N=758; 508 PY			N=323; 169 PY		
	n (%)†	Recurrent	Diagnosis ≤ 3 Months‡	n (%)†	Recurrent	Diagnosis ≤ 3 Months
Patients with Malignancy	10 (1.3)	3/10	9/10	1 (0.3)	0/1	0/1
Kaposi's Sarcoma	2 (0.3)	1	1	0 (0)	-	-
Non-Hodgkin's Lymphoma§	3 (0.4)	1	3	0 (0)	-	-
Squamous Cell Carcinoma – Anogenital‖	1 (0.1)	-	1	0 (0)	-	-
Squamous Cell Carcinoma – Other	1 (0.1)	-	1	1 (0.3)	-	-
Rectal Cancer	1 (0.1)	-	1	0 (0)	-	-
Hepatocellular Carcinoma	1 (0.1)	-	1	0 (0)	-	-
Non-Melanoma Skin Cancer¶	1 (0.1)	1	1	0 (0)	-	-

† Crude incidence (100 x n/N).
‡ Diagnosis of neoplasm occurred within 3 months of initiating study therapy.
§ Includes B-cell lymphoma, T-cell lymphoma.
‖ Includes anal CIS.
¶ Includes squamous cell cancer – skin.
PY = Patient years of exposure.
Patients with multiple events may be counted more than once in different terms, but only once in one term.

Figure 19 displays Kaplan-Meier estimates of time to malignancies for the double-blind phase of Protocols 004, 005, 018, and 019. Of note, no events occurred in the raltegravir arm after month 4 in this analysis.

Figure 19

Kaplan-Meier Plot of Time to Malignancy-Double-Blind Phase
Phase II and III Studies
Original Application



Number at Risk

MK-0518*	758	741	725	493	266	205	155	68	24
Comparator*	323	317	302	123	50	39	32	15	4

*: +OBT for P005, P018 and P019; +3TC +TFV for P004

Double Blinded, Double Blind plus Open Label Analyses of Protocols 004, 005, 018, and 019, and Other Analyses Included in the Original Application

As presented in the original application, 120 patients from the comparator arms crossed over to open-label arms of the trials and received raltegravir, providing an additional 111 patient-years of follow-up in patients receiving raltegravir (total duration of follow-up on raltegravir equals 619 patient-years). During the open label phase, two (2) additional patients experienced malignancy while on open-label raltegravir; one (1) patient experienced a recurrence of Hodgkin's disease and 1 patient experienced Hodgkin's disease and basal cell carcinoma. With this additional limited follow-up, the case rate of malignancy in patients receiving raltegravir remained stable at 1.940 cases per 100 patient-years. The data from the open-label arms did not alter the conclusions regarding malignancy.

For completeness, the original application presented a listing of malignancy cases identified from a review of Worldwide Adverse Event System (WAES) reports, blinded reports from the Phase III treatment-naïve study Protocol 021, and reports from the open-label Expanded access Program. The additional review also did not alter the conclusions regarding malignancy.

Cumulative Update as of 09-Jul-2007

Note: These data have not been reviewed by the FDA.

Double Blinded Analyses of Protocols 004, 005, 018, and 019 in the Cumulative Update as of 09-Jul-2007

In the cumulative update as of 09-Jul-2007, the analyses performed in the original application were repeated with additional follow-up in the same ongoing studies and with the same patients that identified the imbalance in the original application. In the section below, all data is cumulative: all patients presented for the original application are also included in the cumulative analyses below.

As of the cumulative update, in the double blind portions of Protocols 004, 005, 018, and 019, there were 19 patients (2.5%) experiencing malignancies that occurred post-randomization in participants on raltegravir and 5 patients (1.5%) with malignancies occurring in participants on a comparator arm. The time at risk for the raltegravir arms as of the cumulative update for Protocols 004, 005, 018, and 019 was 820 patient-years. For the comparator arms, the time at risk was 261 patient-years.

As of the cumulative update, the patient-year adjusted rates of malignancies per 100 patient-years in the double blind portions of the studies are 2.32 in the raltegravir arms and 1.92 in the comparator arms. This constitutes a Relative Risk of 1.209 (95% confidence interval 0.44, 4,14). By contrast, in the original application, the Relative Risk was 3.328 (95% confidence interval 0.47,144.45).

Table 17 lists the types of malignancies seen in the double blind phase of the studies, through the cumulative update, which still approximate the kinds of malignancies expected in heavily treatment experienced patients.. Patient-year adjusted rates for individual malignancy types are presented in Appendix 24. As in the original application, many of the cancers in the raltegravir were either recurrent, or occurred within a short period ($\leq$3 months) of enrollment.

Table 17

Summary of Malignancy – Double Blind Data
Phase II and III Studies
Cumulative Update as of 09-Jul-2007
Note: These data have not been reviewed by the FDA.

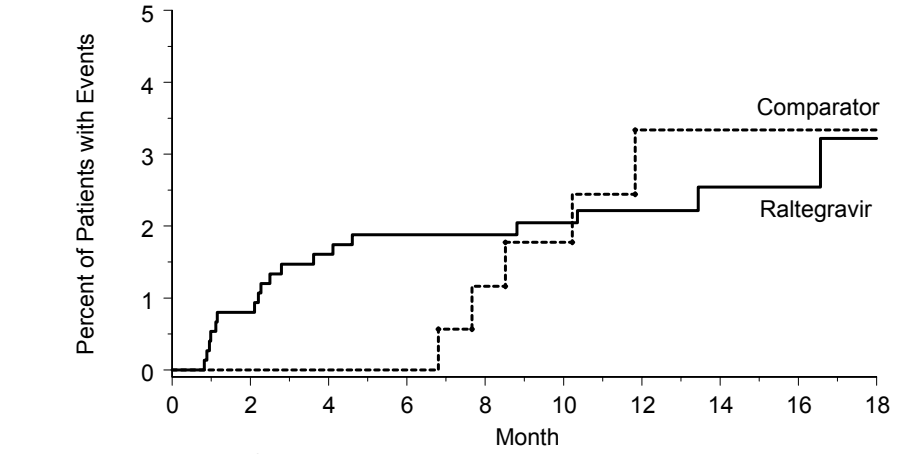
	Raltegravir			Comparator Group		
	N=758; 820 PY			N=323; 261 PY		
	n (%)†	Recurrent	Diagnosis ≤ 3 Months‡	n (%)†	Recurrent	Diagnosis ≤ 3 Months‡
Patients with Malignancy	19 (2.5)	8/19	11/19	5 (1.5)	2/5	0/5
Kaposi's Sarcoma	4 (0.5)	3	1	0 (0)	-	-
Non-Hodgkin's Lymphoma§	3 (0.4)	1	3	1 (0.3)	-	-
Squamous Cell Carcinoma – Anogenital‖	5 (0.7)	2	3	2 (0.6)	-	-
Squamous Cell Carcinoma - Other	1 (0.1)	-	1	1 (0.3)	-	-
Rectal Cancer	1 (0.1)	-	1	0 (0)	-	-
Metastatic Neoplasm NOS	0 (0)	-	-	1 (0.3)	1	
Hepatocellular Carcinoma	1 (0.1)	-	1	0 (0)	-	-
Non-Melanoma Skin Cancer¶	5 (0.7)	2	1	1 (0.3)	1	-

† Crude incidence (100 x n/N).
‡ Diagnosis of neoplasm occurred within 3 months of initiating study therapy.
§ Includes B-cell lymphoma, T-cell lymphoma, and lymphoma – other.
‖ Includes squamous cell carcinoma – anal and squamous cell carcinoma CIS.
¶ Includes squamous cell cancer – skin and basal cell carcinoma.
NOS = Not otherwise specified.
PY = Patient years of exposure.
Patients with multiple events may be counted more than once in different terms, but only once in one term.

Figure 20 displays Kaplan-Meier estimates of time to malignancies for the double blind phase of Protocols 004, 005, 018 and 019 cumulatively seen over 18 months of therapy in this updated malignancy analysis.

Figure 20

Kaplan-Meier Plot of Time to Malignancy-Double-Blind Phase
Phase II and III Studies
Cumulative Update as of 09-Jul-2007†
Note: These data have not been reviewed by the FDA.



Number of Patients at Risk

Raltegravir*	758	739	727	666	612	573	406	238	145	141
Comparator*	323	317	305	192	163	150	100	52	35	34

† Note: This time-to-event plot displays events diagnosed through 18 months of study follow-up. One additional malignancy in a patient on raltegravir occurring after 18 months of follow-up is not shown in this plot but is included in the tables.

Double Blinded, and Double Blind plus Open Label Analyses of Protocols 004, 005, 018, and 019 in the Cumulative Update as of 09-Jul-2007

As in the original application, an additional analysis was done including the available follow-up from the open-label parts of these studies, using the 09-Jul-2007 visit cut-off date.

One-hundred fifty-eight (158) patients from the comparator arms crossed over to open-label arms of the trials and received raltegravir, providing an additional 298 patient-years of follow-up in patients receiving raltegravir (total duration of follow-up on raltegravir equals 1118 patient-years). Including those in both the double blind portions (presented above) and open label parts of these studies, there were 26 patients (2.8%) with 29 malignancy events in the raltegravir group including open label exposure. In the open label phase, the 8 cancers that occurred in 7 patients during the open label phase included: 1 patient with Kaposi's sarcoma, 1 patient with 2 cancers (Hodgkin's lymphoma and basal cell carcinoma), 1 patient with recurrent Hodgkin's lymphoma, 1 patient with non-Hodgkin's lymphoma in the CNS, 2 patient with squamous cell carcinoma – anogenital (1 with anal squamous cell carcinoma and 1 with anal carcinoma in situ) and 1 patient with squamous cell carcinoma – skin that was recurrent. With this additional follow-up, the case rate of malignancy in patients receiving raltegravir remained stable at 2.32 cases per 100 patient-years.

Malignancy Discussion

It is unclear through which mechanism raltegravir could potentially increase malignancies. As discussed in Section 4, raltegravir was not demonstrated to be genotoxic in a battery of *in vitro* and *in vivo* assays designed to detect mutagenicity, direct DNA damage, or clastogenicity.

In the original application an imbalance was observed in the rates of malignancies occurring in the Phase II and Phase III clinical development program. However, based on an updated analysis of the same study cohorts, this imbalance in number of malignancies has not been sustained with additional follow-up.

Table 18 compares the malignancy data presented in the original application with the data obtained in the cumulative update.

Table 18

Summary of Malignancy Rates and Relative Risk
Double Blind Data
Note: The Cumulative Update data have not been reviewed by the FDA.

	Raltegravir (N=758)			Comparator Group (N=323)			
Timing	Cases	PY	Rate[§]	Cases	PY	Rate[§]	Relative Risk (95% CI)
Original Application[†]	10	508	2.0	1	169	0.6	3.3 (0.5, 144)
Cumulative Update[‡]	19	820	2.3	5	261	1.9	1.2 (0.4, 4.1)

† Data through 13-Dec-2006
‡ Data through 9Jul07
§ Per 100 PY.
PY = Patient years of exposure.

To put into perspective the type and rates of neoplasm observed in the raltegravir clinical trials, an extensive literature review of studies of cancer incidence in HIV-infected people was conducted. The natural history of HIV disease has evolved over the past 20 years with changing treatment paradigms. This literature review focused on experience in the HAART era as this experience was considered most relevant to the study population in this application. A comprehensive Medline search on HIV and cancer, identified papers published since 1998. We further selected population-based cohort studies using HIV/AIDS registries or prospective follow-up cohorts of HIV/AIDS patients. Only studies with at least either 5,000 person-years (PY) of follow-up or 1,500 subjects were selected for review. Several of the publications meeting these selection criteria did not provide incidence rates of cancer nor sufficient information to calculate them (e.g., number of cancers observed and data allowing the computation of person-time). For example, many articles only provided the standardized incidence rate ratios (SIRs) without giving the person-time of follow-up. For papers that did not provide incidence rates directly, we were able to calculate them by dividing the number of observed cancer cases by the total person-time of follow-up when this information was available. Whenever possible, we reported the incidence rates of cancer only among study HIV/AIDS patients in the highly active antiretroviral therapy (HAART) era (i.e. treated 1996 onwards) in order to optimize the comparability to the patient population in the raltegravir clinical trials. Of note, most papers in the final selection included advanced

HIV-infected patients, and several papers reviewed included only AIDS patients. The incidence rates from these observational studies are summarized in Table 19, which displays incidence rates for cancer overall as well as for selected cancers particularly frequent in the HIV-infected population.

Table 19

Incidence Rates of Selected Cancers in HIV/AIDS Patients in the Published Literature

	Published Studies Rate Ranges†	Citation number
Patients with Neoplasm	0.73-4.8	[483; 402; 478; 490; 484]
Kaposi's sarcoma	0.12-4.5	[386; 406; 405; 404; 483; 402; 478; 477; 474; 490; 481; 492; 479; 484; 485]
Non-Hodgkin's lymphoma	0.11-1.6	[386; 406; 405; 404; 483; 402; 478; 477; 474; 490; 481; 492; 479; 484; 485]
Hodgkin's lymphoma	0.03-0.10	[405; 404; 402; 480; 478; 492; 485]
Anal cancer	0.01-0.15	[404; 480; 478; 474; 475; 482; 490; 492; 484]
Non-melanoma skin cancer	0.01-0.36	[404; 402; 480; 478; 490; 484; 485]
Rectal cancer	0.01-0.23	[483; 402; 480; 478; 474; 490; 492]
Hepatic neoplasm	0.01-0.22	[483; 402; 474; 490; 487; 489; 486; 492; 485; 488]
PY = Patient years of exposure † Incidence rate expressed as events per 100 patient-years		

Overall, the rates and kinds of malignancies seen in patients receiving raltegravir in the clinical development program approximate the rates and kinds of malignancies reported in the literature for patients with HIV/AIDS.

It is also noteworthy that in the patients receiving raltegravir who ultimately developed a malignancy, the median CD4 cell count was 122 cells/mm^3 and all patients with malignancy had a history of AIDS, a known independent risk factor for malignancy. Most of the malignancies encountered are associated with well known risk factors for malignancy such as AIDS, oncogenic viruses (papillomavirus infection, hepatitis B virus infection), and tobacco.

Rates of malignancies, along with other serious adverse events will be monitored in ongoing clinical trials, post-licensure active surveillance, and assessed in our proposed comprehensive risk management plans (see Section 9).

Malignancy Conclusions

- In the original application, an imbalance in rates of malignancies was noted. The malignancy types and rates in the raltegravir group are those anticipated in a severely immunodeficient HIV/AIDS population and are consistent with reported rates in the literature. A history of malignancy prior to enrollment was common and many of the malignancies in the raltegravir group were likely present at time of study entry or were recurrences of prior diagnosed malignancies.
- Based on an updated analysis of the same study cohorts, the imbalance in rates of malignancies has not been sustained with additional follow-up. This is consistent with the possibility that the original imbalance was a function of small numbers of cases and relatively imprecise estimates of rates.
- While the updated analysis is reassuring, the total amount of safety follow-up is limited and additional data are needed. Further follow-up is proposed in the Risk Management Plan.

8.2.6 Discussion of Specific Adverse Experiences Associated with HIV Therapy

As described above, raltegravir was well tolerated throughout the clinical development program. However, adverse events that are of general concern in HIV therapy and/or are known to be associated with the previously licensed antiretroviral agents used in OBT were, as expected, reported in all arms of all studies. In this section, we review the safety data from the raltegravir clinical development program as it pertains to these adverse events.

Lipodystrophy/lipoatrophy

In treatment-experienced patients receiving raltegravir 400 mg b.i.d. or placebo (each with OBT) from Protocol 005 and the Phase III studies, the frequency of treatment emergent lipodystrophy or lipoatrophy reported as adverse experiences was low (<1%) in both treatment groups. Previous history prior to study enrollment was relatively common for lipodystrophy and lipoatrophy, 27.4% and 12.0%, respectively.

In Protocol 004, body circumference measurements over time were performed. These measurements were found to be similar among treatment groups over 48 weeks. Body circumference measurements in Protocol 005 also showed similar trends in the raltegravir plus OBT groups and the placebo plus OBT groups.

In summary, available data do not suggest that raltegravir is associated with lipodystrophy or lipoatrophy.

Rash

The proportion of patients with rash (including terms of rash, rash follicular, rash generalized, rash macular, rash maculopapular, rash papular, and rash pruritic) was 6.7% (34/507) for the raltegravir group and 3.9% (11/282) for the placebo group. There were no discontinuations due to rash, and no rashes were reported as serious in either treatment group. Several patients reported more than one rash (3 in the raltegravir group and 1 in the placebo group). In the raltegravir group, the intensity of rash was mild-moderate for most patients (33 of 34 or 97.1%) and most patients (25 of 34 or 73.5%) recovered from rash. In the placebo group all rashes were mild to moderate, and most patients (8 of 11 or 72.7%) recovered from rash. It should be noted that the many of the patients in the raltegravir group who had rash (23 of 34 or 67.6%) were taking two or more concomitant medication commonly associated with rash, such as atovaquone, sulfadiazine, sulfamethoxazole + trimethoprim, or OBTs associated with rash such as abacavir, amprenavir, atazanavir, darunavir, efavirenz, fosamprenavir, and tipranavir; in the placebo group 3 of 11 patients (27.3%) used 2 or more of these agents. Interestingly, when comparing the incidence of *drug-related* rash (and related terms as delineated above) between the raltegravir and placebo arms, the difference in incidence noted above was not seen, with drug related rash being reported in 2.0% (10/507) of the raltegravir arm and 2.5% (7/282) of the placebo arm.

Overall, while rash occurred somewhat more frequently in the raltegravir group than in the placebo group, it was generally benign and did not limit study therapy.

Immune Reconstitution Syndrome

Immune Reconstitution Syndrome (IRS) has been reported with highly active antiretroviral therapy regimens. There were 3 patients receiving raltegravir for whom IRS was reported as an adverse experience; 2 patients in the raltegravir treatment group in the double-blind cohort, and 1 patient in the OLPVF phase who was originally randomized to placebo. Only the patient in the OLPVF phase had IRS recorded as being drug-related. All 3 cases were considered serious adverse experiences. Study therapy was interrupted for 1 patient in the double-blind phase. Two (2) patients had recovered from the IRS, but the IRS was still listed as ongoing for 1 patient, at the time of the database freeze. The occurrence of IRS in this study population is not unexpected in light of the prompt and potent antiretroviral response observed in the raltegravir treatment group in highly immunodeficient patients.

Intrinsic Factors

Adverse experiences and laboratory abnormality profiles were generally similar in patient subgroups based on gender (N for male = 445; for female = 62), age (N for <65 years = 498 and N for ≥ 65 years = 9), and race (N for White = 336; N for Black = 71; N for Hispanic = 58; N for Asian = 16; N for Multi-Racial = 26), taking into account small sample sizes for some categories. Limitations of the safety data in the elderly population (age ≥65) are acknowledged. There were no patients ≥75 years of age.

Extrinsic Factors

Hepatitis Band/or C Co-infection: Safety data were reviewed for subgroups of patients with hepatitis B and/or C virus co-infection in Section 8.2.3.2.

Drug Interactions: Safety data from patients who used ARTs that are known to be associated with increased hepatic aminotransferases (tipranavir), and ARTs that have been shown to increase plasma levels of raltegravir have been reviewed.

- A review of patients whose OBT included (or did not include) tipranavir was performed; slightly higher rates of AST and ALT elevations as adverse experiences and PDLC were seen for both raltegravir and comparator treatment groups in those whose OBT contained tipranavir versus the complement. This is likely due to tipranavir itself which has a known association with LFT abnormalities [397]. It is not likely due to a drug-drug interaction because tipranavir modestly lowers exposure of raltegravir.
- The safety profile of patients receiving raltegravir with TFV and/or atazanavir was generally similar to that of the complement population, suggesting that there is no increased toxicity apparent at the highest exposures to raltegravir studied to date.

8.2.7 Updated Safety Information From the 2-Month Safety Update Report

As of the 2-month Safety Update Report (SUR), the conclusions regarding the safety of raltegravir are unchanged. The SUR repeats the safety analyses presented in the original application using data through 16-Feb-2007. Adverse event information from the ongoing trials and the Expanded Access environment are provided below.

Protocols 004, 005, 018, and 019 (Double Blind and OLPVF)

Two additional deaths occurred during the SUR period, 1 from Protocol 005 who was receiving open-label raltegravir (fatal SAEs of pleural effusion, splenic abscess, and lymphadenopathy) and 1 from the raltegravir arm (double blind) of Protocol 019 (fatal SAE of coronary artery disease).

Seven (7) additional non-fatal drug-related serious clinical adverse events occurred during the SUR period, 5 from the raltegravir group and 2 from the placebo group. These included: herpes simplex (double-blind raltegravir Protocol 018); chronic renal failure/renal tubular necrosis in one patient (double-blind raltegravir Protocol 018); second episode of gastritis (double-blind raltegravir Protocol 019); accidental overdose (double-blind raltegravir Protocol 019); hepatic toxicity (placebo Protocol 018) and renal failure (placebo Protocol 019). One serious drug related laboratory adverse event (Protocol 005-decreased platelets) occurred during the SUR period.

Overall, these experiences are not unexpected in a population with advanced HIV infection and immunosuppression.

Malignant Neoplasm

All data on malignant neoplasms identified in the SUR were part of the data included in the Cumulative Update as of 09-Jul-2007 that is presented in Section 8.2.5.

Protocol 021 - Raltegravir Versus Efavirenz in Treatment-Naïve HIV-Infected Patients, Each in Combination With TRUVADA™

There were no serious adverse experiences (SAEs) reported for the 50 patients enrolled in Protocol 021 as of 01-Dec-2006 in the original application. As of 16-Feb-2007, there were 290 patients enrolled in Protocol 021 and 5 of those patients had reported at least 1 SAE (accidental overdose, pneumonia, appendicitis, herpes zoster, and cytomegalovirus colitis). The only drug-related SAE was an accidental overdose in patient AN 23195. It is important to note that these patients are still blinded with respect to treatment group assignment. There were no serious laboratory adverse experiences reported as of 16-Feb-2007.

Expanded Access Environment

As of 16-Feb-2007, SAEs had been reported by 36 of approximately 827 patients enrolled in the expanded access environment. Review of these cases showed that the number and types of adverse experiences are not unexpected in a population with advanced HIV infection and immunosuppression, and no new safety signals were identified.

8.3 Safety Conclusions

1. In treatment-experienced patients failing antiretroviral therapy with triple-class resistant HIV, raltegravir 400 mg b.i.d. administered in combination with Optimized Background Therapy (OBT), as compared to placebo in combination with OBT:
    - is generally well tolerated
    - does not appear to be associated with lipodystrophy or lipoatrophy
    - is generally well tolerated irrespective of gender and race
    - is generally well tolerated in patients with active hepatitis B and/or hepatitis C co-infection.
2. In antiretroviral treatment-naïve patients, raltegravir when administered with tenofovir and lamivudine, as compared with efavirenz plus tenofovir and lamivudine over 48 weeks of treatment:
    - has a generally similar safety profile
    - has no adverse effect on fasting lipids.
3. In dose-ranging Phase II studies, and in patients using tenofovir and/or atazanavir in OBT, there is no evidence that higher doses or higher exposure due to drug-drug interactions lead to increased drug toxicity.
4. In the original application, an imbalance in the rates of malignancies was noted. However, based on an updated analysis of the same study cohorts, the imbalance in the rates of malignancies has not been sustained with further follow-up.
5. However, the total amount of safety follow-up is limited, and additional data are needed. Further follow-up is proposed in the Risk Management Plan.

9. Risk Management Plan

In accordance with US FDA and EMEA regulatory guidances, Merck & Co., Inc. has developed and submitted a Risk Management Plan (RMP). In order to identify potential safety risks, safety data from the pre-clinical and clinical programs have been reviewed and evaluated throughout the development of raltegravir, including the review of integrated pivotal safety summary data, prior to submission of the NDA.

The proposed indication for raltegravir is in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy. Raltegravir has shown a favorable safety profile and high potency in treatment-experienced patients, achieving virological suppression even in patients with limited options and late stage HIV disease. The proposed risk management plan presents a significant number of activities that range from routine passive surveillance to active surveillance, ongoing and planned clinical trials (comparative and non-comparative) that will add thousands of additional of person-years of exposure, a pregnancy registry, and the proposed product label which includes information about the product's safety. New clinical trials will add information on naïve and experienced-controlled populations; the proposed active surveillance study becomes an excellent source of comparative data in treatment-experienced populations.

Safety Issues Evaluated in Pre-clinical Studies

Extensive pre-clinical studies, conducted to evaluate the non-clinical safety of raltegravir, have demonstrated the antiviral properties of raltegravir and have demonstrated that raltegravir is well tolerated in several animal species. Specific observations of note include:

- Negative genotoxicity studies evaluating mutagenicity and clastogenicity.
- Well tolerated in long-term chronic preclinical animal safety studies at several exposure multiples over the recommended clinical dose.
- Identification of hepatotoxicity in preclinical studies occurred only after administration of high intravenous doses which produced AUC and C_{max} values in animals which were 23-fold and 71-fold, respectively, greater than human AUC and C_{max} values at the recommended dose.
- In ongoing 105 week animal carcinogenicity studies, squamous cell carcinoma of the nose/nasopharynx was identified in 3 high-dose rats (see Section 4.5.2). These neoplasms are considered to result from local deposition and/or aspiration of drug on the mucosa of the nose/nasopharynx during dosing and are considered an expected consequence of chronic irritation and inflammation. In addition, a single nasal chondrosarcoma was observed in one mid-dose rat and likely resulted also from topic chronic irritation. All other carcinogenicity studies were within historical incidence ranges for spontaneous occurrences. These observations are considered to have little relevance to humans when raltegravir is taken orally as prescribed.

Summary of Safety Issues Evaluated in Clinical Studies

In considering the safety profile of raltegravir, it is important to consider the study population and the duration of exposure to raltegravir during the clinical development program. There were a total of 875[4] persons exposed to raltegravir in Phase II and III studies (representing 536.6 person-years of exposure-See Section 6.2.3 for comparison of exposure versus duration of follow-up/time at risk). Raltegravir has been studied in different demographic groups and populations including in patients with hepatitis B virus and/or C virus co-infection; there is very limited data in the pediatric population (adolescents age 16 and older were eligible for Phase II studies) and elderly patients (above 65 years of age). There is no experience with raltegravir in pregnant or lactating females, patients with extreme hepatic dysfunction (AST, ALT, and/or alkaline phosphatase ≥5 times the upper limit of normal), and patients with severe renal insufficiency (serum creatinine ≥ 2 times the upper limit of normal) or urinary obstructive

[4] This does not include three patients from Protocol 004 Part 1 monotherapy who did not participate in the combination part of the study (Part 2).

disease. While extensive efforts were made to enroll higher percentages of patients of different races and genders, there was a predominance of whites (62%) and males (86%) exposed to raltegravir in clinical trials. Nevertheless, the safety profile of raltegravir was consistent among these different demographic groups and populations studied.

Raltegravir was generally well tolerated. Upon detailed review of the clinical safety database and taking into account adverse event profiles seen in heavily treatment experienced HIV-infected patients, several issues of interest were identified:

- ***Immune reconstitution inflammatory syndrome (IRS)***: IRS has been described in patients initiating ART, generally within the first 2 to 3 months of therapy, and is an expected consequence of effective antiretroviral therapy. As one would anticipate given the demonstrated potency of raltegravir-based regimens, events of IRS were reported in patients receiving raltegravir.
- ***Viral resistance***: Development of resistance by HIV during treatment has been described with all antiretroviral agents, particularly with monotherapy, either as a single agent or in the setting of functional monotherapy in an inadequate combination regimen. HIV from patients failing raltegravir-based regimens demonstrated mutations in the integrase gene. It is of particular importance to note, however, that the best response rates with raltegravir-based therapies occurred when raltegravir was combined with at least one other potent active agent.
- ***Malignancies***: Patients with AIDS are at high risk of developing malignancies, including AIDS-defining and non-AIDS-defining malignancies. In the Phase II and Phase III studies, a numerically higher number of malignancies were noted in patients receiving raltegravir in comparison to those receiving control study medications. The malignancies reported were consistent with the types anticipated in this highly immunodeficient population. For malignancies for which published rates in the HIV population are available, the observed rates of individual malignancies among raltegravir groups are similar to previously published rates. Furthermore, the overall rate of malignancies did not increase with increased duration of treatment. Several of the malignancies represented recurrences of previously diagnosed cases. Many of the malignancies were identified within 3 months after study entry, suggesting the cancers were pre-existing conditions. More importantly, based on an updated analysis of the same study cohorts, the imbalance in the rates of malignancies has not been sustained with additional follow-up. Overall, based on a complete review of the data, there is no evidence of a direct drug relationship for these events.

- ***Drug-Drug interactions***: HIV-infected patients are treated with a multitude of medications. In preclinical and clinical investigation, the major pathway of metabolism of raltegravir involves glucuronidation, primarily by UGT1A1. Based on *in vitro* and *in vivo* data, raltegravir has very low potential to produce clinically significant changes in levels of other drugs. Drugs that are potent inducers and inhibitors of UGT1A1 were assessed in a number of drug interaction studies with raltegravir and demonstrated that, in general, effects were slight to modest in degree and not considered to be clinically meaningful. Rifampin, a potent inducer of drug metabolizing enzymes, resulted in a modest decrease in raltegravir levels; however, based on the extent of the effect, it is recommended as a conservative measure to consider a dose increase of raltegravir to 800 mg twice daily when co administered with rifampin and the similarly potent broad inducers phenytoin and phenobarbital. Clinical trial data demonstrated that raltegravir has broad therapeutic efficacy with potent efficacy across all doses studied including in the presence of inducers and inhibitors of UGT1A1. Similarly, no dose limiting toxicities were identified including in the presence of inhibitors of UGT1A1. With the exception of rifampin, phenytoin, and phenobarbital, no dose adjustment of raltegravir is required in combination with other drugs.

Conclusion

Considering all the data summarized above, IRS, drug resistance, and drug interaction are the only important identified safety risks. Malignancy is considered a potential risk due to a numeric imbalance in the original application; however, there did not appear to be evidence of a direct drug relationship to this event, considering that cancer is a common condition in HIV infected patients, particularly those with advanced disease, and all the other factors previously mentioned. Also noteworthy was the updated analysis of the same study cohorts, in which the imbalance in the rates of malignancies was not been sustained with additional follow-up. Potential exposure during pregnancy and long-term safety data (populations studied and populations insufficiently studied/not studied e.g., children, elderly, patients with severe hepatic impairment) are considered important missing information.

Risk Management Planned Actions

To address the important safety issues, Merck & Co., Inc. proposes a comprehensive Risk Management Plan that includes the following activities:

1) Routine Pharmacovigilance:

Post-marketing reports of IRS, HIV resistance and/or virologic failure, known and potential drug interactions, pregnancy outcomes, and any other important safety issues that are identified will be reviewed and evaluated on an ongoing basis. Clinical study data pertaining to any of these targeted safety issues will also be monitored and evaluated. For the first 3 years following licensure post-marketing and clinical study reports/data on these issues will be discussed in the 6-month Periodic Safety Update Reports (PSURs).

2) Ongoing/Planned Clinical Trials:

The ongoing/planned clinical trials for raltegravir include 6 pharmacokinetic studies as well as 9 clinical trials. In addition, a pediatric program (Protocol 022) is planned which will evaluate the safety and tolerability of raltegravir added to initial stable background therapy in children. Seven of the ongoing/planned clinical studies (Protocols 004, 005, 018, 019, 021, 032, 033), several of which had been extended to 3 years, are anticipated to contribute an additional estimated exposure of 1,382 person-years as therapy in highly treatment-experienced patients and 1,210 person-years in comparative naïve/experienced-controlled populations. This is in addition to the current exposure available. The expanded access environment will provide additional non-comparative exposure in highly treatment-experienced patients. All these studies will provide information on thousands of treated patients including 156 weeks of cumulative exposure that will strengthen the safety database of raltegravir. Table 20 below provides a high level summary of the ongoing and planned clinical trials:

Table 20

Summary of Ongoing and Planned Clinical Trials

Protocol[#]	Type of study	Type of patient	Raltegravir Exposure (person-years)	Status
005[†], 018, 019[‡]	Comparative	Adult treatment-experienced	1,382 post FF	Ongoing
023¥	Non-comparative	Adult treatment-experienced	>2,000 patients[¶]	Ongoing
004[§], 021[‖],032, 033[∞]	Comparative	Adult naïve/ experienced-controlled	1,210 post FF[#]	Ongoing (004, 021)/Planned (032,033)
022	Non-comparative	Pediatric treatment-experienced	120	Planned

[†] 005 is double-blind, controlled for at least 24 weeks (duration of double blind varies from 24 weeks to 72 weeks depending on when patient was enrolled and when amendment occurred at sites), then open-label for an additional 96 weeks. All patients, including those originally randomized to the control group, received raltegravir during open-label. In addition, patients who failed study therapy could receive raltegravir by enrolling in an "open-label post virologic failure arm" after at least 16-weeks of study therapy.

[‡] 018 and 019 are double-blind, controlled for 156 weeks duration; patients who failed study therapy could receive raltegravir by enrolling in an "open-label post virologic failure arm" after at least 16-weeks of study therapy.

¥ 023 is an early access study of raltegravir in combination with OBT in highly treatment experienced HIV-1 infected patients with limited to no treatment options.

[§] 004 is double-blind, controlled for 144 weeks duration.

[‖] 021 is double-blind, controlled for 96 weeks duration.

∞ 032 and 033 are multicenter, double-blind, randomized, active-controlled studies to evaluate the safety and antiretroviral activity of raltegravir versus Kaletra™ in HIV-infected patients switched from a stable Kaletra™-based regimen for 48 weeks

[¶] Exposure depends on enrollment.

[#] Post frozen-file (FF) exposure estimated based on numbers of patients per group at FF continuing.

3) Active safety surveillance

In addition to the routine pharmacovigilance activities (which include regular analysis of postmarketing safety data), Merck & Co., Inc. proposes an active post-licensure observational prospective cohort safety surveillance study to monitor malignancies and other important safety issues involving a large number of subjects. The objectives of this active observational safety surveillance study will be to:

a) Assess the incidence of medical outcomes of interest in HIV-infected patients treated with raltegravir in routine post-licensure use

b) For comparison purposes, describe background incidence rates of these medical outcomes in two control cohorts:

1. A pre-licensure historical control cohort of treatment-experienced HIV-infected patients who would have been eligible to receive raltegravir, had it been available

2. A post-licensure concurrent control cohort of treatment-experienced HIV-infected patients not treated with raltegravir

The incidence rates and characteristics of medical outcomes observed in the control cohorts will be described and used to put into perspective the outcomes observed in patients treated with raltegravir.

Study databases and cohorts will be established in which raltegravir prescriptions and medical outcomes in HIV-infected patients can be linked. HIV-infected patients will be followed after a raltegravir prescription in order to assess the occurrence of neoplasms and general safety outcomes resulting in hospitalizations or emergency room visits. An independent, external Safety Monitoring Committee (SMC) will be established to review the data and study progress on a regularly scheduled basis.

Merck & Co., Inc. is currently exploring the feasibility of such active observational surveillance in several large medical insurance databases and cohorts in order to establish a study population of HAART treatment-experienced patients that can be followed after the licensure of raltegravir. Active surveillance is proposed to be conducted for 3 years post-licensure and until at least 1,000 patient-years of exposure to raltegravir are accrued. A sample size of 1,000 person-years of raltegravir exposure allows reasonably good power to monitor health outcomes. For example, the proposed study will have 80% power to detect a 2.5 fold increase and approximately 93% power to detect a 3-fold increase in the incidence of a health outcome that has an annual background rate of 0.5% (1/200 person-years) (assuming one-sided alpha=0.05 using exact binomial statistics). If the background rate of the health outcome is 0.2% (i.e., 1/500 person-years), the study will have 80% power to detect a 4-fold increase in incidence. Data will be collected and analyzed on an ongoing basis, with updates on the study progress being reported in the 6-month PSUR (e.g., accumulated person-years of exposure). The results of this active surveillance will be presented in a report first provided after a year of data accrual following the implementation of the project and then on an annual basis, with a final report at the end of the project.

4) Participation in the Antiretroviral Pregnancy Registry (APR)

The APR is an international collaborative project to monitor reported exposures to antiretroviral drugs during pregnancy. The Registry is designed to provide an early signal of teratogenicity with prenatal use of the drugs monitored through the Registry.

The APR interim analysis report describes the ongoing surveillance experience of pregnancy outcomes for the antiretroviral therapies being followed in the Registry and is produced at 6-month intervals. The latest report will be attached to the following PSUR for raltegravir.

5) Routine Pharmacovigilance for Pregnancy Exposures

Reports of birth defects and serious, unlabeled maternal/fetal/newborn adverse experiences following exposure during pregnancy to raltegravir (both in clinical trials and the post-marketing environment) will be monitored and evaluated. Pregnancy exposures to raltegravir will be reviewed and included in the 6-month PSUR.

6) Product Labeling

This activity will inform health professionals about the safety profile of raltegravir, including a summary of safety data related to raltegravir use. The important identified and potential risks are included in product labeling for raltegravir.

Conclusions: Risk Management Plan for Raltegravir

Raltegravir has a favorable safety profile. Given the identified and/or potential safety risks, Merck & Co., Inc. has developed a comprehensive Risk Management Plan that combines traditional passive pharmacovigilance activities with a proactive surveillance program and appropriate product labeling information. Additionally, a substantial amount of clinical trial data from the ongoing and planned studies, including new comparative data in naïve and experienced-controlled populations (at least 2,500 patient-years of additional comparative exposure), will contribute significant additional data to further characterize the safety profile of raltegravir.

10. Conclusions and Recommendations

10.1 Rationale for the Proposed Dosing Recommendations

In Section 7.2.2, the rationale for the choice of the 400 mg b.i.d. dose of raltegravir in the pivotal Phase III trials was presented. In this section, efficacy, safety, drug interaction and food-effect data that support the final dosing recommendations for raltegravir are discussed.

The proposed dose of raltegravir is 400 mg b.i.d. without regard to food.

It is important to note that pharmacodynamic analyses utilizing intensive pharmacokinetic (PK) sampling from Protocol 004 and sparse population PK sampling from Protocols 004, 005, 018, and 019 did not identify clinically meaningful correlations. This suggests that the range of concentrations obtained in the Phase II and Phase III studies falls near the top of the concentration-response curve, where treatment response has, at most, only a modest concentration-dependency. Furthermore, these analyses indicate that raltegravir concentrations throughout the range of clinical experience from Phase II and III are associated with a similar high level of efficacy. As such, the efficacy and safety data from the clinical studies provide the key information to support the proposed raltegravir dose and the dosing regimen.

All doses used throughout the Phase II and Phase III studies have demonstrated potent efficacy and a favorable safety profile. During the Phase II clinical development program, raltegravir was tested at doses as low as 100 mg b.i.d. and as high as 600 mg b.i.d. and was dosed without regard to food. No dose-response relationship was observed in either treatment-naïve patients or treatment-experienced patients for any safety parameters. In both studies, antiviral activity of all doses was sustained through the double-blind portions of the studies, 48 weeks for Protocol 004 and 24 weeks for Protocol 005. In addition, in Protocol 005, antiviral activity was sustained through 48-weeks based on combined data from the double-blind phase and the open-label raltegravir 400 mg b.i.d. phase.

Phase III studies were conducted using the dose of 400 mg b.i.d. taken without regard to food. Raltegravir demonstrated superior efficacy as compared to placebo in both Protocol 018 and Protocol 019 at Week 16, and partial data at Week 24 demonstrated comparable efficacy (as did complete Week 24 data in the update). The Phase III dose was chosen based on the efficacy and tolerability observed in the Phase II studies and taking into consideration potential drug-drug interactions. A broad range of antiretroviral drugs and other concomitant medications were used in combination with raltegravir in the Phase II and Phase III studies, including some with the potential to alter raltegravir plasma levels. Overall, these data strongly support the potency of this dose and this dosing regimen when used as a component of HIV therapy, which contains multiple medications.

However, dose adjustment to 800 mg b.i.d. should be considered when raltegravir is co-administered with rifampin, phenytoin or phenobarbital, 3 broad and potent inducers of drug metabolizing enzymes.

Rationale for Comparability Bounds Defining a Clinically Significant Change in Raltegravir Pharmacokinetics

Summary

Effects up to a 2-fold increase in exposure (AUC) and a 60% decrease (equivalent to GMR of 0.4) in trough concentration (C_{12hr}) were considered to be not clinically relevant based on available clinical experience from Phase I and Phase II studies with regard to safety and efficacy (see Sections 5.5.2, 5.6, and 8).

Defining a Lower Comparability Bound for a Clinically Significant Change in Raltegravir Pharmacokinetics

The association between C_{12hr} and short term viral load reduction described in Section 5.6 and experience in other classes of antiretrovirals support trough as the pharmacokinetic target likely to be the most sensitive to predict viral response. Strongly favorable efficacy has been obtained with raltegravir in the clinical program and no dose or concentration-dependencies in longer-term efficacy measures have been identified. This indicates that the lower bound of pharmacokinetic exposures in the clinical experience

can be used to define the fold-reduction in C_{12hr} demonstrated not to be associated with an increased risk of reduced long-term efficacy. Mean C_{12hr} values for the lower doses studied in Phase II (Protocol 004 and Protocol 005) were ~100 nM, 60% lower than the mean value of ~271 nM obtained at the clinical dose of 400 mg twice-daily in the sparse pharmacokinetic data from the Phase III studies, supporting a 60% reduction in trough concentration as the lower limit of broad clinical experience.

Also important was the clinical experience in the Phase III trials of combination therapy with tipranavir/ritonavir. The combination of tipranavir/ritonavir is an inducer of drug metabolizing enzymes that modestly decreases raltegravir levels (C_{12hr} decreases of ~50-55%; see Table 1). It is assumed that this decrease in raltegravir levels is mediated by induction of UGT1A1. Tipranavir/ritonavir use in the OBT was allowed in Phase III studies and was used in ~21% (n/N= 98/462 [Protocols 018 and 019 combined]) of the patients who received raltegravir. In an analysis of tipranavir/ritonavir as a prognostic factor (Section 7.5.3), potent efficacy of raltegravir was observed as compared to placebo regardless of the presence of phenotypic or genotypic susceptibility to tipranavir/ritonavir. This also supports the robustness of the lower comparability bound, and the recommendation for no dose adjustment for combination therapy of raltegravir and tipranavir/ritonavir (see below).

Defining an Upper Comparability Bound for a Clinically Significant Change in Raltegravir Pharmacokinetics

In general AUC or C_{max} are the pharmacokinetic parameters most likely to be associated with toxicity. There have been no acute safety findings in the raltegravir clinical program that were temporally associated with peak concentrations supporting that AUC is the most appropriate pharmacokinetic parameter to judge the clinical significance of elevations in raltegravir concentrations. Overall, raltegravir has been generally well tolerated with no dose related toxicities identified; therefore, the upper bound of broad clinical experience was used to define the fold-elevation in AUC demonstrated not to be associated with an increased risk of clinically meaningful alterations in safety and tolerability. The highest exposure to raltegravir in the Phase II studies was in patients taking the highest dose (600 mg) in combination with atazanavir or tenofovir, which represented an approximately 2-fold increase over the AUC at the clinical dose of 400 mg twice-daily. These data support an upper comparability bound of up to a 2-fold increase in exposure not having clinical relevance.

Analyses investigating important potential drug-drug interactions, specifically, inducers and inhibitors of UGT1A1 and food interactions, are discussed in the text that follows.

***Drugs that decrease raltegravir levels*:**

As mentioned above, the combination of tipranavir/ritonavir is an inducer of drug metabolizing enzymes that modestly decreases raltegravir levels, with decreases equivalent to the lower bound of clinical significance. However, based on the analyses described above, it can be concluded that the interaction between the drugs is not clinically meaningful and that tipranavir/ritonavir can be coadministered with raltegravir 400 mg b.i.d. without dose adjustment.

The impact of rifampin, a broad potent inducer of drug-metabolizing enzymes, on raltegravir levels was evaluated in a formal drug-drug interaction study as a probe study for the impact of potent inducers on raltegravir. Other potent inducers such as phenytoin and phenobarbital were not formally evaluated but are assumed to have similar inductive potential as rifampin and to have a similar effect on raltegravir. Rifampin decreased raltegravir levels presumably due to induction of UGT1A1. Decreases seen were equivalent to the lower bound of clinical significance. Rifampin, phenytoin, and phenobarbital were prohibited concomitant medications in the Phase II and Phase III clinical studies; in contrast to tipranavir/ritonavir, no clinical data efficacy data is available. In light of the slightly greater effect of rifampin on raltegravir levels than for tripranavir/ritonavir and the lack of actual clinical data for concomitant use of these drugs, it is a conservative recommendation that a doubling of the raltegravir dose should be considered when co-administered with rifampin, phenytoin, or phenobarbital.

Drugs that increase raltegravir levels:

Atazanavir, either alone or in combination with ritonavir, is an inhibitor of UGT1A1 that modestly increases raltegravir levels. Patients receiving raltegravir in combination with an atazanavir containing regimen, therefore, are exposed to higher concentrations of raltegravir. In the Phase II treatment-experienced study, Protocol 005, atazanavir was not used in Substudy A but was used in Substudy B. As briefly mentioned above, treatment effects were comparable between the substudies, and the adverse experience profile in patients receiving atazanavir-containing regimens was similar to that in patients not receiving atazanavir-containing regimens. Review of the safety profile of raltegravir in combination with atazanavir containing regimens from all the Phase II and Phase III treatment experienced studies also demonstrated a satisfactory safety profile.

Tenofovir was found to modestly increase raltegravir levels; the mechanism for the increase in raltegravir levels is not understood. In Protocol 004, all patients received tenofovir (and lamivudine) in combination with either raltegravir or efavirenz. Efficacy and tolerability was comparable across the range of raltegravir doses tested. Review of the safety profile of raltegravir in combination with tenofovir containing regimens from all the Phase II and Phase III treatment-experienced studies also demonstrated a satisfactory safety profile. It is possible that the combination of atazanavir and tenofovir

could increase raltegravir levels to a greater degree than each individual drug alone. However, the safety profile of raltegravir use in patients receiving atazanavir and tenofovir as components of their OBT was evaluated for patients in the Phase II and Phase III treatment-experienced studies and demonstrated a satisfactory safety profile.

Overall, these data support that no dose adjustment is required for patients receiving drugs that modestly increase raltegravir levels.

Food Effects: The effect of food on the pharmacokinetics of raltegravir was evaluated. There was no clinically meaningful effect of food demonstrated on total exposure to raltegravir as measured by AUC, but a high-fat meal did slow the rate of absorption, causing a 34% decrease in C_{max} and an 8.5-fold increase in C_{12hr}. As the total exposure is unchanged and the C_{max} is decreased in the presence of food, it is unlikely that this effect of food will impact the safety profile of raltegravir. Indeed in the Phase II and Phase III studies in which raltegravir was dosed without regard to food, raltegravir demonstrated an excellent safety profile that was similar to the comparator regimens. Food appears to increase pharmacokinetic variability somewhat as compared to the fasted state and, consequently, a similar lower range of individual C_{12hr} values was observed in cross-study comparison, suggesting that food does not consistently increase C_{12hr} values (see Section 5). While the available data indicate that, on average, C_{12hrs} is increased by administration with food, there is no evidence that this increase would provide a therapeutic advantage, given the associated increase in pharmacokinetic variability. This is supported further by pharmacokinetic/pharmacodynamic (PK/PD) analyses which do not suggest an association of drug concentration with viral response (see Section 5.6). In all Phase II and Phase III studies, raltegravir was dosed without regard to food and the raltegravir treatment regimens were highly efficacious in both treatment-naïve and treatment-experienced patients. Overall, the efficacy and safety data generated in the Phase II and Phase III studies support dosing raltegravir without regard to food.

In summary, the 400 mg b.i.d. dose of raltegravir given without regard to food is highly effective in combination regimens which provide potent sustained antiviral activity and is generally well tolerated. The 400 mg b.i.d. dose provides a margin of efficacy and safety that can accommodate factors that modestly increase or modestly decrease raltegravir plasma levels. Dose adjustment to 800 mg b.i.d. should be considered when raltegravir is co-administered with rifampin, phenytoin or phenobarbital, 3 known broad and potent inducers of drug metabolizing enzymes.

10.2 Overall Benefit and Risk of Raltegravir

Medical Need for Treatment of HIV-Infected Patients With Triple-Class Resistant Virus

Despite the progress made with HAART over the last decade, there is still an urgent medical need for an effective ART for patients failing current therapies with multi-drug resistant virus. Although there are approximately 22 licensed ARTs, all except one belong to only 3 classes of ARTs (NRTIs, NNRTIs, and PIs) that target 2 HIV enzymes. There is significant cross-resistance within each class. Overcoming the increased levels of resistance and cross-resistance that follow each successive therapeutic failure is a major challenge faced by clinicians. Recent data [67] strongly indicate that a new ART from a novel class offers benefits to this patient population given lack of cross-resistance to existing classes. Raltegravir, the first HIV integrase strand transfer inhibitor, has provided convincing evidence of its benefits in HIV-1 infected patients, in particular those who are refractory to currently available treatment.

Impact of Raltegravir on the HIV Treatment Armamentarium

Benefits

The available efficacy data from all 3 Phase II and III trials in treatment-experienced patients support the conclusion that raltegravir has potent antiretroviral effect in the targeted patient population. The 48-week results from Protocol 005 suggest that this potent antiretroviral effect is sustained. To date, rescue antiretroviral therapy in patients failing previous regimens has been inadequate, given that patients generally do not have more than one active ART in the regimen. Functional monotherapy quickly leads to therapeutic failure and further development of resistance. The landscape for HIV treatment in heavily-treatment-experienced patients is evolving rapidly with the possibility of having more than one new agent available in approximately the same timeframe to allow truly effective combination therapy. Thus, the timing for access of raltegravir is extremely important for these patients, so that the most recently approved ARTs can partner with raltegravir for the construction of an effective combination therapy.

In addition to efficacy benefits, the favorable tolerability and safety profile of raltegravir to date in this advanced-HIV patient population provides a significant therapeutic benefit. Toxicity is an important barrier to effective antiretroviral therapy and accounts for the most common reasons for treatment failure [204; 367]. The rate of discontinuation due to adverse experiences in all studies in the clinical development program for raltegravir was low. In treatment-naïve patients in whom it is feasible to assess the potential impact on lipid levels, raltegravir treatment was not associated with increases in serum cholesterol, triglycerides, or LDL-C, suggesting an important potential advantage over currently available regimens.

The low propensity of raltegravir for drug interaction represents another important benefit. In situations where raltegravir is co-dosed with ARTs that may lower or raise its plasma exposure, the high margin of efficacy and safety exhibited in the dose-ranging studies, supports the administration of raltegravir without dose adjustment. This would simplify the dosing instructions for raltegravir, and potentially facilitate compliance. In addition, the low pill burden (one pill twice daily) may also facilitate compliance, an important factor for therapeutic success.

Risks

Consistent with all clinical development programs for HIV drugs, the safety database is relatively limited both in terms of size and of duration. Overall, raltegravir has been generally well tolerated with low discontinuation rates due to adverse experiences. The adverse experience profile, clinical and laboratory, of raltegravir in combination with other ARTs is similar to that of placebo with ARTs. No specific safety issues were identified that would preclude the approval of raltegravir for the proposed indication. Although a numerically greater rate of malignant neoplasms was reported in the raltegravir treatment groups, a thorough review of the data does not provide any direct evidence of drug relationship to any of these events of cancer. Also noteworthy was the updated analysis of the same study cohorts, in which the imbalance in the rates of malignancies was not been sustained with additional follow-up. This risk, however, must continue to be actively assessed as the total amount of safety follow-up is limited. The current database will be supplemented with 48-week data from Protocols 018 and 019 when available. As raltegravir is the first in a new class of ARTs, an appropriate postmarketing monitoring plan has been established (Section 9), which includes longer-term safety data from ongoing clinical trials (Protocols 004, 005, 018, 019, which are currently planned for a total of 3 years duration; and the Phase III treatment-naïve study for a total of 96-weeks).

Overall Benefits/Risks Assessment

Overall, the data presented support the proposed indication: Raltegravir is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy.

Taking into account the observed safety profile, the benefits/risks profile of raltegravir for the requested indication is favorable.

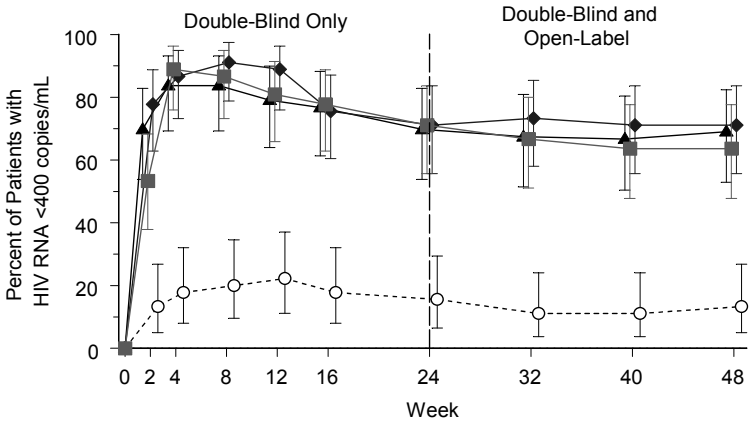
11. Plans for Completing Requirements for Traditional Approval

Week 48 data from the Phase III treatment-experienced studies (Protocol 018 and Protocol 019) will be provided once the final analyses and clinical trial reports are completed. These 48 week data are intended to support the application for traditional approval.

12. Appendices

Appendix 1

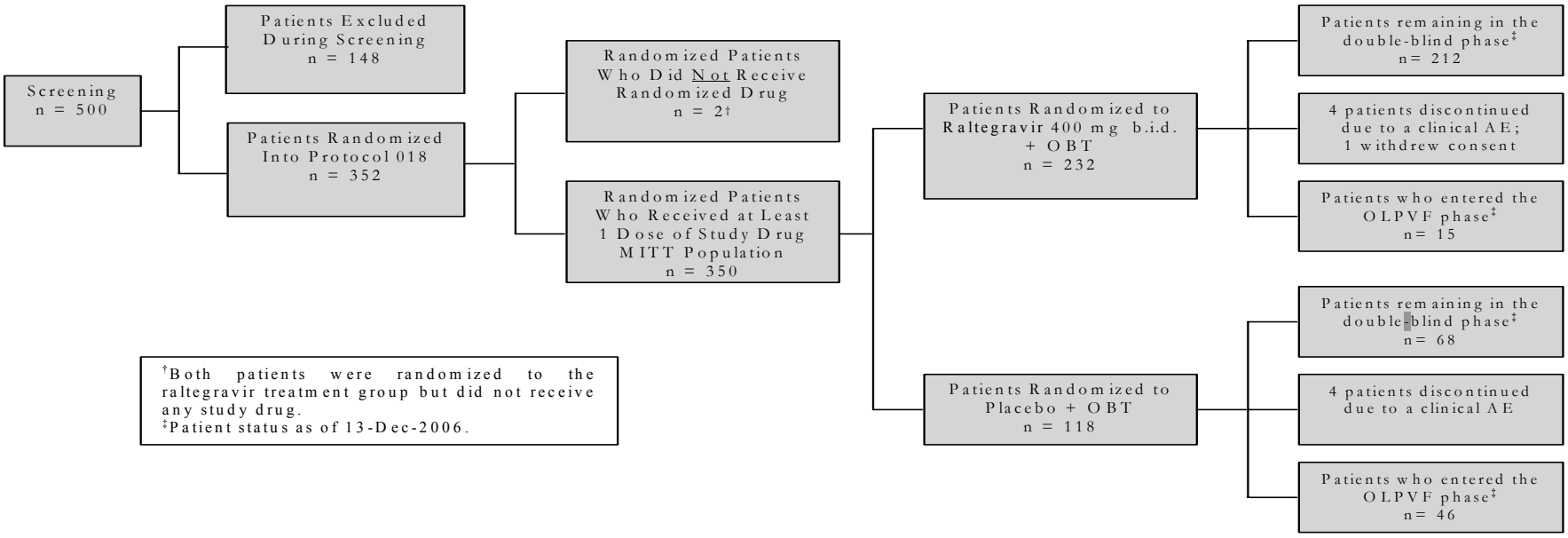
Percent (95% CI) of Patients With HIV RNA <400 Copies/mL Over Time
by Originally Randomized Treatment Group─Protocol 005
(Substudies A and B Combined; Entire Study Period)
(Non-Completer = Failure Approach)



▲ Raltegravir 200 mg b.i.d.	43	43	43	43	43	43	43	43	42	42
■ Raltegravir 400 mg b.i.d.	45	45	45	45	42	45	45	45	44	44
◆ Raltegravir 600 mg b.i.d.	45	45	45	45	45	45	45	45	45	45
○ Placebo	45	45	45	45	45	45	45	45	45	45

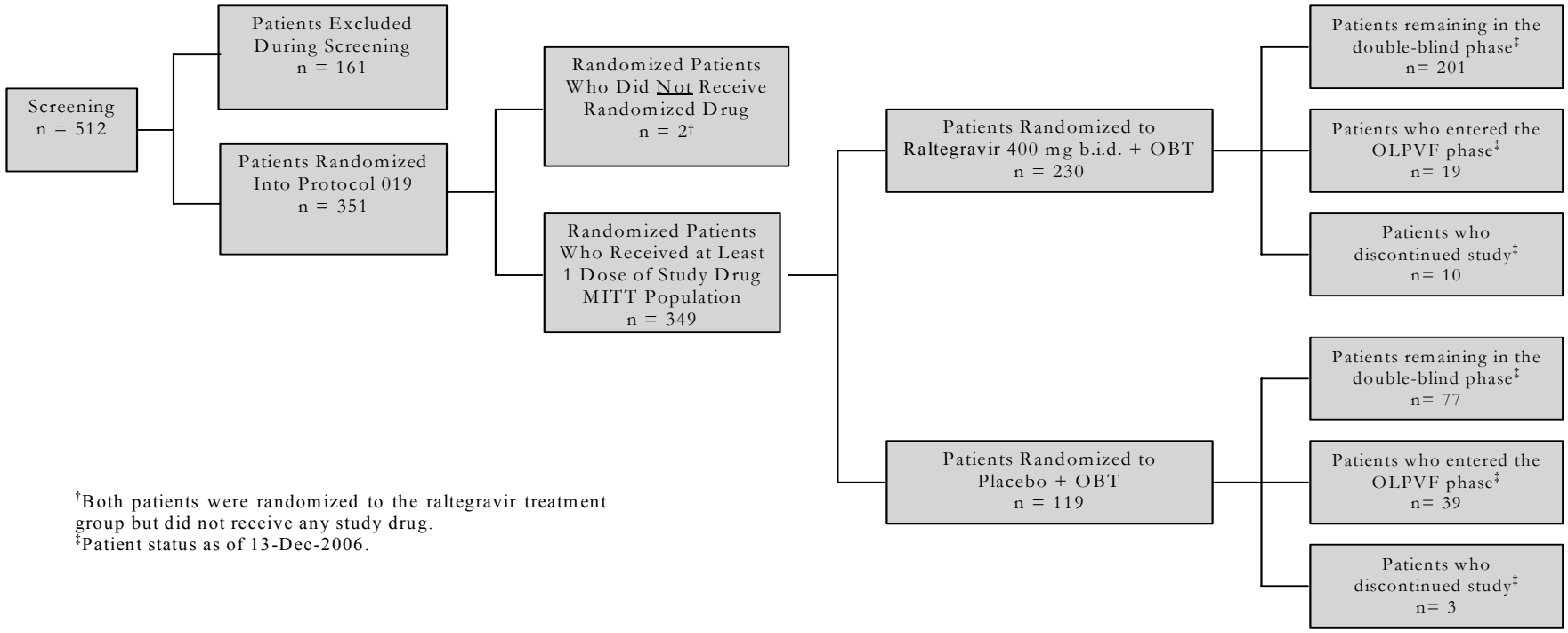
Appendix 2

Summary of Patients Contributing to the Summary of Clinical Efficacy (Protocol 018)



Appendix 3

Summary of Patients Contributing to the Summary of Clinical Efficacy (Protocol 019)



†Both patients were randomized to the raltegravir treatment group but did not receive any study drug.
‡Patient status as of 13-Dec-2006.

Appendix 4

Patient Baseline Characteristics by Treatment Group (Protocol 018)

	Raltegravir 400 mg b.i.d. (N = 232)	Placebo (N = 118)	Total (N = 350)
Gender n (%)			
Male	195 (84.1)	103 (87.3)	298 (85.1)
Female	37 (15.9)	15 (12.7)	52 (14.9)
Race n (%)			
White	175 (75.4)	96 (81.4)	271 (77.4)
Black	18 (7.8)	5 (4.2)	23 (6.6)
Asian	14 (6.0)	5 (4.2)	19 (5.4)
Hispanic	6 (2.6)	1 (0.8)	7 (2.0)
Others	19 (8.2)	11 (9.3)	30 (8.6)
Region n (%)			
Central/South America	23 (9.9)	11 (9.3)	34 (9.7)
Asia Pacific	38 (16.4)	20 (16.9)	58 (16.6)
Europe	171 (73.7)	87 (73.7)	258 (73.7)
Age (years)			
Mean (SD)	46.1 (8.5)	43.7 (8.2)	45.3 (8.5)
Median (min, max)	45.5 (16 to 74)	43.0 (19 to 64)	45.0 (16 to 74)
CD4 Cell Count (cells/mm^3)			
Mean (SD)	156.4 (139.0)	152.8 (152.0)	155.2 (143.3)
Median (min, max)	140.0 (1 to 792)	104.5 (3 to 759)	130.0 (1 to 792)
Plasma HIV RNA (log_{10} copies/mL)			
Mean (SD)	4.6 (0.8)	4.5 (0.8)	4.6 (0.8)
Median (min, max)	4.8 (3 to 6)	4.6 (2 to 6)	4.7 (2 to 6)
Plasma HIV RNA (copies/mL)			
Geometric Mean	40519.2	31827.9	37351.7
Median (min, max)	61750.0 (441 to 750000)	42700.0 (200 to 750000)	50950.0 (200 to 750000)
History of AIDS n (%)			
Yes	217 (93.5)	106 (89.8)	323 (92.3)
Prior Use of ART			
Year of ART Use: Median (min,max)	10.6 (0.3 to 18.8)	10.3 (1.3 to 15.4)	10.5 (0.3 to 18.8)
Number of ART: Median (min,max)	12.0 (2 to 19)	12.0 (3 to 18)	12.0 (2 to 19)
Hepatitis Co-infection[†] n (%)			
No Hepatitis B or C	183 (78.9)	91 (77.1)	274 (78.3)
Hepatitis B only	14 (6.0)	3 (2.5)	17 (4.9)
Hepatitis C only	31 (13.4)	22 (18.6)	53 (15.1)
Hepatitis Co-infection of B and C	4 (1.7)	2 (1.7)	6 (1.7)

Appendix 4 (Cont.)

Patient Baseline Characteristics by Treatment Group
(Protocol 018)

	Raltegravir 400 mg b.i.d. (N = 232)	Placebo (N = 118)	Total (N = 350)
Stratum n (%)			
Enfuvirtide in OBT	88 (37.9)	43 (36.4)	131 (37.4)
Resistant to ≥ 2 PI	225 (97.0)	112 (94.9)	337 (96.3)

† Hepatitis B surface antigen positive or hepatitis C antibody positive.
Note: Raltegravir and Placebo were administered with Optimized Background Therapy (OBT).
N = Number of patients in each treatment group.
n (%) = Number (percent) of patients in each subcategory.

Appendix 5

Patient Baseline Characteristics by Treatment Group (Protocol 019)

	Raltegravir 400 mg b.i.d. (N = 230)	Placebo (N = 119)	Total (N = 349)
Gender n (%)			
Male	210 (91.3)	107 (89.9)	317 (90.8)
Female	20 (8.7)	12 (10.1)	32 (9.2)
Race n (%)			
White	126 (54.8)	77 (64.7)	203 (58.2)
Black	48 (20.9)	21 (17.6)	69 (19.8)
Asian	2 (0.9)	1 (0.8)	3 (0.9)
Hispanic	47 (20.4)	18 (15.1)	65 (18.6)
Native American	1 (0.4)	0 (0.0)	1 (0.3)
Others	6 (2.6)	2 (1.7)	8 (2.3)
Region n (%)			
North America	192 (83.5)	99 (83.2)	291 (83.4)
Central/South America	38 (16.5)	20 (16.8)	58 (16.6)
Age (years)			
Mean (SD)	45.3 (8.6)	46.5 (7.8)	45.7 (8.3)
Median (min, max)	45.0 (16 to 67)	47.0 (17 to 70)	45.0 (16 to 70)
CD4 Cell Count (cells/mm^3)			
Mean (SD)	146.4 (143.4)	163.2 (149.3)	152.1 (145.5)
Median (min, max)	101.5 (1 to 757)	132.0 (0 to 674)	111.0 (0 to 757)
Plasma HIV RNA (log_{10} copies/mL)			
Mean (SD)	4.7 (0.8)	4.7 (0.7)	4.7 (0.8)
Median (min, max)	4.8 (2 to 6)	4.7 (2 to 6)	4.7 (2 to 6)
Plasma HIV RNA (copies/mL)			
Geometric Mean	48366.1	47788.6	48168.4
Median (min, max)	56750.0 (200 to 750000)	46700.0 (200 to 750000)	52900.0 (200 to 750000)
History of AIDS n (%)			
Yes	209 (90.9)	110 (92.4)	319 (91.4)
Prior Use of ART			
Year of ART Use: Median (min,max)	9.6 (0.0 to 18.9)	10.1 (0.0 to 19.4)	9.7 (0.0 to 19.4)
Number of ART: Median (min,max)	12.0 (0 to 21)	12.0 (0 to 22)	12.0 (0 to 22)
Hepatitis Co-infection[†] n (%)			
No Hepatitis B or C	202 (87.8)	110 (92.4)	312 (89.4)
Hepatitis B only	22 (9.6)	4 (3.4)	26 (7.4)
Hepatitis C only	6 (2.6)	5 (4.2)	11 (3.2)

Appendix 5 (Cont.)

Patient Baseline Characteristics by Treatment Group
(Protocol 019)

	Raltegravir 400 mg b.i.d. (N = 230)	Placebo (N = 119)	Total (N = 349)
Stratum n (%)			
Enfuvirtide in OBT	87 (37.8)	46 (38.7)	133 (38.1)
Resistant to ≥ 2 PI	222 (96.5)	114 (95.8)	336 (96.3)

† Hepatitis B surface antigen positive or hepatitis C antibody positive.
Note: Raltegravir and Placebo were administered with Optimized Background Therapy (OBT).
N = Number of patients in each treatment group.
n (%) = Number (percent) of patients in each subcategory.

Appendix 6

Summary of Potential Prognostic Factors and Active Antiretroviral Therapies (ARTs) in OBT (Protocol 018)

Baseline Characteristic	Raltegravir 400 mg b.i.d. (N = 232) n (%)	Placebo (N = 118) n (%)	Total (N = 350) n (%)
Baseline Plasma HIV RNA (copies/mL)			
≤ 50,000	110 (47.4)	64 (54.2)	174 (49.7)
> 50,000	122 (52.6)	54 (45.8)	176 (50.3)
≤ 100,000	155 (66.8)	85 (72.0)	240 (68.6)
> 100,000	77 (33.2)	33 (28.0)	110 (31.4)
Baseline CD4 Cell Counts (cells/mm^3)			
≤ 50	69 (29.7)	40 (33.9)	109 (31.1)
> 50 and ≤ 200	89 (38.4)	43 (36.4)	132 (37.7)
> 200	73 (31.5)	35 (29.7)	108 (30.9)
missing	1 (0.4)	0 (0.0)	1 (0.3)
Number of ARTs in OBT			
Median (min, max)	4.0 (1 to 7)	4.0 (2 to 6)	4.0 (1 to 7)
Enfuvirtide Use in OBT			
No	144 (62.1)	75 (63.6)	219 (62.6)
Yes in enfuvirtide exp. patients	40 (17.2)	19 (16.1)	59 (16.9)
Yes in enfuvirtide naïve patients	48 (20.7)	24 (20.3)	72 (20.6)
Darunavir Use in OBT			
No	156 (67.2)	83 (70.3)	239 (68.3)
Yes in Darunavir exp. patients	14 (6.0)	5 (4.2)	19 (5.4)
Yes in Darunavir naïve patients	62 (26.7)	30 (25.4)	92 (26.3)
Number of Active PI in OBT by Phenotypic Resistance Test[†]			
0	100 (43.1)	55 (46.6)	155 (44.3)
1 or more	123 (53.0)	61 (51.7)	184 (52.6)
Missing	9 (3.9)	2 (1.7)	11 (3.1)
Phenotypic Sensitivity Score (PSS)[‡]			
0	44 (19.0)	21 (17.8)	65 (18.6)
1	67 (28.9)	39 (33.1)	106 (30.3)
2	67 (28.9)	33 (28.0)	100 (28.6)
3 or more	44 (19.0)	21 (17.8)	65 (18.6)
Missing	10 (4.3)	4 (3.4)	14 (4.0)

Appendix 6 (Cont.)

Summary of Potential Prognostic Factors and Active Antiretroviral Therapies (ARTs) in OBT (Protocol 018)

Baseline Characteristic	Raltegravir 400 mg b.i.d. (N = 232) n (%)	Placebo (N = 118) n (%)	Total (N = 350) n (%)
Genotypic Sensitivity Score (GSS)[‡]			
0	70 (30.2)	34 (28.8)	104 (29.7)
1	76 (32.8)	48 (40.7)	124 (35.4)
2	57 (24.6)	22 (18.6)	79 (22.6)
3 or more	26 (11.2)	13 (11.0)	39 (11.1)
Missing	3 (1.3)	1 (0.8)	4 (1.1)

[†] Darunavir use in OBT in darunavir naïve patients 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 patients viral isolate showed phenotypic sensitivity and genotypic sensitivity, respectively, based upon phenotypic and genotypic resistance tests. Enfuvirtide use in OBT in enfuvirtide-naïve patients was counted as one active drug in OBT and added to the GSS and PSS. Darunavir use in OBT in darunavir-naïve patients was counted as one active drug in OBT and added to the PSS and GSS.

Note: 14 patients were missing baseline genotypic and/or phenotypic tests results. For those, "number of active PI in OBT determined by phenotypic resistance test" =1 or more if first time use darunavir in OBT.

Note: Raltegravir and Placebo were administered with Optimized Background Therapy(OBT).

N = Number of patients in each treatment group.

n (%) = Number (percent) of patients in each subcategory.

Appendix 7

Summary of Potential Prognostic Factors and Active Antiretroviral Therapies (ARTs) in OBT (Protocol 019)

Baseline Characteristic	Raltegravir 400 mg b.i.d. (N = 230) n (%)	Placebo (N = 119) n (%)	Total (N = 349) n (%)
Baseline Plasma HIV RNA (copies/mL)			
≤ 50,000	107 (46.5)	61 (51.3)	168 (48.1)
> 50,000	123 (53.5)	58 (48.7)	181 (51.9)
≤ 100,000	143 (62.2)	74 (62.2)	217 (62.2)
> 100,000	87 (37.8)	45 (37.8)	132 (37.8)
Baseline CD4 Cell Counts (cells/mm^3)			
≤ 50	77 (33.5)	38 (31.9)	115 (33.0)
> 50 and ≤ 200	84 (36.5)	42 (35.3)	126 (36.1)
> 200	69 (30.0)	39 (32.8)	108 (30.9)
Number of ARTs in OBT			
Median (min, max)	4.0 (2 to 6)	4.0 (2 to 7)	4.0 (2 to 7)
Enfuvirtide Use in OBT			
No	143 (62.2)	73 (61.3)	216 (61.9)
Yes in enfuvirtide exp. patients	43 (18.7)	22 (18.5)	65 (18.6)
Yes in enfuvirtide naïve patients	44 (19.1)	24 (20.2)	68 (19.5)
Darunavir Use in OBT			
No	122 (53.0)	55 (46.2)	177 (50.7)
Yes in Darunavir exp. patients	4 (1.7)	4 (3.4)	8 (2.3)
Yes in Darunavir naïve patients	104 (45.2)	60 (50.4)	164 (47.0)
Number of Active PI in OBT by Phenotypic Resistance Test[†]			
0	66 (28.7)	42 (35.3)	108 (30.9)
1 or more	155 (67.4)	76 (63.9)	231 (66.2)
Missing	9 (3.9)	1 (0.8)	10 (2.9)
Phenotypic Sensitivity Score (PSS)[‡]			
0	23 (10.0)	23 (19.3)	46 (13.2)
1	78 (33.9)	32 (26.9)	110 (31.5)
2	75 (32.6)	33 (27.7)	108 (30.9)
3 or more	41 (17.8)	27 (22.7)	68 (19.5)
Missing	13 (5.7)	4 (3.4)	17 (4.9)

Appendix 7 (Cont.)

Summary of Potential Prognostic Factors and Active Antiretroviral Therapies (ARTs) in OBT (Protocol 019)

Baseline Characteristic	Raltegravir 400 mg b.i.d. (N = 230) n (%)	Placebo (N = 119) n (%)	Total (N = 349) n (%)
Genotypic Sensitivity Score (GSS)‡			
0	45 (19.6)	31 (26.1)	76 (21.8)
1	102 (44.3)	48 (40.3)	150 (43.0)
2	54 (23.5)	27 (22.7)	81 (23.2)
3 or more	25 (10.9)	10 (8.4)	35 (10.0)
Missing	4 (1.7)	3 (2.5)	7 (2.0)

† Darunavir use in OBT in darunavir naïve patients 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 patients viral isolate showed phenotypic sensitivity and genotypic sensitivity, respectively, based upon phenotypic and genotypic resistance tests. Enfuvirtide use in OBT in enfuvirtide-naïve patients was counted as one active drug in OBT and added to the GSS and PSS. Darunavir use in OBT in darunavir-naïve patients was counted as one active drug in OBT and added to the PSS and GSS.

Note: 17 patients missing baseline genotypic and/or phenotypic tests results. For those, " number of active PI in OBT determined by phenotypic resistance test" =1 or more if first time use darunavir in OBT.

Note: Raltegravir and Placebo were administered with Optimized Background Therapy(OBT).

N = Number of patients in each treatment group.

n (%) = Number (percent) of patients in each subcategory.

Appendix 8

Treatment Outcome at Week 16
Protocol 018
(All Randomized and Treated Patients)

Outcome at Week 16	Raltegravir 400 mg b.i.d. (N=232) n (%)	Placebo (N=118) n (%)
Patients with HIV RNA less than 400 copies/mL	178 (76.7)	48 (40.7)
Patients with HIV RNA less than 50 copies/mL	141 (60.8)	39 (33.1)
Patients with greater than 1 Log_{10} drop in HIV RNA or HIV RNA less than 400 copies/mL	197 (84.9)	49 (41.5)
Mean HIV RNA change from baseline (Log_{10} copies/mL)	-1.85	-0.78
Mean CD4 cell count change from baseline (cells/mm^3)	82.7	31.3
Virologic Failure (confirmed)[†]	32 (13.8)	63 (53.4)
Non responder	4 (1.7)	44 (37.3)
Rebound	28 (12.1)	19 (16.1)
Death	3 (1.3)	3 (2.5)
Adjudicated AIDS-Defining Conditions (ADC)	6 (2.6)	2 (1.7)
Discontinuation due to clinical adverse experiences	4 (1.7)	4 (3.4)
Discontinuation due to laboratory adverse experiences	0 (0.0)	0 (0.0)
Discontinuation due to other reasons[‡]	1 (0.4)	0 (0.0)

[†] Virologic failure: defined as non-responders who did not achieve >1.0 log_{10} HIV RNA reduction or <400 HIV RNA copies/mL by Week 16, or viral rebound , which was defined as: (a) HIV RNA >400 copies/mL (on 2 consecutive measurements at least 1 week apart) after initial response with HIV RNA <400 copies/mL, or (b) >1.0 log_{10} increase in HIV RNA above nadir level (on 2 consecutive measurements at least 1 week apart).

[‡] Includes loss to follow-up, patient withdrew consent, noncompliance, protocol violation and other reasons.

Note: Raltegravir and Placebo were administered with Optimized Background Therapy (OBT).

N = Number of patients in each treatment group.

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

Appendix 9

Treatment Outcome at Week 24
Protocol 018
(All Randomized and Treated Patients)
(Week 24 Partial Data)

Outcome at Week 24	Raltegravir 400 mg b.i.d. (N=232) n (%)	Placebo (N=118) n (%)
Patients with Week 24 data	**158**	**81**
Patients with HIV RNA less than 400 copies/mL	119 (75.3)	32 (39.5)
Patients with HIV RNA less than 50 copies/mL	96 (60.8)	27 (33.3)
Patients with greater than 1 Log_{10} drop in HIV RNA or HIV RNA less than 400 copies/mL	128 (81.0)	35 (43.2)
Mean HIV RNA change from baseline (Log_{10} copies/mL)	-1.75	-0.79
Mean CD4 cell count change from baseline (cells/mm^3)	86.0	30.4
Virologic Failure (confirmed)[†]	34 (14.7)	63 (53.4)
Non responder	4 (1.7)	44 (37.3)
Rebound	30 (12.9)	19 (16.1)
Death	3 (1.3)	3 (2.5)
Adjudicated AIDS-Defining Conditions (ADC)	9 (3.9)	3 (2.5)
Discontinuation due to clinical adverse experiences	4 (1.7)	4 (3.4)
Discontinuation due to laboratory adverse experiences	0 (0.0)	0 (0.0)
Discontinuation due to other reasons[‡]	1 (0.4)	0 (0.0)

[†] Virologic failure: defined as non-responders who did not achieve >1.0 log_{10} HIV RNA reduction or <400 HIV RNA copies/mL by Week 16, or viral rebound , which was defined as: (a) HIV RNA >400 copies/mL (on 2 consecutive measurements at least 1 week apart) after initial response with HIV RNA <400 copies/mL, or (b) >1.0 log_{10} increase in HIV RNA above nadir level (on 2 consecutive measurements at least 1 week apart).

[‡] Includes loss to follow-up, patient withdrew consent, noncompliance, protocol violation and other reasons.

Note: Raltegravir and Placebo were administered with Optimized Background Therapy (OBT).

N = Number of patients in each treatment group.

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

Appendix 10

Treatment Outcome at Week 16
Protocol 019
(All Randomized and Treated Patients)

Outcome at Week 16	Raltegravir 400 mg b.i.d. (N=230) n (%)	Placebo (N=119) n (%)
Patients with HIV RNA less than 400 copies/mL	177 (77.0)	51 (42.9)
Patients with HIV RNA less than 50 copies/mL	142 (61.7)	43 (36.1)
Patients with greater than 1 Log_{10} drop in HIV RNA or HIV RNA less than 400 copies/mL	190 (82.6)	60 (50.4)
Mean HIV RNA change from baseline (Log_{10} copies/mL)	-1.92	-1.06
Mean CD4 cell count change from baseline (cells/mm^3)	85.1	39.7
Virologic Failure (confirmed)[†]	38 (16.5)	57 (47.9)
Non responder	9 (3.9)	34 (28.6)
Rebound	29 (12.6)	23 (19.3)
Death	3 (1.3)	0 (0.0)
Adjudicated AIDS-Defining Conditions (ADC)	5 (2.2)	3 (2.5)
Discontinuation due to clinical adverse experiences	3 (1.3)	1 (0.8)
Discontinuation due to laboratory adverse experiences	1 (0.4)	0 (0.0)
Discontinuation due to other reasons[‡]	5 (2.2)	1 (0.8)

[†] Virologic failure: defined as non-responders who did not achieve >1.0 log_{10} HIV RNA reduction or <400 HIV RNA copies/mL by Week 16, or viral rebound , which was defined as: (a) HIV RNA >400 copies/mL (on 2 consecutive measurements at least 1 week apart) after initial response with HIV RNA <400 copies/mL, or (b) >1.0 log_{10} increase in HIV RNA above nadir level (on 2 consecutive measurements at least 1 week apart).

[‡] Includes loss to follow-up, patient withdrew consent, noncompliance, protocol violation and other reasons.

Note: Raltegravir and Placebo were administered with Optimized Background Therapy (OBT).

N = Number of patients in each treatment group.

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

Appendix 11

Treatment Outcome at Week 24
Protocol 019
(All Randomized and Treated Patients)
(Week 24 Partial Data)

Outcome at Week 24	Raltegravir 400 mg b.i.d. (N=230) n (%)	Placebo (N=119) n (%)
Patients with Week 24 data	**128**	**69**
Patients with HIV RNA less than 400 copies/mL	97 (75.8)	27 (39.1)
Patients with HIV RNA less than 50 copies/mL	83 (64.8)	23 (33.3)
Patients with greater than 1 Log_{10} drop in HIV RNA or HIV RNA less than 400 copies/mL	103 (80.5)	30 (43.5)
Mean HIV RNA change from baseline (Log_{10} copies/mL)	-1.98	-0.90
Mean CD4 cell count change from baseline (cells/mm^3)	93.1	40.3
Virologic Failure (confirmed)†	40 (17.4)	58 (48.7)
Non responder	9 (3.9)	34 (28.6)
Rebound	31 (13.5)	24 (20.2)
Death	3 (1.3)	0 (0.0)
Adjudicated AIDS-Defining Conditions (ADC)	5 (2.2)	3 (2.5)
Discontinuation due to clinical adverse experiences	4 (1.7)	1 (0.8)
Discontinuation due to laboratory adverse experiences	1 (0.4)	0 (0.0)
Discontinuation due to other reasons‡	5 (2.2)	1 (0.8)

† Virologic failure: defined as non-responders who did not achieve >1.0 log_{10} HIV RNA reduction or <400 HIV RNA copies/mL by Week 16, or viral rebound , which was defined as: (a) HIV RNA >400 copies/mL (on 2 consecutive measurements at least 1 week apart) after initial response with HIV RNA <400 copies/mL, or (b) >1.0 log_{10} increase in HIV RNA above nadir level (on 2 consecutive measurements at least 1 week apart).

‡ Includes loss to follow-up, patient withdrew consent, noncompliance, protocol violation and other reasons.

Note: Raltegravir and Placebo were administered with Optimized Background Therapy (OBT).

N = Number of patients in each treatment group.

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

Appendix 12

Proportion of Patients With Plasma HIV RNA <400 Copies/mL at Week 16 by Prognostic Factors Protocols 018 and 019 Combined (Observed Failure Approach)

Prognostic Factor	Response: Raltegravir 400 mg b.i.d. (Group A) n/N	Raltegravir 400 mg b.i.d. (Group A) % (95% CI)	Placebo (Group B) n/N	Placebo (Group B) % (95% CI)	Difference in Percent Response % (95% CI)
Total	355/447	79.4 (75.4, 83.1)	99/230	43.0 (36.6, 49.7)	36.4 (28.8, 43.6)
Baseline Plasma HIV RNA (copies/mL)					
≤ 50,000	187/209	89.5 (84.5, 93.3)	72/121	59.5 (50.2, 68.3)	30.0 (20.4, 39.7)
> 50,000	168/238	70.6 (64.4, 76.3)	27/109	24.8 (17.0, 34.0)	45.8 (35.2, 55.1)
Baseline Plasma HIV RNA (copies/mL)					
≤ 100,000	253/288	87.8 (83.5, 91.4)	85/155	54.8 (46.7, 62.8)	33.0 (24.4, 41.7)
> 100,000	102/159	64.2 (56.2, 71.6)	14/75	18.7 (10.6, 29.3)	45.5 (32.9, 56.0)
Baseline CD4 Cell Counts (cells/mm^3)					
≤ 50	88/140	62.9 (54.3, 70.9)	18/75	24.0 (14.9, 35.3)	38.9 (25.4, 50.5)
> 50 and ≤ 200	145/168	86.3 (80.2, 91.1)	38/82	46.3 (35.3, 57.7)	40.0 (27.8, 51.5)
> 200	121/138	87.7 (81.0, 92.7)	43/73	58.9 (46.8, 70.3)	28.8 (16.5, 41.3)
Missing	1/1	100.0 (2.5, 100.0)			(N/A)
Number of Active PI in OBT by Phenotypic Resistance Test[†]					
0	106/157	67.5 (59.6, 74.8)	16/96	16.7 (9.8, 25.6)	50.8 (39.5, 60.4)
1 or more	237/272	87.1 (82.6, 90.9)	81/131	61.8 (52.9, 70.2)	25.3 (16.3, 34.6)
Missing	12/18	66.7 (41.0, 86.7)	2/3	66.7 (9.4, 99.2)	0.0 (-39.4, 52.5)
Phenotypic Sensitivity Score (PSS)[‡]					
0	38/62	61.3 (48.1, 73.4)	2/44	4.5 (0.6, 15.5)	56.7 (41.5, 69.0)
1	107/141	75.9 (68.0, 82.7)	28/68	41.2 (29.4, 53.8)	34.7 (20.7, 47.7)
2	122/138	88.4 (81.9, 93.2)	31/63	49.2 (36.4, 62.1)	39.2 (25.8, 52.2)
3 or more	72/84	85.7 (76.4, 92.4)	32/47	68.1 (52.9, 80.9)	17.6 (3.0, 33.4)
Missing	16/22	72.7 (49.8, 89.3)	6/8	75.0 (34.9, 96.8)	-2.3 (-32.1, 36.6)
Genotypic Sensitivity Score (GSS)					
0	63/111	56.8 (47.0, 66.1)	6/63	9.5 (3.6, 19.6)	47.2 (34.3, 58.0)
1	144/170	84.7 (78.4, 89.8)	40/93	43.0 (32.8, 53.7)	41.7 (30.0, 52.6)
2	100/109	91.7 (84.9, 96.2)	37/48	77.1 (62.7, 88.0)	14.7 (3.1, 29.1)
3 or more	41/50	82.0 (68.6, 91.4)	13/22	59.1 (36.4, 79.3)	22.9 (1.0, 45.7)
Missing	7/7	100.0 (59.0, 100.0)	3/4	75.0 (19.4, 99.4)	25.0 (-19.1, 71.4)

[†] Darunavir use in OBT in darunavir-naïve patients 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 patients viral isolate showed phenotypic sensitivity and genotypic sensitivity, respectively, based upon phenotypic and genotypic resistance tests. Enfuvirtide use in OBT in enfuvirtide-naïve patients was counted as one active drug in OBT and added to the GSS and PSS. Darunavir use in OBT in darunavir-naïve patients was counted as one active drug in OBT and added to the PSS and GSS.

Note: Missing refers to patients whose baseline genotypic and/or phenotypic test results are not available, or whose baseline CD4 cell count is not available.

Note: Raltegravir and Placebo were administered with Optimized Background Therapy (OBT).

N = Number of patients in each treatment group.

n = Number of patients in each subcategory.

CI = confidence interval

Appendix 13

Proportion of Patients With Plasma HIV RNA <400 Copies/mL at Week 16 by Subpopulation─Protocols 018 and 019 Combined (Observed Failure Approach)

	Response				Difference in Percent Response [Group A Minus Group B]	
	Raltegravir 400 mg bid (Group A)		Placebo (Group B)			
Subpopulation	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)	p-Value
Total	355/447	79.4 (75.4, 83.1)	99/230	43.0 (36.6, 49.7)	36.4 (28.8, 43.6)	
Age (years)						
16-64	348/440	79.1 (75.0, 82.8)	97/228	42.5 (36.0, 49.2)	36.5 (29.0, 43.8)	N/A
≥ 65	7/7	100.0 (59.0, 100.0)	2/2	100.0 (15.8, 100.0)	0.0 (-38.2, 68.4)	
Age (years)						
≤ median	175/232	75.4 (69.4, 80.8)	50/126	39.7 (31.1, 48.8)	35.7 (25.3, 45.5)	0.553
> median	180/215	83.7 (78.1, 88.4)	49/104	47.1 (37.2, 57.2)	36.6 (25.7, 47.1)	
Gender						
Female	40/54	74.1 (60.3, 85.0)	10/27	37.0 (19.4, 57.6)	37.0 (14.3, 56.4)	0.907
Male	315/393	80.2 (75.9, 84.0)	89/203	43.8 (36.9, 51.0)	36.3 (28.3, 44.0)	
Race						
White	238/292	81.5 (76.6, 85.8)	71/166	42.8 (35.1, 50.7)	38.7 (29.8, 47.2)	0.400
Black	46/65	70.8 (58.2, 81.4)	11/26	42.3 (23.4, 63.1)	28.5 (6.1, 48.6)	
Asian	14/15	93.3 (68.1, 99.8)	2/6	33.3 (4.3, 77.7)	60.0 (17.6, 86.5)	
Hispanic	36/50	72.0 (57.5, 83.8)	6/19	31.6 (12.6, 56.6)	40.4 (14.2, 61.1)	
Native American	1/1	100.0 (2.5, 100.0)			100.0 (0.0, 100.0)	
Others	20/24	83.3 (62.6, 95.3)	9/13	69.2 (38.6, 90.9)	14.1 (-13.2, 44.3)	
Region						
North America	148/185	80.0 (73.5, 85.5)	45/97	46.4 (36.2, 56.8)	33.6 (22.0, 44.7)	0.738
Central/South America	48/59	81.4 (69.1, 90.3)	14/31	45.2 (27.3, 64.0)	36.2 (15.6, 54.9)	
Asia Pacific	32/37	86.5 (71.2, 95.5)	12/18	66.7 (41.0, 86.7)	19.8 (-2.7, 45.0)	
Europe	127/166	76.5 (69.3, 82.7)	28/84	33.3 (23.4, 44.5)	43.2 (30.6, 54.3)	
Viral Subtype						
Clade B	320/401	79.8 (75.5, 83.6)	89/211	42.2 (35.4, 49.2)	37.6 (29.7, 45.2)	0.340
non-Clade B	28/39	71.8 (55.1, 85.0)	7/15	46.7 (21.3, 73.4)	25.1 (-3.3, 51.3)	

p-Value were generated using the Breslow-Day test for homogeneity.
Note: Raltegravir and Placebo were administered with Optimized Background Therapy (OBT).
N = Number of patients in each treatment group.
n = Number of patients in each subcategory.

Appendix 14

Proportion of Patients With Plasma HIV RNA <50 Copies/mL at Week 16 by Subpopulation─Protocols 018 and 019 Combined (Observed Failure Approach)

	Response				Difference in Percent Response [Group A Minus Group B]	
	Raltegravir 400 mg bid (Group A)		Placebo (Group B)			
Subpopulation	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)	p-Value
Total	283/447	63.3 (58.7, 67.8)	82/230	35.7 (29.5, 42.2)	27.7 (19.9, 35.1)	
Age (years)						
16-64	277/440	63.0 (58.3, 67.5)	80/228	35.1 (28.9, 41.7)	27.9 (20.0, 35.3)	0.340
≥ 65	6/7	85.7 (42.1, 99.6)	2/2	100.0 (15.8, 100.0)	-14.3 (-53.5, 58.4)	
Age (years)						
≤ median	133/232	57.3 (50.7, 63.8)	42/126	33.3 (25.2, 42.3)	24.0 (13.3, 34.0)	0.350
> median	150/215	69.8 (63.2, 75.8)	40/104	38.5 (29.1, 48.5)	31.3 (19.8, 42.0)	
Gender						
Female	35/54	64.8 (50.6, 77.3)	9/27	33.3 (16.5, 54.0)	31.5 (8.3, 51.1)	0.719
Male	248/393	63.1 (58.1, 67.9)	73/203	36.0 (29.4, 43.0)	27.1 (18.8, 35.1)	
Race						
White	186/292	63.7 (57.9, 69.2)	57/166	34.3 (27.2, 42.1)	29.4 (20.0, 38.1)	0.453
Black	37/65	56.9 (44.0, 69.2)	10/26	38.5 (20.2, 59.4)	18.5 (-4.3, 38.9)	
Asian	12/15	80.0 (51.9, 95.7)	2/6	33.3 (4.3, 77.7)	46.7 (0.9, 77.4)	
Hispanic	31/50	62.0 (47.2, 75.3)	5/19	26.3 (9.1, 51.2)	35.7 (9.2, 56.0)	
Native American	1/1	100.0 (2.5, 100.0)			100.0 (0.0, 100.0)	
Others	16/24	66.7 (44.7, 84.4)	8/13	61.5 (31.6, 86.1)	5.1 (-25.3, 37.1)	
Region						
North America	119/185	64.3 (57.0, 71.2)	38/97	39.2 (29.4, 49.6)	25.1 (12.9, 36.6)	0.893
Central/South America	40/59	67.8 (54.4, 79.4)	12/31	38.7 (21.8, 57.8)	29.1 (7.4, 48.3)	
Asia Pacific	29/37	78.4 (61.8, 90.2)	10/18	55.6 (30.8, 78.5)	22.8 (-2.8, 48.2)	
Europe	95/166	57.2 (49.3, 64.9)	22/84	26.2 (17.2, 36.9)	31.0 (18.3, 42.3)	
Viral Subtype						
Clade B	254/401	63.3 (58.4, 68.1)	72/211	34.1 (27.8, 40.9)	29.2 (21.1, 36.9)	0.344
non-Clade B	24/39	61.5 (44.6, 76.6)	7/15	46.7 (21.3, 73.4)	14.9 (-13.9, 41.9)	

p-Value were generated using the Breslow-Day test for homogeneity.
Note: Raltegravir and Placebo were administered with Optimized Background Therapy (OBT).
N = Number of patients in each treatment group.
n = Number of patients in each subcategory.

Appendix 15

Change From Baseline in CD4 Cell Count (Cells/mm^3) at Week 16 by Subpopulation─Protocols 018 and 019 Combined (Observed Failure Approach)

	Response						Difference in Percent Response [Group A Minus Group B]	
	Raltegravir 400 mg bid (Group A)			Placebo (Group B)				
Subpopulation	N	Baseline Mean	Mean Change From Baseline (95% CI)	N	Baseline Mean	Mean Change From Baseline (95% CI)	(95% CI)	p-Value
Total	446	152.6	83.9 (75.0, 92.8)	229	157.8	35.6 (26.0, 45.1)	48.3 (35.2, 61.3)	
Age (years)								
16-64	439	151.3	84.6 (75.6, 93.7)	227	157.8	35.5 (25.9, 45.1)	49.1 (36.0, 62.3)	0.416
≥ 65	7	230.9	34.4 (2.8, 66.0)	2	158.5	43.5 (-153.4, 240.4)	-9.1 (-78.2, 60.1)	
Age (years)								
≤ median	232	147.5	83.6 (72.6, 94.6)	125	151.0	33.7 (20.9, 46.5)	49.9 (33.1, 66.7)	0.803
> median	214	158.1	84.1 (69.8, 98.4)	104	165.9	37.8 (23.2, 52.5)	46.3 (25.9, 66.7)	
Gender								
Female	57	166.0	99.4 (74.9, 123.9)	27	138.3	58.4 (21.5, 95.4)	40.9 (-2.7, 84.6)	0.713
Male	389	150.6	81.6 (72.0, 91.2)	202	160.4	32.5 (22.8, 42.2)	49.1 (35.4, 62.7)	
Race								
White	294	157.4	80.3 (70.4, 90.2)	165	152.9	35.9 (24.8, 47.0)	44.4 (29.5, 59.2)	0.440
Black	65	119.2	95.2 (69.2, 121.2)	26	131.8	36.2 (14.3, 58.2)	59.0 (25.5, 92.4)	
Asian	15	79.5	87.9 (48.0, 127.8)	6	165.5	40.8 (-55.1, 136.7)	47.0 (-49.9, 144.0)	
Hispanic	49	170.5	75.9 (50.3, 101.5)	19	236.3	-5.7 (-35.2, 23.8)	81.6 (43.5, 119.7)	
Native American	1	97.0	350.0 (N/A)				(N/A)	
Others	22	199.4	100.6 (22.9, 178.4)	13	153.2	87.8 (26.9, 148.6)	12.9 (-82.1, 107.8)	
Region								
North America	184	130.9	93.4 (78.8, 108.1)	97	133.8	45.9 (31.8, 60.0)	47.6 (27.3, 67.8)	0.754
Central/South America	56	216.2	70.9 (38.0, 103.9)	31	245.6	38.1 (1.1, 75.1)	32.8 (-15.9, 81.6)	
Asia Pacific	37	146.2	96.0 (70.8, 121.2)	18	213.4	55.1 (15.5, 94.7)	40.9 (-4.9, 86.8)	
Europe	169	156.5	75.1 (62.6, 87.5)	83	140.9	18.4 (5.1, 31.6)	56.7 (38.6, 74.8)	

Appendix 15 (Cont.)

Change From Baseline in CD4 Cell Count (Cells/mm^3) at Week 16 by Subpopulation─Protocols 018 and 019 Combined (Observed Failure Approach)

	Response						Difference in Percent Response [Group A Minus Group B]	
	Raltegravir 400 mg bid (Group A)			Placebo (Group B)				
Subpopulation	N	Baseline Mean	Mean Change From Baseline (95% CI)	N	Baseline Mean	Mean Change From Baseline (95% CI)	(95% CI)	p-Value
Viral Subtype								
Clade B	400	155.2	84.3 (75.0, 93.6)	210	157.2	34.3 (24.3, 44.2)	50.1 (36.5, 63.6)	0.498
non-Clade B	39	121.6	76.4 (42.7, 110.1)	15	159.1	45.3 (0.8, 89.7)	31.1 (-23.0, 85.2)	

p-Value were generated using F-test from general linear model.
Note: Raltegravir and Placebo were administered with Optimized Background Therapy (OBT).
N = Number of patients in each treatment group.

Appendix 16

Patient Status by Treatment Group
Protocol 018
(Week 24 Data with All Patients)
Note: These data have not yet been reviewed by the FDA

	Raltegravir 400 mg b.i.d. n (%)	Placebo n (%)	Total n (%)
DOUBLE-BLIND PHASE (DB)			
Total Enter	234 (100)	118 (100)	352 (100)
Never Treated	2 (0.9)	0 (0.0)	2 (0.6)
Treated	232 (99.1)	118 (100)	350 (99.4)
Continuing in DB	203 (86.8)	58 (49.2)	261 (74.1)
Discontinued study before completing Week 24	5 (2.1)	4 (3.4)	9 (2.6)
Lack of Efficacy	0 (0.0)	0 (0.0)	0 (0.0)
Clinical adverse experience	4 (1.7)	4 (3.4)	8 (2.3)
Laboratory adverse experience	0 (0.0)	0 (0.0)	0 (0.0)
Consent withdrawn	1 (0.4)	0 (0.0)	1 (0.3)
Loss to follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Protocol violation	0 (0.0)	0 (0.0)	0 (0.0)
Other†	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued study after completing Week 24	0 (0.0)	1 (0.8)	1 (0.3)
Lack of Efficacy	0 (0.0)	0 (0.0)	0 (0.0)
Clinical adverse experience	0 (0.0)	0 (0.0)	0 (0.0)
Laboratory adverse experience	0 (0.0)	0 (0.0)	0 (0.0)
Consent withdrawn	0 (0.0)	1 (0.8)	1 (0.3)
Loss to follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Protocol violation	0 (0.0)	0 (0.0)	0 (0.0)
Other†	0 (0.0)	0 (0.0)	0 (0.0)
Virologic failure, entering Open-Label Post Viral Failure (OLPVF)	24 (10.3)	55 (46.6)	79 (22.4)
Open-Label Post Viral Failure (OLPVF)			
Total Entered	24 (10.3)	55 (46.6)	79 (22.4)
Discontinued from OLPVF	3 (1.3)	0 (0.0)	3 (0.9)
Continuing in OLPVF	21 (9.0)	55 (46.6)	76 (21.6)

†Including patients who moved or relocated or the clinical trial was terminated at the site.

Note: Raltegravir and Placebo were administered with Optimized Background Therapy(OBT).

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

Appendix 17

Patient Status by Treatment Group
Protocol 019
(Week 24 Data with All Patients)
Note: These data have not yet been reviewed by the FDA

	Raltegravir 400 mg b.i.d. n (%)	Placebo n (%)	Total n (%)
DOUBLE-BLIND PHASE (DB)			
Total Enter	232 (100)	119 (100)	351 (100)
Never Treated	2 (0.9)	0 (0.0)	2 (0.6)
Treated	230 (99.1)	119 (100)	349 (99.4)
Continuing in DB	189 (81.5)	66 (55.5)	255 (72.6)
Discontinued study before completing Week 24	9 (3.9)	3 (2.5)	12 (3.4)
Lack of Efficacy	0 (0.0)	1 (0.8)	1 (0.3)
Clinical adverse experience	3 (1.3)	1 (0.8)	4 (1.1)
Laboratory adverse experience	1 (0.4)	0 (0.0)	1 (0.3)
Consent withdrawn	4 (1.7)	0 (0.0)	4 (1.1)
Loss to follow-up	1 (0.4)	1 (0.8)	2 (0.6)
Protocol violation	0 (0.0)	0 (0.0)	0 (0.0)
Other[†]	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued study after completing Week 24	2 (0.9)	1 (0.8)	3 (0.9)
Lack of Efficacy	0 (0.0)	0 (0.0)	0 (0.0)
Clinical adverse experience	2 (0.9)	0 (0.0)	2 (0.6)
Laboratory adverse experience	0 (0.0)	0 (0.0)	0 (0.0)
Consent withdrawn	0 (0.0)	1 (0.8)	1 (0.3)
Loss to follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Protocol violation	0 (0.0)	0 (0.0)	0 (0.0)
Other[†]	0 (0.0)	0 (0.0)	0 (0.0)
Virologic failure, entering Open-Label Post Viral Failure (OLPVF)	30 (12.9)	49 (41.2)	79 (22.5)
Open-Label Post Viral Failure (OLPVF)			
Total Entered	30 (12.9)	49 (41.2)	79 (22.5)
Discontinued from OLPVF	2 (0.9)	1 (0.8)	3 (0.9)
Continuing in OLPVF	28 (12.1)	48 (40.3)	76 (21.7)

[†]Including patients who moved or relocated or the clinical trial was terminated at the site.

Note: Raltegravir and Placebo were administered with Optimized Background Therapy(OBT).

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

Appendix 18

Patient Status by Treatment Group
Protocols 018 and 019 Combined
(Week 24 Data With All Patients)
Note: These data have not yet been reviewed by the FDA

	Raltegravir 400 mg b.i.d. n (%)	Placebo n (%)	Total n (%)
DOUBLE-BLIND PHASE (DB)			
Total Enter	466 (100)	237 (100)	703 (100)
Never Treated	4 (0.9)	0 (0.0)	4 (0.6)
Treated	462 (99.1)	237 (100)	699 (99.4)
Continuing in DB	392 (84.1)	124 (52.3)	516 (73.4)
Discontinued study before completing Week 24	14 (3.0)	7 (3.0)	21 (3.0)
Lack of Efficacy	0 (0.0)	1 (0.4)	1 (0.1)
Clinical adverse experience	7 (1.5)	5 (2.1)	12 (1.7)
Laboratory adverse experience	1 (0.2)	0 (0.0)	1 (0.1)
Consent withdrawn	5 (1.1)	0 (0.0)	5 (0.7)
Loss to follow-up	1 (0.2)	1 (0.4)	2 (0.3)
Protocol violation	0 (0.0)	0 (0.0)	0 (0.0)
Other[†]	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued study after completing Week 24	2 (0.4)	2 (0.8)	4 (0.6)
Lack of Efficacy	0 (0.0)	0 (0.0)	0 (0.0)
Clinical adverse experience	2 (0.4)	0 (0.0)	2 (0.3)
Laboratory adverse experience	0 (0.0)	0 (0.0)	0 (0.0)
Consent withdrawn	0 (0.0)	2 (0.8)	2 (0.3)
Loss to follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Protocol violation	0 (0.0)	0 (0.0)	0 (0.0)
Other[†]	0 (0.0)	0 (0.0)	0 (0.0)
Virologic failure, entering Open-Label Post Viral Failure (OLPVF)	54 (11.6)	104 (43.9)	158 (22.5)
Open-Label Post Viral Failure (OLPVF)			
Total Entered	54 (11.6)	104 (43.9)	158 (22.5)
Discontinued from OLPVF	5 (1.1)	1 (0.4)	6 (0.9)
Continuing in OLPVF	49 (10.5)	103 (43.5)	152 (21.6)

[†]Including patients who moved or relocated or the clinical trial was terminated at the site.

Note: Raltegravir and Placebo were administered with Optimized Background Therapy(OBT).

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

Appendix 19

Treatment Outcome at Week 24
Protocol 018
(All Randomized and Treated Patients)
(Week 24 Data with All patients)
Note: These data have not yet been reviewed by the FDA

Outcome at Week 24	Raltegravir 400 mg b.i.d. (N=232) n (%)	Placebo (N=118) n (%)
Patients with HIV RNA less than 400 copies/mL	175 (75.4)	46 (39.0)
Patients with HIV RNA less than 50 copies/mL	140 (60.3)	39 (33.1)
Patients with greater than 1 Log_{10} drop in HIV RNA or HIV RNA less than 400 copies/mL	189 (81.5)	50 (42.4)
Mean HIV RNA change from baseline (Log_{10} copies/mL)	-1.78	-0.79
Mean CD4 cell count change from baseline (cells/mm^3)	86.1	35.3
Virologic Failure (confirmed)[†]	41 (17.7)	65 (55.1)
Non responder	4 (1.7)	43 (36.4)
Rebound	37 (15.9)	22 (18.6)
Death	3 (1.3)	3 (2.5)
Adjudicated AIDS-Defining Conditions (ADC)	10 (4.3)	3 (2.5)
Discontinuation due to clinical adverse experiences	4 (1.7)	4 (3.4)
Discontinuation due to laboratory adverse experiences	0 (0.0)	0 (0.0)
Discontinuation due to other reasons[‡]	1 (0.4)	0 (0.0)

[†] Virologic failure: defined as non-responders who did not achieve >1.0 log_{10} HIV RNA reduction or <400 HIV RNA copies/mL by Week 16, or viral rebound , which was defined as: (a) HIV RNA >400 copies/mL (on 2 consecutive measurements at least 1 week apart) after initial response with HIV RNA <400 copies/mL, or (b) >1.0 log_{10} increase in HIV RNA above nadir level (on 2 consecutive measurements at least 1 week apart).

[‡] Includes loss to follow-up, patient withdrew consent, noncompliance, protocol violation and other reasons.

Note: Raltegravir and Placebo were administered with Optimized Background Therapy (OBT).

N = Number of patients in each treatment group.

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

Appendix 20

Treatment Outcome at Week 24
Protocol 019
(All Randomized and Treated Patients)
(Week 24 Data with All Patients)
Note: These data have not yet been reviewed by the FDA

Outcome at Week 24	Raltegravir 400 mg b.i.d. (N=230) n (%)	Placebo (N=119) n (%)
Patients with HIV RNA less than 400 copies/mL	172 (74.8)	49 (41.2)
Patients with HIV RNA less than 50 copies/mL	149 (64.8)	41 (34.5)
Patients with greater than 1 Log_{10} drop in HIV RNA or HIV RNA less than 400 copies/mL	182 (79.1)	55 (46.2)
Mean HIV RNA change from baseline (Log_{10} copies/mL)	-1.85	-0.94
Mean CD4 cell count change from baseline (cells/mm^3)	81.2	37.6
Virologic Failure (confirmed)†	43 (18.7)	62 (52.1)
Non responder	9 (3.9)	34 (28.6)
Rebound	34 (14.8)	28 (23.5)
Death	4 (1.7)	0 (0.0)
Adjudicated AIDS-Defining Conditions (ADC)	6 (2.6)	3 (2.5)
Discontinuation due to clinical adverse experiences	5 (2.2)	1 (0.8)
Discontinuation due to laboratory adverse experiences	1 (0.4)	0 (0.0)
Discontinuation due to other reasons‡	5 (2.2)	2 (1.7)

† Virologic failure: defined as non-responders who did not achieve >1.0 log_{10} HIV RNA reduction or <400 HIV RNA copies/mL by Week 16, or viral rebound , which was defined as: (a) HIV RNA >400 copies/mL (on 2 consecutive measurements at least 1 week apart) after initial response with HIV RNA <400 copies/mL, or (b) >1.0 log_{10} increase in HIV RNA above nadir level (on 2 consecutive measurements at least 1 week apart).

‡ Includes loss to follow-up, patient withdrew consent, noncompliance, protocol violation and other reasons.

Note: Raltegravir and Placebo were administered with Optimized Background Therapy (OBT).

N = Number of patients in each treatment group.

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

Appendix 21

Treatment Outcome at Week 24
Protocols 018 and 019 Combined
(All Randomized and Treated Patients)
(Week 24 Data with All Patients)
Note: These data have not yet been reviewed by the FDA

Outcome at Week 24	Raltegravir 400 mg b.i.d. (N=462) n (%)	Placebo (N=237) n (%)
Patients with HIV RNA less than 400 copies/mL	347 (75.1)	95 (40.1)
Patients with HIV RNA less than 50 copies/mL	289 (62.6)	80 (33.8)
Patients with greater than 1 Log_{10} drop in HIV RNA or HIV RNA less than 400 copies/mL	371 (80.3)	105 (44.3)
Mean HIV RNA change from baseline (Log_{10} copies/mL)	-1.82	-0.87
Mean CD4 cell count change from baseline (cells/mm^3)	83.7	36.5
Virologic Failure (confirmed)†	84 (18.2)	127 (53.6)
Non responder	13 (2.8)	77 (32.5)
Rebound	71 (15.4)	50 (21.1)
Death	7 (1.5)	3 (1.3)
Adjudicated AIDS-Defining Conditions (ADC)	16 (3.5)	6 (2.5)
Discontinuation due to clinical adverse experiences	9 (1.9)	5 (2.1)
Discontinuation due to laboratory adverse experiences	1 (0.2)	0 (0.0)
Discontinuation due to other reasons‡	6 (1.3)	2 (0.8)

† Virologic failure: defined as non-responders who did not achieve >1.0 log_{10} HIV RNA reduction or <400 HIV RNA copies/mL by Week 16, or viral rebound , which was defined as: (a) HIV RNA >400 copies/mL (on 2 consecutive measurements at least 1 week apart) after initial response with HIV RNA <400 copies/mL, or (b) >1.0 log_{10} increase in HIV RNA above nadir level (on 2 consecutive measurements at least 1 week apart).

‡ Includes loss to follow-up, patient withdrew consent, noncompliance, protocol violation and other reasons.

Note: Raltegravir and Placebo were administered with Optimized Background Therapy (OBT).

N = Number of patients in each treatment group.

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

Appendix 22

Number (%) of Patients With a Laboratory Predefined Limit of Change (PDLC)[†] by Treatment Group
(Double-Blind Phase - Protocols 005, 018 and 019)

Laboratory Test (Unit)	PDLC Criteria	Grade	Number (%) With PDLC	
			Raltegravir 400 mg b.i.d. (N=507) n/m (%)	Placebo (N=282) n/m (%)
hematology laboratory test				
absolute neutrophil count (10[3]/microL)	1.00 - 1.30	Grade 1	34/507 (6.7)	33/282 (11.7)
	0.75 - 0.999	Grade 2	17/507 (3.4)	22/282 (7.8)
	0.50 - 0.749	Grade 3	12/507 (2.4)	6/282 (2.1)
	<0.50	Grade 4	5/507 (1.0)	3/282 (1.1)
hemoglobin (gm/dL)	8.5 - 10.0	Grade 1	23/507 (4.5)	19/282 (6.7)
	7.5 - 8.4	Grade 2	5/507 (1.0)	7/282 (2.5)
	6.5 - 7.4	Grade 3	4/507 (0.8)	1/282 (0.4)
	< 6.5	Grade 4	0/507 (0.0)	0/282 (0.0)
platelet count (10[3]/microL)	100 - 124.999	Grade 1	17/507 (3.4)	21/282 (7.4)
	50 - 99.999	Grade 2	18/507 (3.6)	14/282 (5.0)
	25 - 49.999	Grade 3	2/507 (0.4)	1/282 (0.4)
	<25	Grade 4	4/507 (0.8)	1/282 (0.4)

Appendix 22 (Cont.)

Number (%) of Patients With a Laboratory Predefined Limit of Change (PDLC)† by Treatment Group - Treatment-Experienced Raltegravir 400 mg b.i.d. Double-Blind Cohort (Double-Blind Phase - Protocols 005, 018 and 019)

Laboratory Test (Unit)	PDLC Criteria	Grade	Number (%) With PDLC	
			Raltegravir 400 mg b.i.d. (N=507) n/m (%)	Placebo (N=282) n/m (%)
blood chemistry test				
fasting(non-random) serum LDL-C (mg/dL)	130 - 159	Grade 1	68/471 (14.4)	28/249 (11.2)
	160 - 189	Grade 2	36/471 (7.6)	12/249 (4.8)
	≥190	Grade 3	18/471 (3.8)	6/249 (2.4)
fasting(non-random) serum cholesterol (mg/dL)	200 - 239	Grade 1	114/506 (22.5)	49/276 (17.8)
	240 - 300	Grade 2	74/506 (14.6)	35/276 (12.7)
	>300	Grade 3	23/506 (4.5)	10/276 (3.6)
fasting(non-random) serum triglyceride (mg/dL)	500 - 750	Grade 2	24/506 (4.7)	21/276 (7.6)
	751 - 1200	Grade 3	16/506 (3.2)	8/276 (2.9)
	>1200	Grade 4	7/506 (1.4)	5/276 (1.8)
fasting(non-random) serum glucose test (mg/dL)	110 -125	Grade 1	44/507 (8.7)	23/280 (8.2)
	126 - 250	Grade 2	42/507 (8.3)	17/280 (6.1)
	251 - 500	Grade 3	5/507 (1.0)	4/280 (1.4)
	>500	Grade 4	0/507 (0.0)	0/280 (0.0)
total serum bilirubin (mg/dL)	1.1 - 1.5 x ULN	Grade 1	22/507 (4.3)	10/282 (3.5)

Appendix 22 (Cont.)

Number (%) of Patients With a Laboratory Predefined Limit of Change (PDLC)† by Treatment Group - Treatment-Experienced Raltegravir 400 mg b.i.d. Double-Blind Cohort (Double-Blind Phase - Protocols 005, 018 and 019)

Laboratory Test (Unit)	PDLC Criteria	Grade	Number (%) With PDLC	
			Raltegravir 400 mg b.i.d. (N=507) n/m (%)	Placebo (N=282) n/m (%)
	1.6 - 2.5 x ULN	Grade 2	28/507 (5.5)	18/282 (6.4)
	2.6 - 5.0 x ULN	Grade 3	15/507 (3.0)	7/282 (2.5)
	>5.0 x ULN	Grade 4	3/507 (0.6)	0/282 (0.0)
	>2.5 - 5.0 x Baseline‡		21/507 (4.1)	16/282 (5.7)
	>5.0 -10.0 x Baseline‡		19/507 (3.7)	8/282 (2.8)
	>10.0 x Baseline‡		6/507 (1.2)	2/282 (0.7)
serum direct bilirubin (mg/dL)	>2.5 - 5.0 x Baseline‡		11/507 (2.2)	4/282 (1.4)
	>5.0 - 10.0 x Baseline‡		0/507 (0.0)	2/282 (0.7)
	>10.0 x Baseline‡		4/507 (0.8)	0/282 (0.0)
serum indirect bilirubin (mg/dL)	>2.5 - 5.0 x Baseline‡		13/507 (2.6)	9/282 (3.2)
	>5.0 - 10.0 x Baseline‡		15/507 (3.0)	8/282 (2.8)
	>10.0 x Baseline‡		10/507 (2.0)	2/282 (0.7)
serum creatinine (mg/dL)	1.1 - 1.3 x ULN	Grade 1	37/507 (7.3)	21/282 (7.4)
	1.4 - 1.8 x ULN	Grade 2	11/507 (2.2)	4/282 (1.4)
	1.9 - 3.4 x ULN	Grade 3	4/507 (0.8)	3/282 (1.1)
	≥3.5 x ULN	Grade 4	0/507 (0.0)	0/282 (0.0)

Appendix 22 (Cont.)

Number (%) of Patients With a Laboratory Predefined Limit of Change (PDLC)† by Treatment Group - Treatment-Experienced Raltegravir 400 mg b.i.d. Double-Blind Cohort (Double-Blind Phase - Protocols 005, 018 and 019)

Laboratory Test (Unit)	PDLC Criteria	Grade	Number (%) With PDLC	
			Raltegravir 400 mg b.i.d. (N=507) n/m (%)	Placebo (N=282) n/m (%)
	>2.5 x Baseline‡		1/507 (0.2)	0/282 (0.0)
serum aspartate aminotransferase (IU(aminot.)/L)	1.25 - 2.5 x ULN	Grade 1	91/507 (17.9)	74/282 (26.2)
	2.6 - 5.0 x ULN	Grade 2	45/507 (8.9)	13/282 (4.6)
	5.1 - 10.0 x ULN	Grade 3	10/507 (2.0)	6/282 (2.1)
	>10.0 x ULN	Grade 4	2/507 (0.4)	1/282 (0.4)
	>2.5 - 5.0 x Baseline‡		29/507 (5.7)	13/282 (4.6)
	>5.0 x Baseline‡		10/507 (2.0)	7/282 (2.5)
serum alanine aminotransferase (IU(aminot.)/L)	1.25 - 2.5 x ULN	Grade 1	94/507 (18.5)	57/282 (20.2)
	2.6 - 5.0 x ULN	Grade 2	34/507 (6.7)	22/282 (7.8)
	5.1 - 10.0 x ULN	Grade 3	13/507 (2.6)	4/282 (1.4)
	>10.0 x ULN	Grade 4	3/507 (0.6)	1/282 (0.4)
	>2.5 - 5.0 x Baseline‡		38/507 (7.5)	19/282 (6.7)
	>5.0 x Baseline‡		16/507 (3.2)	7/282 (2.5)
serum alkaline phosphatase (IU(alk phos)/L)	1.25 - 2.5 x ULN	Grade 1	47/507 (9.3)	25/282 (8.9)
	2.6 - 5.0 x ULN	Grade 2	9/507 (1.8)	1/282 (0.4)
	5.1 - 10.0 x ULN	Grade 3	2/507 (0.4)	3/282 (1.1)

Appendix 22 (Cont.)

Number (%) of Patients With a Laboratory Predefined Limit of Change (PDLC)† by Treatment Group - Treatment-Experienced Raltegravir 400 mg b.i.d. Double-Blind Cohort (Double-Blind Phase - Protocols 005, 018 and 019)

Laboratory Test (Unit)	PDLC Criteria	Grade	Number (%) With PDLC	
			Raltegravir 400 mg b.i.d. (N=507) n/m (%)	Placebo (N=282) n/m (%)
	>10.0 x ULN	Grade 4	2/507 (0.4)	1/282 (0.4)
	>2.5 - 5.0 x Baseline‡		7/507 (1.4)	3/282 (1.1)
	>5.0 x Baseline‡		1/507 (0.2)	1/282 (0.4)
serum pancreatic amylase test (IU(amylase)/L)§	1.1 - 1.5 x ULN	Grade 1	8/507 (1.6)	3/282 (1.1)
	1.6 - 2.0 x ULN	Grade 2	7/507 (1.4)	2/282 (0.7)
	2.1 - 5.0 x ULN	Grade 3	16/507 (3.2)	6/282 (2.1)
	>5.0 x ULN	Grade 4	1/507 (0.2)	0/282 (0.0)
serum lipase test (IU(lipase)/L)	1.1 - 1.5 x ULN	Grade 1	26/507 (5.1)	19/282 (6.7)
	1.6 - 3.0 x ULN	Grade 2	15/507 (3.0)	4/282 (1.4)
	3.1 - 5.0 x ULN	Grade 3	3/507 (0.6)	0/282 (0.0)
	>5.0 x ULN	Grade 4	1/507 (0.2)	0/282 (0.0)

† For inclusion in this analysis, both a baseline and at least one on-treatment laboratory value had to be present. A patient was included as a Grade X event if his/her highest grade during treatment was X and the laboratory value was worse than baseline.
‡ A patient was included in the event of '>X-fold Baseline' if his/her highest laboratory value during treatment fell in this category and was more extreme than the upper limit of normal (ULNA).
§ Defined as (the number of patients meeting the specific serum pancreatic amylase criteria) / (the number of patients with serum amylase test result).
Note: Raltegravir and Placebo were administered with Optimized Background Therapy (OBT).
N = total number of patients randomized in the treatment group.
n/m = number of patients with PDLC/number of patients with laboratory test. For the criteria using baseline, m=number of patients with baseline values for that laboratory test.
LLN = Lower limit of normal range. ULN = Upper limit of normal range.

Appendix 23

Summary of Malignancy Rates– Double Blind Data
Phase II and III Studies
Original Application

	Raltegravir (N = 758) 508 Patient-Years		Control Group (N = 323) 169 Patient-Years	
	N (%)[†]	Rate[‡]	n (%)[†]	Rate[‡]
Total number of patients with Endpoint	**10 (1.3)**	**2.0**	**1 (0.3)**	**0.6**
Kaposi's sarcoma	**2 (0.3)**	**0.4**	**0 (0.0)**	**0.0**
Non-Hodgkin's lymphoma	**3 (0.4)**	**0.6**	**0 (0.0)**	**0.0**
---B-cell lymphoma	2 (0.3)	0.4	0 (0.0)	0.0
---T-cell lymphoma	1 (0.1)	0.2	0 (0.0)	0.0
Squamous cell carcinoma - anogenital	**1 (0.1)**	**0.2**	**0 (0.0)**	**0.0**
---Squamous cell carcinoma - CIS - anal	1 (0.1)	0.2	0 (0.0)	0.0
Squamous cell carcinoma - other	**1 (0.1)**	**0.2**	**1 (0.3)**	**0.6**
Rectal cancer	**1 (0.1)**	**0.2**	**0 (0.0)**	**0.0**
Hepatocellular carcinoma	**1 (0.1)**	**0.2**	**0 (0.0)**	**0.0**
Non-melanoma skin cancer	**1 (0.1)**	**0.2**	**0 (0.0)**	**0.0**
---Squamous cell carcinoma - skin	1 (0.1)	0.2	0 (0.0)	0.0

Note: Patients with multiple events may be counted more than once in different terms, but only once in one term.
[†] Crude incidence (100×n/N).
[‡] Events per 100 patient-years, with patient-years at risk (PYR) calculated based on the overall endpoint.

Appendix 24

Summary of Malignancy Rates– Double Blind Data
Phase II and III Studies
Cumulative Update as of 09-Jul-2007
Note: These data have not been reviewed by the FDA.

	Raltegravir (N = 758) 820 Patient-Years		Control Group (N = 323) 261 Patient-Years	
	n (%)[†]	Rate[‡]	n (%)[†]	Rate[‡]
Total number of patients with Endpoint	**19 (2.5)**	**2.3**	**5 (1.5)**	**1.9**
Kaposi's sarcoma	**4 (0.5)**	**0.5**	**0 (0.0)**	**0.0**
Non-Hodgkin's lymphoma	**3 (0.4)**	**0.4**	**1 (0.3)**	**0.4**
---B-cell lymphoma	2 (0.3)	0.2	0 (0.0)	0.0
---T-cell lymphoma	1 (0.1)	0.1	0 (0.0)	0.0
---Lymphoma - other	0 (0.0)	0.0	1 (0.3)	0.4
Squamous cell carcinoma - anogenital	**5 (0.7)**	**0.6**	**2 (0.6)**	**0.8**
---Squamous cell carcinoma - anal	2 (0.3)	0.2	2 (0.6)	0.8
---Squamous cell carcinoma - CIS - anal	3 (0.4)	0.4	0 (0.0)	0.0
Squamous cell carcinoma - other	**1 (0.1)**	**0.1**	**1 (0.3)**	**0.4**
Rectal cancer	**1 (0.1)**	**0.1**	**0 (0.0)**	**0.0**
Metastatic Neoplasm, NOS	**0 (0.0)**	**0.0**	**1 (0.3)**	**0.4**
Hepatocellular carcinoma	**1 (0.1)**	**0.1**	**0 (0.0)**	**0.0**
Non-melanoma skin cancer	**5 (0.7)**	**0.6**	**1 (0.3)**	**0.4**
---Squamous cell carcinoma - skin	4 (0.5)	0.5	0 (0.0)	0.0
---Basal cell carcinoma	2 (0.3)	0.2	1 (0.3)	0.4

Note: Patients with multiple events may be counted more than once in different terms, but only once in one term.
[†] Crude incidence (100×n/N).
[‡] Events per 100 patient-years, with patient-years at risk (PYR) calculated based on the overall endpoint.

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