MEMORANDUM

DATE: August 8, 2007

TO: Advisory Committee Members and Guests

FROM: Raltegravir Review Team

THROUGH: Debra Birnkrant, M.D.
Division Director
Division of Antiviral Products

SUBJECT: Background Package for NDA 22-145; raltegravir

I. Summary of Regulatory Issues and Purpose of Meeting

This document provides background information for the September 5, 2007, Antiviral Drugs Advisory Committee meeting on raltegravir. On this day, the committee will be asked to consider efficacy and safety data submitted to support the approval of raltegravir for the treatment of HIV-1 infection.

Raltegravir (also known as MK-0518) is the first agent of the pharmacological class of antiretroviral agents known as integrase inhibitors to be submitted to FDA for review for marketing approval. HIV-1 integrase is 1 of 3 enzymes required for viral replication. In the cycle of viral replication, HIV-1 ribonucleic acid (RNA) is first converted into deoxyribonucleic acid (DNA) within the host cell. HIV-1 DNA is then integrated into the DNA of the host cell; this step is catalyzed by the integrase enzyme. Raltegravir blocks the strand transfer step of the integration process.

This new drug application (NDA) was submitted in accordance with regulations and guidance for submission of drugs for accelerated approval; demonstration of efficacy of this drug is based on surrogate endpoint analyses of plasma HIV RNA and CD4+ cell counts in antiretroviral highly treatment-experienced HIV-infected subjects after 16 and 24 weeks of treatment.

FDA analyses of the safety and efficacy data submitted in the NDA support the applicant's findings. Phase 2 and 3 trial data provide evidence that the antiviral activity of raltegravir is superior to optimized background therapy (OBT) in treatment-experienced patients with few or no remaining treatment options. In addition, a small dose-finding study of raltegravir in combination with lamivudine/tenofovir (3TC/TDF) in treatment-naïve patients showed similar activity to efavirenz (EFV) in combination with 3TC/TDF at 48 weeks; however, this study was not powered to convincingly demonstrate similarity or to fully evaluate safety in this population. A large Phase 3 study in treatment-naïve patients is currently being conducted.

The Division is convening this meeting to solicit the committee's comments on the following questions:

Questions for the Advisory Committee

1) Do the available data support accelerated approval of raltegravir for the treatment of HIV-1 infection?

   If no, what additional studies are recommended?
   If yes, please answer Question 2.

2) Raltegravir proposed indication – "In combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy."

   a) Do the data from Protocols 005, 018 and 019 support the proposed indication for treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy?
   b) Should the indication be restricted to the population enrolled in the pivotal studies, specifically patients with few or no remaining treatment options?

3) Please discuss the pros and cons of the following potential treatment strategies in future clinical trials used to support drug development, and more specifically, if you would like to see these studies conducted using raltegravir as post-marketing commitments.
   a) Nucleoside-sparing regimens in treatment-naïve patients using either two-drug/two-class or three-drug/three-class regimens
   b) Nucleoside-sparing regimens or three-drug/three class regimens in first treatment failure patients

4) What additional studies would you like to see undertaken as post-marketing commitments?

5) What strategies would help increase study enrollment of women and minorities?

Preclinical Development Summary

The safety profile of raltegravir has been extensively characterized in rats, mice, rabbits, and dogs. The absorption, distribution, metabolism, and excretion (ADME) profiles of raltegravir in these species are similar to that in humans making them appropriate animal models for nonclinical safety evaluation. Toxicologic, genotoxic, allergenic, immunologic, and reproductive toxicological potential and potential effects on cardiovascular, neurologic, respiratory, gastrointestinal, renal and other systems were evaluated. Two year carcinogenicity studies in rats and mice are ongoing; the dosing phase is expected to end in the 4th quarter of 2007.

All of the pivotal toxicology studies employed an adequate range of doses and produced sufficient systemic exposures and safety margins over the clinical dose of 400 mg twice daily. Raltegravir was found to readily cross blood-brain and blood-placental barriers. It is not known whether raltegravir is secreted in human milk. The highest doses explored following chronic oral administration of raltegravir were 360 mg/kg/day in dogs (12 month administration) and 600 mg/kg/day in rats (6 month administration). Exposures at these doses were 5- and 3-fold greater than exposures observed with the proposed dose of 400 mg twice daily. At these doses, raltegravir was found to be well tolerated and produced few or no adverse effect; one notable exception was irritation to mucosal surfaces that came in contact with raltegravir.

Mucosal irritation was dose- and duration-related but was independent of age. Raltegravir at doses ≥ 120 mg/kg/day caused dose-related salivation, increases in the incidence of glandular mucosal degeneration/erosions in stomach, and incidence and severity of inflammation in nose and nasopharynx (presumably due to aspiration of drug) in adult rats. Similar irritation to mucosal surfaces was also observed in young rats. No additional toxicities were noted in juvenile rats, indicating that juvenile rats were not more sensitive to drug effects than adult rats. In mice, the mucosal irritation was manifested as dose-related increases in the incidences of gastrointestinal bloating. Irritation to mucosal surfaces is dose-limiting (mortality in rats and mice and >10% reduction in body weight gain in rats) and is independent of formulation. The toxicity was likely related to the local concentration of raltegravir rather than the systemic exposure. In contrast to the findings in rats and mice, no adverse events were observed in dogs, although dogs had the highest and longest duration of systemic exposure to raltegravir.

Raltegravir was evaluated in three *in vitro* and one *in vivo* genotoxicity assays and was found not to be mutagenic or clastogenic. The carcinogenic potential of raltegravir is being evaluated in two-year carcinogenicity studies in rats and mice; as noted, studies are ongoing. Histomorphologic examination in all prematurely necropsied animals through Week 76 showed that 5 out of 24 high dose males examined had squamous cell carcinoma in the nasopharynx or nose. In mice, histomorphologic examination in all prematurely necropsied animals through Week 76 did not detect any tumors. However, dose-related increases in the incidence of squamous metaplasia were seen in nose and

nasopharynx of both males and females at doses ≥ 50 mg/kg/day. These results confirm the irritability of raltegravir and suggest that rats are most sensitive to this toxicity. There is no indication of gastrointestinal irritation in clinical studies so far.

The safety of raltegravir was also investigated in a variety of *in vitro* and local tolerance studies. It is not a dermal sensitizer in the mouse local lymph node assay or a skin irritant in *in vivo* rabbit dermal irritation model or *in vitro* EpiDerm Skin Model. It is not phototoxic or hemolytic *in vitro* to blood cells isolated from rats, dogs, and humans. As expected, because of its irritability to mucosal surfaces, it is considered a severe irritant in the *in vitro* bovine corneal opacity test with *in vitro* score higher than that for the positive control, imidazol.

In conclusion, except for the irritation to mucosal surfaces observed in rodents, raltegravir has a favorable safety profile in animals at multiples of exposure in humans.

Clinical Development Summary

This NDA contains clinical data collected primarily from four clinical studies, including the two pivotal studies Protocol 018 and Protocol 019. Protocols 018 and 019 are international, multi-center, double-blind, randomized, placebo-controlled trials comparing raltegravir in combination with optimized background therapy (OBT) to OBT alone in highly treatment-experienced HIV-infected subjects. The studies were identical except for the location of the study sites. Protocol 018 was conducted in Europe, Asia/Pacific, and South America, while Protocol 019 was conducted in North and South America. Eligible subjects were HIV-1 infected patients who had failed therapy as documented by HIV RNA >1,000 copies/mL while on stable therapy and documented resistance to at least 1 drug in each of 3 classes of licensed oral ARVs (NNRTI, NRTI, and PI).

Several supportive studies were also submitted, including Protocol 004, a dose-finding study in treatment-naïve patients and Protocol 005, a dose-finding study in treatment-experienced patients that evaluated doses of 200 mg, 400 mg, and 600 mg of raltegravir versus OBT for 48 weeks. Dose selection for Phase 3 was based on Week 24 study data.

A pediatric study is currently underway, but no pediatric data were submitted in support of this NDA. Other ongoing studies include expanded access Protocol 023 and a large Phase 3 trial in treatment-naïve patients, Protocol 021.

Summaries of these trials are provided in Table 1.

TABLE 1 - Summary of Clinical Trials

Study	Design	Raltegravir Regimens (mg)	Comparator (mg)	Background	# Enrolled	Pt Population	Endpoint
004	Part 1: 10 d Randomized Double - Blinded	100 mg bid 200 mg bid 400 mg bid 600 mg bid	Placebo	n/a	35	Treatment naïve	ΔHIV RNA from B/L at Day 10
	Part 2: 48 wks plus extension Randomized Double - Blinded	100 mg bid 200 mg bid 400 mg bid 600 mg bid	Efavirenz 600 mg qhs	3TC/TDF	198	Treatment naïve	HIV RNA <400 at Week 24
005	Randomized Double - Blinded	200 mg bid 400 mg bid 600 mg bid	Placebo	OBT	178	Treatment experienced	ΔHIV RNA from B/L at Week 24
018[1]	Randomized Double - Blinded	400 mg bid	Placebo	OBT	350	Treatment experienced	HIV RNA <400 Week 16
019[1]	Randomized Double - Blinded	400 mg bid	Placebo	OBT	349	Treatment experienced	HIV RNA <400 Week 16
021	Randomized Double - Blinded	400 mg bid	Efavirenz 600 mg qhs	FTC/TDF	290[2] (550)[3]	Treatment naïve	HIV RNA <50 Week 48
022	Pediatric	Dose ranging	None	OBT	(140[3]	Treatment-experienced Age 2 to 18 years	PK/PD and safety
023	Expanded Access Protocol	400 mg bid	none	OBT	827[2]	Treatment experienced	Percent BLQ

[1]Pivotal studies used to support NDA submission
[2]Current enrollment
[3]Targeted enrollment

Phase 3 Study Results

Table 2 summarizes select patient demographics and baseline patient characteristics from Protocols 018 and 019. These results reflect FDA analyses which are consistent with the sponsor's analyses.

Please note that demographics and baseline characteristics are reported by protocol and not by treatment arm; no significant imbalance was noted between patients randomized to placebo versus control.

TABLE 2 – Patient Demographics and Baseline Characteristics

	Protocol 018	**Protocol 019**
# of Subjects Treated	350	349
Age (Years)		
Mean	45	46
Median	45	45
Range	16, 74	16, 70
Sex – n (%)		
Male	298 (85)	317 (91)
Female	52 (15)	32 (9)
Race – n (%)		
White	271 (77)	203 (58)
Black	23 (7)	69 (20)
Hispanic	7 (2)	65 (19)
Asian	19 (5)	3 (1)
Other	30 (9)	8 (2)
CD4+ Cell Count (cells/mm^3)		
Mean	155	152
Median	130	111
< 50 - n (%)	109 (31)	115 (33)
> 50 and ≤ 200 - n (%)	132 (38)	126 (36)
> 200 - n (%)	108 (31)	108 (31)
HIV RNA (log_{10} copies/mL)		
Mean	4.6	4.7
Median	4.7	4.7
N < 100,000 - n (%)	240 (69)	217 (62)
N ≥ 100,000 - n (%)	110 (31)	132 (38)

TABLE 2 CONTINUED – Demographics and Baseline Characteristics

	Protocol 018	Protocol 019
# of Subjects Treated	350	349
Median Time on Prior ARV [years (min, max)]	11 (0, 19)	10 (0, 19)
Median Number of Prior ARV [number (min, max)]	12 (2, 19)	12 (1, 22)
History of AIDS - n (%)	323 (92)	319 (91)
Hepatitis B and/or C Co-infection n (%)	76 (22)	37 (10)
Phenotypic Sensitivity Score (PSS)[1] – n (%)		
0	65 (19)	46 (13)
1	106 (30)	110 (32)
2	100 (29)	108 (31)
≥ 3	65 (19)	68 (20)
Missing	14 (4)	17 (5)
Genotypic Sensitivity Score (GSS)[1] – n (%)		
0	104 (30)	76 (22)
1	124 (35)	150 (43)
2	79 (23)	81 (23)
≥ 3	39 (11)	35 (10)
Missing	4 (1)	7 (2)
T-20 Use in OBT – n (%)		
Naïve Use	72 (21)	68 (20)
Experienced Use	59 (17)	65 (19)
No Use	219 (63)	216 (62)
Darunavir Use in OBT – n (%)		
Naïve Use	92 (26)	164 (47)
Experienced Use	19 (5)	8 (2)
No Use	239 (68)	177 (51)

[1]PSS and GSS scores were defined as the total oral ARVs in OBT to which a patient's viral isolate showed phenotypic sensitivity and genotypic sensitivity, respectively, based on phenotypic resistance 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.

Table 3 provides FDA analyses of Week 24 outcomes for Protocols 018 and 019. Please note at the time of submission all patients had reached Week 16 and just over 60% of patients had reached Week 24. FDA analyses of both timepoints were performed, however, only Week 24 data is displayed in this document. Small discrepancies between FDA analyses and Merck analyses may be noted because of different definitions of the visit window and different missing data imputation approaches. Please also note that all events included in the table are from the double-blind portion of the study. Subjects discontinuing blinded treatment were counted as treatment failures; however, they were given the option to receive open-label raltegravir and continue on study.

TABLE 3 – Week 24 Outcomes

	Protocol 018		**Protocol 019**	
	Raltegravir + OBT N=232	Placebo + OBT N=118	Raltegravir + OBT N=230	Placebo + OBT N=119
Patients w/ Week 24 Data[1] – n (%)	158 (68)	81 (69)	128 (56)	69 (58)
< 400 copies/mL[2,3] – n (%)	120 (76)	33 (41)	97 (76)	27 (39)
< 50 copies/mL[2,3] – n (%)	95 (60)	28 (35)	83 (65)	23 (33)
CD4+ cell count change from baseline – Mean (SD)[2,4]	83 (98)	33 (71)	92 (98)	39 (72)
Virologic failure[5] – n (%)	36 (15)	63 (53)	40 (17)	58 (49)
Week 16 Nonresponder	5 (2)	44 (37)	9 (4)	33 (28)
Week 24 Rebound	31 (13)	19 (16)	31 (13)	25 (21)
Discontinuation by Week 24 – n (%)				
due to Adverse Events	4 (2)	4 (3)	4 (2)	1 (1)
due to Other	1 (<1)	0 (0)	5 (2)	2 (2)
Death by Week 24 – n (%)	3 (1)	3 (3)	3 (1)	0 (0)

[1]The analysis population at Week 24 included the patients who were randomized before 07/01/06, received at least one dose of study drug, and had Week 24 data available at the database locked on 12/13/06.

[2]These parameters were calculated using the analysis population at Week 24.

[3]A subject was considered to fail if he/she discontinued from the study or switched to receive open-label raltegravir. If the HIV RNA level was missing at Week 24 but not missing at Week 32, then the one at Week 32 was carried backwards for Week 24; otherwise if HIV RNA levels were missing at both Weeks 24 and 32, then the one at Week 16 was carried forwards for Week 24.

[4]If the $CD4^+$ cell count was missing at Week 24 but not missing at Week 32, then the one at Week 32 was carried backwards for Week 24; otherwise if the $CD4^+$ cell counts were missing at both Weeks 24 and 32, then the one at Week 16 was carried forwards for Week 24.

[5]Virologic failure was defined as non-responders who did not achieve > 1.0 $\log_{10}$ HIV RNA reduction and < 400 HIV RNA copies/mL by Week 16, or viral rebound at Week 24, which was defined as: 1) HIV RNA > 400 copies/mL (on 2 consecutive measurements at least 1 week apart) after initial response with HIV RNA < 400 copies/mL, or 2) > 1.0 $\log_{10}$ increase in HIV RNA above nadir level (on 2 consecutive measurements at least 1 week apart).

Additional analyses were performed to examine the impact of baseline characteristics and optimized background therapy on patient outcomes. Select analyses are displayed in Table 4.

TABLE 4 – Selected Subgroup Analyses at Week 24
Proportion of Patients Achieving HIV RNA < 50 copies/mL

	Protocol 18		Protocol 19		Total	
Responders/Evaluable (%)	Raltegravir + OBT N=232	Placebo + OBT N=118	Raltegravir + OBT N=230	Placebo + OBT N=119	Raltegravir + OBT N=462	Placebo + OBT N=237
Patients w/ Week 24 Data N	158	81	128	69	286	150
Phenotypic Susceptibility Score (PSS)[1] of OBT						
0	13/32 (41)	1/15 (7)	5/12 (42)	0/11 (0)	18/44 (41)	1/26 (4)
1	30/43 (70)	9/26 (35)	29/46 (63)	7/24 (29)	59/89 (66)	16/50 (32)
2	33/51 (65)	9/23 (39)	33/44 (75)	4/13 (31)	66/95 (69)	13/36 (36)
≥ 3	13/26 (50)	7/14 (50)	13/22 (59)	11/19 (58)	26/48 (54)	18/33 (55)
Number of Active PIs in OBT by Phenotype						
0	38/69 (55)	6/39 (15)	18/37 (49)	4/23 (17)	56/106 (52)	10/62 (16)
≥ 1	52/84 (62)	21/41 (51)	64/90 (71)	19/46 (41)	116/174 (67)	40/87 (46)
Naïve ENF	26/37 (70)	9/16 (56)	25/27 (93)	9/12 (75)	51/64 (80)	18/28 (64)
Naïve DRV	28/47 (60)	13/22 (59)	42/59 (71)	18/37 (49)	70/106 (66)	31/59 (53)
Naïve ENF and naïve DRV	10/16 (62)	6/7 (86)	14/15 (93)	6/7 (86)	24/31 (77)	12/14 (86)
Naïve ENF and no DRV	16/21 (76)	3/9 (33)	11/12 (92)	3/5 (60)	27/33 (82)	6/14 (43)
No ENF and naïve DRV	12/20 (60)	7/12 (58)	18/28 (64)	6/20 (30)	30/48 (62)	13/32 (41)
No ENF and no DRV	44/65 (68)	12/38 (32)	26/48 (54)	2/21 (10)	70/113 (62)	14/59 (24)

[1]PSS score was defined as the total oral ARVs in OBT to which a patient's viral isolate showed phenotypic sensitivity based on phenotypic resistance test. Enfuvirtide use in OBT in enfuvirtide-naïve patients was counted as one active drug in OBT and added to the PSS. Darunavir use in OBT in darunavir-naïve patients was counted as one active drug in OBT and added to the PSS.

Summary of Important Clinical Pharmacology Findings

The clinical pharmacology of raltegravir has been characterized in healthy and HIV-1 infected subjects, as well as in vitro studies using human biomaterials. The clinical pharmacology characteristics of raltegravir observed in these studies are summarized in the following sections.

Clinical Pharmacology Conclusions

1. Raltegravir exhibits high pharmacokinetic variability (range of geometric mean C_{12hr} on 400 mg twice daily = 12 to 9151 nM in pivotal studies).
2. The potential sources of variability include: food, pH dependent solubility, UGT1A1 polymorphism, UGT1A1 expression and drug interactions.
3. Defining a clinically significant concentration threshold for potential dose adjustment is challenging because observed raltegravir plasma concentrations span over a 5-log range.
    a. Within the concentration range studied, the virologic success rate is similar (77%) for patients with lower C_{12hr} (median C_{12hr} 76nM) compared to those with higher C_{12hr} (median C_{12hr} 1085 nM). This relationship needs careful interpretation in the presence of high within subject variability.
    b. It is difficult to define the maximum safe raltegravir concentration because of the size of the current safety database at high exposure levels and the high pharmacokinetic variability

Pharmacokinetics (Absorption, Distribution, Metabolism, Excretion)

After oral administration of single doses of raltegravir in healthy subjects in the fasted state, raltegravir $AUC_{0-\infty}$ and C_{max} are dose proportional over the dose range of 100 to 1600 mg. However, the variability is quite large (increasing with increasing dose levels), which implies a large degree of uncertainty in raltegravir exposure levels (See Assessment of Pharmacokinetic Variability section). In treatment naïve HIV-1 infected patients who received raltegravir 400 mg twice daily monotherapy, raltegravir drug exposures were similar to exposures in healthy subjects.

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. The median time to maximum plasma concentration (T_{max}) is ~3 hours in the fasted state. Steady state is achieved after two days of dosing at all dose levels.

Raltegravir is approximately 83% bound to human plasma proteins and is minimally distributed into red blood cells (blood-to-plasma partitioning ratio of 0.6). No data are available regarding human central nervous system (CNS) or brain penetration. Raltegravir is a substrate of human P-gp *in vitro*, which may limit CNS penetration in humans.

The results from a single dose study of 200 mg [^{14}C] raltegravir given to young healthy subjects indicate hepatic clearance via glucuronidation plays a major role in the clearance of raltegravir in

humans while renal clearance of unchanged drug is a minor pathway of elimination of raltegravir.

The *in vitro* metabolism of raltegravir was studied in human hepatic microsomes and hepatocytes. Data indicate glucuronidation of the parent compound to M2 is the major metabolic pathway in humans. Raltegravir is not a substrate of cytochrome P450 enzymes. Correlation and specific chemical inhibition studies in pooled human liver microsomes confirm the glucuronidation of raltegravir is mainly catalyzed by UGT1A1 with a minor contribution from UGT1A9 and 1A3.

UGT1A1 is a polymorphic enzyme. A single-dose, open-label study in healthy subjects with UGT1A1*1/*1 and UGT1A1*28/*28 genotypes is ongoing.

Food Effect

A high-fat meal, on average, resulted in a 19% increase in AUC, 34% decrease in C_{max}, 750% increase in C_{12hr} and 7.3 hour delay in T_{max} with raltegravir final market image (FMI) formulation. However, the food effect is variable between subjects (See Assessment of Pharmacokinetic Variability section).

Based on the results from the high-fat meal study and the fact that raltegravir was dosed with or without food in Phase 2 and Phase 3 trials, raltegravir can be taken with or without food.

A study to investigate the effects of low, moderate, and high-fat meals on multiple dose pharmacokinetics of raltegravir in healthy volunteers is ongoing.

Special Populations

The effects of HIV status, age, gender, weight, and race on raltegravir pharmacokinetics were assessed by evaluation of raltegravir plasma trough concentrations in Phase 2/3 trials. The data indicate age, gender, weight, race and HIV status do not have an impact on raltegravir exposure. No clinically important effect of moderate hepatic insufficiency on the raltegravir pharmacokinetic profile was observed in a study of subjects with Child Pugh scores of 7 to 9. No dosage adjustment is recommended for patients with mild to moderate hepatic insufficiency. No clinically important effect of severe renal insufficiency on the raltegravir pharmacokinetic profile was observed in a study of subjects with 24-hour creatinine clearance of <30 mL/min/1.73 m^2. No dosage adjustment is recommended for patients with renal insufficiency.

Drug-Drug Interactions

In Vitro Results: Drug-Drug Interaction Potential

- Raltegravir is a UGT1A1 substrate.
- Raltegravir is an avid P-gp substrate.
- Raltegravir is not an inhibitor of P-gp.
- Raltegravir is not an inhibitor (IC_{50} >100 μM) of CYP1A2, 2C8, 2C9, 2C19, 2D6, 3A4, and 2B6. Raltegravir (up to 10 μM) has no potential to induce CYP3A4.

- Raltegravir is not a potent inhibitor of UGT1A1 or UGT2B7 (IC_{50} >50 μM).
- No study was conducted to evaluate other transporter pathways.

In Vivo Effects of Other Drugs on Raltegravir
Raltegravir is a UGT1A1 and P-gp substrate. Because raltegravir will be co-administered with drugs that affect UGT1A1 and P-gp activity, the effects of drugs on raltegravir pharmacokinetics were studied in Phase 1 clinical trials. Table 5 summarizes the effect of other drugs on raltegravir.

Table 5 - Summary of the Effect of Other Drugs on Raltegravir

Co-administered drug and dose	N	Study Design	Ratio (90% CI) of raltegravir pharmacokinetic parameters with/without co-administered drug (no effect = 1.00)		
			C_{min}	AUC_{tau}	C_{max}
UGT1A1 Inhibitors					
Atazanavir 400 mg QD	10	SD/MD	1.95 (1.30, 2.92)	1.72 (1.47, 2.02)	1.53 (1.11, 2.12)
Atazanavir/ritonavir 300/100 mg QD	10	MD/MD	1.77 (1.39, 2.25)	1.41 (1.12, 1.78)	1.24 (0.87, 1.77)
UGT1A1 Inducers					
Ritonavir	10	SD/MD	0.99 (0.70, 1.40)	0.84 (0.70, 1.01)	0.76 (0.55, 1.04)
Efavirenz 600 mg QD	10	SD/MD	0.79 (0.49, 1.28)	0.64 (0.52, 0.80)	0.64 (0.41, 0.98)
Rifampicin 600 mg QD	10	SD/MD	0.39 (0.30, 0.51)	0.60 (0.39, 0.91)	0.62 (0.37, 1.04)
Tipranavir/ritonavir 500/200 mg BID	18	MD/MD	0.45 (0.31, 0.66)	0.76 (0.49, 1.19)	0.82 (0.46, 1.46)
Etravirine (TMC125) 200 mg BID	20	MD/MD	0.66 (0.34, 1.26)	0.90 (0.68, 1.18)	0.89 (0.68, 1.15)
Other Drugs					
Tenofovir 300 mg BID	10	MD/MD	1.03 (0.73, 1.45)	1.49 (1.15, 1.94)	1.64 (1.16, 2.32)

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.

The effect of ritonavir (100 mg twice-daily) on the pharmacokinetics of raltegravir is not significant. The observed results may be due to counteracting effects of ritonavir on UGT1A1 (induction) and on P-gp (inhibition). Ritonavir is a potent UGT1A1 inducer and a P-gp inhibitor, and raltegravir is a dual substrate of UGT1A1 and P-gp.

As anticipated, raltegravir plasma levels were increased with co-administration with atazanavir alone and in combination with ritonavir, which is consistent with inhibition of

UGT1A1. However, concomitant use of raltegravir and atazanavir was well tolerated in the Phase 2 and Phase 3 studies. Based on these data, atazanavir may be co-administered with raltegravir without dose adjustment of raltegravir.

Rifampin and tipranavir/ritonavir are potent inducers of a broad range of drug-metabolizing enzymes as well as P-gp. Thus, the reduction in raltegravir exposure could be due to the combination of UGT1A1 and P-gp induction.

Based on these drug interaction data, the applicant's recommendation for a dose increase of raltegravir to 800 mg twice daily when co-administered with rifampin, phenytoin and phenobarbital is under review.

Tipranavir/ritonavir has a similar effect on raltegravir exposure compared to rifampin. Approximately 100 patients received raltegravir in combination with tipranavir/ritonavir in Phase 3 trials. Comparable efficacy was observed in this subgroup relative to patients not receiving tipranavir/ritonavir. Based on these data, tipranavir/ritonavir may be co-administered with raltegravir without dose adjustment of raltegravir.

The applicant's proposals that raltegravir exposure changes up to a 2-fold increase in exposure (AUC) for safety and a 60% decrease (equivalent to geometric mean ratio of 0.4) in trough concentration ($C_{12\ hr}$) for efficacy are not clinically relevant based on available clinical experience. The cut-off values are under review (See Assessment of Pharmacokinetic Variability section).

Effects of Raltegravir on Other Drugs

Raltegravir is unlikely to significantly alter plasma exposure of co-administered drugs that are metabolized by cytochrome P450 enzymes, UGT enzymes and P-gp.

Drug interaction studies demonstrated that raltegravir did not alter pharmacokinetics of midazolam, tenofovir and etravirine (TMC125).

Potential sources that contribute to pharmacokinetic variability of raltegravir

As indicated in Assessment of Pharmacokinetic Variability section, raltegravir plasma concentrations were highly variable in clinical studies. The high pharmacokinetic variability observed across these clinical studies could be due to the combination of the following factors:

1. High variability in hepatic UGT1A1 protein expression levels (>50-fold) from human liver samples
2. UGT1A1 polymorphism
3. High variability in intestinal P-gp expression levels
4. pH-dependent solubility (Solubility increases with increasing pH)

5. Food effect on $C_{12\ hr}$ values (Raltegravir was administered with or without food in Phase 2/3 trials)
6. Drug interactions affecting UGT1A1 and/or P-gp

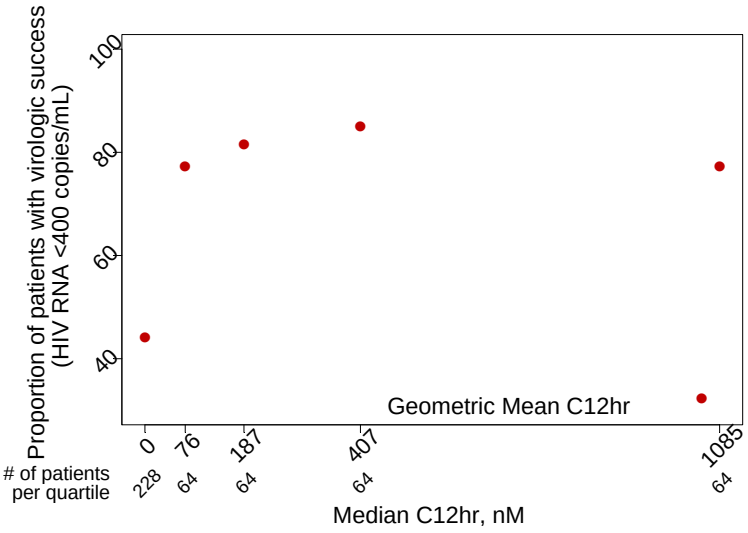
Exposure-Response Analysis

The data from two large double-blind placebo controlled trials (Protocols 018 and 019) in HIV-infected patients with documented resistance to at least 1 drug in each of the 3 classes of licensed oral antiretroviral therapies were used in the exposure-response analyses. These trials were conducted using the FMI formulation, which exhibits considerable food effect on C_{12hr} (described later). A total of 483 subjects (225 raltegravir treated and 228 placebo treated) were included in the analyses. Approximately 200 subjects were excluded due to lack of sufficient PK information. Plasma trough concentrations (C_{12hr}) were used as an exposure variable. Two individual exposure estimates were derived from the observed values in the sparse data set: the geometric mean observed C_{12hr} (determined from the geometric mean concentration of all samples taken between 11 and 13 hours post-dose in a given individual); and the minimum observed C_{12hr} (determined as the minimum concentration from all samples taken between 11 and 13 hours post-dose in a given individual). Due to poor predictive performance, the population pharmacokinetic model does not provide reliable individual exposure estimates.

Several binary endpoints indicating virologic success, such as protocol defined failure at 16 weeks, viral load <50 copies/mL at 16 weeks, viral load <400 copies/mL at 16 weeks, were investigated. Analyses to establish predictors of virologic success are currently ongoing. According to preliminary results, geometric mean observed C_{12hr}, baseline viral load, naïve use of enfuvirtide or darunavir and the presence of tipranavir/ritonavir are the important predictors of virologic success. Using logistic regression analyses, various covariates (patient disease information, medication information and demographic information) that could impact the C_{12hr}-virologic success relationship will be evaluated.

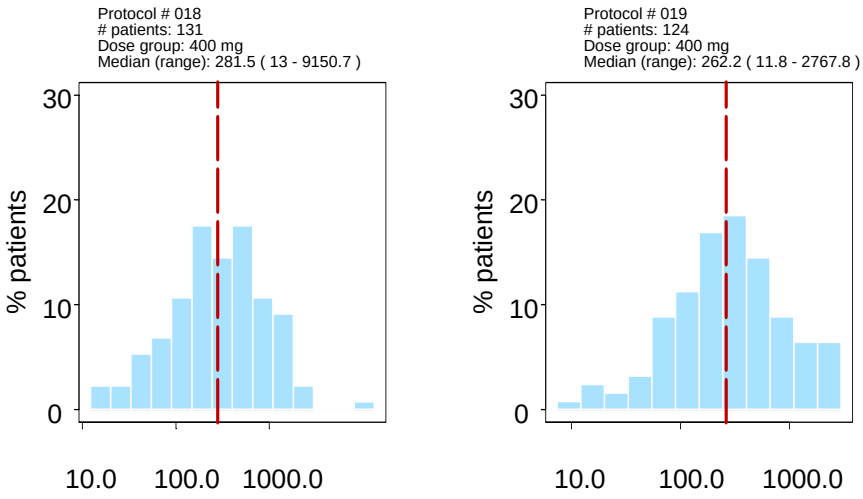
Figure 1 illustrates the relationship between the probability of virologic success (<400 copies/mL) and geometric mean observed C_{12hr}. Within the concentration range studied, the C_{12hr}-virologic success relationship is shallow. However, this relationship needs careful interpretation in the presence of high within subject variability.

Figure 1: C_{12hr}-virologic success relationship. The C_{12hr}=0 represents placebo-treated patients; raltegravir-treated patients were divided into four quartiles.



The overall variability in C_{12hr} is considerably high, with a range of 12 to 9151 nM. Figure 2 illustrates distribution of geometric mean observed C_{12hr} in the pivotal studies.

Figure 2: Distribution of geometric mean observed C_{12hr} (nM)



Assessment of Pharmacokinetic Variability

An attempt was made to understand the factors leading to variability in C_{12hr}. As noted earlier, administration of raltegravir with a high fat meal was found to slow the rate of raltegravir absorption, causing a mean increase in C_{12hr} of 750%. The effect of food on

raltegravir C_{12hr} was variable between subjects. Because raltegravir dosing in pivotal studies was done without regard to food, over the course of the trials (Protocols 018 and 019), day-to-day variability was likely influenced by variability in food intake. In other words, a given patient could have 8 fold higher C_{12hr} on a day when raltegravir was taken with food compared to days when raltegravir was taken without food. In addition to food, there are other determinants of raltegravir pharmacokinetics, such as, UGT1A1 polymorphism and drug interactions.

Figure 3 illustrates the within-subject variability in raltegravir concentrations. The figure includes pre-dose and post-dose trough concentrations (C_{0hr} and C_{12hr}) for treatment-naïve HIV-infected subjects who received their assigned dose (100 to 600 mg twice daily) for 10 days. The diagonal line in the graph represents the "line of unity". If low within subject variability was observed, data points would fall on or near the line. High within subject variability is demonstrated by the lack of correlation between pre-dose and post-dose trough concentrations.

Figure 3: Within subject variability in raltegravir trough concentrations (Inset: Data within 0–500 nM)

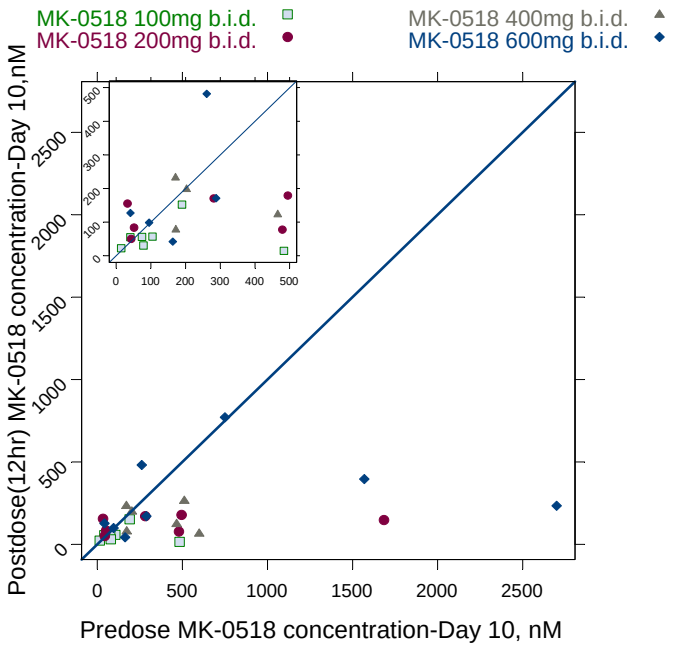
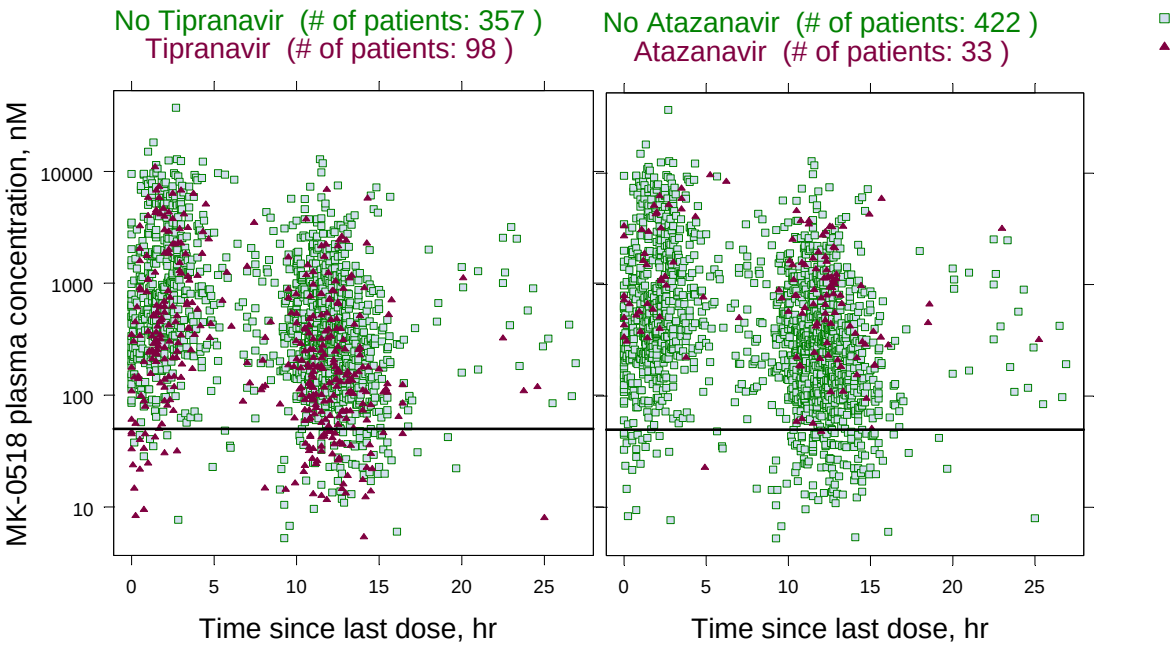


Figure 4 illustrate the high variability in raltegravir C_{12hr} observed in Protocols 018 and 019. The C_{12} values span a 5-log range. The figure also illustrates the impact of interactions with tipranavir and atazanavir within the context of high pharmacokinetic variability. The Phase 1 drug interaction studies indicated atazanavir/ritonavir increased raltegravir C_{12hr} by 77% and tipranavir/ritonavir decreased raltegravir C_{12hr} by 55%. The mean changes in raltegravir C_{12hr} due to atazanavir/ritonavir and tipranavir/ritonavir were similar between the Phase 1 studies and Protocols 018 and 019. However, because of the

high variability in raltegravir concentrations, the range of raltegravir concentrations observed with or without either co-administered drug is similar.

Figure 4 Effect of tipranavir and atazanavir on raltegravir plasma concentrations in Protocols 018 and 019. (The horizontal line represents 50 nM, an in vitro IC95 using 50% human serum) Plasma concentrations are normalized to time after dose, but were obtained over the entire trial duration.



The size of the current safety database at high raltegravir exposure levels and high variability make defining a clinically significant threshold for dose adjustment challenging. The applicant's proposals that raltegravir exposures spanning a 2-fold increase in AUC for safety and a 60% decrease in $C_{12\ hr}$ for efficacy are not clinically relevant based on available clinical experience. The cut-off values are under review. Based on the applicant's rationale, a dose adjustment in the presence of atazanavir/ritonavir or tipranavir/ritonavir is not needed. Safety and efficacy data from Protocols 018 and 019 support the administration of raltegravir 400 mg twice daily with either tipranavir/ritonavir or atazanavir/ritonavir, with no dose adjustment. However, doubling of the dose to 800 mg twice daily is proposed in presence of rifampin, phenobarbital or phenytoin. Protocols 018 and 019 prohibited use of phenobarbital, phenytoin, rifabutin, and rifampin. When the protocols were amended, rifabutin (a less potent CYP3A, UGT1A1 inducer) was no longer prohibited. Dose adjustment is under review.

Summary of Nonclinical/Clinical Microbiology

Mechanism of Action

As stated previously, HIV-1 integrase (IN) catalyzes integration of the unintegrated linear viral DNA, made by reverse transcription of the viral genomic RNA, into the host chromosome. Integration is essential for HIV-1 replication. The integration reaction requires three steps: (1) assembly of a stable preintegration complex at the termini of the viral DNA; (2) 3'-end endonucleolytic processing to remove the terminal dinucleotide from each 3' end of viral DNA; (3) strand transfer in which the viral DNA 3' ends are covalently linked to the cellular DNA.

Raltegravir has been shown to specifically inhibit the strand transfer step in a biochemical reaction with an IC_{50} value of 2 to 7 nM. No significant inhibitory activity was observed against the DNA polymerase and RNaseH activities of HIV-1 reverse transcriptase (RT) at concentrations up to 100 μM and 25 μM, respectively, and human DNA polymerases α, β, and γ at concentrations up to 50 μM.

Antiviral Activity in Cell Culture

The antiviral activity of raltegravir was assessed in MT4 cells infected with the H9/IIIB laboratory isolate of HIV-1 for 5 days. The EC_{95} values for raltegravir, determined by reduction in p24 Ag using an ELISA assay, were 18.7 ± 14 nM in the presence of 10% fetal bovine serum and 31 ± 20 nM in the presence of 50% normal human serum. In addition, raltegravir showed anti-HIV activity against multiple clinical isolates from HIV-1-infected persons in PBMCs with EC_{95} values ranging from 6 to 50 nM.

Resistance Development in Cell Culture

HIV-1 variants resistant to raltegravir were selected by serially passaging the laboratory HIV-1 isolate IIIB in H9 cells in the presence of increasing concentrations of raltegravir. A Q148K substitution in the HIV-1 IN coding region first emerged during selection and was followed sequentially by substitutions E138A, G140A, I208M, S230R, D10F and Y143C. Additional substitutions F181L and D279G were observed in a small number of clones.

The glutamine residue at position 148 is highly conserved among HIV-1 isolates and is located within the central core domain of IN containing the 3 active site amino acid residues D62, D116, and E152.

Phenotypic evaluations of these mutations using a single-cycle HIV-1 infection assay showed that the Q148K substitution conferred 46-fold reduced susceptibility in cell culture to raltegravir. Sequential addition of E138A and G140A substitutions increased overall resistance to 90-fold and 508-fold, respectively. The E138A substitution alone did not reduce susceptibility, while the G140A substitution and the E138A/G140A combination conferred 3-fold and 4-fold reduced susceptibility, respectively.

Thus, it appeared that the Q148K substitution is a primary contributor to resistance to raltegravir, and the E138A and G140A substitutions play a secondary role in augmenting resistance.

Clinical Resistance Analyses

In an as-treated analysis of the Phase 3 studies, paired amino acid sequences of HIV-1 IN from screening and on-treatment samples from 27 evaluable patients experiencing virologic failure on raltegravir were analyzed. A median of 3 (range 1 to 8) amino acid substitutions in HIV-1 IN were detected from the viruses of 26 patients. A total of 48 codons (16.7% of codons in the HIV-1 IN domain) were found to be mutated. Most were mutated once or twice. Seven amino acid changes were observed in 3 or more patients:

- 148 (Q148H/K/R)*
- 155 (N155H)*
- 92 (E92Q)
- 140 (G140A/S)
- 143 (Y143C/H/R)
- 151 (V151I)
- 230 (S230N/R)

*key pathways

These mutations were not observed in patients with virologic response to raltegravir treatment (4 patients from Studies 005 and 018) or with virologic failure to placebo therapy (12 patients from Study 005).

The N155H substitution was the most frequent mutation observed (11 patients [40.7%]) and conferred 13.2-fold resistance to raltegravir in cell culture. N155H was associated with E92Q (5 patients) and/or V151I (3 patients). The addition of E92Q, which by itself conferred 3-fold reduced susceptibility, increased resistance to 64-fold. V151I alone conferred no reduction in susceptibility to raltegravir.

Substitutions of Q148 with basic amino acid residues, arginine (R), histidine (H), or lysine (K) were noted in 7 patients (25.9%) and conferred 24-fold, 46-fold, and 27-fold resistance, respectively. Associated substitutions included E92Q (1 patient), G140A/S (4 patients), V151I (1 patient), and S230N/R (1 patient). Addition of G140A or G140S to Q148 variants substantially increased resistance to 257-fold and 521-fold, respectively. G140A and G140S alone conferred 3-fold and 2-fold reduced susceptibility, respectively.

Viruses from 4 patients harbored the Y143C/H/R substitutions in combination with either E92Q (2 patients) or S230N/R (2 patients). No phenotypic data of these mutations containing Y143C/H/R are currently available.

Protocol 005 (Phase 2 dose-ranging study) yielded a resistance profile of raltegravir similar to that of Protocols 018 and 019. Out of 50 evaluable patients experiencing

virologic failure to raltegravir treatment, key amino acid changes were observed at Q148 (27 patients), N155 (18 patients) and Y143 (2 patients). In addition to key changes at Q148 and N155, E92Q (2 patients), G140A/S (23 patients), V151I (5 patients), and S230N/R (6 patients) substitutions were also observed.

In summary, at least 2 major pathways, the Q148 pathway and the N155 pathway, appear to be involved independently in emergence of raltegravir resistance. Substitution of Q148 with any of the basic amino acids, H, K, or R, and the N155H substitution decreased susceptibility in cell culture to raltegravir 24- to 46-fold and 13-fold respectively. A third pathway is amino acid substitution at Y143 (Y143C/H/R). These substitutions were frequently found with additional amino acid changes.

The list of raltegravir resistance-associated substitutions observed to date includes L74M/R, E92Q, T97A, E138A/K, G140A/S, Y143C/H/R, Q148H/K/R, V151I, N155H, G163R, H183P, Y226C/D/F/H, S230N/R, and D232N.

Clinical Safety Results

General Safety:

A total of 902 HIV-infected subjects received at least one dose of raltegravir during the Phase 2 and Phase 3 studies at the time of the Safety Update Report (SUR, Frozen File date 2/16/07): 758 subjects by initial randomization, 138 subjects by switch from placebo to open label raltegravir after virologic failure, and 6 subjects by switch from placebo to open label raltegravir in the extension phase of Protocol 05. The proposed dose of 400 mg twice daily was received by 41 treatment-naïve and 651 treatment-experienced subjects.

In general, in dose-finding treatment-naïve Protocol 004 and dose-finding treatment-experienced Protocol 005, no relationship with dose and any adverse event was observed. Safety analyses of common adverse events (AE) and laboratory abnormalities pooled subjects from the Phase 2 and Phase 3 treatment-experienced studies receiving 400 mg raltegravir twice daily or placebo in combination with an optimized background regimen (OBT). The majority of AE analyses were limited to the double-blind treatment period to allow a more direct comparison among treatment arms. For some analyses, clinical AE data from the Safety Update Report (SUR, Frozen File data 2/16/07) was used to capture the most recent AE profile of raltegravir, given the limited duration of exposure in the current ongoing Phase 3 studies. This difference accounts for small discrepancies between Merck results and FDA results.

Clinical AEs were common in study subjects, occurring in >85% of all subjects receiving either 400 mg raltegravir twice daily or placebo. The majority of AEs were mild to moderate in intensity. The most common AEs occurring in $\geq$ 10% were diarrhea, injection site reactions (due to enfuvirtide use), nausea, and headache, and were observed with similar frequency in each study arm (**Appendix 1**). Adverse events that occurred at

a higher frequency in raltegravir-treated subjects included: rash (5.3% versus 2.5%) and blood creatine phosphokinase increase (3.7% versus 1.1%).

Eighteen treatment-experienced subjects receiving either 400 mg raltegravir twice daily or placebo discontinued therapy because of adverse events (12, 2.4% versus 6, 2.1%). Overall, these 18 subjects reported 25 AEs as reasons for discontinuation, and 7 were considered at least possibly related to study drug. Raltegravir subjects discontinued due to hepatitis in the setting of bronchopneumonia; recurrent cryptococcal meningitis, hepatomegaly, and lactic acidosis, the latter attributed to concomitant NRTIs; renal failure in the setting of dehydration and concomitant tenofovir use; and flatulence. Placebo subjects discontinued due to lipoatrophy and nausea.

In Protocols 018 and 019, potential AIDS-defining conditions (ADC) identified by the investigator and/or sponsor were reviewed by an external adjudicator who was blinded to treatment assignment. A total of 32 subjects experienced 40 ADCs, 15 "presumptive" and 25 "definitive" diagnoses. The majority of ADCs occurred during the double-blind treatment period (N=34). During the double-blind treatment period, the incidence of ADCs was 4.1% (N=19) in the raltegravir arm and 6.3% (N=15) in the placebo arm (**Appendix 2**). Notably, the original NDA submission reported more ADCs in the raltegravir arm compared to placebo (3.0% versus 2.5%); however, with longer follow-up from the SUR, more ADCs were reported in the placebo arm than the raltegravir arm.

Further analyses of deaths, neoplasms, rash, hepatic and creatine kinase abnormalities are presented in more detail in the following sections.

Deaths:

A total of 16 deaths have occurred during treatment with study drugs up to the 2/16/07 database lock for the SUR and are summarized in Table 6. All deaths occurred in HIV-positive treatment-experienced adult subjects. Thirteen out of 595 raltegravir-randomized subjects and three out of 282 placebo-randomized subjects died. Adverse events leading to death occurred in the double-blind phase of the study in 11 subjects, in the open-label phase in 2 subjects, and in 1 subject each in the pre-treatment, post-study, and open-label post virologic failure phase.

Table 6: Summary of Deaths in Phase 2 and 3 Studies Through 2/16/07

AN	Study Drug, Dose	Cause of Death	Study Phase at Time of AE Onset	Total Days on Therapy	Days Post-Therapy to Death
Protocol 05					
3286	Raltegravir, 200 mg	Laceration, Suicide	Post-Treatment Dbl-Blind	4	9
3261	Raltegravir, 200 mg	Lymphadenopathy Splenic abscess Pleural effusion	Open-Label	510	20
3876	Raltegravir, 400 mg	Acute Myocardial Infarction	Open-Label	375	On Tx
3243	Raltegravir, 600 mg	Sepsis, Shock Bradycardia Cardio-respiratory Arrest	Dbl-Blind	137	3
Protocol 018					
7056	Placebo	Mycobacterium avium complex, End Stage AIDS	Pre-Treatment	78	5
7088	Placebo	Urosepsis	Post-Study	86	16
8266	Placebo	Pneumonia	Dbl-Blind	19	6
7005	Raltegravir, 400 mg	B-cell Lymphoma	Dbl-Blind	280	42
8204	Raltegravir, 400 mg	Mycobacterial Infection Lymphoma, Shock Multi-organ Failure	Dbl-Blind	93	2
8325	Raltegravir, 400 mg	Bronchopneumonia Rectal Hemorrhage Septic Shock	Dbl-Blind	73	11
8353	Raltegravir, 400 mg	Cryptococcal Meningitis	Dbl-Blind	78	12
Protocol 019					
15028	Raltegravir, 400 mg	Lymphoma	Dbl-Blind	62	7
16239	Raltegravir, 400 mg	Hepatic Neoplasm Malignant	Dbl-Blind	75	3
16254	Raltegravir, 400 mg	Progressive Multifocal Leukoencephalopathy	OLPVF	185	53
16314	Raltegravir, 400 mg	Aspergillosis Tuberculosis	Post-Treatment Dbl-Blind	31	20
16318	Raltegravir, 400 mg	Coronary Artery Disease	Dbl-Blind	200	On Tx

Source: AE and DEMODATA datasets for Protocol 05, 018, and 019
AN= allocation number, OLPVF = open-label post virologic failure

As noted in Table 6, the majority of deaths were related to infections (N=10), and/or malignancy (N=4). Two deaths were related to cardiac disease and one death was due to suicide. In general, the causes of death were similar to those observed in clinical trials enrolling similar patient populations. No deaths were considered possibly related to raltegravir administration.

An analysis of baseline age, HIV RNA, and CD4+ cell counts was performed to compare the subjects who died to the randomized population (Table 7). Protocols 05, 018, and 019 were evaluated because these protocols enrolled similar populations. All subject deaths occurred in these protocols.

Table 7: Select Demographics of Treatment-Experienced Subjects Who Died During Protocols 005, 018, 019

	Deaths on Raltegravir N=13	Deaths on Placebo N=3	Raltegravir Treated Subjects N=582	Placebo Treated Subjects N=279
Mean (Median)Age	45.4 (47)	52.3 (51)	45.4 (45)	44.8 (44)
Mean (Median) Baseline HIV RNA	192,692 (142,000)	335,407 (254,000)	125,852 (54,450)	125,453 (45,500)
Mean (Median) Baseline CD4*	102.7 (65)	4.7 (4)	170.2 (142)	178.5 (138)
Proportion Baseline CD4 <50*	46.2%	100%	24.1%	26.9%
Mean (Median) Last CD4	136.4 (108)	6.7 (7)	277.9 (241)	252.8 (214)

Source: QHIVRNA, AE (Safety Update Report Frozen File 2/16/07), QCD4CC (Safety Update Report updated Frozen File 2/16/07) datasets for Protocols 05, 018 and 019.
* N=582 for raltegravir treated subjects with baseline CD4 measurements.

Subjects who died were generally sicker at baseline with higher baseline HIV RNA and lower baseline CD4+ cell counts. In addition, last on study CD4+ cell counts were lower.

An analysis of all-cause mortality in HIV treatment-experienced subjects was performed for the double-blind study period. Patients 3261, 3876, 7005 and 16254, all randomized to raltegravir, are excluded from this analysis because death occurred during open-label post virologic failure treatment.

Table 8: Mortality by Treatment Group for Protocols 005, 018, and 019 (HIV Treatment-Experienced Subjects), Double-Blind Phase, Frozen File 2/16/07

	Total Number of Subjects	Total Number of Deaths	Crude Mortality (%)	Person Years at Risk (PYR)	Deaths/ PYR (Mortality Rate, per 100 Patient-Years)
Raltegravir	595	9	1.5	395	9/395 (2.3%)
Placebo	282	3	1.1	150	3/150 (2.0%)

The subjects enrolled in these trials were highly treatment-experienced patients, and the number of reported deaths does not appear to be in excess of the expected mortality rates in this population. The mortality rates observed in raltegravir clinical trials appear to fall within the range observed in other clinical trials enrolling similar patient populations. A relationship between study drug dose, duration, or other factors and the report of deaths among subjects in the safety population is not apparent.

Table 9: Mortality per 100 Patient-Years in Other Clinical Trials

ENF Mortality at Wk 24 Analysis of TORO trials		TPV/RTV Mortality at Wk 24 Analysis of RESIST trials		DRV/RTV Mortality at Wk 24 Analysis of POWER trials	
ENF +/- OBR	OBR	TPV/RTV+/- OBR	CPI/RTV +/- OBR	DRV/RTV+/- OBR	CPI/RTV+/- OBR
10/663 (1.5%)	5/334 (1.5%)	12/582 (2.0%)	7/577 (1.2%)	6/513 (1.2%)	0/124 (0 %)
Mortality rate = 3.3	Mortality rate = 3.3	Mortality rate = 4.5	Mortality rate = 2.6	Mortality rate = 2.6	Mortality rate = 0.0

Source: NDA 21-897 Team Leader Memorandum
ENF = enfuvirtide; OBR = optimized background regimen; TPV/RTV = tipranavir/ritonavir; CPI/RTV = comparator protease inhibitor/ritonavir; DRV/RTV = darunavir/ritonavir

Malignancies

At the time of database lock for the SUR, an imbalance was noted in rate of malignancies observed in raltegravir-treated subjects as compared to control/placebo-treated subjects. A total of 20 subjects experienced 21 malignant neoplasms through the SUR frozen file date. Twenty malignancies in 19 subjects occurred in raltegravir arms (including one subject who switched from placebo to open-label raltegravir, and two subjects from the expanded access program) and one in the efavirenz arm of Protocol 04 (squamous cell carcinoma of the vocal cord). No placebo-treated subject experienced a malignancy.

Malignancies reported in raltegravir-treated subjects were as follows:

- Squamous cell carcinoma: anogenital (4)
  - Anal (1)
  - Carcinoma in situ (CIS) (3)
- Lymphoma (4)
- Squamous cell carcinoma: other (4)
- Kaposi's sarcoma (3)
- Hodgkin's disease (2)
- Rectal cancer (1)
- Hepatic neoplasm malignant (1)
- Basal cell carcinoma (1)

Raltegravir-treated subjects with malignancies appear to have more advanced disease at baseline as evidenced by higher baseline HIV RNA (median HIV RNA 90,600 copies/mL versus 56,050 copies/mL in subjects with and without malignancy) and lower baseline CD4+ cell counts (median CD4+ cell count 34 cells/mm^3 versus 140 cells/mm^3 in subjects with and without malignancy). The malignancy rate for treatment-experienced subjects during the double-blind treatment period was 2.2% (13/595) in the raltegravir arm versus 0% in placebo. Adjusted for 395 patient-exposure years, the rate was 3.3 per 100 patient-exposure years.

Although an imbalance was observed initially in the malignancy rate between raltegravir arms and placebo/control arms, the overall malignancy rate observed in raltegravir-treated subjects was consistent with rates observed in other trials enrolling similar study populations. The identified malignancies are not unexpected in this heavily treatment-experienced HIV population, and no apparent pattern to the types of malignancies was observed. The initial imbalance appeared to reflect more a paucity of malignancies in control/placebo-treated subjects than an increased rate of malignancies in general or an increase in a specific malignancy.

Importantly, a more recent update of malignancies now shows similar rates of malignancies in raltegravir-treated subjects as compared to control/placebo-treated subjects. During the double-blind period 19 patients (2.5%) experienced 21 malignancies in the raltegravir arms and 5 patients (1.5%) experienced 6 malignancies in control/placebo arms. As calculated by the sponsor, the patient-year adjusted incidence rates are 2.32 and 1.92 per 100 patient-years for the raltegravir and control/placebo arms, respectively, resulting in a relative risk of 1.209 with an associated 95% confidence interval of (0.44, 4.14).

<u>Rash:</u>

In the completed Phase 1 studies, there were 17 reports (5.1%, 17/334) of cutaneous adverse events that included the preferred terms dermatitis, pruritus, rash, rash maculo-papular, rash vesicular, and urticaria. None of these AEs resulted in study drug discontinuation and all were mild in intensity. Two (2) of the seven reports of rash and four of the five reports of pruritus were considered either "possibly" or "probably" drug-

related by the investigator. All cases of dermatitis (3 reported) and urticaria (1 reported) were not considered by the investigator to be drug-related. Of the drug-related adverse experience reports of rash, one subject was taking 400 mg of efavirenz alone and the other subject was taking a combination of 400 mg of raltegravir, 500 mg of tipranavir, and 200 mg of ritonavir. Of the drug-related adverse experience reports of pruritus, all 4 subjects were taking raltegravir alone.

Protocol 029 is an ongoing open-label, sequential, 2-period study evaluating the safety, tolerability, and pharmacokinetics of multiple doses of raltegravir administered alone or with multiple does of darunavir and ritonavir. In Period 1, subjects receive 400 mg raltegravir twice daily for four (4) days, immediately followed by Period 2. In Period 2, the same subjects receive 400 mg raltegravir twice daily with 600 mg darunavir and 100 mg ritonavir twice daily for 12 days. At the time of the SUR, four discontinuations due to rash were reported. These four discontinuations were determined by the investigator to be "definitely" related to co-administration of darunavir, ritonavir, and raltegravir. All were Grade 2 (defined as diffuse macular, maculopapular, or morbilliform rash; and/or presence of target lesions), and all occurred during Period 2 after at least nine days of co-administration of darunavir, ritonavir, and raltegravir. One of the subjects who discontinued experienced an SAE. This subject completed Period 1 without complication and initiated Period 2; on Day 12 of darunavir, ritonavir, and raltegravir, the subject developed a diffuse maculopapular rash on the trunk and extremities associated with a temperature of 100.7 °F. The subject was discontinued form the study. Skin biopsy showed superficial perivascular chronic inflammation with rare intravascular neutrophils consistent with a delayed hypersensitivity reaction. Rash was observed in healthy volunteer studies when darunavir was administered with other drugs (Source: Team Leader Memorandum NDA 21-897). Given the temporal relationship of rash onset to darunavir initiation, it is more likely that darunavir was the cause of rash.

No cases of Stevens-Johnson syndrome were found in the entire Phase 2 and 3 AE database. One case of erythema multiforme occurred in the efavirenz arm of Protocol 04.

Analyses of rash events were performed for the Phase 2 and Phase 3 studies using AE data at the time of the SUR. To allow more focused analyses, the following preferred terms were selected: exfoliative rash, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular, and drug eruption.

A total of 87 subjects experienced 91 rash events; none were SAEs. Eight subjects with rash events discontinued from study; seven subjects receiving raltegravir and one subject receiving efavirenz. In all cases, the dates of study discontinuation were greater than 60 days from the onset of the rash event, and the reason for discontinuation was not related to rash.

Four subjects interrupted study therapy due to rash: three subjects receiving raltegravir and one receiving placebo; however, all four subjects resumed study therapy.

The majority of rash events occurred during the double-blind treatment period (N=73); therefore, to allow a more direct comparison among treatment arms, the following analyses of rash events are limited to the double-blind treatment period.

The majority of rash events were mild/moderate in intensity. One subject in the raltegravir arm of Protocol 019 experienced a rash of severe intensity on Day 10 lasting 15 days. The OBT consisted of abacavir, efavirenz, and lamivudine. The rash was assessed by the investigator as probably not study drug related, and study drug and OBT were continued.

A total of 27 rash events were considered to be drug-related by the investigator. Drug-related was defined as definitely, probably, or possibly drug-related. The proportion of subjects with a drug-related rash in the raltegravir arms was 2.4% (18/755) versus 3.1% (10/320) in the placebo/comparator arms. Five of these rash events were considered related to OBT; the rash resolved in 3 subjects with discontinuation of a component of the OBT (fosamprenavir, enfuvirtide, and abacavir).

Twenty-three (23) additional rash events in 20 subjects occurred outside the double-blind treatment period with all subjects receiving raltegravir either in the extension/open-label phase in Protocols 04 and 05, in the interim phase in Protocol 04, or in the OLPVF phase. One subject experienced a second rash in the post-treatment period. None of the rashes were serious in intensity. Eight rash events were considered drug-related by the investigator, including one due to open-label raltegravir occurring 16 days after starting raltegravir with an unchanged OBT.

Six rash events were determined to be OBT-related by the investigator: three due to abacavir (two in the same subject separated by 23 days), one due to amoxicillin, one due to emtricitabine/tenofovir, and one due to delavirdine.

In summary, the majority of rash events in raltegravir-treated subjects were mild to moderate in intensity and no study discontinuations due to rash were reported in the Phase 2 and 3 development program. A clear pattern of rash has not been established and many of the rash events have been confounded by use of concomitant medications associated with rash such as darunavir, abacavir, and delavirdine. All reported rashes in drug-drug interaction Protocol 029, for example, occurred after darunavir was added to raltegravir. In an analysis limited to drug-related rash, no imbalance between the raltegravir and placebo/comparator arms was observed. Therefore, although rash events have occurred during treatment with raltegravir, no consistent pattern is observed and, in general, the events have not led to raltegravir discontinuation.

Hepatic events:

Analyses of hepatic events were performed for the Phase 2 and Phase 3 studies, limited to the double-blind treatment period. The following preferred terms were combined to define “hepatic event”: abdominal pain upper, ascites, gastric varices, haematemesis, oesophageal varices haemorrhage, varices oesophageal, cytolytic hepatitis, hepatic

function abnormal, hepatic pain, hepatic steatosis, hepatitis, hepatitis acute, hepatitis toxic, hepatomegaly, hepatosplenomegaly, hepatotoxicity, hyperbilirubinemia, jaundice, liver tenderness, portal hypertension, portal hypertensive gastropathy, ALT increased, AST increased, blood alkaline phosphatase increased, blood bilirubin increased, blood unconjugated bilirubin increased, GGT increased, spleen palpable, hepatic neoplasm malignant.

A total of 129 subjects experienced 189 hepatic events. There was no apparent dose-response relationship; therefore, the raltegravir dose groups are combined.

Table 10: Hepatic Events in Phase 2 and Phase 3 Studies, Double-Blind Treatment Period

Protocol	Raltegravir[1]		Placebo/Comparator[2]	
	n	%	n	%
04	33	20.6%	10	26.3%
05	37	27.8%	2	5.0%
018	37	15.9%	15	12.7%
019	37	16.1%	18	15.1%

Source: AE (Safety Update Report Frozen File 2/16/07) datasets for Protocols 04, 05, 018 and 019.
[1] All RALTEGRAVIR doses: Protocol 04 N=160, Protocol 05 N=133, Protocol 018 N=232, Protocol 019 N=230
[2] Placebo/Comparator: Protocol 04 N=38, Protocol 05 N=45, Protocol 018 N=118, Protocol 019 N=119

A higher rate of laboratory-related hepatic events was reported in the raltegravir arm; however, the remainder of the hepatic AEs were balanced between the two groups.

Seven hepatic AEs occurring in five subjects were reported as SAEs, all occurred in the Phase 3 studies: one in the placebo arm (hepatitis toxic in the setting of tipranavir therapy) and four in the raltegravir arm (two subjects with hepatitis in the setting of pneumonia, one subject with history of hepatomegaly incidentally discovered to have portal hypertension and esophageal varices, and one subject with hepatocellular carcinoma attributed to hepatitis B). The subject diagnosed with hepatocellular carcinoma died.

Liver enzyme data submitted at the time of NDA submission were examined for hepatic abnormalities. Table 11 shows the rates of AST, ALT, alkaline phosphatase and bilirubin abnormalities from the raltegravir and placebo arms of the Phase 2 and Phase 3 studies.

Table 11: Grade 1 – 4 AST, ALT, Alkaline Phosphatase, Total Bilirubin Laboratory Data in Phase 2 and Phase 3 Studies, Double-Blind Treatment Period

Laboratory Parameter	Limit	Treatment Arm			
		Raltegravir N=755		Placebo N=320	
		n	%	n	%
Serum ALT (IU/L)					
Grade 1	1.25-2.5 x ULN	139	18.4%	72	22.5%
Grade 2	2.6-5.0 x ULN	44	5.8%	24	7.5%
Grade 3	5.1-10.0 x ULN	15	2.0%	6	1.9%
Grade 4	>10.0 x ULN	3	0.4%	1	0.3%
Serum AST (IU/L)					
Grade 1	1.25-2.5 x ULN	135	17.9%	86	26.9%
Grade 2	2.6-5.0 x ULN	53	7.0%	17	5.3%
Grade 3	5.1-10.0 x ULN	10	1.3%	7	2.2%
Grade 4	>10.0 x ULN	5	0.7%	1	0.3%
Serum Alkaline Phosphatase (IU/L)					
Grade 1	1.25-2.5 x ULN	66	8.7%	32	10.0%
Grade 2	2.6-5.0 x ULN	12	1.6%	1	0.4%
Grade 3	5.1-10.0 x ULN	3	0.4%	3	0.9%
Grade 4	>10.0 x ULN	2	0.3%	1	0.4%
Total Serum Bilirubin (mg/dL)					
Grade 1	1.1-1.5 x ULN	40	5.3%	11	3.4%
Grade 2	1.6-2.5 x ULN	45	6.0%	18	5.6%
Grade 3	2.6-5.0 x ULN	23	3.0%	7	2.2%
Grade 4	>5.0 x ULN	5	0.7%	0	0

Source: FDALABGD dataset for Protocols 04, 05, 018, 019

Overall, the rates of liver enzyme elevations were similar between the raltegravir and placebo arms. A higher rate of Grade 3/4 total bilirubin was observed in the raltegravir arm. The majority of subjects with elevated total bilirubin levels had elevated indirect bilirubin (85.7%, 24/28), and all of these subjects were receiving atazanavir as part of the OBT. Additional analyses are ongoing to identify and define potential Hy's Law cases.

Increased Creatine Kinase:

An analysis was performed for elevated creatine kinase (CK) and associated musculoskeletal AEs. This analysis used data submitted at the time of NDA submission from Phase 2 and 3 studies, limited to the double-blind treatment period. A total of 63 subjects experienced Grade 2 - Grade 4 CK elevations, displayed in Table 12. For the purpose of this analysis, all raltegravir doses were combined as no dose-response relationship was observed for elevated CK levels.

Table 12: Elevated Creatine Kinase (CK) in Phase 2 and Phase 3 Studies, Double-Blind Treatment Period

CK Grade	Limit	Raltegravir N=755		Placebo/Comparator N=320	
		n	%	n	%
Grade 2	6.0–9.9 x ULN	18	2.4%	5	1.6%
Grade 3	10.0–19.9 x ULN	16	2.1%	5	1.6%
Grade 4	≥20.0 x ULN	16	2.1%	3	0.9%
All Grades 2-4		50	6.6%	13	4.1%

Source: FDALABGD dataset for Protocols 04, 05, 018, and 019

Overall, there was a small increase in the rates of CK elevations in the raltegravir arms compared to the placebo arms.

The AE database for Protocols 2 and 3 was examined for potential AEs associated with elevated CK, including: arthralgia, myalgia, myositis, blood creatine phosphokinase increased, rhabdomyolysis, musculoskeletal pain, muscle fatigue, muscle strain. The following table reports the rates of elevated CK values, defined as Grade 1 or higher, and potential CK-related AEs. Of note, no AEs were associated with Grade 1 CK levels.

Table 13: Number (%) of Subjects with Potential Creatine Kinase (CK)-Related Adverse Experiences in Phase 2 and Phase 3 Studies, Double Blind Treatment Period

Preferred Term	CK Grade	Raltegravir N=755		Placebo/Comparator N=320	
		n	%	n	%
Blood CPK Increased					
	Grade 2	6	0.8%	1	0.3%
	Grade 3	5	0.7%	1	0.3%
	Grade 4	14	1.9%	1	0.3%
	All Grades	25	3.3%	3	0.9%
Myalgia					
	Grade 3	1	0.1%	0	0
	Grade 4	1	0.1%	2	0.6%
	All Grades	2	0.3%	2	0.6%
Myositis					
	Grade 2	1	0.1%	0	0
	Grade 4	1	0.1%	0	0
	All Grades	2	0.3%	0	0
Arthralgia					
	Grade 3 (All)	2	0.3%	0	0

The association between CK elevations and the clinical AEs of myalgia, myositis, and arthralgia were balanced between the two groups. There were no reported SAEs or study discontinuations due to elevated CK levels. The "blood CPK increased" preferred term occurred at a higher rate in the raltegravir arms; however, this preferred term

categorization was determined by the investigator and the laboratory data provides a more accurate reflection of the CK data.

Overall, there was a modest increase in Grade 2 – 4 CK elevations in the raltegravir arm; however, association with clinical symptoms was balanced between the two groups. In addition, no SAEs or study discontinuations were associated with elevated CK levels.

In conclusion, raltegravir appeared to be well-tolerated in the Phase 2 and Phase 3 clinical studies with relatively few subjects discontinuing for adverse events. No clinically significant imbalance was observed in mortality rates and ADCs. A higher number of malignancies was observed in raltegravir-treated subjects initially; however, the imbalance appeared to reflect more a paucity of malignancies in control/placebo-treated subjects than an increased rate of malignancies in general or an increase in a specific malignancy. Analyses of rash, hepatic, and CK-related AEs did not detect a specific safety signal associated with raltegravir and additional analyses pertaining to hepatic events are ongoing. Based on review of the available safety data, the benefits of raltegravir in HIV-1 treatment-experienced subjects outweigh the currently identified risks.

Appendix 1: Most Common AEs by MedDRA Preferred Terms Reported in ≥ 2% of Subjects Without Regard to Causality (Protocols 05, 018, 019 400 mg Twice Daily Raltegravir and Placebo arms), Frozen File Date 2/16/07

	Raltegravir 400 mg bid N=507		Placebo N=282		Total N=789	
	n	**%**	**n**	**%**	**n**	**%**
Subjects with one or more AE	**438**	**86.4%**	**247**	**87.5%**	**685**	**86.8%**
Diarrhoea	84	16.6%	55	19.5%	139	17.6%
Injection site reaction	**52**	**10.3%**	**28**	**9.9%**	**80**	**10.1%**
Nausea	50	9.9%	40	14.2%	90	11.4%
Headache	49	9.7%	33	11.7%	82	10.4%
Fatigue	**40**	**7.9%**	**13**	**4.6%**	**53**	**6.7%**
Vomiting	35	6.9%	23	8.2%	58	7.4%
Nasopharyngitis	**31**	**6.1%**	**11**	**3.9%**	**42**	**5.3%**
Upper respiratory infection	27	5.3%	16	5.7%	43	5.4%
Rash	**27**	**5.3%**	**7**	**2.5%**	**34**	**4.3%**
Abdominal pain	**26**	**5.1%**	**11**	**3.9%**	**37**	**4.7%**
Pyrexia	25	4.9%	29	10.3%	54	6.8%
ALT increased	**24**	**4.7%**	**5**	**1.8%**	**29**	**3.7%**
Cough	**24**	**4.7%**	**8**	**2.8%**	**32**	**4.1%**
AST increased	**23**	**4.5%**	**7**	**2.5%**	**30**	**3.8%**
Herpes zoster	**21**	**4.1%**	**2**	**0.7%**	**23**	**2.9%**
Herpes simplex	20	3.9%	12	4.3%	32	4.1%
Dizziness	**20**	**3.9%**	**6**	**2.1%**	**26**	**3.3%**
Insomnia	**20**	**3.9%**	**10**	**3.5%**	**30**	**3.8%**
Blood CPK increased	**19**	**3.7%**	**3**	**1.1%**	**22**	**2.8%**
Blood triglycerides increased	**19**	**3.7%**	**10**	**3.5%**	**29**	**3.7%**
Lymphadenopathy	**17**	**3.4%**	**8**	**2.8%**	**25**	**3.2%**
Bronchitis	17	3.4%	10	3.5%	27	3.4%
Asthenia	16	3.2%	11	3.9%	27	3.4%
Sinusitis	**16**	**3.2%**	**7**	**2.5%**	**23**	**2.9%**
Pain in extremity	**16**	**3.2%**	**7**	**2.5%**	**23**	**2.9%**
Flatulence	15	3.0%	9	3.2%	24	3.0%
Influenza	15	3.0%	5	1.8%	20	2.5%
Blood cholesterol increased	**15**	**3.0%**	**6**	**2.1%**	**21**	**2.7%**
Gastroenteritis	**14**	**2.8%**	**5**	**1.8%**	**19**	**2.4%**
Arthralgia	**14**	**2.8%**	**7**	**2.5%**	**21**	**2.7%**
Pruritus	**14**	**2.8%**	**6**	**2.1%**	**20**	**2.5%**
Abdominal distension	13	2.6%	8	2.8%	21	2.7%
Depression	13	2.6%	8	2.8%	21	2.7%
Hypertension	**13**	**2.6%**	**4**	**1.4%**	**17**	**2.2%**
Abdominal pain upper	12	2.4%	11	3.9%	23	2.9%
Night sweats	12	2.4%	8	2.8%	20	2.5%

Anogenital warts	11	2.2%	4	1.4%	15	1.9%
Folliculitis	11	2.2%	2	0.7%	13	1.6%
Pneumonia	11	2.2%	7	2.5%	18	2.3%
Anorexia	**11**	**2.2%**	**6**	**2.1%**	**17**	**2.2%**
Anaemia	10	2.0%	8	2.8%	18	2.3%
Constipation	10	2.0%	1	0.4%	11	1.4%
Blood creatinine increased	**10**	**2.0%**	**5**	**1.8%**	**15**	**1.9%**
Back pain	10	2.0%	7	2.5%	17	2.2%
Myalgia	10	2.0%	7	2.5%	17	2.2%
Skin papilloma	10	2.0%	7	2.5%	17	2.2%
Pharyngolaryngeal pain	9	1.8%	11	3.9%	20	2.5%
Muscle spasms	8	1.6%	7	2.5%	15	1.9%
Oral candidiasis	6	1.2%	15	5.3%	21	2.7%
Urinary tract infection	6	1.2%	6	2.1%	12	1.5%
Weight decreased	5	1.0%	7	2.5%	12	1.5%
Blood phosphorous decreased	4	0.8%	6	2.1%	10	1.3%
Neutrophil count decreased	4	0.8%	6	2.1%	10	1.3%
Oesophageal candidiasis	3	0.6%	6	2.1%	9	1.1%
Eczema	3	0.6%	6	2.1%	9	1.1%

Appendix 2: AIDS Defining Conditions (ADC) in Phase 3 Studies, as of Frozen File Date 2/16/07

	Raltegravir 400 mg bid N=462		**Placebo N=237**	
	n	%	n	%
All ADCs	19	4.1%	15	6.3%
Esophageal candidiasis[1]	4	0.9%	6	2.5%
Lymphoma[2]	3	0.6%	0	-
Cytomegalovirus[3]	2	0.4%	3	1.3%
Herpes simplex[4]	2	0.4%	0	-
Kaposi's sarcoma	2	0.4%	0	-
Cryptococcal meningitis	2	0.4%	0	-
Mycobacterium avium complex	1	0.2%	2	0.8%
Encephalopathy	1	0.2%	0	-
Microsporidiosis	1	0.2%	0	-
Recurrent pneumonia	1	0.2%	1	0.4%
Cryptosporidiosis	0	-	2	0.8%
Salmonella bacteremia	0	-	1	0.4%

Source: QARF (Safety Update Report Frozen File 2/16/07) datasets for Protocols 018 and 019.

[1]Esophageal candidiasis includes recurrent esophageal candidiasis (N=1)

[2]Lymphoma includes B-cell (N=1) and T-cell lymphoma (N=1)

[3]Cytomegalovirus (CMV) includes CMV colitis (N=2), retinitis (N=2), and recurrent retinitis (N=1)

[4]Herpes simplex includes chronic ulcers (N=1) and esophagitis (N=1)