CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-145

MEDICAL REVIEW

Team Leader's Memorandum

NDA:	22-145
Drug and Indication:	ISENTRESS (raltegravir), in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.
Proposed Dose:	400 mg twice daily
Dosage Form:	400 mg tablet
Letter Date: **Stamp Date**:	April 13, 2007 April 13, 2007
Date of Memorandum:	October 11, 2007

Background

Raltegravir (RAL, tradename Isentress) is a novel HIV-1 integrase inhibitor under development by the Applicant (Merck) for the treatment of HIV-1 infection. 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 heavily treatment-experienced HIV-infected subjects after 16 and 24 weeks of treatment.

The clinical development package submitted to support the efficacy of raltegravir consists primarily of data from four clinical studies, two dose-finding studies and two pivotal studies. Protocol 004 is a two part dose-finding study in treatment-naïve subjects and Protocol 005 is a dose-finding study in treatment-experienced subjects. The two large pivotal Phase 3 studies were initiated following dose selection.

The pivotal Phase 3 studies, Protocol 018 and Protocol 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 study site locations. 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 antiretroviral therapy as documented by HIV RNA >1,000 copies/mL while on stable antiretroviral medications (ARVs) with documented resistance to at least 1 drug in each of 3 classes of licensed oral ARVs (NNRTI, NRTI, and PI).

FDA agreed to accept Week 16 data from these Phase 3 studies for NDA submission due to the robust antiviral activity observed in the Phase 2 dose-finding studies. Week 16 data was supported by Week 24 data from about 60% of randomized study subjects.

Inclusion Criteria, Patient Demographics and Baseline Characteristics

Table 1 summarizes select patient demographics and baseline patient characteristics from Protocols 018 and 019. Randomization was stratified by enfuvirtide use and protease inhibitor resistance; no significant imbalances were observed between raltegravir and placebo arms within each study; therefore, raltegravir and placebo arms are combined in the table.

TABLE 1 – 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 1 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)

Source: FDA Raltegravir Advisory Committee Backgrounder

[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.

Efficacy Analyses

Select efficacy analyses are summarized in Table 2. The primary endpoint for Protocol 018 and Protocol 019 is HIV-1 RNA <400 copies/mL at Week 16. Over 75% of raltegravir-treated subjects achieved a viral load of <400 copies/mL at Week 16 versus 40% in placebo; the treatment difference was highly statistically significant for each protocol ($p<0.001$). In addition, over 60% of raltegravir-treated subjects achieved a viral load <50 copies/mL compared with 35% in placebo. The mean increase in CD4+ cell count from baseline in raltegravir-treated subjects was over twice that of placebo subjects. Week 24 analyses support the Week 16 results.

Table 2: FDA Week 16 Efficacy Analyses for Protocols 018 and 019 (All Treated)[1]

	Protocol 018		Protocol 019	
	Raltegravir N=232	Placebo N=118	Raltegravir N=230	Placebo N=119
<400 copies/mL – n (%)*	179 (77)	49 (42)	180 (78)	51 (43)
<50 copies/mL– n (%)	146 (63)	40 (34)	143 (62)	43 (36)
HIV-1 RNA change from baseline (log_{10}) – mean (SD)	-2.3 (1.1)	-1.0 (1.3)	-2.4 (1.2)	-1.3 (1.3)
CD4+ cell count change from baseline (cells/mm^3) – mean (SD)	81 (94)	32 (73)	84 (96)	39 (74)

Source: Statistical Review of NDA 22-145 by Dr. Karen Qi

*p value <0.001 for each protocol

[1]If the measurement at a visit was missing and the one at next visit was available, then the one at the next visit was used. If the one at the next visit was missing as well, then the one at the previous visit was carried forwards to Week 16. For example, if a patient did not have HIV RNA value at Week 16, but had one at Week 24, then the one at Week24 was used to impute the missing measurement at Week 16. If HIV RNA at Week 24 was missing as well, then Week 12 RNA level was carried forwards to Week 16.

Select Subgroup Analyses: Number of Active PIs in OBT, PSS, GSS

Over 60% of raltegravir-treated subjects achieved a virologic response of <400 copies/mL when no active PIs were in the OBT compared with <20% in placebo. In addition, over 50% of raltegravir-treated subjects with a PSS or GSS of zero achieved <400 copies/mL compared with <10% in placebo. As the number of active agents in the background regimen increased, the treatment effect between the two groups diminished.

Table 3 - FDA Week 16 Efficacy Analyses for Protocols 018 and 019
HIV-1 RNA <400 copies/mL (All Treated):
Number of Active PIs, PSS, and GSS

	Protocol 018		Protocol 019		Total	
Responders / Evaluable (%)	**RAL**	**Placebo**	**RAL**	**Placebo**	**RAL**	**Placebo**
Number of active PI in OBT by phenotypic resistance test						
0	70/100 (70)	9/55 (16)	40/66 (61)	7/42 (17)	110/166 (66)	16/97 (16)
1 or more	102/123 (83)	39/61 (64)	135/155 (87)	43/76 (57)	237/278 (85)	82/137 (60)
Missing	7/9 (78)	1/2 (50)	5/9 (56)	1/1 (100)	12/18 (67)	2/3 (67)
Phenotypic Sensitivity Score (PSS)						
0	25/44 (57)	1/21 (5)	14/23 (61)	1/23 (4)	39/67 (58)	2/44 (5)
1	52/67 (78)	17/39 (44)	57/78 (73)	12/32 (38)	109/145 (75)	29/71 (41)
2	61/67 (91)	14/33 (42)	63/75 (84)	17/33 (52)	124/142 (87)	31/66 (47)
3 or more	33/44 (75)	14/21 (67)	37/41 (90)	18/27 (67)	70/85 (82)	32/48 (67)
Missing	8/10 (80)	3/4 (75)	9/13 (69)	3/4 (75)	17/23 (74)	6/8 (75)
Genotypic Sensitivity Score (GSS)						
0	40/70 (57)	4/34 (12)	23/45 (51)	2/31 (6)	63/115 (55)	6/65 (9)
1	65/76 (86)	21/48 (44)	84/102 (82)	20/48 (42)	149/178 (84)	41/96 (43)
2	53/57 (93)	16/22 (73)	47/54 (87)	21/27 (78)	100/111 (90)	37/49 (76)
3 or more	18/26 (69)	8/13 (62)	22/25 (88)	5/10 (50)	40/51 (78)	13/23 (57)
Missing	3/3 (100)	0/1 (0)	4/4 (100)	3/3 (100)	7/7 (100)	3/4 (75)

Source: Statistical Review of NDA 22-145 by Dr. Karen Qi

Select Subgroup Analyses: Use of Enfuvirtide and/or Darunavir in OBT
Approximately 60% of raltegravir-treated subjects without use of either ENF or DRV achieved HIV-1 RNA <400 copies/mL at Week 16 compared to approximately 25% in placebo. Reflecting the PSS and GSS data, the treatment difference between raltegravir and placebo groups decreased when initial use of both agents was incorporated into the background regimen; however, 95-96% of raltegravir-treated subjects in this group achieved virologic response.

Table 4 - FDA Week 16 Efficacy Analyses for Protocols 018 and 019
HIV-1 RNA <400 copies/mL (All Treated)
Use of Enfuvirtide (ENF) and/or Darunavir (DRV) in the OBT

	Protocol 018		Protocol 019		Total	
Responders / Evaluable (%)	**RAL**	**Placebo**	**RAL**	**Placebo**	**RAL**	**Placebo**
Naïve ENF use and naïve DRV use	19/20 (95)	8/9 (89)	24/25 (96)	12/14 (86)	43/45 (96)	20/23 (87)
Naïve ENF use and no DRV use	26/28 (93)	9/15 (60)	15/18 (83)	6/10 (60)	41/46 (89)	15/25 (60)
No ENF use and naïve DRV use	23/28 (82)	9/16 (56)	48/53 (91)	18/33 (55)	71/81 (88)	27/49 (55)
No ENF use and no DRV use	82/109 (75)	19/55 (35)	60/88 (68)	7/38 (18)	142/197 (72)	26/93 (28)

Source: Statistical Review of NDA 22-145 by Dr. Karen Qi

Clinical Resistance Analyses
The following section summarizes Dr. Sung Rhee's clinical resistance analyses. Please see Dr. Rhee's review for additional details.

In an as-treated analysis of the Phase 3 studies, paired amino acid sequences of HIV-1 integrase (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

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.

Summing up, 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.

Summary of Safety Review

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 or higher was received by 41 treatment-naïve and 651 treatment-experienced subjects for any treatment duration; 592 of these subjects received the proposed dose for at least 24 weeks.

Overall, raltegravir appeared to be well tolerated with few study discontinuations due to adverse events. While clinical adverse events (AEs) were common in study subjects, occurring in >85% of all subjects receiving either 400 mg raltegravir twice daily or placebo, the majority were mild to moderate in intensity. The most common AEs occurring in ≥ 10% of subjects were diarrhea, injection site reactions (ISRs) due to enfuvirtide use, nausea and headache, and were observed with similar frequency in raltegravir and placebo arms. In dose-finding treatment-naïve Protocol 004 and dose-finding treatment-experienced Protocol 005, no relationships with dose and any adverse event were observed, with the exception of rash.

In Phase 3 studies, adverse events that occurred at a higher frequency in raltegravir-treated subjects as compared to placebo-treated subjects included rash (5.3% versus

2.5%). 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 was not established and many of the rash events were confounded by use of concomitant medications associated with rash such as darunavir, abacavir, and delavirdine. Four study discontinuations due to rash were reported from Phase 1 drug-drug interaction Protocol 029; however, all events occurred after darunavir was added to raltegravir. In summary, although rash events occurred during treatment with raltegravir, no consistent pattern was observed and, in general, the events did not result in raltegravir discontinuation.

Another event observed at higher frequency in raltegravir-treated subjects was Grade 2-4 blood creatine phosphokinase (CK) elevation (6.8% versus 3.9%); however, no SAEs or study discontinuations were associated with elevated CK levels in Phase 2 and 3 studies. A minority of raltegravir-treated subjects briefly interrupted study therapy due to elevated CK levels, but temporal correlation with confounding factors such as ISRs or use of trimethoprim/sulfamethoxazole or fibrates makes attributing an association with raltegravir use difficult. A total of 3 cases of rhabdomyolysis and 2 cases of myopathy were reported in the Phase 3 and Expanded Access Programs. One subject appeared to have a positive rechallenge with elevated CK levels after restarting their raltegravir-based regimen; however, the subject was asymptomatic and CK values normalized without interrupting study therapy. Although a causal relationship with raltegravir is unclear at this time, the Applicant has agreed to include language regarding CK laboratory data, rhabdomyolysis and myopathy in the package insert. Longer term data and safety monitoring will be collected as a post-marketing commitment to allow further characterization of any potential relationship between raltegravir, elevated CK levels and clinical adverse events.

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, of which 7 were considered at least possibly related to study drug. These adverse events included, for raltegravir subjects, 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.

Malignancies

At the time of database lock for the SUR, an imbalance was noted in malignancies observed in raltegravir-treated subjects as compared to control/placebo-treated subjects. Twenty malignancies were reported in 19 raltegravir-treated subjects (including one subject who switched from placebo to open-label raltegravir, and two subjects from the expanded access program), while only one malignancy was reported in a control subject from the efavirenz arm of Protocol 004. No placebo-treated subject experienced a malignancy.

Although an imbalance in malignancies between treatment arms was observed, the overall malignancy rate in raltegravir-treated subjects was consistent with rates observed in other trials enrolling similar study populations. The identified malignancies are expected in this heavily treatment-experienced HIV population (i.e. Kaposi's sarcoma, lymphoma) and no apparent pattern to the types of malignancies was observed. 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.

An update of malignancies occurring by a July 9, 2007 data lock was submitted to FDA in August 2007. By this time, 36 malignancies had been reported in 31 subjects: 30 in raltegravir-treated subjects (including 2 in subjects switching from placebo to OLPVF) and 6 in control; in summary, the imbalance observed initially appears to have decreased with additional follow-up.

Deaths

A total of 16 deaths occurred during treatment with study drugs up to SUR data lock. All deaths occurred in treatment-experienced subjects. Thirteen out of 595 raltegravir-randomized subjects and 3 out of 282 placebo-randomized subjects died. Subjects who died were more advanced at baseline with higher baseline HIV-1 RNA, lower baseline CD4+ cell counts, and lower last on study CD4+ cell counts compared with surviving subjects. The mortality rate per 100 patient-years for raltegravir-treated subjects was similar to rates observed in other clinical trials enrolling similar study populations.

The majority of deaths were related to either opportunistic infection (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 are similar to those observed in clinical trials enrolling similar patient populations. No deaths are considered possibly related to raltegravir administration.

Conclusion

I agree with the primary reviewer's conclusion. Raltegravir 400 mg twice daily is safe and effective in combination with other antiretroviral agents for the treatment of HIV-1 infection in antiretroviral treatment-experienced adult patients with limited treatment options. The risks associated with taking this medication are balanced by the robust efficacy observed in this population. Raltegravir is not indicated for treatment-naïve patients or for pediatric patients.

Kendall A. Marcus, M.D.
Medical Team Leader

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/s/

Kendall Marcus
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MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-145
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Letter Date	April 13, 2007
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PDUFA Goal Date	October 12, 2007
Reviewer Name	Sarah M. Connelly, MD
Review Completion Date	October 11, 2007
Established Name	Raltegravir
(Proposed) Trade Name	ISENTRESS™
Therapeutic Class	Integrase inhibitor
Applicant	Merck
Priority Designation	P
Formulation	400 mg tablet
Dosing Regimen	400 mg, twice daily
Indication	Treatment of HIV-1 infection
Intended Population	HIV-1 treatment-experienced adults

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Accelerated approval of raltegravir is recommended for the management of HIV-1 infected treatment-experienced adults. This recommendation is based on the finding of virologic suppression in a patient population with few remaining treatment options. The efficacy of raltegravir was demonstrated with Week 16 results of two large double-blind randomized placebo-controlled trials, Protocols 018 and 019. Over 75% of raltegravir-treated subjects achieved an HIV-1 viral load <400 copies/mL at Week 16 versus approximately 40% of placebo-treated subjects; the treatment difference was statistically significant for each protocol. Analyses of Week 24 data, available for approximately 60% of subjects supported the Week 16 results.

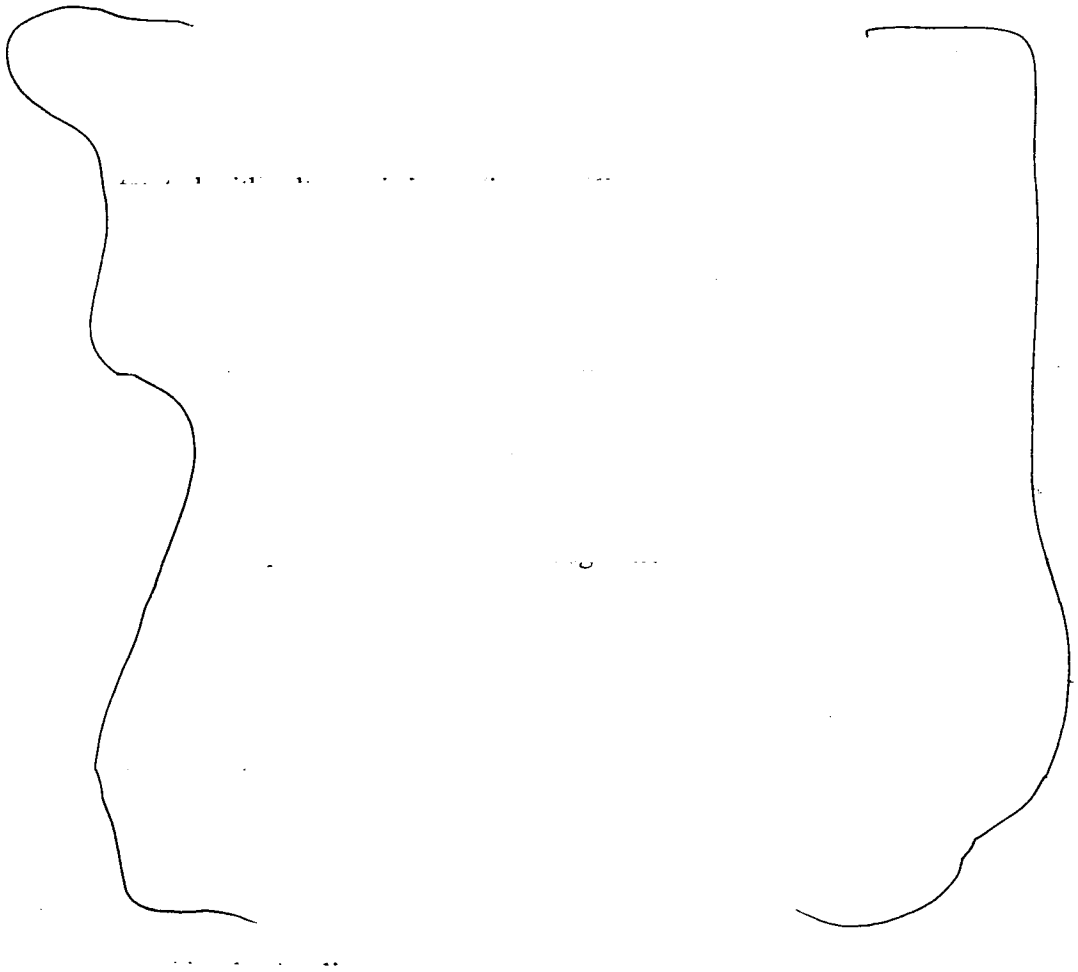
Overall, raltegravir appeared to be well tolerated with few subjects discontinuing for adverse events considered potentially related to raltegravir use. One safety concern observed during the clinical development of raltegravir was an imbalance in the rate of malignancy between raltegravir and control subjects; however, with longer follow up the imbalance initially observed diminished. Overall, rash events were more common in raltegravir arms (7.2%) as compared to control arms (5.3%); however, no raltegravir-treated subject discontinued for rash in any Phase 2 or 3 trial, no clear pattern was observed and the majority were mild/moderate in intensity. A modest increase in Grade 2 – 4 CK elevations was observed in raltegravir arms as compared to control; however, association with clinical symptoms was balanced between the two groups. A total of 3 cases of rhabdomyolysis and 2 cases of myopathy have been reported in the Phase 3 and Expanded Access Programs. Several raltegravir-treated subjects temporarily interrupted therapy due to CK elevations; however, all were able to resume raltegravir without recurrence. In addition, more raltegravir-treated subjects reported herpes zoster as compared to control subjects.

In summary, based on the demonstrated virologic efficacy of raltegravir in treatment-experienced adults with HIV-1 and supportive safety data, accelerated approval under 21 CFR 312 subpart H is recommended.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The FDA Office of Surveillance and Epidemiology was consulted to review the Applicant's proposed Risk Management Plan. OSE concluded the risks of immune reconstitution syndrome (IRS), drug resistance, and drug interactions are common to antiretrovirals and the Applicant's intended pharmacovigilance plan is appropriate to monitor those events.



1.2.2 Required Phase 4 Commitments

The following post-marketing commitments (PMCs) have been proposed and have been accepted by the Applicant.

Accelerated Approval PMCs

1. By December 31, 2008, submit study reports for Week 48 data analyses for the ongoing Phase 3 Studies 018 and 019.
2. Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric subjects from 2 to 18 years of age. This study will determine raltegravir exposure (pharmacokinetic profile) followed by 24 weeks of dosing. Efficacy will be based on viral load reduction through 24 weeks of dosing and safety will be monitored for a minimum of 24 weeks to support raltegravir dose selection, safety, and efficacy in this population.

Protocol Submission Date: Ongoing
Final Study Report Submission Date: June 30, 2011

3. Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric subjects from 4 weeks to 2 years of age. This study will determine raltegravir exposure (pharmacokinetic profile) followed by 24 weeks of dosing. Efficacy will be based on viral load reduction through 24 weeks of dosing and safety will be monitored for a minimum of 24 weeks to support raltegravir dose selection, safety, and efficacy in this population.
   Protocol Submission Date: September 30, 2008
   Final Study Report Submission Date: June 30, 2011

PMCs

1. Submit Week 96 reports and datasets for Protocols 018 and 019.
   Protocol Submission Date: Completed
   Week 96 Reports and Datasets Submission Date: December 31, 2009
2. Conduct a five-year follow-up for subjects in Protocols 018 and 019 focusing on safety evaluations, which should include but not be limited to assessment of mortality, malignancy, herpes zoster, creatine kinase elevations, and other adverse events.
   Protocol Submission Date: May 31, 2008
   Final Study Report Submission Date: December 31, 2012
3. Submit Week 48 reports and datasets for Protocol 021.
   Protocol Submission Date: Completed
   Week 48 Reports and Datasets Submission Date: March 31, 2009
4. Conduct a non-interventional, prospective, observational study to provide additional safety data on important clinical events. The duration of the study will be 5 years from initiation of the study; data will be reviewed on an interim basis every 6 months during the course of the study.
   Protocol Submission Date: March 31, 2008
   Final Study Report Submission Date: December 31, 2014
5. Complete the ongoing carcinogenicity study in mice and submit the final report.
   Protocol Submission Date: Completed
   Final Study Report Submission Date: July 25, 2008
6. Complete the ongoing carcinogenicity study in rats and submit the final report.
   Protocol Submission Date: Completed
   Final Study Report Submission Date: August 15, 2008
7. Determine the susceptibility in cell culture of HIV-1 harboring Y143C/H/R, individually and in combination with L74M, E92Q, T97A, G163R, and S230R in a common genetic background.
   Protocol Submission Date: December 31, 2007
   Final Study Report Submission Date: September 30, 2008
8. Evaluate the contributions of L74M/R, T97A, V151I, G163R, H183P, Y226C/D/F/H, and S230N/R substitutions on raltegravir resistance by site-directed mutagenesis.

9. Conduct a 48-week, open-label, non-randomized, single arm, diversity cohort study in 200 HIV-positive patients to assess efficacy and safety. At least 50% of the total enrollment will be African American patients and at least 25% of the total enrollment will be female patients in order to characterize the efficacy and safety of raltegravir in a population that closely reflects the United States HIV-1 infected patient population.
   Protocol Submission Date: July 31, 2008
   Final Study Report Submission Date: March 31, 2012
10. Conduct an in vitro study (e.g., in human hepatocytes) to evaluate the relative UGT1A1 induction potency of phenytoin, phenobarbital, rifabutin, and rifampin using raltegravir as a probe substrate.
   Protocol Submission: December 31, 2007
   Final Report Submission: November 30, 2008
11. Conduct an in vitro study (e.g., in human hepatocytes) to evaluate the potential of raltegravir to induce CYP1A2 and CYP2B6.
   Protocol Submission: December 31, 2007
   Final Report Submission: November 30, 2008

1.2.3 Other Phase 4 Requests

The following post-marketing requests are also under negotiation with the Applicant.

1. Perform genotypic and genotypic analyses of HIV-1 from patients who experience virologic failure to raltegravir (plus OBT) therapy out to 48 and 96 weeks in ongoing clinical trials.
2. Contact leading investigators studying RAG1/2 recombinase in a timely fashion about conducting studies to evaluate raltegravir's potential for inhibiting RAG1/2, and provide raltegravir to interested researchers.
3. Characterize phenotypically and genotypically virus selected in cell culture for resistance to raltegravir using distantly related non-clade B HIV-1 isolates.
   Protocol Submission Date: December 31, 2007
   Final Study Report Submission Date: December 31, 2009
4. Submit the final reports of the UGT1A1 polymorphism study, the rifampin plus 800 mg raltegravir study, and the omeprazole-raltegravir drug interaction study.
5. Conduct a drug interaction study of rifabutin and raltegravir.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Raltegravir is an HIV-1 integrase inhibitor, blocking the strand transfer step of the integration process. It is a new molecular entity, and the Applicant has proposed that it be indicated, in combination with other antiretroviral agents, for treatment-experienced adult patients infected with HIV-1. Data from Protocols 018 and 019 formed the principal basis for characterizing the safety and efficacy of raltegravir in treatment-experienced patients with HIV-1 infection. Pooled

analyses of the study data from these two trials were a prominent component of this review as the trials had identical designs with the exception of different geographic locations. Two dose-finding Phase 2 studies provided additional efficacy and safety data. Protocol 004 was performed in HIV-1 infected treatment-naïve subjects and compared 100, 200, 400, and 600 mg twice daily raltegravir doses to efavirenz, each in combination with tenofovir (TDF) and lamivudine. Protocol 005 was performed in HIV-1 treatment-experienced subjects and compared 200, 400, and 600 mg twice daily raltegravir doses with placebo, each in combination with an optimized background regimen.

1.3.2 Efficacy

Raltegravir was superior to placebo with respect to virologic suppression in treatment-experienced subjects with HIV-1 using multiple endpoints. A total of 77% of subjects in Protocol 018 and 78% subjects in Protocol 019 achieved HIV-1 viral load <400 copies/mL at Week 16 compared to 42% and 43% in the placebo arms, respectively. Over 60% of raltegravir-treated subjects achieved viral load <50 copies/mL at Week 16 compared with approximately 35% in placebo. In addition, the increase in CD4+ cell count in raltegravir-treated subjects was greater than twice that observed with placebo (81, 84 versus 32, 39 cells/mm^3 for Protocols 018 and 019, respectively). Approximately 60% of subjects had reached Week 24 at the time of the database lock for NDA submission. Week 24 efficacy analyses were performed and supported the Week 16 efficacy findings.

1.3.3 Safety

An increase in the number of reported malignancies was identified in raltegravir-treated subjects as compared to control subjects at the time of the original NDA submission; however with longer follow up the imbalance initially observed has diminished.

There was a slight increase in mortality with raltegravir in the treatment-experienced trials, 2.2% in the raltegravir group versus 1.1% in placebo. An analysis of baseline characteristics demonstrated subjects who died were more advanced at baseline as evidenced by higher baseline HIV-1 viral load, lower baseline CD4+ cell count, and lower last CD4+ cell count compared with surviving subjects. An analysis of Week 24 mortality, adjusted for exposure, resulted in mortality rates per 100 patient-years of 2.8 in the raltegravir group versus 2.5 in placebo. Cross study comparison with other clinical trials enrolling similar HIV-1 treatment-experienced subjects demonstrated similar morality rates to those observed in the raltegravir development program. The majority of deaths were due to infection and/or malignancy. All deaths were assessed as not related to study drug; after review of the deaths in raltegravir-treated subjects I am in agreement with the investigators' assessments. Therefore, no evidence of an increase in mortality associated with raltegravir is apparent based on the available clinical data.

Overall, rash events were more common in raltegravir arms (7.2%) as compared to control arms (5.3%); however, no raltegravir-treated subject discontinued for rash in any Phase 2 or 3 trial, no clear pattern was observed and the majority were mild/moderate in intensity. An increase in

creatine kinase elevations, and herpes zoster was observed in the raltegravir arms of the Phase 2 and 3 protocols.

1.3.4 Dosing Regimen and Administration

The proposed dosing regimen for raltegravir is 400 mg twice daily in adults.

1.3.5 Drug-Drug Interactions

Raltegravir is a UDP-glucuronosyltransferase (UGT) 1A1 and P-gp substrate. Phase 1 drug-drug interaction studies with atazanavir (ATV), a UGT1A1 inhibitor demonstrated increased raltegravir plasma levels with co-administration of ATV alone and in combination with ritonavir. However, concomitant use of raltegravir and ATV was well tolerated in the Phase 2 and Phase 3 studies.

Rifampin and tipranavir (TPV)/ritonavir are potent inducers of P-gp as well as a broad range of drug-metabolizing enzymes; raltegravir exposure was decreased with co-administration of each drug. Of note, efficacy in the Phase 3 subgroup receiving TPV/ritonavir as part of the optimized background regimen was similar to efficacy in patients not receiving TPV/ritonavir. No raltegravir dose adjustments are recommended based on concomitant medication use.

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, TDF and etravirine (TMC125).

1.3.6 Special Populations

Raltegravir was studied in individuals 16 years and older, therefore no pediatric information is currently available. In addition, insufficient numbers of subjects age 65 years and older were enrolled in the clinical studies to determine whether this population responds differently from younger subjects. In developmental toxicity studies in rats, an increase in the incidence of supernumerary ribs relative to control was found at a dose approximately 3.4-fold higher than anticipated with the proposed human dose. No external or visceral abnormalities and no other fetal or postnatal developmental effects were observed at this dose. In rabbits, no fetal malformations were found at the maximum raltegravir dose. No adequate studies have been performed in pregnant women. Because animal reproduction studies are not necessarily predictive of human response, raltegravir should be used during pregnancy only if the potential benefit justifies the potential risk.

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 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.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Generic (trade) name: Raltegravir (ISENTRESS™)

Chemical class: New molecular entity

Pharmacological class: HIV integrase strand transfer inhibitor

Proposed indication: ISENTRESS in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.

Dosing regimens: 400 mg twice daily

Dosage form: 400 mg tablet

Age groups: indication for adults and adolescents $\geq$ 16 years of age

Raltegravir is an HIV integrase strand transfer inhibitor in development for the treatment of HIV-1 infection. The Applicant has evaluated and submitted data in support of raltegravir's efficacy and safety in heavily treatment-experienced adults, and is proposing an indication for the treatment of HIV-1 infection in treatment-experienced adult patients. Treatment-naïve and pediatric studies are ongoing.

2.2 Currently Available Treatment for Indications

There are currently 24 drugs approved for the treatment of HIV-1 infection (not including fixed dose combinations or different formulations). These drugs fall into five classes based on mechanism of action in the HIV life cycle: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion/entry inhibitors, and CCR5 antagonists (Table 2.2.A).

TABLE 2.2.A : Currently Approved Antiretrovirals

Drug Class	Generic Name	Trade Name
NRTI	Zidovudine (AZT)	Retrovir®
	Didanosine (ddI)	Videx®
	Zalcitabine (ddC)	Hivid®
	Stavudine (d4T)	Zerit®
	Lamivudine (3TC)	Epivir®
	Abacavir	Ziagen®
	Tenofovir	Viread®
	Emtricitabine (FTC)	Emtriva®
NNRTI	Delavirdine	Rescriptor®
	Nevirapine	Viramune®
	Efavirenz	Sustiva®
PI	Indinavir	Crixivan®
	Ritonavir	Norvir®
	Saquinavir, hard gel	Invirase®
	Saquinavir, soft gel	Fortavase®
	Nelfinavir	Viracept®
	Amprenavir	Agenerase®
	fos-amprenavir	Lexiva®
	Atazanavir	Reyataz®
	Lopinavir/ritonavir fixed dose combination	Kaletra®
	Tipranavir	Aptivus®
	Darunavir	Prezista®
Fusion/Entry Inhibitor	Enfuvirtide (ENF)	Fuzeon®
CCR5 receptor antagonist	Maraviroc	Selzentry®

According to the 2006 DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents "the primary goals of antiretroviral therapy are to: reduce HIV-related morbidity and mortality, improve quality of life, restore and preserve immunologic function, and maximally and durably suppress viral load". Obstacles in achieving these goals include drug side effects, drug intolerance and drug resistance. The use of antiretroviral drugs in combination has decreased the morbidity and mortality of HIV disease. However, treatment with combination therapy is often associated with drug toxicities such as fat redistribution, hyperglycemia, pancreatitis, and lactic acidosis. In addition, inconvenience, drug intolerance and adherence issues limit the success of these antiretroviral drug combinations.

The prevalence of drug resistance in HIV-positive, treatment-experienced patients and the incidence of drug resistance in treatment-naïve patients are increasing. Raltegravir targets a novel step in the HIV-1 replication process, and the development of raltegravir specifically targeted a highly treatment-experienced population with limited treatment options.

2.3 Availability of Proposed Active Ingredient in the United States

This product is a new molecular entity and is not currently marketed in the United States.

2.4 Important Issues With Pharmacologically Related Products

Raltegravir is a new molecular entity targeting a novel step in HIV-1 replication. Currently, no pharmacologically related products have received FDA approval.

2.5 Presubmission Regulatory Activity

The first-in-man study of raltegravir was a randomized, double-blind, placebo-controlled, two-period Phase 1 drug interaction study to evaluate the influence of ritonavir on the pharmacokinetics of raltegravir. It was submitted by Merck to the FDA under IND 69,928; Serial No. 000 on June 1, 2004. At that time, raltegravir was assigned the drug name L-900612. Subsequent drug development included pre-clinical testing and additional Phase 1 and Phase 2 studies, with the Division of Antiviral Products (DAVP) providing feedback on study design and populations, clinical endpoints, and safety monitoring. In September 2005, L-900612 was changed to drug name MK-0518. The generic name adopted by the United States Adopted Name (USAN) Council was raltegravir, and was submitted to the FDA on February 9, 2007.

On June 29, 2005 an End-of-Phase 1 meeting was held between Merck and DAVP. Merck presented updated blinded safety and efficacy summary data from the two ongoing Phase 2 clinical studies, Protocols 004 and 005. Agreement was reached on submission of 2-year carcinogenicity studies after anticipated filing provided no significant safety issues arose. The discussion resulted in the following action items:

- Submission of a request for Fast Track designation (granted on November 9, 2005).
- Agreement to evaluate the inhibitory potency of raltegravir on P-gp in an *in vitro* system.
- Submission of available efficacy data unblinded by treatment group once preliminary dose selection is made.
- Review and feedback from DAVP for Phase 3 draft protocols prior to dose selection.

On December 5, 2005 an End-of-Phase 2 meeting was held between Merck and DAVP to discuss the available safety and efficacy data from the completed/ongoing Phase 1-2 clinical studies, the proposed plan to initiate Phase 3 clinical studies in adult subjects, and plans to establish a Data Safety Monitoring Board (DSMB) for the Phase 3 studies to address safety and efficacy considerations. Merck agreed to provide a summary of the dose-confirmation interim analysis from the Phase 2 studies (Protocols 004 and 005) to support Phase 3 dose selection. This analysis was submitted to DAVP on January 11, 2006. The preliminary safety and efficacy data

from Protocol 004 was similar in all raltegravir treatment arms. However, in Protocol 005, there was some evidence of a lesser raltegravir treatment effect at the 200 mg twice daily dose (statistically significant lower changes in CD4+ cell counts) and evidence of increased safety concerns for subjects receiving 600 mg twice daily (increased frequency of skin AEs). DAVP provided concurrence on January 25, 2006 that the Phase 2 data confirmed the 400 mg twice daily dose was the appropriate one for use in Phase 3 studies of raltegravir.

DAVP agreed that a priority review with a six month review cycle was appropriate for Merck's clinical program. As a result, DAVP requested the Applicant to submit a request for Rolling Review designation and submit a formal meeting request for a Type C meeting to discuss NDA component roll-out plans prior to the Pre-NDA meeting. DAVP granted Rolling Review designation on January 20, 2006.

A Type C planning meeting was held between Merck and DAVP on August 9, 2006. DAVP agreed the NDA would be filed with 16-week Phase 3 data; however, the NDA would also include 24 week analyses as this would be used for labeling. The new primary endpoint for the Phase 3 studies (Protocols 018 and 019) would be HIV-1 RNA <400 copies/mL at Week 16. The Applicant agreed to include information on 48 week "all cause mortality" in the Phase 3 48 week Clinical Study Reports (CSRs). Finally, agreement was reached on a roll-out plan whereby reviewable units of the NDA would be provided beginning in January 2007 with the final reviewable units submitted in April 2007.

On December 1, 2006 a pre-NDA teleconference was held between Merck and DAVP to discuss and gain concurrence on the issues pertaining to the planned April 2007 NDA filing. DAVP requested reevaluation of the pediatric development program given the robust virologic response to raltegravir in the 24-week data submitted from the Phase 2 studies and the critical need to determine safety in this population, and recommended a pharmacokinetic study in children/adolescents be performed as soon as possible to support use of raltegravir in the pediatric population.

2.6 Other Relevant Background Information

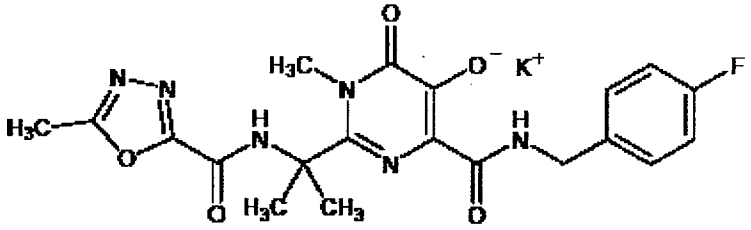
At this time, no additional information is available from regulatory actions in other countries.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Chemical name: *N*-[(4-Fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-1-methyl-2-[1-methyl-1-[[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino]ethyl]-6-oxo-4-pyrimidinecarboxamide monopotassium salt

Chemical structure:



Chemical formula: $C_{20}H_{20}FKN_6O_5$

Molecular weight: 482.51 g/mole

Formulations: 400 mg tablet

Code: MK-0518

For full details regarding review of the chemistry, manufacturing, and controls (CMC) data submitted in the NDA, please see the Chemistry Review conducted by Drs. George Lunn and Ted Chang. Raltegravir is supplied as a film-coated tablet, each containing 434.4 mg of raltegravir as the potassium salt, equivalent to 400 mg of the free phenol. The final market image tablets are the poloxamer 407 formulation, which contains and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, calcium phosphate dibasic, hypromellose, poloxamer 407 (contains 0.01% butylated hydroxytoluene), sodium stearyl fumarate, magnesium stearate. The film coating is pink which contains polyvinal alcohol- , titanium dioxide /PEG 3350 talc, red and black iron oxide. Raltegravir is soluble in water. The pH of a saturated solution of raltegravir in water is . No concerns regarding the CMC data were raised during the review cycle. The manufacturing sites were inspected prior to this approval and no significant concerns were raised.

The final market image tablet was used in the Phase 3 studies. The poloxamer formulation used in all Phase 2 studies differed from the final market image in color (for Phase 2 and pink for Phase 3), thickness of the film coating, and in the debossing used for the Phase 3 formulation.

3.2 Animal Pharmacology/Toxicology

Please refer to Dr. Ita Yuen's Animal Pharmacology/Toxicology Review for a detailed analysis of the raltegravir pharmacology and toxicity data. This following is a summary of Dr. Yuen's findings.

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 detected two types of carcinomas in the respiratory tract (squamous cell carcinoma and chondrosarcoma) likely due to aspiration and irritation of drug product to the respiratory tract. 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* ——————————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.

Male and female fertility were assessed either by direct oral dosing to young (5-56 days old) and adult rats or by exposure *in utero* and via breast milk. The results indicated that fertility was not affected at doses as high as 600 mg/kg (about 3-times human exposure) in rats. *In utero* exposure to raltegravir did not adversely affect embryo and fetal survival, weight, and external, skeletal, and visceral development in rabbits at doses up to 1000 mg/kg/day (4-fold human exposure at 800 mg/day). Fetal plasma drug concentrations were about 2% of those in maternal plasma at 1 and 24 hours postdose, respectively. However, an increased incidence of supernumerary ribs in rat fetuses exposed *in utero* to 600 mg/kg/day (3-fold human exposure at 800 mg/day) raltegravir was observed. Mean drug concentrations in rat fetal plasma were approximately 1.5- to 2.5-fold greater than those in maternal plasma at 1 and 24 hours postdose, respectively. Based on the skeletal finding in rats, raltegravir will be classified under "Pregnancy Category C" and is not recommended for use during pregnancy unless necessary. It was also secreted into rat milk. Mean drug concentration in milk at 2 hours postdose was approximately 3-fold that in maternal plasma. Exposure to this drug *in utero* or in milk did not affect pup delivery or neonatal development in rats. The second generations exhibited normal behavior and postnatal development, growth, sexual maturity, and fertility. Young rats had similar sensitivity to raltegravir as adult rats. The same type of mucosal surface irritability was observed in 5-56 day-old rats administered the same dose range as adults. The No-adverse-effect level (NOAEL) for reproductive toxicity is 1000 mg/kg/day for rabbits (3.7-fold human exposure at 800 mg/day) and 300 mg/kg/day for rats (2.2-fold human exposure at 800 mg/day).

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.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Data from Protocols 018 and 019 formed the principal basis for characterizing the safety and efficacy of raltegravir in treatment-experienced subjects with HIV-1 infection. Protocols 018 and 019 were international, multi-center, double-blind, randomized, placebo-controlled trials comparing 400 mg twice daily 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-1 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 antiretrovirals (NNRTI, NRTI, and PI).

Two 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 Phase 2 study data.

4.2 Tables of Clinical Studies

The two pivotal studies and key supportive studies submitted to the raltegravir NDA for review are summarized in Table 4.2.A. Additionally, the applicant submitted pharmacokinetic and safety data from 18 clinical pharmacology (Phase 1) studies. These studies are reviewed in detail by our Clinical Pharmacology/Biopharmaceutics Reviewer, Dr. Derek Zhang.

Table 4.2.A: Phase 2 and 3 Clinical Studies Analyzed in this Review

Study	Design	Raltegravir Regimens	Comparator	Background Regimen	# Enrolled and Treated	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	Randomized Double - Blinded	400 mg bid	Placebo	OBT	350	Treatment experienced	HIV RNA <400 Week 16
019	Randomized Double - Blinded	400 mg bid	Placebo	OBT	349	Treatment experienced	HIV RNA <400 Week 16

4.3 Review Strategy

I conducted the Clinical Review of NDA 22-145. This review focused primarily on the results from two Phase 3 studies, Protocols 018 and 019, conducted in HIV-1 infected treatment-experienced subjects. The safety review integrated data from the Phase 3 studies, and included data from the Phase 2 studies for key analyses. The Safety Update Report (SUR) submitted two months after the original NDA submission was reviewed for additional safety data. I collaborated with the statistical reviewers, Drs. Karen Qi and Fraser Smith, throughout the review process, and a number of the efficacy analyses in this review were performed by the FDA statisticians. In addition, I also obtained valuable input from the clinical pharmacology, microbiology, pharmacology-toxicology and product evaluation groups.

4.4 Data Quality and Integrity

A routine consult was submitted to the Division of Scientific Investigations (DSI) on March 19, 2007, in response to the submission of the raltegravir NDA. Please refer to the DSI review by Dr. Antoine El-Hage for further details. Four clinical sites were inspected (Table 4.4.A). Three minor protocol deviations were noted at two of the four sites, and these deviations did not adversely impact data integrity. Therefore, the data from the inspected sites are acceptable in support of the pending application.

Table 4.4.A: Listing of Division of Scientific Investigations Evaluation of Clinical Inspections

Name of CI and site #, if known	City, State	Protocol	Inspection Date	EIR Received Date	Final Classification
	Barcelona, Spain	018	6/18/07	7/16/07	NAI
	St. New Haven, CT	019	7/17/07	pending	NAI*
	Atlanta , GA	019	5/30/07	8/20/07	NAI
	New York, NY	019	8/2/07	Pending	NAI*

Source: Division of Scientific Investigations Evaluation of Clinical Inspections for NDA 22-145 by Dr. Antoine El-Hage
* based on e-mail summary information or telephone call from the field investigators.
CI = clinical investigator
Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations. Data unreliable.

4.5 Compliance with Good Clinical Practices

The protocol and informed consent documents were reviewed and approved by the Institutional Review Boards and Independent Ethics Committees for each of the investigational centers that participated in Protocols 018 and 019. The Applicant certified these studies were conducted in compliance with the ethical principles described in the Declaration of Helsinki, and in compliance with International Conference on Harmonisation Good Clinical Practice guidelines. In addition, the FDA DSI inspected four clinical sites, and data from all four were considered acceptable (see Section 4.4). For a more detailed discussion of the DSI audit, please refer to the Clinical Inspection Summary, by Dr. Antoine El-Hage, Regulatory Pharmacologist.

Protocol violations occurring in Protocols 018 and 019 are summarized in the following table:

Table 4.5.A: Protocol Violations in Protocols 018 and 019

	Raltegravir	Placebo	Total
# Subjects Randomized and Treated	462	237	699
Protocol deviation for enrollment – n (%)	6 (1.3)	5 (2.1)	11 (1.6)
OBT changed for reasons other than lack of efficacy or toxicity – n (%)	21 (4.5)	6 (2.5)	27 (3.9)
Prematurely unblinded – n (%)	2 (0.4)	1 (0.4)	3 (0.4)
Took prohibited medication – n (%)	10 (2.2)	2 (0.8)	12 (1.7)

Source: Applicant MRL Clinical Study Report for Protocols 018 and 019

There were more violations due to change in OBT and use of prohibited medications in the raltegravir group. The Applicant states 27 subjects changed OBT due to "administrative reasons" which included: subject and/or physician misunderstanding (5 raltegravir, 1 placebo), dose simplification (2 raltegravir), non-availability of fixed dose combination (1 raltegravir), new formulation (3 raltegravir), subject self-discontinuation (7 raltegravir, 1 placebo), initiation of OBT days after randomization (2 raltegravir, 2 placebo), weight adjustment (2 raltegravir), insurance coverage issues (1 placebo).

The Protocol 018 CSR states seven randomized subjects took prohibited medication during the study; however, nine subjects are listed and, therefore, nine subjects are included in the summary table. Five of these subjects (four in the raltegravir group) received rifabutin under the original protocol. Subsequently this drug was removed from the list of prohibited medications in the protocol extensions. One raltegravir-treated subject received phenobarbital during the study. Three raltegravir-treated subjects received an immunosuppressive medication (thalidomide) prohibited by the protocol. In Protocol 019, one raltegravir-treated subject took TMC-125 without the investigator's knowledge until three months into the study, and after review by the Applicant, this subject was allowed to continue in the study. One raltegravir-treated subject received a single dose of phenytoin, and one placebo treated subject received interferon-gamma for MAC prophylaxis from Day -25 to Day 6.

In summary, protocol violations were uncommon and do not appear to impact the overall conclusions from these studies.

4.6 Financial Disclosures

The Applicant examined financial data regarding significant payments and equity for all investigators per 21 CFR Part 54. A total of 918 investigators participated in the Phase 1, 2, and 3 protocols submitted with the NDA. The Applicant provided a certification for 896 (97.6%) of the investigators, indicating the majority had no financial arrangement (884, 96%), six had received significant payments, two disclosed equity interest, and two disclosed proprietary or financial interest. The two investigators disclosing equity interest were involved in [redacted] and included one investigator [redacted] granted [redacted] shares since February 24, 1998 and exercised [redacted] shares as reported by the investigator on February 19, 2007, and one investigator holding [redacted] shares assessed at approximately [redacted] as of an April 2006 calculation. The two investigators disclosing proprietary interests were [redacted]

Based on the low proportion of investigators with a financial interest and the double-blind nature of the Phase 2 and 3 protocols, the likelihood study results were substantively biased based on financial interest is low.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

This section provides a brief summary of the pharmacokinetics of raltegravir. Please refer to the FDA Clinical Pharmacology Review by Dr. Derek Zhang for additional information.

Absorption

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 large (increasing with increasing dose levels), implying a large degree of uncertainty in raltegravir exposure levels. 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.

Distribution

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.

Metabolism

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.

Elimination

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.

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. 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 5.1.A summarizes the effect of other drugs on raltegravir.

Table 5.1.A: 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)

Source: Table 5 from FDA Background Package for NDA 22-145
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 ATV alone and in combination with ritonavir, which is consistent with inhibition of UGT1A1. However, concomitant use of raltegravir and ATV was well tolerated in the Phase 2 and Phase 3 studies. Based on these data, ATV may be co-administered with raltegravir without dose adjustment of raltegravir.

Rifampin, a potent inducer of UGT1A1, reduces plasma concentrations of raltegravir. Therefore, caution should be used when co-administering raltegravir with rifampin or other potent inducers of UGT1A1. The impact of other inducers of drug metabolizing enzymes, such as phenytoin and phenobarbital, on UGT1A1 is unknown. Other less potent inducers (e.g., efavirenz, nevirapine, rifabutin) may be used with the recommended dose of raltegravir.
TPV/ritonavir is a potent inducer of a broad range of drug-metabolizing enzymes as well as P-gp, and raltegravir exposure was decreased with co-administration. Of note, comparable efficacy was observed in the Phase 3 subgroup receiving TPV/ritonavir as part of the optimized background regimen relative to patients not receiving TPV/ritonavir. No raltegravir dose adjustments are recommended based on concomitant TPV/ritonavir use.

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, TDF and etravirine (TMC125).

Potential sources that contribute to pharmacokinetic variability of raltegravir

As indicated in Assessment of Pharmacokinetic Variability section (Section 5.3), 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

5.2 Pharmacodynamics

Please refer to Section 5.3

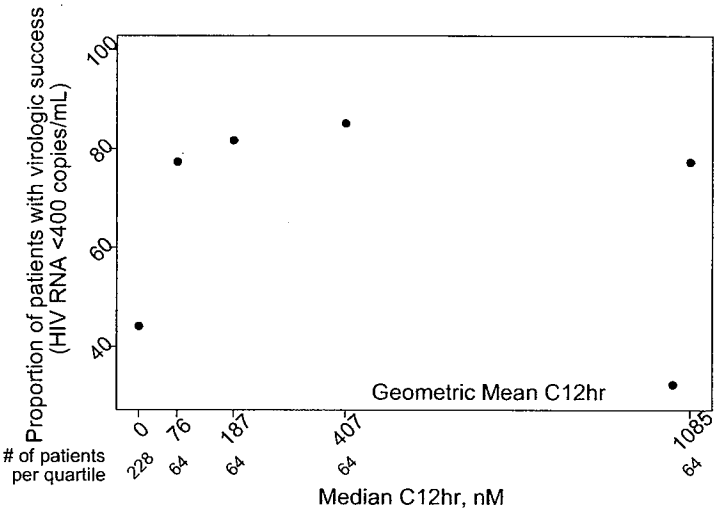
5.3 Exposure-Response Relationships

This section provides a brief summary of the FDA Pharmacometric Review of raltegravir. Please refer to the review by Dr. Pravin Jadhav for additional information.

Data from Protocols 018 and 019 were used in the exposure-response analyses. In the univariate analyses, the virologic success rate was similar (77%) for subjects with lower C_{12hr} (median C_{12hr} 76nM) compared to those with higher C_{12hr} (median C_{12hr} 1085 nM).

Figure 5.3.A 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 5.3.A: C_{12hr}-virologic success relationship. C_{12hr}=0 represents placebo-treated subjects; raltegravir-treated subjects divided into four quartiles



Source: FDA Pharmacometrics Review for NDA 22-145 by Dr. Pravin Jadhav

A total of 483 subjects (255 raltegravir treated and 228 placebo treated) were included in the pharmacokinetic-pharmacodynamic analyses. Approximately 200 subjects were excluded due to lack of sufficient pharmacokinetic 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

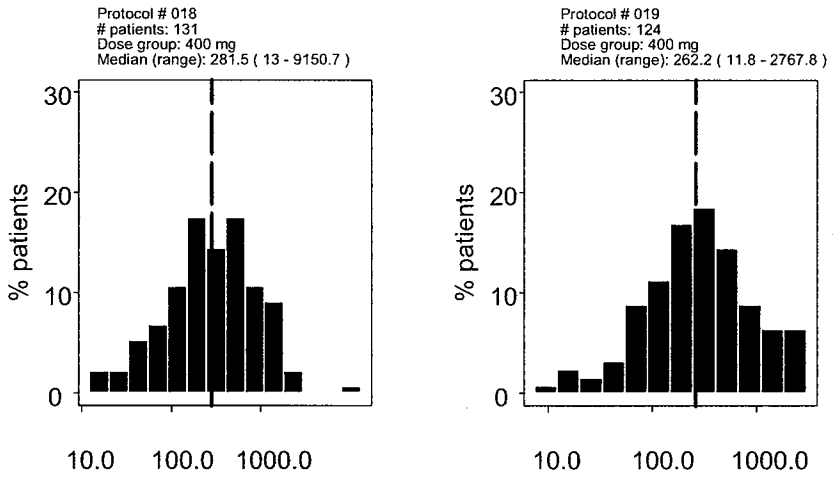
individual); and the minimum observed C_{12hr} (determined as the minimum concentration from all samples taken between 11 and 13 hours post-dose in a given individual).

A preliminary analysis using generalized additive modeling indicated the probability of virologic success was higher at higher C_{12hr} and/or higher baseline CD4+ cell count and/or lower baseline HIV RNA. However, further analyses revealed local noise in the exposure response data and thus little dependency of virologic success on the C_{12hr}, with the concentration range studied. The noise could be introduced by high within subject variability (described below) or due to high potency (maximum IC95~50nM in 50% human serum) of raltegravir such that the exposures are in the asymptotic region of the C_{12hr}-virologic success relationship.

Assessment of Pharmacokinetic Variability

The overall variability in C_{12hr} is high, with a range of 12 to 9151 nM. Figure 5.3.B illustrates distribution of geometric mean observed C_{12hr} in the pivotal studies.

Figure 5.3.B: Distribution of geometric mean observed C_{12hr} (nM)

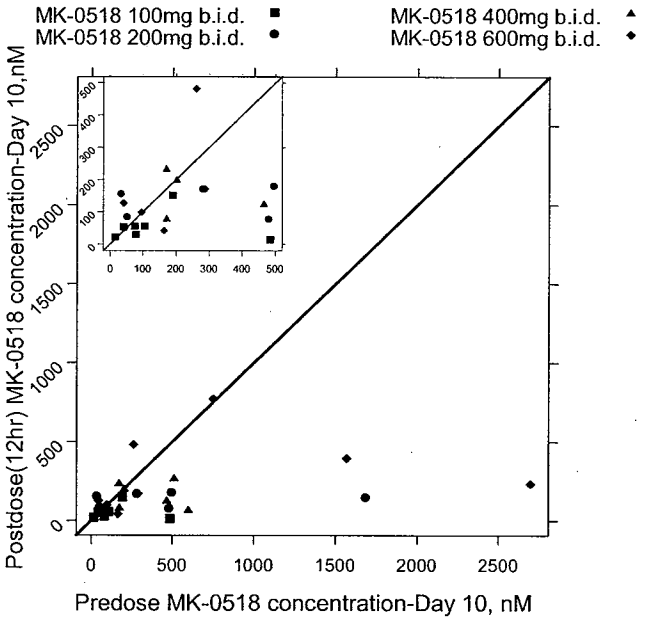


Source: FDA Pharmacometrics Review for NDA 22-145 by Dr. Pravin Jadhav

An attempt was made to understand the factors leading to variability in C_{12hr}. 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. A given subject 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 5.3.C 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 identity". 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.

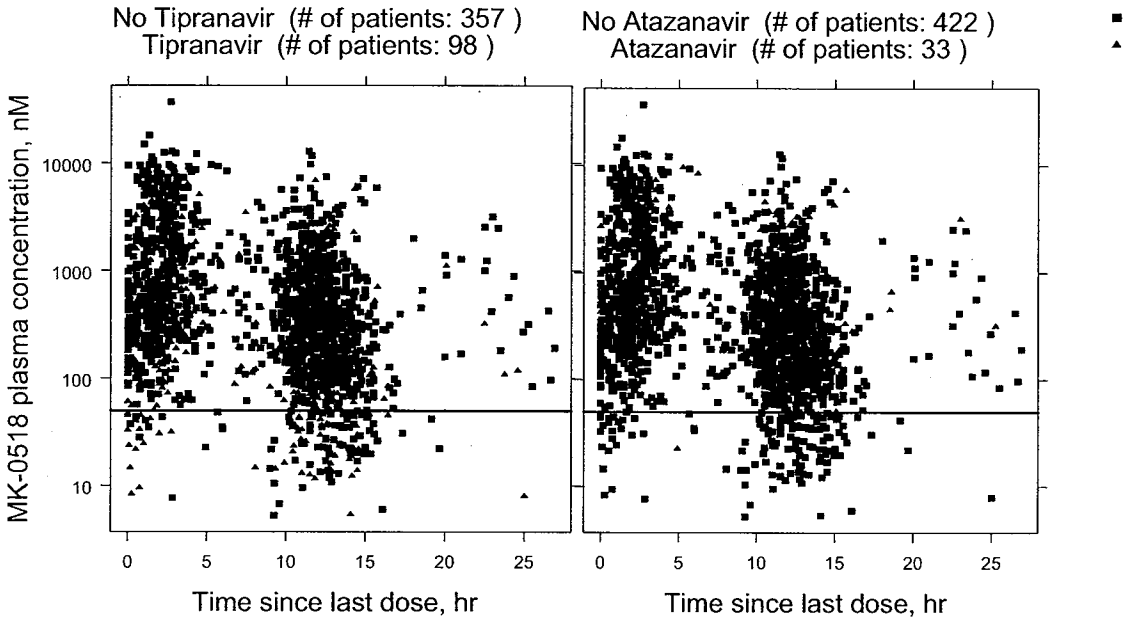
Figure 5.3.C: Within subject variability in raltegravir trough concentrations (Inset: Data within 0–500 nM)



Source: FDA Pharmacometrics Review for NDA 22-145 by Dr. Pravin Jadhav

Figure 5.3.D illustrates 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 TPV and ATV within the context of high pharmacokinetic variability. The Phase 1 drug interaction studies indicated ATV/ritonavir increased raltegravir C_{12hr} by 77% and TPV/ritonavir decreased raltegravir C_{12hr} by 55%. The mean changes in raltegravir C_{12hr} due to ATV/ritonavir and TPV/ritonavir were similar between the Phase 1 studies and Protocols 018 and 019. However, because of the high variability in raltegravir plasma levels, the range of raltegravir plasma levels observed with or without either co-administered drug is similar.

Figure 5.3.D: Effect of tipranavir and atazanavir on raltegravir plasma levels s in Protocols 018 and 019. (The horizontal line represents 50 nM, an in vitro IC95 using 50% human serum) Plasma levels are normalized to time after dose, but were obtained over the trial duration.



Source: FDA Pharmacometrics Review for NDA 22-145 by Dr. Pravin Jadhav

The size of the current safety database at high raltegravir exposure levels and the high variability make defining a clinically significant threshold for dose adjustment challenging. No major adverse events of concern were found to be associated with high (top 10%) raltegravir exposures. Given the overall pharmacokinetic (PK) variability, a temporal association between raltegravir plasma concentrations and adverse events was weak. Exposure dependent safety concerns were not found, however, the safety data base at high exposures is limited. The impact of these findings on the long term safety is not clear.

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 subjective and not based on extensive clinical experience. Based on the Applicant's rationale, a dose adjustment in the presence of ATV/ritonavir or TPV/ritonavir is not needed. Safety and efficacy data from Protocols 018 and 019 support the administration of raltegravir 400 mg twice daily with either TPV/ritonavir or ATV/ritonavir, with no dose adjustment.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The final agreed upon indication is ISENTRESS in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.

6.1.1 Methods

Week 24 efficacy data for the two Phase 3 pivotal trials, Protocol 018 (BENCHMRK-1) and Protocol 019 (BENCHMRK-2) were reviewed in support of the proposed indication. A total of 62% of subjects enrolled in the Phase 3 trials had completed Week 24 at the time of database lock. All subjects completed Week 16, and therefore, Week 16 efficacy data for the Phase 3 trials was also reviewed.

6.1.2 General Discussion of Endpoints

The FDA Guidance, *Antiretroviral Drugs Using Plasma HIV RNA Measurements- Clinical Considerations for Accelerated and Traditional Approval*, states "the Division of Antiviral Drug Products advisory committee concurred that treatment-induced decreases in HIV RNA levels were highly predictive of meaningful clinical benefit and that HIV RNA measurements could serve as endpoints in trials designed to support both accelerated and traditional approvals". The use of this endpoint is supported by analyses showing an association between change in viral load and clinical outcome. In addition, the Guidance recommends HIV RNA reduction at 24 weeks as the basis for accelerated approval, and that changes in CD4+ cell counts should be consistent with the observed HIV-1 RNA changes.

The primary endpoint for the integrated analysis of Protocols 018 and 019 was the proportion of subjects with HIV-1 RNA <400 copies/mL at Week 16. Additional analyses were performed on the 62% of subjects with Week 24 data.

Secondary endpoints for the integrated analysis of the Phase 3 trials were:

- Proportion of subjects with virologic response at Week 16. The following two definitions were used for two different categories of virologic response and analyzed separately:
  1. Either HIV-1 RNA <400 copies/mL at Week 16, or reduction from baseline in HIV-1 RNA (log_{10} copies/mL) exceeding 1.0 log_{10} copies/mL at Week 16
  2. HIV-1 RNA <50 copies/mL
- Change from baseline in HIV-1 RNA (log_{10} copies/mL) at Week 16
- Change from baseline in CD4+ cell count at Week 16

6.1.3 Study Design

Protocols 018 and 019 were international, multi-center, double-blind, randomized, placebo-controlled trials comparing 400 mg twice daily raltegravir in combination with optimized background therapy (OBT) to OBT alone in highly treatment-experienced HIV-infected subjects. Subjects were randomized 2:1 to raltegravir or placebo. 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. The protocols have been amended to continue for 156 weeks.

The major eligibility criteria for enrollment included:

- HIV-1 infected adults at least 16 years of age
- HIV-1 RNA > 1,000 copies/mL
- Documented resistance to at least of drug in each of the three classes: NNRTI, NRTI, PI
- Antiretroviral therapy-experienced and on stable antiretroviral therapy for $\geq$ 2 months

At baseline, the investigator selected the OBT based on the subject's prior treatment history, the results from the HIV-1 genotypic and phenotypic antiretroviral resistance testing at screening, and prior antiretroviral resistance testing, if available. Subjects were stratified by use of enfuvirtide (ENF) in the OBT and the degree of PI resistance at study entry (resistant to 1 PI or >1 PI). Use of darunavir (DRV) and TPV was allowed in the OBT. Subjects with chronic HBV and/or HCV were allowed to enroll if clinically stable and serum AST and ALT values were $\leq$5 times the upper limit of normal (ULN).

The Phenotypic Sensitivity Score (PSS) and the Genotypic Sensitivity Score (GSS) were defined as the total oral antiretrovirals (ART) in OBT to which a subject's viral isolate showed phenotypic sensitivity and genotypic sensitivity, respectively, based upon phenotypic and genotypic resistance tests. ENF use in OBT in ENF-naïve subjects was counted as one active drug in OBT and added to the GSS and PSS. DRV use in OBT in DRV-naïve patients was counted as one active drug in OBT and added to the PSS and GSS.

The schedule of subject monitoring procedures performed during the double blind phase of Protocols 018 and 019 are presented in Table 6.1.3.A.

Table 6.1.3.A: Phase 3 Schedule of Subject Monitoring Procedures

Schedule of Clinical Observations and Laboratory Measurements for the Double-Blind Treatment Phase

	Weeks (Postinitiation of Combination Therapy)										
Visit No	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11
	Screen	Fasting[3] Randomization (Day 1)	Week 2	Week 4	Week 8	Fasting[3] Week 12	Week 16	Fasting[3] Week 24	Week 32	Week 40	Fasting[3] Week 48
Medical History	X										
12-lead ECG	X							X			
Chest x-ray	X										
Physical examination	X	X[4]	X	X	X	X	X	X	X	X	X
Blood and urine for safety (Appendix 1)	X	X[4]	X	X	X	X	X	X	X	X	X
Pregnancy test[1]	X[2]	X[2,4]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
HIV RNA	X	X[4]	X	X	X	X	X	X	X	X	X
CD4 cell count	X	X[4]	X	X	X	X	X	X	X	X	X
Plasma for viral resistance	X							X			X
Predrug PK plasma sample		X[4]									
Population PK blood draws[5]				X	X	X	X	X	X		
Blood, archiving		X[4]									
Contact Interactive Voice Response System (IVRS)	X[11]	X[4,11]		X[11]	X[11]	X[11]	X[11]	X[11]	X[11]	X[11]	X[11]

[1] For women of childbearing potential.
[2] Serum pregnancy test (central laboratory).
[3] Fasting; 8 hours.
[4] Urine pregnancy test (central laboratory kit).
[5] One sample for population pharmacokinetics (PK) was collected. At Weeks 12 and 24, the sample had to be collected pre-AM dose. At all other weeks, the samples could have been collected irrespective of time of dose.
[6] Prior to first dose on Day 1.
[7] Not needed if obtained at virologic failure confirmation visit.
[11] To register patients at screening.
[11] To allocate patients (Day 1) and for assignment and management of clinical supplies.

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	Weeks (Postinitiation of Combination Therapy)											
Visit No	V30	V31	V32	V33	V34	V35	V36	V37	V38	V99	U	U
	Week 60	Fasting[3] Week 72	Week 84	Fasting[3] Week 96	Week 108	Fasting[3] Week 120	Week 132	Fasting[3] Week 144	Week 156	Fasting[3] 14-Day Posttherapy Follow-up	Virologic Failure Confirmation	Discontinuation[11]
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X
Blood and urine for safety (Appendix 1)	X	X	X	X	X	X	X	X	X	X		X
Pregnancy test[1]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]		
HIV RNA	X	X	X	X	X	X	X	X	X	X	X	X
CD4 cell count	X	X	X	X	X	X	X	X	X	X	X	X
Plasma for viral resistance									X		X	X[6]
Population PK blood draws[5]		X		X		X		X				
Contact Interactive Voice Response System (IVRS)[4]	X	X	X	X	X	X	X	X	X			

[1] For women of childbearing potential, serum pregnancy test (central laboratory).
[5] One sample for population PK will be collected irrespective of time of dose.
[3] Fasting; 8 hours.
[4] For management of clinical supplies and to register discontinuation
[7] Not needed if obtained at virologic failure confirmation visit.
[11] Limited information (mortality and participation in any other antiretroviral clinical study) will be collected for patients who discontinue prior to Week 48.

Source: Table 9-1 from Applicant MRL Clinical Study Report for Protocols 018 and 019

Subjects who met the definition of virologic failure at Week 16 or beyond were permitted to switch to open-label treatment with a re-optimized background regimen. These subjects remained in the study and continued in the open-label post virologic failure (OLPVF) treatment phase; however, any subject entering the OLPVF phase was counted as a failure in the primary efficacy analysis. Virologic failure was defined as:

- Nonresponders who did not achieve > 1.0 $\log_{10}$ HIV-1 RNA reduction and <400 HIV-1 RNA copies/mL by Week 16
  – OR –
- Rebound, defined as (a) HIV-1 RNA >400 copies/mL (on 2 consecutive measurements at least 1 week apart) after initial response with HIV-1 RNA <400 copies/mL, or (b) > 1.0 $\log_{10}$ increase in HIV-1 RNA above nadir level (on 2 consecutive measurements at least 1 week apart).

6.1.4 Efficacy Findings

A total of 1012 subjects were screened for entry into Protocols 018 and 019, of whom 703 were randomized and 699 received at least one dose of study drug (462 raltegravir, 237 placebo). Baseline characteristics of subjects enrolled in Protocols 018 and 019 are summarized in Table 6.1.4.A below. The majority of subjects were white (65-73%) males (87-89%) with a median age of 45 years, median baseline viral load of 4.66-4.78 $\log_{10}$, and median baseline CD4+ cell count of 119-123 cells/mm^3. Subjects were advanced and highly treatment-experienced with a median of 10 years prior antiretroviral therapy. Approximately one-third of subjects had CD4+ cell counts $\leq$50 cells/mm^3 and one-third had HIV-1 RNA >100,000 copies/mL. Almost half of the subjects had a phenotypic sensitivity score (PSS) of $\leq$1, and over 60% had a genotypic sensitivity score (GSS) of $\leq$1.

Table 6.1.4.A: Protocols 018 and 019: Baseline Characteristics

	Protocol 018		**Protocol 019**		**Pooled**	
	Raltegravir (N=232)	**Placebo (N=118)**	**Raltegravir (N=230)**	**Placebo (N=119)**	**Raltegravir (N=462)**	**Placebo (N=237)**
Gender n (%)						
Male	195 (84%)	103 (87%)	210 (91%)	107 (90%)	405 (88%)	210 (89%)
Female	37 (16%)	15 (13%)	20 (9%)	12 (10%)	57 (12%)	27 (11%)
Race n (%)						
White	175 (75%)	96 (81%)	126 (55%)	77 (65%)	301 (65%)	173 (73%)
Black	18 (8%)	5 (4%)	48 (21%)	21 (18%)	66 (14%)	26 (11%)
Asian	14 (6%)	5 (4.2%)	2 (0.9%)	1 (0.8%)	16 (3.5%)	6 (2.5%)
Hispanic	6 (3%)	1 (<1%)	47 (20%)	18 (15%)	53 (12%)	19 (8%)
Other	19 (8%)	11 (9%)	7 (3%)	2 (2%)	26 (6%)	13 (6%)
Age (years)						
Median (min,max)	45.5 (16, 74)	43 (19, 64)	45 (16, 67)	47 (17, 70)	45 (16, 74)	45 (17, 70)
Geographic Region n (%)						
North America	-	-	202 (88%)	102 (86%)	202 (44%)	102 (43%)
South America	23 (10%)	11 (9%)	28 (12%)	17 (14%)	51 (11%)	28 (12%)
Europe	171 (74%)	87 (74%)	-	-	171 (37%)	87 (37%)
Australia	25	15	-	-	25	15

	(11%)	(13%)			(5%)	(6%)
Asia	13 (6%)	5 (4%)	-	-	13 (3%)	5 (2%)
CD4+ Cell Count[1]:					N=461	N=237
Median (min, max) cells/mm3	140 (1,792)	104.5 (3,759)	101.5 (1,757)	132 (0,674)	119 (1, 792)	123 (0, 759)
≤50 cells/mm3, n (%)	69 (30%)	40 (34%)	77 (34%)	38 (32%)	146 (32%)	78 (33%)
>50 and ≤200 cells/mm3, n (%)	89 (38%)	43 (36%)	84 (37%)	42 (35%)	173 (37%)	85 (36%)
Plasma HIV-1 RNA						
Median (min,max) log_{10} copies/mL	4.79 (2.64, 5.88)	4.63 (2.30, 5.88)	4.75 (2.30, 5.88)	4.67 (2.30, 5.88)	4.78 (2.30, 5.88)	4.66 (2.30, 5.88)
>100,000 copies/mL, n (%)	79 (34%)	33 (28%)	87 (38%)	45 (38%)	166 (36%)[2]	78 (33%)
History of AIDS n (%)	217 (94%)	106 (90%)	209 (91%)	110 (92%)	426 (92%)	216 (91%)
Prior Use of Antiretroviral Therapy (ART), Median (1st Quartile, 3rd Quartile)						
Years of ART use	10.6 (7.7, 12.6)	10.3 (8.0, 12.3)	9.6 (6.5, 11.6)	10.1 (7.4, 13.1)	10.1 (7.3, 12.1)	10.2 (7.9, 12.4)
Number of ART	12 (8, 14)	12 (9, 14)	12 (9, 15)	12 (9, 14)	12 (9, 15)	12 (9, 14)
Phenotypic Sensitivity Score[3]						
0	44 (19%)	21 (18%)	23 (10%)	23 (19%)	67 (15%)	44 (19%)
1	67 (29%)	39 (33%)	78 (34%)	32 (27%)	145 (31%)	71 (30%)
2	67 (29%)	33 (28%)	75 (33%)	33 (28%)	142 (31%)	66 (28%)
3+	44 (19%)	20 (17%)	41 (18%)	26 (22%)	85 (18%)	48 (20%)
Missing	10 (4%)	4 (3%)	13 (6%)	4 (3%)	23 (5%)	8 (3%)
Genotypic Sensitivity Score[3]						
0	70 (30%)	34 (29%)	45 (20%)	31 (26%)	115 (25%)	65 (27%)
1	76 (33%)	48 (41%)	102 (44%)	48 (40%)	178 (39%)	96 (41%)
2	57 (25%)	22 (19%)	54 (24%)	27 (23%)	111 (24%)	49 (21%)
3+	26 (11%)	13 (11%)	25 (11%)	10 (8%)	51 (11%)	23 (10%)
Missing	3 (1%)	1 (<1%)	4 (2%)	3 (3%)	7 (2%)	4 (2%)

Hepatitis Co-infection n (%)						
HBV	14 (6%)	3 (3%)	22 (10%)	4 (3%)	36 (8%)	7 (3%)
HCV	31 (13%)	22 (19%)	6 (3%)	5 (4%)	37 (8%)	27 (11%)
HBV/HCV	4 (2%)	2 (2%)	0	0	4 (<1%)	2 (<1%)
Stratum						
ENF in OBT	88 (38%)	43 (36%)	87 (38%)	46 (39%)	175 (38%)	89 (38%)
Resistant to ≥2 PI	225 (97%)	112 (95%)	222 (97%)	114 (96%)	447 (97%)	226 (95%)

Source: QHIVRNA, QCD4CC, DEMOG, RNADBNC, DEMODATA, GPNSCORE datasets for Protocols 018 and 019

1 CD4+ cell count N=461 in raltegravir arm, subject AN 8406 has no baseline CD4+ cell count value

2 FDA analysis of the QHIVRNA datasets for Protocols 018 and 019 resulted in 166 subjects in the raltegravir arm with HIV-1 RNA>100,000 copies/mL. The proposed package insert lists 164 subjects.

3 The Phenotypic Sensitivity Score (PSS) and the Genotypic Sensitivity Score (GSS) were defined as the total oral antiretrovirals (ART) in OBT to which a subject's viral isolate showed phenotypic sensitivity and genotypic sensitivity, respectively, based upon phenotypic and genotypic resistance tests. Enfuvirtide (ENF) use in OBT in ENF-naïve subjects 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.

Each subject in the Phase 3 studies used study drug in combination with OBT. The use of specific OBT agents was balanced between the treatment groups. The most commonly used OBT agents are summarized in the following table. DRV, TPV, and lopinavir/ritonavir were given to approximately 3/4 of subjects. Over 2/3 of subjects received tenofovir, either in combination with emtricitabine or in combination with another NRTI. Of note, efavirenz was the most often prescribed NNRTI in OBT; however it was used in 7% in Protocol 018 and 5% in Protocol 019.

Table 6.1.4.B: Most Commonly Used Specific OBT Antiretroviral Agents in Phase 3 Studies

	Protocol 018	**Protocol 019**
Ritonavir	74%	80%
Darunavir	34%	50%
Emtricitabine/Tenofovir	37%	49%
Enfuvirtide	38%	38%
Tenofovir	31%	35%
Tipranavir	25%	17%
Lopinavir/Ritonavir	21%	13%

Source: Table 10-6 from Applicant MRL Clinical Study Report for Protocols 018 and 019

Efficacy analysis

The following section highlights the major findings of the NDA Statistical Review by Dr. Karen Qi. All tables reflect data from the double-blind portion of the Phase 3 studies. Subjects discontinuing blinded treatment were counted as treatment failures in the analyses.

The primary endpoint for the pivotal Phase 3 studies was HIV-1 RNA <400 copies/mL at Week 16 (Table 6.1.4.C). Over 75% of raltegravir-treated subjects achieved a viral load of <400 copies/mL at Week 16 versus 40% in placebo; this was highly statistically significant for both protocols ($p<0.001$). In addition, over 60% of raltegravir-treated subjects achieved a viral load <50 copies/mL at Week 16 compared with 35% in placebo. The mean change in HIV-1 RNA from baseline in raltegravir-treated subjects was -2.3 to 2.4 $\log_{10}$ compared to -1.0 to 1.3 $\log_{10}$ in placebo. The increase in CD4+ cell count from baseline was over twice that of placebo.

Table 6.1.4.C: FDA Week 16 Efficacy Analysis for Protocols 018 and 019 (All Treated)[1]

	Protocol 018		Protocol 019	
	Raltegravir N=232	**Placebo N=118**	**Raltegravir N=230**	**Placebo N=119**
<400 copies/mL – n (%)*	179 (77)	49 (42)	180 (78)	51 (43)
<50 copies/mL– n (%)	146 (63)	40 (34)	143 (62)	43 (36)
HIV-1 RNA change from baseline ($\log_{10}$) – mean (SD)	-2.3 (1.1)	-1.0 (1.3)	-2.4 (1.2)	-1.3 (1.3)
CD4+ cell count change from baseline (cells/mm^3) – mean (SD)	81 (94)	32 (73)	84 (96)	39 (74)

Source: Statistical Review of NDA 22-145, by Dr. Karen Qi

* p value <0.001 for each protocol

[1] If the measurement at a visit was missing and the one at next visit was available, then the one at the next visit was used. If the one at the next visit was missing as well, then the one at the previous visit was carried forwards to Week 16. For example, if a patient did not have HIV RNA value at Week 16, but had one at Week 24, then the one at Week 24 was used to impute the missing measurement at Week 16. If HIV RNA at Week 24 was missing as well, then Week 12 RNA level was carried forwards to Week 16.

Approximately 60% of subjects had reached Week 24 at the time of NDA submission. Analysis of Week 24 data is presented in Table 6.1.4.D; the virologic and CD4+ cell count response support the Week 16 results. A total of 50% of placebo subjects experienced VF, with the majority due to lack of virologic response at Week 16. A total of 15% of raltegravir-treated subjects experienced virologic failure (VF), with the majority due to rebound. Paired screening and on-treatment samples in Protocols 018 and 019 were available from 27 evaluable raltegravir-treated virologic failure subjects, with 22 due to rebound. An earlier November 15, 2006 cutoff date allowing time for sample amplification and sequencing accounts for the smaller number of subjects. A median of 3 (range 1 to 8) amino acid substitutions in HIV-1 integrase were detected from the viruses of 26 subjects. At least two major pathways, Q148 and N155, appear to be involved independently in emergence of raltegravir resistance (Section 6.1.5).

Table 6.1.4.D: FDA Week 24 Efficacy Analysis for Protocols 018 and 019 (All Treated)

	Protocol 018		Protocol 019	
	Raltegravir N=232	Placebo N=118	Raltegravir N=230	Placebo N=119
*Subjects with 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)
HIV-1 RNA change from baseline (log_{10})[2,3] – mean (SD)	-2.2 (1.2)	-1.1 (1.3)	-2.4 (1.3)	-1.1 (1.4)
CD4+ cell count change from baseline (cells/mm^3) – Mean (SD)[2,4]	83 (98)	33 (71)	92 (98)	39 (71)
Virologic failure – n (%) Week 16 Nonresponder Week 24 Rebound	36 (15) 5 (2) 31 (13)	63 (53) 44 (37) 19 (16)	40 (17) 9 (4) 31 (13)	58 (49) 33 (28) 25 (21)
Discontinuation by Week 24 – n (%) Due to Adverse Events Due to Other	4 (2) 1 (<1)	4 (3) 0 (0)	5 (2) 5 (2)	1 (1) 2 (2)
Death by Week 24 – n (%)	3 (1)	3 (3)	3 (1)	0 (0)

Source: Statistical Review of NDA 22-145, by Dr. Karen Qi

[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.

Two discontinuations were due to "Other" reasons in the placebo group; however, in the package insert only one discontinuation is reported in this category. The definition for discontinuation due to other reasons in the package insert does not include discontinuation due to lack of efficacy (N=1 in the placebo arm of Protocol 019), and this accounts for the difference.

Subgroup Analysis

The following tables present subgroup analyses of gender, race, GSS, PSS, degree of PI resistance, and use of ENF and/or DRV in the OBT using the Week 16 HIV-1 RNA <400 copies/mL endpoint. Each raltegravir-treated subgroup had a higher proportion of subjects achieving HIV-1 RNA<400 copies/mL than placebo. Additional subgroup analyses using Week

16 HIV-1 RNA <50 copies/mL, Week 24 HIV-1 RNA <400 copies/mL, and Week 24 HIV-1 RNA <50 copies/mL endpoints yielded similar results.

Gender/Race

White and Asian subjects had modestly higher response rates compared with Blacks and Hispanics, although subject numbers in most subgroups are small.

Table 6.1.4.E: Protocols 018 and 019: HIV-1 RNA <400 copies/mL at Week 16 (All Treated): Gender and Race

	Protocol 018		Protocol 019		Total	
Responders / Evaluable (%)	**Raltegravir**	**Placebo**	**Raltegravir**	**Placebo**	**Raltegravir**	**Placebo**
Gender						
Female	27/37 (73)	7/15 (47)	14/20 (70)	3/12 (25)	41/57 (72)	10/27 (37)
Male	152/195 (78)	42/103 (41)	166/210 (79)	48/107 (45)	318/405 (79)	90/210 (43)
Race						
White	133/175 (76)	36/96 (38)	107/126 (85)	35/77 (45)	242/301 (80)	72/173 (42)
Black	11/18 (61)	2/5 (40)	34/48 (71)	9/21 (43)	45/66 (68)	11/26 (42)
Asian	12/14 (86)	2/5 (40)	2/2 (100)	0/1 (0)	14/16 (88)	2/6 (33)
Hispanic	6/6 (100)	0/1 (0)	31/47 (66)	6/18 (33)	37/53 (70)	6/19 (32)
Native American	0/0	0/0	1/1 (100)	0/0	1/1 (100)	0/0
Other	15/19 (79)	8/11 (73)	5/6 (83)	1/2 (50)	20/25 (80)	9/13 (69)

Source: Statistical Review of NDA 22-145, by Dr. Karen Qi

Number of Active PIs in OBT, PSS, GSS

Over 60% of raltegravir-treated subjects achieved a virologic response of <400 copies/mL when no active PIs were in the OBT compared with <20% in placebo. In addition, over 50% of raltegravir-treated subjects with a PSS or GSS of zero achieved <400 copies/mL compared with <10% in placebo. The rates of virologic response in raltegravir-treated subjects increased with inclusion of more active agents in the OBT. A statement will be included in the package insert Indications and Usage section to reflect this outcome. As the number of active agents in the background regimen increased, the treatment effect between the two groups diminished, particularly with GSS and PSS scores ≥ 3.

Table 6.1.4.F: Protocols 018 and 019: HIV-1 RNA <400 copies/mL at Week 16 (All Treated): Number of Active PIs, PSS, and GSS

	Protocol 018		Protocol 019		Total	
Responders / Evaluable (%)	**Raltegravir**	**Placebo**	**Raltegravir**	**Placebo**	**Raltegravir**	**Placebo**
Number of active PI in OBT by phenotypic resistance test						
0	70/100 (70)	9/55 (16)	40/66 (61)	7/42 (17)	110/166 (66)	16/97 (16)
1 or more	102/123 (83)	39/61 (64)	135/155 (87)	43/76 (57)	237/278 (85)	82/137 (60)
Missing	7/9 (78)	1/2 (50)	5/9 (56)	1/1 (100)	12/18 (67)	2/3 (67)
Phenotypic Sensitivity Score (PSS)						
0	25/44 (57)	1/21 (5)	14/23 (61)	1/23 (4)	39/67 (58)	2/44 (5)
1	52/67 (78)	17/39 (44)	57/78 (73)	12/32 (38)	109/145 (75)	29/71 (41)
2	61/67 (91)	14/33 (42)	63/75 (84)	17/33 (52)	124/142 (87)	31/66 (47)
3 or more	33/44 (75)	14/21 (67)	37/41 (90)	18/27 (67)	70/85 (82)	32/48 (67)
Missing	8/10 (80)	3/4 (75)	9/13 (69)	3/4 (75)	17/23 (74)	6/8 (75)
Genotypic Sensitivity Score (GSS)						
0	40/70 (57)	4/34 (12)	23/45 (51)	2/31 (6)	63/115 (55)	6/65 (9)
1	65/76 (86)	21/48 (44)	84/102 (82)	20/48 (42)	149/178 (84)	41/96 (43)
2	53/57 (93)	16/22 (73)	47/54 (87)	21/27 (78)	100/111 (90)	37/49 (76)
3 or more	18/26 (69)	8/13 (62)	22/25 (88)	5/10 (50)	40/51 (78)	13/23 (57)
Missing	3/3 (100)	0/1 (0)	4/4 (100)	3/3 (100)	7/7 (100)	3/4 (75)

Source: Statistical Review of NDA 22-145, by Dr. Karen Qi

Use of Enfuvirtide and/or Darunavir in OBT

Approximately 60% of raltegravir-treated subjects without use of either ENF or DRV achieved HIV-1 RNA <400 copies/mL at Week 16 compared to approximately 25% in placebo. Reflecting the PSS and GSS data, the treatment effect between raltegravir and placebo groups decreased when initial use of both agents was incorporated into the background regimen; however, 95-96% of raltegravir-treated subjects in this group achieved virologic response.

Table 6.1.4.G: Protocols 018 and 019: HIV-1 RNA <400 copies/mL at Week 16 (All Treated): Use of Enfuvirtide (ENF) and/or Darunavir (DRV) in the OBT

	Protocol 018		Protocol 019		Total	
Responders / Evaluable (%)	**Raltegravir**	**Placebo**	**Raltegravir**	**Placebo**	**Raltegravir**	**Placebo**
ENF use in OBT						
No	108/144 (75)	28/75 (37)	108/143 (76)	25/73 (34)	216/287 (75)	53/148 (36)
Yes in ENF exp. subjects	26/40 (65)	4/19 (21)	32/43 (74)	8/22 (36)	58/83 (70)	12/41 (29)
Yes in ENF naïve subjects	45/48 (94)	17/24 (71)	40/44 (91)	18/24 (75)	85/92 (92)	35/48 (73)
DRV use in OBT						
No	119/156 (76)	29/83 (35)	84/122 (69)	13/55 (24)	203/278 (73)	42/138 (30)
Yes in DRV exp. subjects	6/14 (43)	0/5 (0)	2/4 (50)	0/4 (0)	8/18 (44)	0/9 (0)
Yes in DRV naïve subjects	54/62 (87)	20/30 (67)	94/104 (90)	38/60 (63)	148/166 (89)	58/90 (64)
Naïve ENF use and naïve DRV use	19/20 (95)	8/9 (89)	24/25 (96)	12/14 (86)	43/45 (96)	20/23 (87)
Naïve ENF use and no DRV use	26/28 (93)	9/15 (60)	15/18 (83)	6/10 (60)	41/46 (89)	15/25 (60)
No ENF use and naïve DRV use	23/28 (82)	9/16 (56)	48/53 (91)	18/33 (55)	71/81 (88)	27/49 (55)
No ENF use and no DRV use	82/109 (75)	19/55 (35)	60/88 (68)	7/38 (18)	142/197 (72)	26/93 (28)

Source: Statistical Review of NDA 22-145, by Dr. Karen Qi

Use of Tipranavir in OBT, by Number of Active PIs in OBT

Drug-drug interaction studies found TPV/ritonavir decreases raltegravir plasma concentrations. Therefore, the potential for decreased virologic response rates exists with a TPV/raltegravir combination regimen compared with raltegravir alone. The Phase 3 studies allowed TPV as an OBT option. The following analysis compared response rates by the presence or absence of TPV. Analyses were conducted by the number of active PIs in the OBT (0 or ≥1) and TPV sensitivity (sensitive or resistant), using the Week 16 HIV-1 RNA <400 copies/mL virologic endpoint. Analyses of DRV were included as a comparator.

First, response rates of subjects with no active PIs in the background regimen were evaluated. Subjects who received TPV but were TPV-resistant (R) were compared to subjects without an active PI who did not receive TPV. Results indicate response rates for TPV-R subjects were slightly lower than other subjects without an active PI in the OBT. Allowing for the small number of subjects in this subgroup analysis, clinical significance is uncertain. Furthermore, response rates in DRV-experienced subjects without an active PI in the OBT and using DRV were less than those observed with TPV.

In another analysis, virologic responses were evaluated in subjects who had at least one active PI in their OBT. TPV-sensitive (S) subjects receiving TPV were compared to subjects receiving other PIs to which their viral isolates were susceptible. Responses rates in TPV-S subjects were similar to response rates in subjects receiving at least one active PI other than TPV.

Therefore, a decreased virologic response in raltegravir-treated subjects using TPV in the OBT is not apparent.

Table 6.1.4.H: Analysis of Tipranavir (TPV) and Darunavir (DRV) use in Protocols 018 and 019 comparing Number (#) of Active Protease Inhibitors (PI) in OBT: Week 16 HIV-1 RNA <400 copies/mL

#Active PI in OBT	Raltegravir	Placebo
0		
TPV in OBT (HIV-1 Resistant to TPV)	24/43 (56%)	5/19 (26%)
No TPV in OBT	86/123 (70%)	11/78 (14%)
DRV in OBT (DRV experienced)[1]	8/18 (44%)	0/9 (0%)
No DRV in OBT	102/148 (69%)	16/88 (18%)
≥1		
TPV in OBT (HIV-1 Sensitive to TPV)	44/51 (86%)	10/21 (48%)
No TPV in OBT	193/227 (85%)	72/116 (62%)
DRV in OBT (DRV naïve)[1]	147/166 (89%)	57/90 (63%)
No DRV in OBT	90/112 (80%)	25/47 (53%)
Missing	12/18 (67%)	2/3 (67%)

Source: Statistical Review of NDA 22-145, by Dr. Karen Qi; Applicant Slide 416 from Antiviral Drugs Advisory Committee Meeting, Sept. 5, 2007 for NDA 22-145

[1] For DRV, the terms "naïve" and "experienced" apply because a standard DRV resistance assay was not used during the Phase 3 studies.

Package Insert

The following tables and text reflect the efficacy data reported in the package insert (Tables 6.1.4.I, 6.1.4.J). The raltegravir package insert reports response rates for Protocols 018 and 019. Because the two studies were identical, FDA allowed the applicant to combine the results of Protocols 018 and 019. This data was confirmed by both this reviewer and Dr. Qi. Discrepancies between the Applicant and FDA analyses occur due to differences in determination of study visit windows and missing data imputations; however, because these

discrepancies were small (approximately <1%) and did not affect the conclusion that, in combination with an OBT, raltegravir has superior antiviral efficacy to placebo, the Applicant's analysis was placed in the label.

Table 6.1.4.I: Package Insert Table 7: Outcomes by Treatment Group through Week 24

BENCHMRK 1 and 2 Pooled n (%)	ISENTRESS 400 mg Twice Daily + OBT (N = 462)	Placebo + OBT (N = 237)
Outcome at Week 24	n (%)	n (%)
Subjects with Week 24 data	286	150
Subjects with HIV-1 RNA less than 400 copies/mL*	216 (75.5)	59 (39.3)
Subjects with HIV-1 RNA less than 50 copies/mL*	179 (62.6)	50 (33.3)
Virologic Failure (confirmed)†‡	74 (16.0)	121 (51.1)
Non-responder†‡	13 (2.8)	78 (32.9)
Rebound†‡	61 (13.2)	43 (18.1)
Death‡§	6 (1.3)	3 (1.3)
Discontinuation due to adverse experiences‡§	9 (1.9)	5 (2.1)
Discontinuation due to other reasons‡§¶	6 (1.3)	1 (0.4)

*Based upon the 436 patients with Week 24 data

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

‡Based upon the total 699 subjects randomized and treated, not all subjects complete to Week 24

§Includes available data beyond Week 24

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

The mean changes in plasma HIV-1 RNA from baseline were -1.85 $\log_{10}$ copies/mL in the ISENTRESS 400 mg twice daily arm and -0.84 $\log_{10}$ copies/mL for the control arm. The mean increase from baseline in CD4+ cell counts was higher in the arm receiving ISENTRESS 400 mg twice daily (89 cells/mm^3) than in the control arm (35 cells/mm^3).

Table 6.1.4.J: Package Insert Table 8: Virologic Response at Week 24 by Baseline Genotypic/Phenotypic Sensitivity Score

BENCHMRK 1 and 2 Pooled (Noncompleters as failures approach)	Percent with HIV RNA <400 copies/mL at Week 24				Percent with HIV RNA <50 copies/mL at Week 24			
	n	ISENTRESS 400 mg Twice Daily + OBT (N = 286)	n	Placebo + OBT (N = 150)	n	ISENTRESS 400 mg Twice Daily + OBT (N = 286)	n	Placebo + OBT (N = 150)
Phenotypic Sensitivity Score (PSS)*								
0	44	50	26	4	44	41	26	4
1	89	75	50	34	89	66	50	30
2	95	86	36	42	95	70	36	36
3 or more	48	73	33	67	48	56	33	55
Genotypic Sensitivity Score (GSS)*								
0	69	54	40	8	69	41	40	5
1	115	82	64	36	115	70	64	33
2	67	88	27	78	67	75	27	63
3 or more	30	70	18	61	30	53	18	50

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

6.1.5 Clinical Microbiology

This Section provides a brief summary of the FDA Microbiology Review. Please refer to the review by Dr. Sung Rhee for additional information.

Mechanism of Action

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 subjects 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 subjects. 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 subjects:

- 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 subjects with virologic response to raltegravir treatment (4 patients from Protocols 005 and 018) or with virologic failure to placebo therapy (12 subjects from Protocol 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 subjects) and/or V151I (3 subjects). 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 subjects (25.9%) and conferred 24-fold, 46-fold, and 27-fold resistance, respectively. Associated substitutions included E92Q (1 subjects), G140A/S (4 subjects), V151I (1 subjects), and S230N/R (1 subjects). 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 subjects) or S230N/R (2 subjects). 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 subjects experiencing virologic failure to raltegravir treatment, key amino acid changes were observed at Q148 (27 subjects), N155 (18 subjects) and Y143 (2 subjects). In addition to key changes at Q148 and N155, E92Q (2 subjects), G140A/S (23 subjects), V151I (5 subjects), and S230N/R (6 subjects) 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.

6.1.6 Efficacy Conclusions

Raltegravir in combination with OBT displays greater antiviral activity as compared to OBT alone in treatment-experienced subjects with a statistically significant difference in Week 16 HIV-1 RNA <400 copies/mL in the two Phase 3 studies. Raltegravir's superior antiviral activity is supported by results from analyses of Week 16 HIV-1 RNA <50 copies/mL, change in CD4+ cell count and HIV-1 RNA from baseline, and multiple subgroup analyses.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Safety data for this NDA was submitted as final study reports, a clinical safety summary and electronic datasets. Narrative summaries were provided for all subjects who died, developed a serious adverse event (SAE), or discontinued from the study because of an adverse event (AE). Adverse events and laboratory abnormalities were graded using the 2004 Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.

All subjects receiving at least one dose of study drug in the Phase 2 and 3 studies were included in the safety analyses. A total of 902 HIV infected subjects had 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), submitted two months after NDA submission: 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 005. A total of 692 subjects received the proposed dose of 400 mg twice daily for any duration; 548 received the proposed dose for at least 24 weeks.

Safety analyses of common AEs 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 OBT. The majority of AE analyses were limited to the double-blind treatment period to allow a more direct comparison among treatment arms. AEs and SAEs occurring in the open-label period were generally considered separately. SUR data was used to conduct most analyses. Causality analyses using investigator determination of drug-relatedness were applied in appropriate situations. Finally, several analyses included all doses from the Phase 2 studies in

addition to the Phase 3 studies to maximize evaluation of uncommon, potentially clinically important AEs.

Grades were not provided by the Applicant with the SUR laboratory datasets. Therefore, in my review, I applied the DAIDS grading criteria to the laboratory results by creating appropriate formulas within the dataset; this accounts for minor differences between my analyses and the Applicant's analyses.

Summary results of the integrated safety analysis are presented in the following sections. Minor differences between the Applicant's results and FDA's results can be attributed to the differences in definitions of the double-blind treatment period, categorizing of adverse events, and methods for conducting the analyses and do not significantly alter the final conclusions.

Raltegravir was well tolerated in Phase 1 studies. Adverse events were generally mild, and no relationship to dose was observed. No SAEs were reported in the Phase 1 studies submitted to the NDA. Four subjects discontinued: Protocol 003 (raltegravir/EFV) one subject with vomiting on Day 1; Protocol 008 (raltegravir/TDF) one subject with increased AST/ALT on Day 12 (Predose Period 3 after recent 7 days of TDF alone); Protocol 017 (raltegravir/TPV/r) one subject suffered a concussion on Day 9.

In general, in dose-finding treatment-naïve Protocol 004 and dose-finding treatment-experienced Protocol 005, a relationship with dose and any adverse event was not observed; one exception appears to be rash, which is discussed in detail later in this review. 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 ENF use), nausea, and headache, and were observed with similar frequency in each study arm. Notable clinical AEs that occurred at a higher frequency in raltegravir-treated subjects included: rash (5.3% versus 2.5%) and herpes zoster (4.1% versus 0.7%). In addition, an increase in Grade 2 – 4 CK elevations was observed in raltegravir arms as compared to control.

In Phase 3 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. The majority of ADCs occurred during the double-blind treatment period (N=34), and no increase in the raltegravir arm as compared to placebo was observed.

Further analyses of deaths, SAEs, discontinuations due to AEs, and particular AEs of interest are presented in the following sections.

7.1.1 Deaths

For the mortality analysis, SUR data from all raltegravir doses in Phase 2 and 3 studies were examined. 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 7.1.1.A. All deaths occurred in

HIV-positive, treatment-experienced, adult subjects; therefore, mortality analyses are limited to the treatment-experienced studies.

A total of 13 deaths (2.2%, 13/595) occurred in the raltegravir group versus 3 deaths (1.1%, 3/282) in placebo. 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 7.1.1A: Cumulative Death Summary in Phase 2 and 3 Studies (through Frozen File Date of 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 005					
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 (SUR Frozen File 2/16/07) and DEMODATA datasets for Protocols 005, 018, and 019
AN= allocation number, OLPVF = open-label post virologic failure, Dbl-Blind = double-blind, Tx = treatment,

The majority of deaths were related to either opportunistic infection (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-1 RNA, and CD4+ cell counts was performed to compare the subjects who died to the randomized population (Table 7.1.1.B). Protocols 005, 018, and 019 were selected because these protocols enrolled a similar HIV treatment-experienced population. All subject deaths occurred in these protocols.

Table 7.1.1.B: Select Baseline Characteristics of Treatment-Experienced Subjects Who Died, Protocols 005, 018, 019

	Deaths on Raltegravir N=13	**Deaths on Placebo N=3**	**All Other Subjects N=861**
Age - Mean (Median)	45.4 (47)	52.3 (51)	45.2 (45)
Baseline HIV-1 RNA $\log_{10}$ - Mean (Median)	5.3 (5.2)	5.5 (5.4)	5.1 (4.7)
Baseline CD4* - Mean (Median)	103 (65)	5 (4)	173 (140)
Proportion Baseline CD4 ≤50* - %	46.2	100	26
Last CD4 - Mean (Median)	136 (108)	7 (7)	270 (234)

Source: QHIVRNA, AE (SUR Frozen File 2/16/07), QCD4CC (SUR Frozen File 2/16/07) datasets for Protocols 005, 018 and 019.
* N=581 for raltegravir-treated subjects with baseline CD4 measurements.

Subjects who died were more advanced at baseline with higher baseline HIV-1 RNA, lower baseline CD4+ cell counts, and lower last on study CD4+ cell counts compared with surviving subjects.

An analysis of Week 24 all-cause mortality in HIV treatment-experienced subjects was performed for the double-blind study period (Table 7.1.1.C). A total of 11 deaths occurred by Week 24, with 8 in the raltegravir group and 3 in placebo. Due to the 3:1 and 2:1 randomization

in the Phase 2 and 3 studies, there was greater raltegravir exposure compared with placebo; after adjustment for exposure, mortality rates were 2.8 in the raltegravir group versus 2.5 in placebo.

Table 7.1.1.C: Week 24 Mortality per 100 Patient-Years in Treatment-Experienced Subjects: All Treated, Protocols 005, 018, and 019, Double-Blind Treatment Phase (Frozen File 2/16/07)

	Raltegravir (N=595)	Placebo (N=282)
By Week 24		
Number of deaths	8	3
Person years exposure	282.1	120.8
Mortality rate per 100 patient-years	2.8	2.5

Source: Statistical Review of NDA 22-145, by Dr. Karen Qi

Table 7.1.1.D contains Week 24 mortality data from other clinical trials enrolling HIV treatment-experienced subjects, specifically ENF, TPV, and DRV. The mortality rates in the active arms ranged between 2.6 and 4.5. Recognizing the limits of cross study comparisons, this comparative data provides a framework in which to put the mortality rates from the raltegravir trials into context.

Table 7.1.1.D: Week 24 Mortality per 100 Patient-Years in Other HIV Clinical Trials

ENF Mortality at Wk 24 Analysis of TORO trials		TPV/r Mortality at Wk 24 Analysis of RESIST trials		DRV/r Mortality at Wk 24 Analysis of POWER trials	
ENF +/- OBT	OBT	TPV/r +/- OBT	CPI/r +/- OBT	DRV/r +/- OBT	CPI/r +/- OBT
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; OBT = optimized background therapy; TPV/r = tipranavir/ritonavir; CPI/r = comparator protease inhibitor/ritonavir; DRV/r = darunavir/ritonavir

Summary

The subjects enrolled in these trials were highly treatment-experienced, and the number of reported deaths does not appear to be in excess of mortality rates observed in similar patient populations. All deaths were considered unrelated to study therapy by investigators, and review of the narrative summaries supports investigator assessment. A relationship between study drug

dose, duration, or other factors and the report of deaths among subjects in the safety population is not apparent.

7.1.2 Other Serious Adverse Events

Serious Adverse Events

The Phase 2 and Phase 3 studies were examined for serious adverse events (SAEs) using SUR data, limited to the double-blind treatment period. A total of 152 SAEs occurred in raltegravir-treated subjects and 72 SAEs occurred in comparator arms. No dose response relationship was observed in the Phase 2 dose-finding studies; therefore, the raltegravir doses are combined. The following table presents the number of SAEs by protocol.

Table 7.1.2.A: Serious Adverse Events in Phase 2 and 3 Studies, By Protocol Double-Blind Treatment Period

	Raltegravir N=755	Control N=320
Protocol 004	12	3
Protocol 005	21	3
Protocol 018	62	36
Protocol 019	57	30
Total (%)	152 (20.1%)	72 (22.5%)

Source: AE dataset (SUR Frozen File 2/16/07) for Protocols 004, 005, 018 and 019

SAEs reported in two or more subjects are summarized in Table 7.1.2.B. Pneumonia was the most common SAE, occurring in approximately 1% of subjects in each group.

Table 7.1.2.B: Serious Adverse Events in Phase 2 and 3 Studies Occurring in ≥2 Subjects, Double-Blind Treatment Period

	Raltegravir N=755	Control N=320
Pneumonia – n (%)	8 (1.1)	4 (1.3)
Cellulitis – n (%)	4 (0.5)	0 (0)
Anemia – n (%)	3 (0.4)	0 (0)
Dehydration – n (%)	3 (0.4)	0 (0)
Depression – n (%)	3 (0.4)	1 (0.3)
Abdominal pain – n (%)	2 (0.3)	1 (0.3)
Asthma – n (%)	2 (0.3)	0 (0)
Chest pain – n (%)	2 (0.3)	0 (0)
Choriomeningitis lymphocytic – n (%)	2 (0.3)	0 (0)
Coronary artery disease – n (%)	2 (0.3)	1 (0.3)
Herpes simplex – n (%)	2 (0.3)	0 (0)
Hypersensitivity – n (%)	2 (0.3)	0 (0)
Immune reconstitution syndrome – n	2 (0.3)	0 (0)

(%)		
Intentional overdose – n (%)	2 (0.3)	1 (0.3)
Kaposi's sarcoma AIDS related – n (%)	2 (0.3)	0 (0)
Malaise – n (%)	2 (0.3)	0 (0)
Meningitis cryptococcal – n (%)	2 (0.3)	0 (0)
Myocardial infarction – n (%)	2 (0.3)	1 (0.3)
Oedema peripheral – n (%)	2 (0.3)	0 (0)
Pyrexia – n (%)	2 (0.3)	4 (1.3)
Renal failure – n (%)	2 (0.3)	1 (0.3)
Septic shock – n (%)	2 (0.3)	1 (0.3)
Shock – n (%)	2 (0.3)	0 (0)
Squamous cell carcinoma – n (%)	2 (0.3)	1 (0.3)
Esophageal candidiasis – n (%)	1 (0.1)	3 (0.9)
Asthenia – n (%)	0 (0)	2 (0.6)
CMV chorioretinitis – n (%)	0 (0)	2 (0.6)
Neutropenia – n (%)	1 (0.1)	2 (0.6)

Source: AE datasets (SUR Frozen File 2/16/07) for Protocols 004, 005, 018 and 019

Drug-Related Serious Adverse Events

A causality assessment was performed of investigator determined drug-related SAEs. SAEs described as "definitely", "possibly" or "probably" related to study drug in the AE dataset under the CAUSAL column were selected. Review of investigator assessment identified 16 drug-related SAEs in 13 subjects. Nine SAEs assessed by the investigator as drug-related were excluded because narrative review did not support a causal association with study drug.

Eight SAEs occurred in raltegravir-treated subjects (1.1%, 8/755) and included: gastritis, renal failure (N=2; one subject also experienced metabolic acidosis), hepatitis complicated by suspected IRS and treatment for thyrotoxicosis, herpes simplex, and hypersensitivity (N=2 in same subject, see Section 7.1.3 Rash: Hypersensitivity). With the exception of gastritis and herpes simplex, the remaining SAEs are discussed in more detail in later sections of the safety review.

Drug-related SAEs occurring in the control group included: lipoatrophy, nephrolithiasis, renal failure, lacunar infarction, neutropenia, pancreatitis, hyperglycemia, and hepatitis.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

An analysis of dropouts was performed for all Phase 2 and Phase 3 studies, limited to the double-blind treatment period (Table 7.1.3.1.A). There was no observed dose-related response;

therefore, all raltegravir doses are combined. Overall there were few study discontinuations in the Phase 2 and 3 studies and no imbalance between the raltegravir and control groups.

Table 7.1.3.1.A: Study Discontinuation in Phase 2 and 3 Studies, Double-Blind Treatment Period

	Protocol 004		Protocol 005		Protocol 018		Protocol 019		Total	
	Raltegravir N= 160 (%)	EFV N= 38 (%)	Raltegravir N= 133 (%)	Placebo N= 45 (%)	Raltegravir N= 232 (%)	Placebo N= 118 (%)	Raltegravir N= 230 (%)	Placebo N=119 (%)	Raltegravir N =755 (%)	Control N= 320 (%)
Lack of Efficacy	2 (1.3)	0 (0)	1 (0.8)	1 (2.2)	0 (0)	0 (0)	0 (0)	1 (0.8)	3 (0.4)	2 (0.6)
Adverse Event	1 (0.6)	0 (0)	3 (2.3)	1 (2.2)	4 (1.7)	4 (3.4)	6 (2.6)	1 (0.8)	14 (1.9)	6 (1.9)
Lost to Follow Up	3 (1.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.4)	0 (0)	4 (0.5)	0 (0)
Consent With-drawn	4 (2.5)	3 (7.9)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.9)	1 (0.8)	6 (0.8)	4 (1.3)
Other	1 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.1)	0 (0)
Total	11 (6.9)	3 (7.9)	4 (3.0)	2 (4.4)	4 (1.7)	4 (3.4)	9 (3.9)	3 (2.5)	28 (3.7)	12(3.8)

Source: DISPOS datasets (SUR Frozen File 2/16/07) for Protocols 004, 005, 018 and 019
The following subjects were also included in this double-blind analysis: AN 7088 with urosepsis because the last raltegravir dose was not confirmed and AN 3869 because therapy was discontinued during the double-blind phase (Day 60) and the subject ultimately discontinued from the study on Day 135 without ever resuming therapy.

This analysis of study discontinuations uses the SUR database and, therefore, differs from the numbers reported in the package insert in the Clinical Studies section which is limited to the data submitted at the time of the original NDA. The reported numbers in the package insert have been confirmed by this reviewer and are described in Section 6.1.4.

7.1.3.2 Adverse events associated with dropouts

A total of 23 subjects discontinued due to AEs during the Phase 2 and 3 studies at the time of the SUR database lock and are summarized in Table 7.1.3.2.A. Twenty discontinuations due to AEs occurred during the double-blind treatment phase, 2 during the open-label/extension phase of the Phase 2 studies, and 1 during the OLPVF phase of the Phase 3 studies. Case Report Forms were submitted for all discontinuations due to AEs in Protocols 018 and 019. The majority of study discontinuations due to AEs were due to fatal events.

Table 7.1.3.2.A: Study Discontinuations Due to Adverse Events in Phase 2 and 3 Studies, Double-Blind Treatment Period

Study	AN	Age/Sex/Race	Period	AE (Preferred Term)	Ser-ious	Days on SD at AE Onset	Day of SD D/C	Outcome
Raltegravir 200 mg BID								
005	3286	57/M/White	Post-Tx Double-Blind	Laceration	Yes	12	8	Fatal
005	3869	41/M/White	Post-Tx Double-Blind	AST, ALT increased	No	58, 113	135	Recovered
Raltegravir 400 mg BID								
005[1]	3876	48/M/White	Open Label	Acute myocardial infarction	Yes	375	375	Fatal
018	7005	60/M/White	OL PVF	Lymphoma Septic Shock	Yes	279	280	Fatal
018	8341	58/M/Asian	Double Blind	Obsessive thoughts	No	33	36	Not Recovered
018	8325	40/F/Black	Double Blind	Pneumonia Hepatitis Rectal Hemorrhage Septic Shock	Yes	93 102 118 119	108	Fatal
018	8353	38/M/Multi	Double Blind	Hepatomegaly Hyperlactacidemia Cryptococcal meningitis	No No Yes	76 76 76	80 80 80	Fatal
018	8204	45/M/White	Double Blind	Mycobacterial infection T-cell Lymphoma Multi-organ failure Shock	Yes Yes Yes Yes	74 85 93 93	93 93 93 93	Fatal
019[2]	15028	46/M/White	Double Blind	AST/ALT/ bilirubin increased Lymphoma	No Yes	62 64	62	Fatal
019	16314	58/M/Hispa	Double Blind	Dehydration with TB and Aspergillosis	Yes	32	31	Fatal
019	16318	50/M/White	Double Blind	Coronary Artery Disease	Yes	197	200	Fatal
019	16239	47/M/Hispa	Double Blind	Hepatic neoplasm malignant	Yes	69	75	Fatal
019	15115	39/M/Black	Double Blind	Renal failure	Yes	25	26	Not Recovered
019	16210	64/M/White	Double Blind	Flatulence	No	165	179	Not Recovered
Raltegravir 600 mg BID								
004	369	35/F/Multi	Double	AST, ALT	No	29	70	(Not

			Blind	increased				provided)
005	3243	42/M/White	Post-Tx Double Blind	Cardio-respiratory arrest, Shock, Bradycardia	Yes	146	146	Fatal
Placebo								
004	17	37/M/Hispa	Exten-sion	Intentional Overdose	Yes	502	501	Recovered
005	3278	51/M/White	Double Blind	Lipoatrophy	Yes	146	181	Not Recovered
018[1]	7056	42/M/White	Double Blind	End stage AIDS	Yes	-26	78	Fatal
018[1]	7088	64/M/White	Post-study Double Blind	Urosepsis	Yes	101	86	Fatal
018	8266	51/M/White	Double Blind	Pneumonia	Yes	5	25	Fatal
018	8334	42/M/White	Double Blind	Nausea	No	32	75	Not Recovered
019	16290	46/M/White	Double Blind	Hepatitis C	No	34	34	Not Recovered

Source: AE and DISPOS datasets (SUR Frozen File 2/16/07) for Protocols 004, 005, 018 and 019
OLPVF = open label post virologic failure
[1]Subjects AN 3876 and 7088 experienced AEs leading to study discontinuation outside of the double-blind treatment period. Subject AN 7056 the AE of end stage AIDS occurred prior to randomization, however, the subject died during the study. The Applicant does not include these subjects in their analysis of discontinuations due to AEs.

Discontinuations associated with AEs in raltegravir-treated subjects included:

Protocol 004 One subject with a history of TB on anti-TB treatment discontinued due to elevated hepatic enzymes.

Protocol 005 The following fatal events led to study discontinuation: suicide in a subject with a psychiatric history; suspected sepsis and ultimate cardiorespiratory arrest; acute myocardial infarction in a subject with known coronary artery disease. One subject discontinued due to elevated hepatic enzymes determined by the investigator to be secondary to ATV (although I do not agree with the investigator's assessment that ATV use led to hepatic enzyme elevation, association with raltegravir use appears unrelated).

Protocol 018 The following fatal events led to study discontinuation: septic shock due to an infection of an implantable chamber in a subject with underlying lymphoma; pneumonia, elevated liver enzymes, rectal hemorrhage and septic shock; recurrent cryptococcal meningitis; lymphoma, mycobacterial infection, and shock. One subject discontinued due to obsessive thoughts.

Protocol 019 The following fatal events led to study discontinuation: recurrent lymphoma associated with elevated liver enzymes and bilirubin; hepatocellular carcinoma in a subject with HBV; coronary artery disease

in a subject with a history of hypertension and chronic pulmonary heart disease admitted with pulmonary edema who died while awaiting coronary artery bypass grafting; dehydration with TB and aspergillosis. One subject who discontinued due to renal failure was receiving TDF and the episode of renal failure occurred during a hospitalization for clinical clostridium difficile and dehydration.

7.1.3.3 Other significant adverse events

Neoplasms: Safety Update Report Data

An analysis of neoplasms was performed on all subjects in Phase 2 and 3 clinical studies using the updated AE datasets provided with the SUR (Frozen File lock of 2/16/07), limited to *Neoplasms benign, malignant and unspecified* under BODY_SYS. Several subjects had duplicate PTs, therefore, duplicates were deleted. A total of 48 subjects experienced 52 neoplasms.

Table 7.1.3.3.A: All Neoplasms benign, malignant, and unspecified in Phase 2 and Phase 3 studies through Frozen File 2/16/07

Preferred Term	Raltegravir N=755	Control N=320	Total N=1075
Skin papilloma	17 (2.3%)	10 (3.1%)	27 (2.5%)
Squamous cell carcinoma	3 (0.4%)	2 (0.6%)	5 (0.5%)
Kaposi's sarcoma	3 (0.4%)	0	3 (0.3%)
Lymphoma	3 (0.4%)	0	3 (0.3%)
Hodgkin's Disease	2 (0.3%)	0	2 (0.2%)
Rectal cancer	2 (0.3%)	0	2 (0.2%)
Acrochordon	0	1 (0.3%)	1 (0.1%)
Anal cancer	1 (0.1%)	0	1 (0.1%)
Basal cell carcinoma	1 (0.1%)	0	1 (0.1%)
Buccal cavity papilloma	1 (0.1%)	0	1 (0.1%)
Fibrous histiocytoma	0	1 (0.3%)	1 (0.1%)
Hepatic neoplasm malignant	1 (0.1%)	0	1 (0.1%)
Keratoacanthoma	0	1 (0.3%)	1 (0.1%)
Lipoma	1 (0.1%)	0	1 (0.1%)
Seborrhoeic keratosis	1 (0.1%)	0	1 (0.1%)
Uterine leiomyoma	1 (0.1%)	0	1 (0.1%)
Total	**37 (4.9%)**	**15 (4.7%)**	**52 (4.8%)**

Source: AE (SUR Frozen File 2/16/07) datasets for Protocols 004, 005, 018 and 019.

From Table 7.1.3.3.A, neoplasms associated with malignancy were further analyzed: anal cancer, lymphoma, basal cell carcinoma, hepatic neoplasm malignant, Hodgkin's disease, Kaposi's sarcoma, rectal cancer, squamous cell carcinoma. Using this definition, 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 004 (squamous cell carcinoma of the vocal cord). No placebo-treated subject experienced a malignancy.

Table 7.1.3.3.B: Malignant Neoplasms in Phase 2 and 3 Studies by original treatment group randomization, as of Frozen File 2/16/07

Study	AN	Age/Sex/ Race	Preferred Term	Days on SD at AE Onset	Treatment Phase	Outcome
Raltegravir 200 mg bid						
005	3281	52/M/White	Hodgkin's disease Basal cell carcinoma	211 254	OLPVF (Day 157 switch to 600 mg bid; Day 325 switch to 400 mg bid)	Not recovered Recovered
Raltegravir 400 mg bid						
004	12	55/M/White	Kaposi's sarcoma**	409	Double-Blind	Recovered
005	3240	47/M/White	Hodgkin's disease**	441	OLPVF (Day 282 switch to 600 mg bid, Day 295 switch to 400 mg bid)	Not recovered
018	7005	60/M/White	B-cell lymphoma	76	Double-blind	Fatal
018	7026	42/M/White	Kaposi's sarcoma	29	Double-blind	Recovered
018	8204	45/M/White	T-cell Lymphoma	85	Double-blind	Fatal
018	8256	46/M/White	Kaposi's sarcoma**	110	Double-blind	Recovered
018	8288	45/M/White	Anal cancer	181	OLPVF (Day 178)	Recovered
018	8292	60/F/White	Rectal cancer	27	Double-blind	Not recovered
018	8321	46/M/White	Squamous cell carcinoma** (Ear)	35	Double-blind	Recovered
019	15028	46/M/White	Lymphoma	64	Post-treatment Double-blind (Day 62 stopped raltegravir)	Fatal
019	15084	63/M/White	Rectal cancer stage 0**	25	Double-Blind	Not recovered
019	15090	45/M/White	Metastatic squamous cell carcinoma	140	Double-Blind	Not recovered

			(Temple)			
019	15113	41/M/Black	Squamous cell carcinoma – CIS (Buttocks)[1]	30	Double-Blind	Recovered
019	16365	48/M/Black	Squamous cell carcinoma (Vocal cord)	67	Double-Blind	Recovered
019	16239	47/M/Hispa	Hepatic neoplasm malignant	69	Double-Blind	Fatal
EAP	18	50/M	Rectal cancer (Squamous cell CIS)	63	N/A	Non-fatal
EAP	58	52/F	B cell lymphoma (CNS)[2]	21	N/A	Non-fatal
Placebo/Comparator (Efavirenz)						
004	163	48/M/White	Squamous cell carcinoma (Vocal cord)	207	Double-Blind	Recovered
018	7024	57/M/White	Squamous cell carcinoma** (Scalp)	277	OLPVF (Day 184 switched to raltegravir)	Not recovered

Source: AE (SUR Frozen File 2/16/07) datasets for Protocols 004, 005, 018 and 019.
SD = Study Drug, EAP = Expanded Access Program (Protocol 023)
** Recurrent
[1] The preferred term in the AE dataset is "Mass"; however, in the SUR, the *sponsor term* is "Squamous cell carcinoma-carcinoma in situ (CIS)". This subject had a history of papilloma viral infection (HPV), and the Applicant states the CIS had evidence of HPV cytopathic effect. The SUR states the *sponsor term* for a diagnosis is assigned for clarity based on all data available in the Clinical Trials System or Worldwide Adverse Event System database to facilitate the analysis and discussion.
[2] Subject AN 58 had a 2-3 month history of left sided weakness prior to study entry per Applicant report of WAES data.

In summary, 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)

A total of 13 malignancies occurred in the double-blind treatment period. Baseline age, HIV-1 RNA, and CD4+ cell counts are presented in Table 7.1.3.3.C, limited to the double-blind treatment period for the treatment-experienced studies. Raltegravir-treated subjects with

malignancies appeared to have more advanced disease at baseline as evidenced by higher baseline HIV-1 RNA (median HIV-1 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).

Table 7.1.3.3.C: Select Baseline Characteristics of Treatment-Experienced Subjects Who Developed Malignancies, Protocols 005, 018, 019, Double-Blind Treatment Phase (Frozen File 2/16/07)

	Malignancies on Raltegravir N=13	Malignancies on Placebo N=0	Raltegravir Treated Subjects N=582	Placebo Treated Subjects N=282
Mean (Median)Age	48.8 (46)	n/a	45.3 (45)	44.8 (44.5)
Mean (Median) Baseline HIV-1 RNA	205,492 (90,600)	n/a	125,566 (56,050)	127,686 (45,750)
Mean (Median) Baseline CD4*	160 (34)	n/a	169 (140)	177 (135)
Proportion Baseline CD4 <50*	61.5%	n/a	23.8%	27.7%

Source: AE, QHIVRNA, QCD4CC (SUR Frozen File 2/16/07) datasets for Protocols 005, 018, 019
Includes two subjects diagnosed with malignancy <7 days after the double-blind treatment period: AN 15028 was diagnosed with lymphoma only two days after discontinuing raltegravir, and AN 8288 (randomized to raltegravir) was diagnosed with anal cancer three days after switching to open-label post virologic failure.
* N=581 for raltegravir-treated subjects with baseline CD4 measurements.

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.

Neoplasms: July 2007 Update

A more recent July 9, 2007 update of malignancies was submitted to the Agency in August 2007. A total of 36 malignancies were observed in 31 subjects: 30 malignancies in raltegravir-treated subjects (including 2 in subjects switching from placebo to OLPVF) and 6 in control, with 4 in placebo-treated subjects. The distribution of subjects with malignancies is presented by protocol and dose group in Table 7.1.3.3.D. The majority of malignancies occurred in raltegravir-treated subjects receiving the 400 mg twice daily dose.

Table 7.1.3.3.D: Malignancies by Protocol in Phase 2 and 3 Studies, July 2007 Update

Protocol	Treatment Arm	N subjects with Malignancy
004	EFV	1
	200 mg raltegravir	1
	400 mg raltegravir	2
005	200 mg raltegravir	1
	400 mg raltegravir	1
018/019	Placebo	4
	400 mg raltegravir	21

Source: TERMDB (7/9/07 Update) dataset

The types of malignancies consisted of a range of diagnosis and are summarized below.

Raltegravir-treated subjects

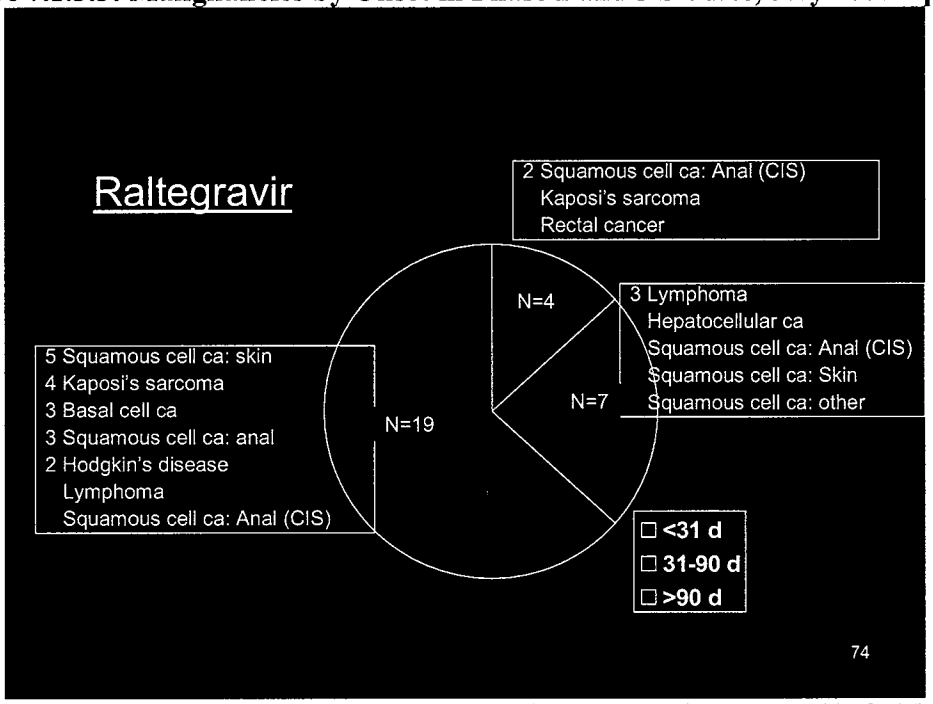
- Squamous cell ca: anogenital N=7
  - Anal (N=3)
  - Carcinoma in situ (N=4)
- Squamous cell carcinoma: skin N=6
- Kaposi's sarcoma N=5
- Lymphoma N=4
- Basal cell carcinoma N=3
- Hodgkin's disease N=2
- Rectal cancer N=1
- Hepatocellular carcinoma N=1
- Squamous cell carcinoma: other N=1

Control subjects

- Squamous cell carcinoma: anogenital N=2
  - Anal (N=2)
- Lymphoma N=1
- Basal cell carcinoma N=1
- Squamous cell carcinoma: other N=1
- Metastatic neoplasm N=1

The time to onset of malignancies in raltegravir-treated subjects was varied, ranging 25 to 557 days. No pattern was observed in the numbers or types of malignancies when evaluated by time of onset.

Figure 7.1.3.3: Malignancies by Onset in Phase 2 and 3 Studies, July 2007 Update



Source: FDA Backup Slide 74 from Antiviral Drugs Advisory Committee Meeting, Sept 5, 2007 for NDA 22-145

Limiting the analysis to the double-blind period of the Phase 2 and 3 studies, a total of 28 malignancies were reported: 22 in raltegravir-treated subjects, 8 of which were recurrences (Table 7.1.3.3.E). The median time to onset was 98 days in the raltegravir group versus 285 in control. The percentage of subjects with at least 1 malignancy was 2.5 in the raltegravir group versus 1.6 in control. Adjusted for exposure, the malignancy rates were 2.3 versus 1.9.

Table 7.1.3.3.E: Malignancies in Phase 2 and 3 Studies, July 2007 Update, Double-Blind Treatment Period

	Raltegravir N=755 PEY=824	Control N=320 PEY=262
# Malignancies	22	6
# Subjects with ≥1 Malignancy	19	5
# Recurrences	8	2
Time to Onset, days - Median	98	285
% Subjects with ≥1 Malignancy	2.5	1.6
Malignancy Rate, adjusted for PEY	2.3	1.9

Source: TERMDB (7/9/07 Update) dataset
PEY = patient exposure years

An additional analysis limited to the treatment-experienced Protocols 005, 018, and 019 resulted malignancy rates adjusted for exposure of 3.0 in raltegravir-treated subjects versus 2.1 in placebo, which is more similar than our earlier analysis using the SUR data (Table 7.1.3.3.F).

Table 7.1.3.3.F: Malignancies in Treatment-Experienced Protocols 005, 018, 019, July 2007 Update, Double-Blind Treatment Period

	Raltegravir N=595 PEY=539	Placebo N=282 PEY=195
# Malignancies	18	4
# Subjects with ≥1 Malignancy	16	4
# Recurrences	6	1
Time to Onset, days - Median	73	285
% Subjects with ≥1 Malignancy	2.7	1.4
Malignancy Rate, adjusted for PEY	3.0	2.1
***Prior SUR Malignancy Rate, adjusted for PEY (Raltegravir=395)**	3.3	0

Source: TERMDB (7/9/07 Update) dataset
PEY = patient exposure years

In summary, the occurrence of malignancies in the raltegravir development program has not been demonstrated to be directly attributable to raltegravir. The initial malignancy imbalance between raltegravir arms and placebo/control arms 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. In addition, with longer follow up, the imbalance diminished. The identified malignancies are expected in this heavily treatment-experienced HIV population, and no apparent pattern to the types of malignancies was observed. Nonetheless, an active surveillance program for malignancies and other potential adverse events will be undertaken by the Applicant as a post-marketing commitment.

AIDS-Defining Conditions

An analysis was performed of AIDS-defining conditions (ADCs) in the Phase 3 studies using SUR data. In Protocols 018 and 019, potential ADCs identified by the investigator and/or the Applicant were reviewed by an external adjudicator who was blinded to treatment assignment. The approach to adjudication was defined by a standard operating procedure. This analysis defines ADCs as those ADCs with a "Final Adjudicator's Diagnosis" of "Presumptive" or "Definitive". This analysis differs from the Applicant's analysis in the Clinical Summary of Efficacy because the Applicant limits their analysis to cases entered into the database prior to 12/13/06, the datalock for original NDA submission. My analysis includes a greater number of ADCs due to longer follow-up.

A total of 32 subjects experienced 40 ADCs as determined by the external adjudicator, 15 were "presumptive" diagnoses and 25 were "definitive" diagnoses. The majority of ADCs occurred during the double-blind treatment period (N=34). The following table lists the ADCs by treatment group occurring during the double-blind treatment period. Overall, no increase in ADCs was observed in the raltegravir group. 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.

Table 7.1.3.3.G: AIDS Defining Conditions in the Phase 3 Studies, Double-Blind Treatment Period

	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 (SUR 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)
PML=progressive multifocal leukoencephalopathy

Rash

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 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 TPV, 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 open-label, sequential, 2-period study evaluating the safety, tolerability, and pharmacokinetics of multiple doses of raltegravir administered alone or with multiple does of DRV and ritonavir. This study was not part of this NDA submission and has not been submitted to FDA for review. In Period 1, subjects received 400 mg raltegravir twice daily for four days, immediately followed by Period 2. In Period 2, the same subjects were co-administered 400 mg raltegravir bid with 600 mg DRV and 100 mg ritonavir bid 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 DRV, ritonavir, and raltegravir. All occurred during Period 2 after at least nine days of co-administration of DRV, ritonavir, and raltegravir. One of the subjects who discontinued experienced an SAE. The subject developed a diffuse maculo-papular rash on the trunk and extremities associated with a temperature of 100.7 °F on Day 12 of Period 2. Skin biopsy showed superficial perivascular chronic inflammation with rare intravascular neutrophils consistent with a delayed hypersensitivity reaction.

These four study discontinuations for rash in Protocol 029 are the only rash events in subjects receiving raltegravir in the NDA development program; given the temporal relationship of rash onset to DRV initiation, it is most likely that DRV was the cause of rash.

No cases of Stevens-Johnson syndrome were reported in subjects receiving raltegravir in the entire Phase 2 and 3 AE database. One case of erythema multiforme occurred in the efavirenz arm of Protocol 004.

In the Phase 2 and Phase 3 studies an analysis of rash adverse events was performed using the SUR AE data, limited to "Skin and Subcutaneous Tissue Disorders" under BODY_SYS.

A total of 293 subjects reported 404 skin and subcutaneous tissue disorder AEs, two were SAEs:

AN 3278	Lipoatrophy occurring in the placebo arm, double-blind phase of Protocol 05 on Day 146 prompting study therapy discontinuation
AN 16234	Henoch-Schonlein purpura occurring in the raltegravir arm, OLPVF phase of Protocol 019 on Day 204 prompting interruption of study therapy Day 204 until 209.

To allow more focused analyses of rash, 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. Several subjects had duplicate PTs or duplicate AEs due to listing of multiple generic medications; therefore, duplicates were deleted.

A total of 87 subjects experienced 91 rash events, none were SAEs. No study discontinuations were due 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 without recurrence of rash.

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. While the incidence of rash appeared to increase slightly with increasing dose as shown in Table 7.1.3.3.H, the difference is small, and no rash resulted in study discontinuation. The efavirenz arm of Protocol 004 has the higher percentage of rash.

Table 7.1.3.3.H: Rash Events in Phase 2 and Phase 3 Studies, Double-Blind Treatment Period

Protocol	Raltegravir dose					
	100 mg[1] n (%) Total N=39	200 mg[2] n (%) Total N=83	400 mg[3] n (%) Total N=548	600 mg[4] n (%) Total N=85	All doses[5] n (%) Total N=755	Control[6] n (%) Total N=320
004	0	2 (5.0%)	1 (2.4%)	3 (7.5%)	6 (3.8%)	5 (13.2%)
005	-	2 (4.7%)	2 (4.4%)	7 (15.6%)	11 (8.3%)	2 (4.4%)
018	-	-	15 (6.5%)	-	15 (6.5%)	4 (3.4%)
019	-	-	24 (10.4%)	-	24 (10.4%)	6 (5.0%)
Total	0	4 (4.8%)	42 (7.6%)	10 (11.8%)	56 (7.4%)	17 (5.3%)

Source: AE (SUR Frozen File 2/16/07) datasets for Protocols 004, 005, 018 and 019.
[1] 100 mg: Protocol 004 N=39
[2] 200 mg: Protocol 004 N=40, Protocol 005 N=43
[3] 400 mg: Protocol 004 N=41, Protocol 005 N=45, Protocol 018 N=232, Protocol 019 N=230
[4] 600 mg: Protocol 004 N=40, Protocol 005 N=45
[5] All raltegravir doses: Protocol 004 N=160, Protocol 005 N=133, Protocol 018 N=232, Protocol 019 N=230
[6] Placebo/Comparator: Protocol 004 N=38, Protocol 005 N=45, Protocol 018 N=118, Protocol 019 N=119

A listing of the individual preferred terms of the "rash" definition, compared between the raltegravir and control arms, is presented in the following table (Table 7.1.3.3.I).

Table 7.1.3.3.1: Number (%) of Subjects with "Rash" Adverse Experiences in Phase 2 and Phase 3 Studies, Double Blind Treatment Period

	Raltegravir[1] N=755		Control[2] N=320	
	n	%	n	%
Subjects with ≥1 Rash AE[3]	**54**	**7.2%**	**17**	**5.3%**
Rash Preferred Term				
Exfoliative rash	0	-	1	0.3%
Rash	35	4.6%	8	2.5%
Rash erythematous	1	0.1%	0	-
Rash follicular	1	0.1%	0	-
Rash generalized	2	0.3%	0	-
Rash macular	4	0.5%	2	0.6%
Rash maculo-papular	5	0.7%	1	0.3%
Rash papular	4	0.5%	5	1.6%
Rash pruritic	3	0.4%	0	-
Rash vesicular	1	0.1%	0	-

Source: AE (SUR Frozen File 2/16/07) datasets for Protocols 004, 005, 018 and 019.
[1] All raltegravir doses: Protocol 004 N=160, Protocol 005 N=133, Protocol 018 N=232, Protocol 019 N=230
[2] Placebo/Comparator: Protocol 004 N=38, Protocol 005 N=45, Protocol 018 N=118, Protocol 019 N=119
[3] Although a subject may have had two or more clinical adverse experiences, the subject is counted only once within a category. The same subject may appear in different categories.

Rash events occurred in approximately 7% of raltegravir-treated subjects and 5% in control. The majority of rash events were mild/moderate in intensity. One subject (AN 16302) in the raltegravir arm of Protocol 019, double-blind treatment phase 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 the rash resolved without drug interruption.

The median time to rash onset in raltegravir-treated subjects was 45 days (range 1-290 days) and the median time to resolution was 20 days (range 3-287). In comparison, in the control group the median time to rash onset and resolution was 16 days (range 4-161 days) and 12 days (range 1-202 days), respectively.

Men had a higher rate of rash compared to women in the raltegravir arm: 8.2% (53/650) versus 2.9% (3/105). However, women had a higher rate of rash compared to men in the control arm: 9.8% (4/41) versus and 4.7% (13/279).

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% (17/755) versus 3.1% (10/320) in control. Three rashes in raltegravir-treated subjects (AN 3277, 7058, and 16272) resolved with discontinuation of a component of the OBT (fosamprenavir, ENF, and abacavir, respectively).

Twenty-three 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 004 and 005, in the interim phase in Protocol 004, or in the OLPVF phase. One subject (AN 3287) 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 that resolved without drug interruption. 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 (FTC)/TDF, and one due to delavirdine.

Rash: Hypersensitivity

A total of 14 hypersensitivity events were reported in 10 subjects during the double-blind treatment period of the Phase 2 and 3 studies (SUR data), occurring in 0.8% (6/755) of raltegravir-treated subjects and 1.3% (4/320) in control. Two hypersensitivity events were SAEs, both in raltegravir-treated subjects:

AN 15100 experienced hypersensitivity on Day 45 with resolution after discontinuation of DRV. This subject was able to resume raltegravir without further hypersensitivity events.

AN 6404 experienced multiple hypersensitivity episodes and treatment interruptions with discontinuation of DRV, ENF, and trimethoprim/sulfamethoxazole. This subject resumed raltegravir as of Day 180 without further reported hypersensitivity events.

Of the remaining four raltegravir-treated subjects, three have alternative causes determined by the investigator: environmental allergy, drug reaction to anti-TB therapy (isoniazid and streptomycin), and drug reaction to lisinopril. All four subjects were able to continue raltegravir with resolution of the hypersensitivity events.

Rash: Summary

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 were confounded by use of concomitant medications associated with rash such as DRV, abacavir, and delavirdine. All rashes reported in drug-drug interaction Protocol 029, for example, occurred after DRV was added to raltegravir. In an analysis limited to drug-related rash, no imbalance between the raltegravir and control arms was observed. Therefore, although rash events occurred during treatment with raltegravir, no consistent pattern was observed and, in general, the events did not result in raltegravir discontinuation.

Pruritus

A separate analysis of the Phase 2 and 3 SUR AE database was performed for pruritus. The following preferred terms were selected to define pruritus: pruritus, pruritus allergic, pruritus generalized. A total of 52 reports of pruritus were observed in 49 subjects: none were SAEs, all were mild to moderate in intensity, and none led to study drug discontinuation.

The majority of pruritus events occurring during the double-blind treatment period (92.3%, 48/52); therefore, further analyses are limited to the double-blind treatment period. No dose response relationship was observed as presented in Table 7.1.3.3.J.

Table 7.1.3.3.J: Pruritus Events in Phase 2 and Phase 3 Studies, Double-Blind Treatment Period

Protocol	Raltegravir dose					
	100 mg[1] n (%)	200 mg[2] n (%)	400 mg[3] n (%)	600 mg[4] n (%)	All doses[5] n (%)	Control[6] n (%)
004	4 (10.3%)	5 (12.5%)	2 (4.9%)	2 (5.0%)	13 (8.1%)	2 (5.3%)
005	-	2 (4.7%)	2 (4.4%)	4 (8.9%)	8 (6.0%)	2 (2.2%)
018	-	-	10 (4.3%)	-	10 (4.3%)	2 (1.7%)
019	-	-	5 (2.2%)	-	5 (2.2%)	4 (3.4%)
Total	4 (10.3%)	7 (8.4%)	19 (3.5%)	6 (7.1%)	36 (4.8%)	10 (3.1%)

Source: AE (SUR Frozen File 2/16/07) datasets for Protocols 004, 005, 018 and 019.
[1] 100 mg: Protocol 004 N=39
[2] 200 mg: Protocol 004 N=40, Protocol 005 N=43
[3] 400 mg: Protocol 004 N=41, Protocol 005 N=45, Protocol 018 N=232, Protocol 019 N=230
[4] 600 mg: Protocol 004 N=40, Protocol 005 N=45
[5] All raltegravir doses: Protocol 004 N=160, Protocol 005 N=133, Protocol 018 N=232, Protocol 019 N=230
[6] Placebo/Comparator: Protocol 004 N=38, Protocol 005 N=45, Protocol 018 N=118, Protocol 019 N=119

The mean and median time to onset of pruritus was 67 and 32.5 days, respectively, with a range between 1 to 325 days. A total of 26 pruritus events were considered drug-related by the investigator. The proportion of subjects with drug-related pruritus in the raltegravir arms was 3.2% (24/755) versus 0.6% (2/320) in the placebo/comparator arms. Five of these pruritus events were considered related to OBT including four raltegravir-treated subjects (AN 3277, 3588, 6404, 8394) where pruritus was considered related to a component of OBT (2 fosamprenavir, TPV, and indinavir, respectively). Three subjects experienced pruritus associated with rash (AN 3243, 3277, 3873), all receiving raltegravir; however, as noted above, the investigator assessed subject AN 3277's pruritus and rash related to fosamprenavir. In two additional subjects receiving raltegravir, pruritus was associated with a subcutaneous nodule in one subject receiving concomitant ENF (AN 7047), and associated with dry skin in another subject (AN 15029).

Overall the observed pruritus events were balanced between the two treatment groups. Investigator-assessment of drug-related pruritus was greater in raltegravir-treated subjects; however, none of the pruritus events were serious and none led to study discontinuation.

Herpes Zoster

Analysis of common AEs using the Phase 2 and 3 SUR database, limited to the double-blind treatment period detected an imbalance in herpes zoster between the raltegravir and control groups [3.8% (29/755) raltegravir, 1.9% (6/320) control]. Further analysis of herpes zoster events found approximately one-third of subjects had a prior history of zoster. The majority of

subjects had an HIV-1 viral load <400 copies/mL and an increase in CD4+ cell count >50 cells/mm^3 at the time of herpes zoster. With the exception of a lower percentage of raltegravir-treated subjects having a change in CD4+ cell count >100 cells/mm^3 at the time of herpes zoster, no other significant differences between the two groups were identified.

Table 7.1.3.3.K: Herpes Zoster and Associated Medical History, Onset, HIV-1 Viral Load, and CD4+ Cell Count, Phase 2 and 3 Studies, Double-Blind Treatment Period

	Raltegravir N=29	Control N=6
Prior history of zoster – n (%)	10 (34 %)	2 (33%)
Onset, days – mean, median	137, 104	98, 94
HIV-1 RNA <400 at time of zoster – n (%)	20 (69%)	5 (83%)
Change in CD4 >100 from baseline at time of zoster - n (%)	10 (34%)	4 (66%)
Change in CD4 >50 from baseline at time of zoster – n (%)	18 (75%)	4 (66%)

Source: AE (SUR Frozen File 2/17/07), MEDHIST, QHIVRNA, and QCD4CC datasets for Protocols 004, 005, 018, 019

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 7.1.3.3.L: Hepatic Events in Phase 2 and Phase 3 Studies, Double-Blind Treatment Period

Protocol	Raltegravir[1]		Control[2]	
	n	%	n	%
004	33	20.6%	10	26.3%
005	37	27.8%	2	5.0%
018	37	15.9%	15	12.7%
019	37	16.1%	18	15.1%

Source: AE (SUR Frozen File 2/16/07) datasets for Protocols 004, 005, 018 and 019.

[1] All raltegravir doses: Protocol 004 N=160, Protocol 005 N=133, Protocol 018 N=232, Protocol 019 N=230
[2] Placebo/Comparator: Protocol 004 N=38, Protocol 005 N=45, Protocol 018 N=118, Protocol 019 N=119

Individual hepatic-related preferred terms are listed in the following table by treatment arm (Table 7.1.3.3.M). A higher rate of laboratory-related hepatic events was reported in the raltegravir arm; however, no significant differences between the two groups were noted in the remainder of hepatic AEs.

Table 7.1.3.3.M: Hepatic-Related AEs in Phase 2 and Phase 3 Studies, Double-Blind Treatment Period

Preferred Term	Raltegravir N=755 n (%)		Control N=320 n (%)	
	n	%	n	%
ALT increased	36	4.8	10	3.1
AST increased	34	4.5	13	4.1
Abdominal pain upper	19	2.5	11	3.4
Blood bilirubin increased	15	2.0	4	1.3
Blood alkaline phosphatase increased	9	1.2	1	0.3
Blood bilirubin unconjugated increased	5	0.7	0	0.0
Hyperbilirubinaemia	4	0.5	0	0.0
Jaundice	4	0.5	1	0.3
Hepatitis	3	0.4	1	0.3
Hepatomegaly	2	0.3	3	0.9
Varices oesophageal	2	0.3	0	0.0
Ascites	1	0.1	0	0.0
GGT increased	1	0.1	0	0.0
Gastric varices	1	0.1	0	0.0
Hepatic neoplasm malignant	1	0.1	0	0.0
Hepatic pain	1	0.1	0	0.0
Hepatic steatosis	1	0.1	0	0.0
Hepatitis acute	1	0.1	0	0.0
Hepatosplenomegaly	1	0.1	0	0.0
Portal hypertension	1	0.1	0	0.0
Portal hypertensive gastropathy	1	0.1	0	0.0
Spleen palpable	1	0.1	0	0.0
Hepatitis toxic	0	0.0	1	0.3
Total	**144**	**19.1%**	**45**	**14.1%**

Source: AE (SUR Frozen File 2/16/07) datasets for Protocols 004, 005, 018 and 019.