CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

NDA/Serial Number:	N22145
Drug Name:	Isentress™ (raltegravir potassium) 400 mg tablets, administered twice daily (bid)
Indication(s):	Treatment of HIV-1 infection in combination with other antiretroviral agents in treatment-experienced patients
Applicant:	Merck Research Laboratories
Date(s):	Submission date: April 13, 2007 PDUFA date: October 12, 2007
Review Priority:	Priority
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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

In April of 2007, Merck submitted the NDA to seek the Agency's accelerated approval of raltegravir, the first antiretroviral drug of the pharmacological class of HIV-1 integrase inhibitors, in the treatment of HIV-infected treatment-experienced patients. The proposed indication was raltegravir 400 mg administered orally, twice daily (bid) with or without food, in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced patients with HIV-1 replication despite ongoing antiretroviral therapy.

After reviewing the efficacy results based on all 16-week data and approximately 60% of the 24-week data from two pivotal Phase III trials in treatment-experienced (i.e., Studies 018 and 019) in the original submission which included the data up to database locked on 12/13/06, the statistical reviewer concluded that raltegravir 400 mg bid in combination of the optimal background therapies (OBT) had superior efficacy over the placebo in combination of OBT for the treatment of HIV treatment-experienced patients. Additionally, based on the updated data from three Phase II or III trials in treatment-experienced patients (i.e., Studies 005, 018 and 019) which included the data up to the database locked on 2/16/07, the statistical reviewer concluded that there was no significant difference in mortality between raltegravir and placebo; however, at the same time, there were not enough deaths to rule out a difference in mortality.

1.2 Brief Overview of Clinical Studies

The NDA included the 48-week data from two dose-ranging Phase II trials (i.e., Study 004 for treatment-naïve patients, and Study 005 for treatment-experienced patients) and the complete 16-week and the partial 24-week data from two Phase III trials in treatment-experienced patients (i.e., Studies 018 and 019). This statistical report focuses on the efficacy of the two Phase III studies and the mortality analysis of the one Phase II and the two Phase III trials in treatment-experienced patients (i.e., Studies 005, 018 and 019).

Studies 018 and 019 were Phase III multicenter, double-blind, randomized, placebo-controlled trials. The primary objective of the studies was to evaluate the antiretroviral activity of raltegravir 400 mg bid compared to placebo, both in combination with OBT, for the treatment of HIV treatment-experienced patients. The two studies were identical in study design with the only difference arising in the geographic region. Study 018 was carried out in Europe, Asia, and central and south America, while Study 019 was conducted in north, central and south America. The patient population included treatment-experienced patients who had failed prior antiretroviral therapy. These patients had failed therapy as documented by HIV RNA > 1000 copies/mL and resistance to at least one drug in each of the three classes of licensed oral ARTs (i.e., NRTI, NNRTI and PI) at screening. In Study 018, a total of 352 patients were randomized in a 2:1 ratio to receive either raltegravir 400 mg bid (N=234) or placebo bid (N=118). Similarly, 351 patients were randomized in Study 019 to receive raltegravir (N=232) or placebo

(N=119). The randomization was stratified by the use of enfuvirtide in OBT (yes vs. no) and the degree of resistance to PI at study entry (resistant to 1 PI vs. >1 PI). The duration of the studies was 156 weeks. The studies consisted of two phases: 1) a double-blind phase during which the patients received the assigned treatment regimen for at least 16 weeks; and 2) an open-label post virologic failure phase during which any patient who met the criteria for virologic failure at Week 16 or beyond was allowed to stay on current treatment, to discontinue the studies, or to switch to receive open-label raltegravir. The primary efficacy endpoint in both studies was the percentage of patients achieving HIV RNA level < 400 copies/mL at Week 16. Other key efficacy endpoints at Week 16 included proportion of patients achieving HIV RNA < 50 copies/mL, mean change from baseline in HIV RNA level, and mean change from baseline in CD4 cell counts.

Study 005 was a Phase II multicenter, double-blind, randomized, dose-ranging, placebo-controlled trial to evaluate the safety, pharmacokinetics and efficacy of raltegravir bid at three different doses (i.e., 200, 400 and 600 mg) compared to placebo, both in combination with the OBT, in HIV-infected patients who have failed therapy. These patients had failed therapy as documented by HIV RNA > 5000 copies/mL and documented resistance to at least one drug in each of the three classes of licensed oral antiretroviral therapies. Because preliminary pharmacokinetic data suggest that co-administration of raltegravir with ATV increases overall drug exposure of raltegravir, there were two substudies depending on whether ATV was in the OBT in double-blind phase: patients who received non-ATV-containing OBT were enrolled in Substudy A and patients who received ATV-containing OBT were enrolled in Substudy B. A total of 179 patients were randomized in Substudies A and B in 1:1:1:1 ratio to the three raltegravir dose groups and the placebo group (raltegravir 200 mg: N=44, raltegravir 400 mg: N=45, raltegravir 600 mg: N=45; placebo: N=45). The randomization was stratified by enfuvirtide use (yes or no) and degree of resistance to PI at study entry (resistance to 1 PI or >1 PI). Similar to the Phase III studies, the study had two phases, namely, double-blind phase when the patients received the assigned treatment and open-label post virologic failure phase when the patients who failed to response at Week 16 or beyond could change to receive raltegravir. When the raltegravir dose of 400 mg bid was selected for the Phase III trials, the protocol was amended (2/28/06) to switch all patients who had completed at least 24 weeks of double-blind phase to receive open-label raltegravir. Also, under the original protocol, patients who switched to open-label post virologic failure phase received raltegravir 600 mg bid. In the protocol amendment, all patients entering open-label post virologic failure phase received raltegravir 400 mg bid. The primary efficacy endpoint was change from baseline in plasma HIV RNA (log_{10} copies/mL) at Week 24.

1.3 Statistical Issues and Findings

Overall, based on the data submitted, the following results were observed:

- In the two pivotal Phase III studies (018 and 019), approximately 78% of the patients in the raltegravir treatment group had HIV RNA viral load <400 copies/mL at Week 16 compared to 41% of the placebo patients in study 018 and 43% of the placebo patients in study 019 (where missing data were imputed

assuming treatment-related discontinuations were treatment failures).

- Raltegravir efficacy compared to placebo was less impressive for treatment-naive enfuvirtide and treatment-naïve darunavir patients and for patients with ≥3 phenotypic susceptibility scores (PSS).

The following issues were raised by the statistical review team:

- Nearly identical results were observed in the raltegravir treatment group in the two pivotal phase III trials for the applicant's primary efficacy endpoint (where missing data were imputed assuming treatment-related discontinuations were treatment failures): 178/228 (78.1%) of the subjects in Study 018 and 177/226 (78.3%) of the patients in Study 019 had HIV RNA viral loads that were less than 400 copies/mL at Week 16.

- Similar trends were also apparent in the two studies for the cumulative distribution of HIV RNA data for the following categories (<50, <400, <1,000, <10,000 and <100,000 copies/mL) and for many of the secondary endpoints.

As part of the data verification process, the review team requested the copies of original source documents for HIV RNA Amplicor, HIV RNA Ultra-sensitive, and CD4 count data for selected sites in studies 018 and 019 and treatment randomization schedules that were to be sent directly to the FDA from the external vendors for studies 004, 005, 018 and 019. In addition, the FDA requested Merck's standard operating procedures for randomization schedule generation and certification from the external vendors that the randomization code documents were obtained from the original electronic file sent to the vendors from Merck prior to study initiation. A sample of treatment codes and laboratory data were compared to corresponding values in the SAS data sets and appeared to match.

To evaluate the robustness of the efficacy results of the two Phase III trials in the treatment-experienced patients, the statistical reviewer used different rules of assigning of viral load results using results from different assays (i.e., standard, ultrasensitive and dilution assays), different definitions of visit windows for measurements of HIV RNA level and CD4 counts, and different approaches to impute missing data. The statistical reviewer's results were quite similar to the applicant's. With regards to the mortality, 16 patients died in the three Phase II or III trials in the treatment-experienced patients based on the updated datasets up to the database locked on 2/16/07 (raltegravir 13 vs. placebo 3 patients). The statistical reviewer calculated the mortality rates per person-year exposure and performed survival analysis using the updated data. There was no significant difference in the mortality between raltegravir and placebo groups; however, at the same time, there were not enough deaths to rule out a difference in mortality due to the short follow-up time.

2. INTRODUCTION

2.1 Overview

The HIV integrase is one of the three HIV-1 enzymes required for viral replication and catalyzes the stepwise process resulting in the integration of the HIV deoxyribonucleic acid (DNA) into the genome of the host cell. Merck has been developing raltegravir, the first HIV integrase strand transfer inhibitor, to treat HIV-infected patients. In this NDA, Merck submitted a series of Phase I studies, the 48-week data from two dose-ranging Phase II trials (i.e., Study 004 in treatment-naïve patients and Study 005 in treatment-experienced patients), and all 16-week data and partial 24-week data from the two pivotal Phase III trials in treatment-experienced patients to seek the Agency's accelerated approval of raltegravir for the treatment of HIV treatment-experienced patients. The proposed indication was raltegravir 400 mg administered orally, twice daily (bid) with or without food, in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced patients with HIV-1 replication despite ongoing antiretroviral therapy.

In this review report, we will review the efficacy of the two Phase III trials and the mortalities of the three Phase II or Phase III trials conducted in the treatment-experienced patients. Table 1 below summarizes the studies reviewed in this report.

Table 1: Summary of Reviewed Studies

Study ID	Study Design	Treatment Arms and Number of Randomized Patients	Geographic Region
Study 018	Phase III, multicenter, double-blind, randomized, placebo-controlled study to evaluate the safety and antiretroviral activity of raltegravir 400 mg bid in combination with an OBT vs. OBT alone in HIV-infected treatment-experienced patients	raltegravir 400 mg: n=354 placebo: n=118	Europe, Asia, Central and South America
Study 019	Phase III, multicenter, double-blind, randomized, placebo-controlled study to evaluate the safety and antiretroviral activity of raltegravir 400 mg bid in combination with an OBT vs. OBT alone in HIV-infected treatment-experienced patients	raltegravir 400 mg: n=232 placebo: n=119	North, Central and South America
Study 005	Phase II, multicenter, double-blind, randomized, dose-ranging, placebo-controlled study to evaluate the safety, pharmacokinetics and efficacy of raltegravir in combination with an OBT versus OBT alone in HIV-infected patients with documented resistance to at least one drug in each of the three classes of licensed oral antiretroviral therapies	raltegravir 200 mg: n=44 raltegravir 400 mg: n=45 raltegravir 600 mg: n=45 placebo: n=45	Europe, Asia, North, Central and South America

2.2 Data Sources

The application was electronic and can be found in FDA internal network drive of \\Cdsesub1\evsprod\NDA022145.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy of Studies 018 and 019

3.1.1 Study Design

Studies 018 and 019 were identical in study design with the only difference arising in that Study 018 was conducted in Europe, Asia, and Central and South America and Study 019 was carried out in North, Central and South America. Both studies were multicenter, double-blind, randomized, placebo-controlled trials in treatment-experienced HIV-infected patients who had failed prior antiretroviral therapy. These patients had failed therapy as documented by HIV RNA > 1000 copies/mL and documented resistance to at least one drug in each of the three classes of licensed oral ARTs (i.e., NRTI, NNRTI, and PI) at screening.

The primary objective of the studies was to evaluate the antiretroviral activity of Raltegravir 400 mg twice daily (bid) compared to placebo, both in combination with OBT, as measured by the proportion of patients achieving HIV RNA < 400 copies/mL at Week 16.

In Study 018, a total of 352 eligible patients were randomized in a 2:1 ratio to receive either Raltegravir 400 mg (N=234) or placebo (N=118), administered twice daily (bid). Similarly, a total of 351 patients were randomized to receive either Raltegravir (N=232) or placebo (N=119) in Study 019. The randomization was stratified by the use of enfuvirtide in OBT (yes vs. no) and the degree of resistance to PI at study entry (resistant to 1 PI vs. >1 PI).

The duration of the studies was 156 weeks. The studies had two phases: 1) a double-blind phase during which the patients received the assigned treatment regimen for at least 16 weeks; and 2) an open-label post virologic failure phase during which any patient who met the criteria for virologic failure at Week 16 or beyond had the following treatment options.

1) stayed on current treatment if the patient and the investigator felt that there was still sufficient benefit, or
2) discontinued the study, or
3) switched to an open-label treatment post virologic failure options where patients were able to change their OBT (if feasible) and received open-label Raltegravir once they had completed 16 weeks of study.

The virologic failure was defined as:

1) a confirmed decrease from baseline plasma HIV RNA < 1.0 $\log_{10}$ and HIV RNA > 400 copies/mL starting at Week 16 or beyond;
2) a virologic relapse starting at Week 16 or beyond that was defined as:
   (a) HIV RNA > 400 copies/mL on two consecutive measurements at least one week apart after initial response with HIV RNA < 400 copies/mL or
   (b) > 1.0 $\log_{10}$ increase in HIV RNA above nadir level on two consecutive measurements at least one week apart.

3.1.2 Efficacy and Safety Assessments

During the double-blind phase, HIV RNA and CD4 cell counts were determined at Screening, Randomization (Day 1), Weeks 2, 4, 8, 12, 16, 24, 32, 40, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156 and 14-day post-therapy follow-up. Plasma for viral resistance samples were collected at Screening, Week 24, Week 48, following virologic failure, and at the discontinuation visit (for patients that discontinued the study early). Blood for archiving were collected pretreatment at Randomization (Day 1) for possible future testing of the polymorphism of UGT1A1 or other drug-metabolizing enzymes.

During the open-label post virologic failure (OLPVF) phase, HIV RNA and CD4 cell count were determined after switching to open-label treatment post virologic failure at OLPVF Weeks 4, 8, 16, 24, 32, 40, 48, 60, 72, 84, 96, 108, 120, 132, final OLPVF visit (156 weeks of total study therapy), and 14-day post-therapy follow-up. Plasma for viral resistance samples were collected at OLPVF Week 24, OLPVF Week 48, and at the discontinuation visit (for patients who discontinued the open-label treatment option before Week 48).

Tables 6 and 7 in Appendix display the detailed schedule of efficacy and safety assessments.

3.1.3 Efficacy Endpoints

The primary efficacy endpoint in the two studies was the proportion of patients achieving HIV RNA <400 copies/mL at Week 16. The secondary efficacy endpoints included the following variables.

1) proportions of patients with either HIV RNA level <400 copies/mL, or reduction from baseline in HIV RNA (log10 copies/mL) exceeding 1.0 log10 copies/mL at Weeks 16 and 48;
2) proportions of patients with HIV RNA < 50 copies/mL at Weeks 16 and 48;
3) change from baseline in HIV RNA (log10 copies/mL) at Weeks 16 and 48;
4) change from baseline in CD4 cell count at Weeks 16 and 48;
5) proportions of patients with HIV RNA < 400 copies/mL at Week 48;
6) Time-to-loss-of-virologic-response (TLOVR) at Week 48.

3.1.4 Patient Disposition, Demographic and Baseline Characteristics

Table 2 displays patient disposition for both studies. In Study 018, a total of 352 patients were randomized, of whom 350 received at least one dose of assigned treatment regimen in Study 018 (raltegravir: 232; placebo: 118). In Study 019, a total of 351 patients were randomized, of whom 349 received at least one dose of assigned treatment regimen (raltegravir: 230; placebo 119). Of the randomized patients who received at least one dose of study medication, a few patients withdrew from the study during the double blind phase in both treatment groups in both studies and most common reason for discontinuation was due to the adverse event. In Study 018, 5 out of the 232 raltegravir-treated patients discontinued during the double-blind phase (4 discontinued due to clinical adverse event, and 1 due to consent withdrawn), compared to 4 out of 118 placebo-treated patients (all due to clinical adverse event). In Study 019, 10 out of the 230 patients in the raltegravir group withdrew from the study during the double-blind phase (4 due to clinical adverse event, 2 due to withdrawal of consent, and 1 due to lab adverse event), while 3 out of 119 placebo-treated patients discontinued the study in the double-blind study (1 due to lack of efficacy, 1 due to clinical adverse event, and 1 due to loss to follow-up). As expected, more patients in the placebo group experienced virologic failure and entered the open-label post virologic failure treatment phase. Specifically, 15 raltegravir-treated and 46 placebo-treated patients in Study 018 received the open-label treatment, and 19 raltegravir-treated and 39 placebo-treated patients in Study 019 entered the open-label treatment phase.

Table 2: Studies 018 and 019 – Patient Disposition

	Study 018			Study 019			Overall		
	Raltegravir	**Placebo**	**Total**	**Raltegravir**	**Placebo**	**Total**	**Raltegravir**	**Placebo**	**Total**
Number of screening – n (%)	500			512			1012		
Double–blind phase – n (%)									
Number of randomized	234 (100)	118 (100)	352 (100)	232 (100)	119 (100)	351 (100)	466 (100)	237 (100)	703 (100)
Number of treated	232 (99)	118 (100)	350 (99)	230 (99)	119 (100)	349 (99)	462 (99)	237 (100)	699 (99)
Discontinued study	5 (2)	4 (3)	9 (3)	10 (4)	3 (3)	13 (4)	15 (3)	7 (3)	22 (3)
Before Week 16[1]	5 (2)	4 (3)	8 (2)	6 (3)	3 (3)	9 (3)	11 (2)	7 (3)	18 (3)
Lack of efficacy	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (<1)	0 (0)	1 (<1)	1 (<1)
Clinical adverse event	4 (2)	4 (3)	8 (2)	3 (1)	1 (1)	4 (1)	7 (2)	5 (2)	12 (2)
Lab adverse event	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)	1 (<1)	0 (0)	1 (<1)
Consent withdrawn	1 (<1)	0 (0)	1 (<1)	2 (1)	0 (0)	2 (1)	3 (1)	0 (0)	3 (<1)
Loss to follow-up	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (<1)	0 (0)	1 (<1)	1 (<1)
After Week 16	0 (0)	0 (0)	0 (0)	4 (2)	0 (0)	4 (1)	4 (1)	0 (0)	4 (1)
Clinical adverse event	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)	1 (<1)	0 (0)	1 (<1)
Consent withdrawn	0 (0)	0 (0)	0 (0)	3 (1)	0 (0)	3 (1)	3 (1)	0 (0)	3 (<1)
Open–label post viral failure – n (%)									
Total entered	15 (6)	46 (39)	61 (17)	19 (8)	39 (33)	58 (17)	34 (7)	85 (36)	119 (17)
Discontinued treatment	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)	1 (<1)	0 (0)	1 (<1)
Continuing treatment	15 (6)	46 (39)	61 (17)	18 (8)	39 (33)	57 (16)	33 (7)	85 (36)	118 (17)
Time Switched from Double–blind phase to Open–label (weeks)									
Median (min, max)	22 (17, 36)	20 (17, 29)	20 (17, 36)	20 (17, 32)	19 (17, 32)	20 (17, 32)	21 (17, 36)	20 (17,32)	20 (17, 36)

Source: Clinical Study Report for Studies 018 and 019, Section 10, Table 10 – 3.
[1]Patient 7088 in Study 018 died on [redacted] which was approximately at 14 weeks after start of therapy, but the applicant regarded him discontinuing on [redacted] which was at 20 weeks after start of therapy in Table 10 – 3.

Tables 8 and 9 in Appendix summarize patient demographics and baseline characteristics. In general, patient demographics and baseline characteristics were balanced between the two treatment groups in both studies with exception of the number of patients infected with hepatitis B and hepatitis C. In Study 018, fewer patients in the raltegravir group had hepatitis B infection than those in the placebo group (raltegravir: 6%; placebo: 3%), but more patients in the raltegravir group than those in the placebo group had hepatitis C infection (raltegravir 13%; placebo 19%). In Study 019, fewer patients in the raltegravir group had hepatitis C infection compared to those in the placebo group (raltegravir 10%; placebo 3%).

A majority of the study patients were male (Study 018: 85%; Study 019: 91%) and white (Study 018: 77%; Study 019: 58%). The median age in the two studies was 45 years. A majority of patients in Study 018 were treated in Europe (74%) and a majority of patients in Study 019 were treated in North America. Above 90% of patients had a prior history of AIDS (Study 018: 92%, Study 019: 91%). Approximately 50% of the patients had baseline HIV RNA <=50,000 copies/mL (Study 018: 50%; Study 019: 48%), and the mean baseline $\log_{10}$ HIV RNA was above 4.5 $\log_{10}$ copies/mL (Study 018: 4.6 $\log_{10}$ copies/mL; Study 019: 4.7 $\log_{10}$ copies/mL). The average baseline CD4 counts for Studies 018 and 019 were 155 and 152 cells/mm^3, respectively. Approximately 20% of patients received enfuvirtide as the first time use (Study 018: 21%; Study 019: 20%). More patients in Study 019 (47%) received darunavir as the first time use than those in Study 018 (26%). The average phenotypic sensitivity scores were 1.5 and 1.6 in Studies 018 and 019, respectively. The average genotypic sensitivity score was 1.2 in both studies.

3.1.5 Statistical Methodologies

The efficacy analysis was conducted on the treated patient population which was defined as all the randomized patients who received at least one dose of study medication. For each of the defined virologic response (successes), the following approaches were used to handle missing values for patients who discontinued the assigned treatment:

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

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

- Non-Completer = Failure (NC=F): Patients who prematurely discontinued the assigned treatment regardless of reasons were considered as failures thereafter.

- The TRD=F approach was the primary approach. Of note, if a patient's OBT was changed due to lack of efficacy during the double-blind treatment period, this patient was considered as a virologic failure starting from the time the OBT was changed. OBT changes due to administrative reasons were not considered as failures.

To analyze the primary efficacy endpoint of proportion of patients achieving HIV RNA < 400 copies/mL at Week 16, the applicant employed a logistical regression model adjusted for the following prognostic factors: the baseline HIV RNA level, enfuvirtide use in OBT in enfuvirtide-naïve patients (yes/no), active PI in OBT determined by phenotypic resistance test (yes/no) and darunavir use in the OBT in darunavir- naïve patients (yes/no). Also, the Kaplan-Meier approach for time to loss of virologic-response (TLOVR) was applied to assess the durability of antiretroviral activity of Raltegravir. TLOVR was the time between randomization and the first HIV RNA value above 400 copies/mL, with non-responders who did not achieve HIV RNA values < 400 copies/mL on two consecutive visits being assigned a failure time of zero. Patients who discontinued assigned therapy were considered as a failure for TLOVR analysis. Similar methods were applied to other secondary efficacy endpoints of virologic response with binary outcome.

HIV RNA changes were calculated based on HIV RNA measured by COBAS Amplicor HIV Monitor standard assay. The values were imputed as 400 copies/mL for the standard assay values reported as "<400 copies/mL HIV RNA Detected", while they were imputed as 200 copies/mL for the standard assay values reported as "<400 copies/mL HIV RNA Not Detected". Baseline measurements were defined as the randomization/Day1 value for each patient. Baseline HIV RNA levels were carried forward for patients who discontinued assigned therapy due to lack of efficacy.

To address the secondary endpoint of change from baseline in CD4 cell count at Week 16, a mixed-effect model (with patients as random effects) adjusted for baseline CD4 cell counts, visit, stratum, and treatment was applied. The following logic, which was similar to the observed failure (OF) approach, was used to handle missing values: baseline CD4 cell count was carried forward for those who discontinued assigned therapy due to lack of efficacy and/or adverse experience.

3.1.6 Applicant's Results and Conclusion

Table 3 summarizes the applicant's analysis for the primary efficacy endpoint which demonstrated that a greater proportion of raltegravir-treated patients achieved HIV RNA < 400 copies/mL at Week 16 than the placebo-treated patients. Specifically, in Study 018, 77% of the patients in the Raltegravir group had HIV RNA < 400 copies/mL at Week 16 compared to 41% of the patients in the placebo group; in Study 019, 77% raltegravir-treated patients experienced HIV RNA < 400 copies/mL at Week 16 compared to 43% of the placebo-treated patients. The analysis included all randomized and treated patients, and regarded those who had missing HIV RNA values at Week 16 as failures. The applicant further conducted additional analyses using different missing data imputation methods, logistics regression and CMH tests. The results supported the superiority of raltegravir over the placebo with respect to the primary efficacy endpoint.

Table 3: Studies 018 and 019 – Applicant's Analysis Results for Primary Efficacy Endpoint of Proportion of Patients Achieving HIV RNA < 400 copies/mL at Week 16 (All Treated)

	Study 018				Study 019			
	Responses by Treatment Group – Responders/ Evaluable (%)		Treatment Difference in Percent Response (Raltegravir – Placebo)		Responses by Treatment Group – Responders/ Evaluable (%)		Treatment Difference in Percent Response (Raltegravir – Placebo)	
	Raltegravir (N=232)	Placebo (N=118)	Odds Ratio (95% CI)	p-value	Raltegravir (N=230)	Placebo (N=119)	Odds Ratio (95% CI)	p-value
Patients with HIV RNA < 400 copies/mL[1]	178/232 (77)	48/118 (41)	Not done	Not done	177/230 (77)	51/119 (43)	Not done	Not done
Additional analyses using different approaches to impute missing data								
Treatment-related discontinuation = Failure	178/228 (78)	48/117 (41)	11 (6, 20)[2] 10 (5, 18)[3]	<0.001[2] <0.001[3]	177/226 (78)	51/118 (43)	10 (5, 18)[2] 8 (4, 16)[3]	<0.001[2] <0.001[3]
Non-completer = Failure	178/230 (77)	48/118 (41)	10 (5, 18)[2] 9 (5, 17)[3]	<0.001[2] <0.001[3]	177/229 (77)	51/119 (43)	8 (4, 15)[2] 7 (4, 14)[3]	<0.001[2] <0.001[3]
Observed failure	178/225 (79)	48/113 (43)	10 (5, 20)[2] 9 (5, 18)[3]	<0.001[2] <0.001[3]	177/222 (80)	51/117 (44)	12 (6, 23)[2] 10 (5, 19)[3]	<0.001[2] <0.001[3]

Source: Clinical Study Report for Studies 018 and 019, Section 11, Tables 11 – 1 and 11 – 4; and Section 14, Table 14-14.
[1]The numerator was the number of patients having HIV RNA < 400 copies/mL in the treatment group, and the denominator was the total number of patients in the treatment group.
[2]The odds ratio and p-value were calculated using a logistic regression model adjusted for baseline HIV RNA level, enfuvirtide use in OBT in enfuvirtide naïve patients, active PI in OBT determined by phenotypic resistance test (not including darunavir use), darunavir use in OBT in darunavir naïve patients, and treatment group.
[3]The odds ratio and p-value were calculated using Cochran-Mantel-Haenszel adjusted for: baseline HIV RNA level, enfuvirtide use in OBT in enfuvirtide naïve patients, active PI in OBT determined by phenotypic resistance test (not including darunavir use), darunavir use in OBT in darunavir naïve patients, and treatment group.

Additionally, raltegravir group was superior to the placebo in the following key secondary efficacy endpoints at Week 16:

1) percentage of patients with HIV RNA < 50 copies/mL (Study 018: raltegravir 61% vs. placebo 33%; Study 019: raltegravir 62% vs. placebo 36%)

2) percentage of patients with > 1 $\log_{10}$ drop in HIV RNA or HIV RNA < 400 copies/mL (Study 018: raltegravir 85% vs. placebo 42%; Study 019: raltegravir 83% vs. placebo 50%)

3) mean change in HIV RNA from baseline (Study 018: raltegravir -1.9 vs. placebo -0.8 $\log_{10}$ copies/mL; Study 019: raltegravir -1.9 vs. placebo -1.1 $\log_{10}$ copies/mL)

4) mean change in CD4 cell count from baseline (Study 018: raltegravir 83 vs. placebo 31 cells/mm3; Study 019: raltegravir 85 vs. placebo 40 cells/mm3)

5) percentage of virologic failure (Study 018: raltegravir 14% vs. placebo 53%; Study 019: raltegravir 17% vs. placebo 48%).

Furthermore, the applicant analyzed the Week 24 efficacy endpoints using the patients who were randomized before 07/01/06 and had Week 24 available at the time of database locked (12/13/06), which consisted of about 68% and 56% of all Week 24 data in Studies 018 and 019, respectively. The raltegravir-treated patients again showed better efficacy in comparison with the placebo-treated patients in the following efficacy endpoints at Week 24.

1) percentage patients with HIV RNA < 400 copies/mL (Study 018: raltegravir 75% vs. placebo 40%; Study 019: raltegravir 76% vs. placebo 39%)

2) percentage of patients with HIV RNA < 50 copies/mL (Study 018: raltegravir 61% vs. placebo 33%; Study 019: raltegravir 65% vs. placebo 33%)

3) percentage of patients with > 1 $\log_{10}$ drop in HIV RNA or HIV RNA < 400 copies/mL (Study 018: raltegravir 81% vs. placebo 43%; Study 019: raltegravir 81% vs. placebo 44%)

4) mean change in HIV RNA from baseline (Study 018: raltegravir -1.8 vs. placebo -0.8 $\log_{10}$ copies/mL; Study 019: raltegravir -2.0 vs. placebo -1.0 $\log_{10}$ copies/mL)

5) mean change in CD4 cell count from baseline (Study 018: raltegravir 86 vs. placebo 30 cells/mm3; Study 019: raltegravir 93 vs. placebo 40 cells/mm3)

6) percentage of virologic failure (Study 018: raltegravir 15% vs. placebo 53%; Study 019: raltegravir 17% vs. placebo 49%).

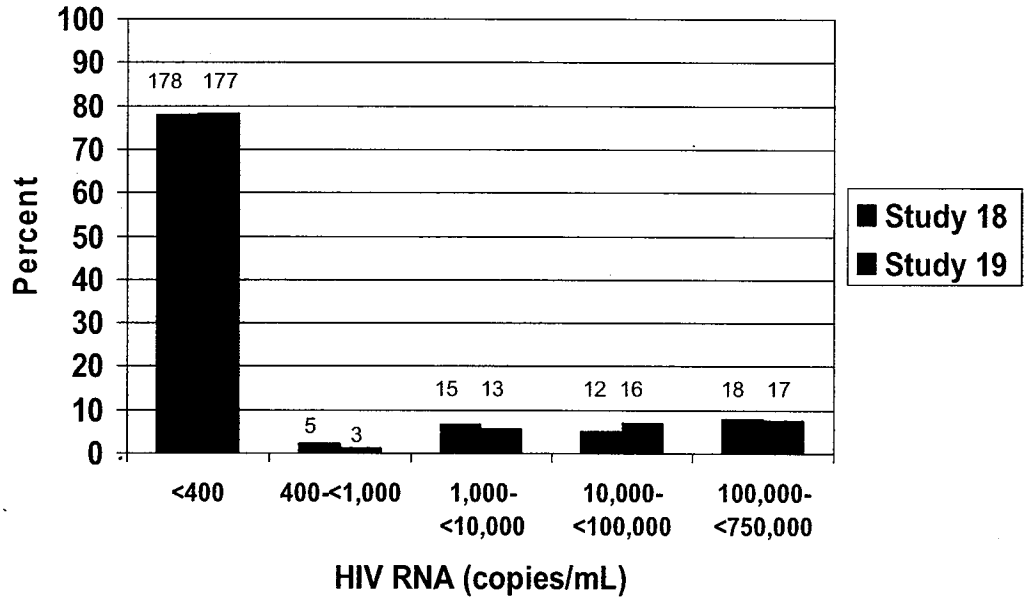
Tables 10 and 11 in Appendix display the applicant's analyses for the key secondary efficacy endpoints at Weeks 16 and 24.

Based on the results for the primary and secondary efficacy analyses, the applicant concluded that raltegravir 400 mg bid in combination with an OBT had superior antiretroviral activity compared with the placebo in combination with an OBT.

3.1.7 Reviewer's Comments

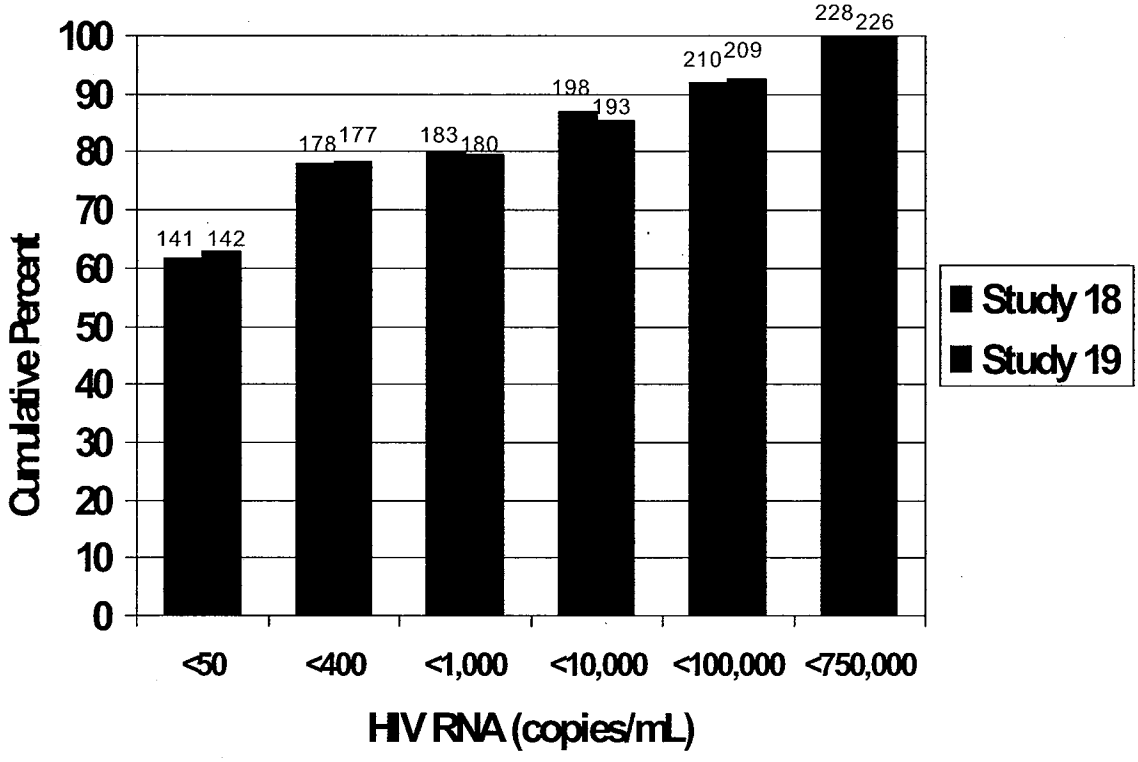
Nearly identical results were observed in the raltegravir treatment group in the two pivotal phase III trials for the applicant's primary efficacy endpoint (where missing data were imputed assuming treatment-related discontinuations were treatment failures); 178/228 (78.1%) of the subjects in study 018 and 177/226 (78.3%) of the subjects in study 019 had HIV RNA viral loads that were less than 400 copies/mL at Week 16.

Figure 1: Distribution of HIV RNA Data from Phase III Studies 018 and 019 for Raltegravir Treatment Group



Similar trends were also apparent in the two studies for the cumulative distribution of HIV RNA data for the following categories (<50, <400, <1,000, <10,000 and <100,000 copies/mL) and for many of the secondary endpoints.

Figure 2: Cumulative Distribution of HIV RNA Data from Phase III Studies 018 and 019 for Raltegravir Treatment Group



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In contrast to the raltegravir treatment group, placebo treatment results differed somewhat in the two studies.

Figure 3: Distribution of HIV RNA Data from Phase III Studies 018 and 019 for Placebo Treatment Group

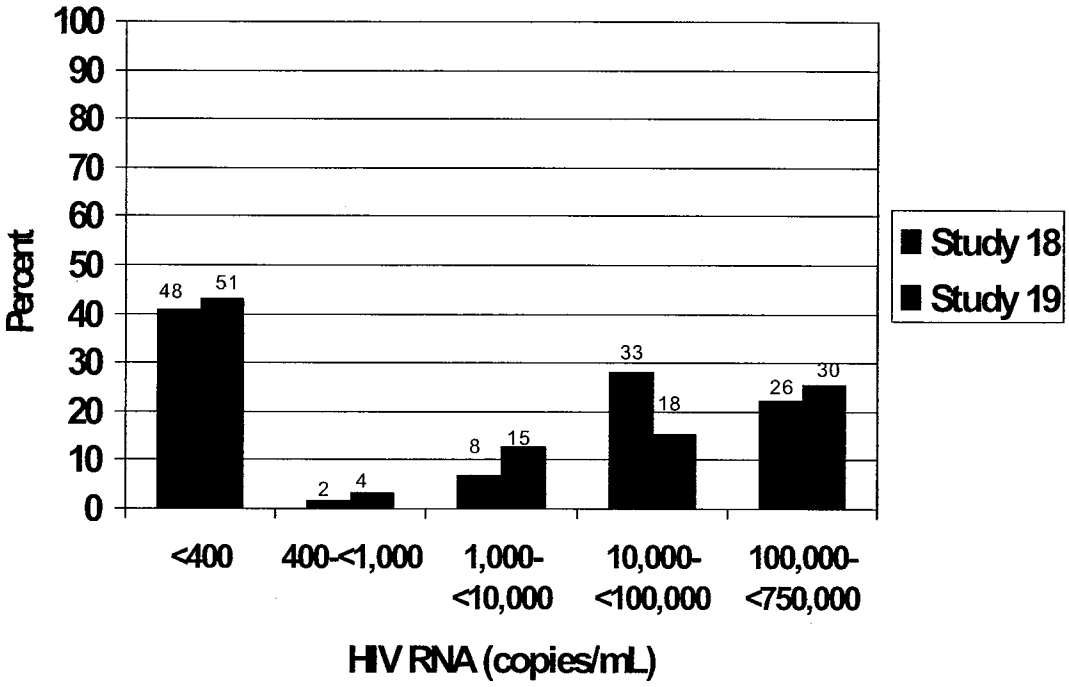

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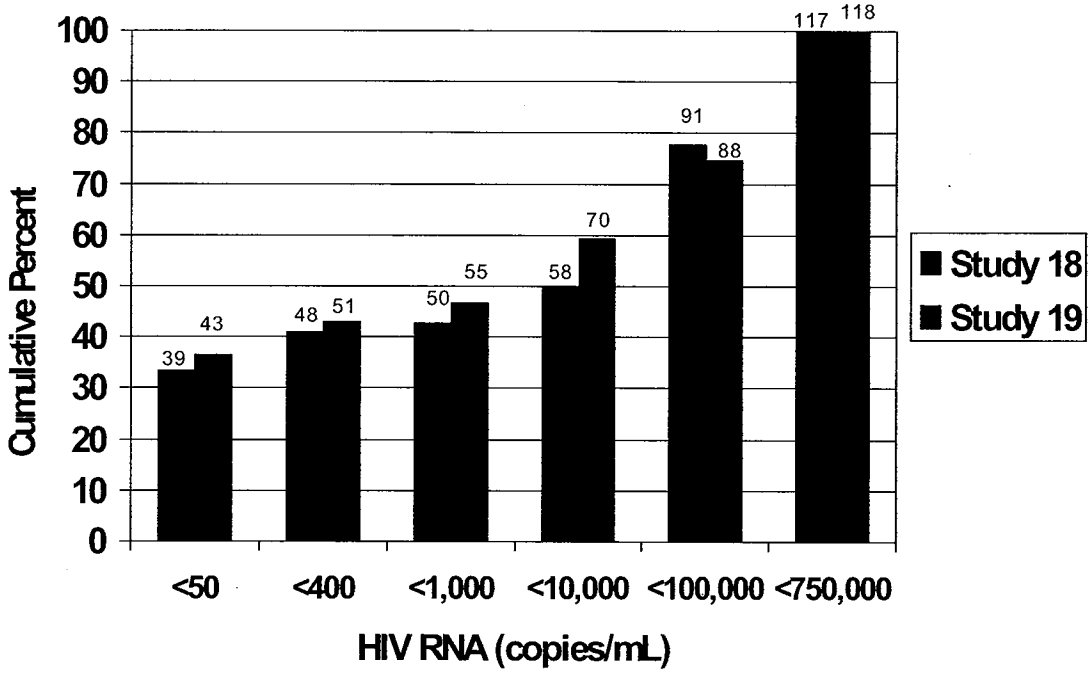
Figure 4: Cumulative Distribution of HIV RNA Data from Phase III Studies 018 and 019 for Placebo Treatment Group



As part of the data verification process, the review team requested copies of original source documents (laboratory reports) for HIV RNA Amplicor, HIV RNA Ultra-sensitive, and CD4 count data for the 4 sites that were inspected for studies 018 and 019, the largest site in study 019 and an additional site in study 018 that had highly significant results in favor of raltegravir. The review team also requested copies of original source documents for treatment randomization schedules be sent directly to the FDA from the external vendors for studies 004, 005, 018 and 019. In addition, the FDA requested Merck's standard operating procedures for randomization schedule generation and certification from the external vendors that the randomization code documents were obtained from the original electronic file sent to the vendors from Merck prior to study initiation. Copies of the original source documents of laboratory data and a 10% sample of treatment codes were examined and found to be consistent with our data listings.

To evaluate the robustness of the efficacy results, the statistical reviewer used different rules of assignment of viral load results when results from different assays (i.e., standard, ultrasensitive and dilution assays), different definitions of visit windows for measurements of HIV RNA level and CD4 counts, and different approaches to impute missing data. The detailed differences between the reviewer's and the applicant's methods are listed in Table 4. The reviewer's results varied slightly from those of the applicant due to these different rules, but they did not change the conclusion that raltegravir had better antiviral efficacy than the placebo. Tables 13 and 14 summarize the statistical reviewer's analysis results.

Table 4: Rules Used by Applicant and Reviewer in Efficacy Analysis

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

to be continued

Table 4: Rules Used by Applicant and Reviewer in Efficacy Analysis (Cont.)

	Applicant	Reviewer
Missing data imputation	The following four approaches were used to analyze the proportions of patients achieving HIV RNA < 400 copies/mL and < 50 copies/mL at a certain visit. 1. The missing values were not imputed. The proportions were calculated as the number of responders divided by the total number of treated patients. 2. Observed failure: patients who discontinued the assigned treatment due to lack of efficacy were considered as failure thereafter. 3. Treatment-related discontinuation = failure: patients who discontinued the assigned treatment due to lack of efficacy or AE were considered as failures thereafter. 4. Non-completer = failure: patients who discontinued the assigned treatment regardless of reasons were considered as failures thereafter.	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. 2. The patients who discontinued the assigned treatment regardless of reasons were regarded as failures.

3.2 Evaluation of Safety

In June of 2007, the applicant submitted the updated safety report and the corresponding datasets up to the database locked on 2/16/07. The statistical reviewer used the updated data from Studies 005, 018 and 019 to evaluate the difference in mortality between raltegravir and placebo groups in treatment-experienced patients. Note that the patients in the three raltegravir dose groups in Study 005 were considered as raltegravir-treated patients regardless of different doses of raltegravir they received.

In total there were 16 deaths (13 in raltegravir group and 3 in placebo group) among the 877 randomized and treated patients in Studies 005, 018 and 019 (raltegravir N=595; placebo N=282). It was noticed that all three deaths in placebo group occurred during the double-blind phase in Study 018.

The statistical reviewer calculated the mortality rate per person-year of exposure by Week 24, by last follow-up visit before 2/16/07 and by 2/16/07, using both ITT and as-treated population. The ITT analysis counted the patients randomized to the placebo group as placebo-treated patients even though they might enter the open-label to receive raltegravir treatment. The as-treated analysis reclassified the patients from their originally assigned treatment as follows: 1) a patient who was randomized to raltegravir was considered as a raltegravir patient; 2) a patient who was randomized to the placebo and continued the placebo treatment without switching to the raltegravir was considered as a placebo patient; and 3) a patient who was randomized to the placebo and switched to receive open-label raltegravir after virologic failure was considered as two patients – one as the placebo from the randomization to the time of switching to the open-label raltegravir, and the other as raltegravir from the time of switching to receive raltegravir to the desired ending time (i.e., Week 24, the last visit before database locked or database locked). The statistical reviewer regards the as-treated analyses are more appropriate than the ITT analysis for safety endpoints. Overall, in spite that there was no death in the placebo group in Studies 005 and 019, there were no apparent differences between the raltegravir and placebo in the mortality rates per person-year of exposure by Week 24 (as-treated analysis: raltegravir 2.8% vs. placebo 2.5%), by last follow-up visit before 2/16/07 (as-treated analysis: raltegravir 2.5% vs. placebo 2.1%) and by 2/16/07 (as-treated analysis: raltegravir 2.2% vs. placebo 1.9%) (Table 5 in next two pages).

The statistical reviewer also performed survival analysis using Kaplan-Meier approach. There was no obvious difference between the two treatment groups due to the short follow-up time (Figure 5).

Therefore, based on the mortality analyses, the statistical reviewer concluded that no apparent difference in mortality between raltegravir and placebo groups and there were not enough deaths to rule out a difference in mortality because the follow-up time was short.

Of note, question was raised in the advisory committee meeting about the statistical significance of comparison of malignancy rates between raltegravir and placebo groups.

According to the medical officer, Dr. Connelly, the results depended on the data included in the analysis. Specifically, based on the data up to 2/16/07, the malignancy rate for treatment-experienced patients during the double-blind treatment period was 2.2% (13/595) in the raltegravir arm versus 0% (0/282) in placebo arm, and the p-value was 0.013 based on the 2-sided Fisher's exact test; however, based on the data up to July of 2007, the malignancy rates were 2.7% (18/595) and 1.4 (4/282) for the raltegravir and placebo groups, respectively; and the p-value based on 2-sided chi-square test was 0.239.

Table 5: Studies 005, 018 and 019 – Mortality Analysis (All Treated)

	Study 005		Study 018		Study 019		Overall	
	Raltegravir (N=133)	Placebo (N=45)	Raltegravir (N=232)	Placebo (N=118)	Raltegravir (N=230)	Placebo (N=119)	Raltegravir (N=595)	Placebo (N=282)
Number of death by 02/16/07	4	0	4	3	5	0	13	3
Survival time in weeks	2, 21, 53, 76	n/a	13, 13, 17, 46	4, 12, 14	7, 10, 11, 28, 34	n/a	See individual studies	See individual studies
ITT analysis[1]								
By Week 24								
Number of deaths	2	0	3	3	3	0	8	3
Person years exposure	61.6	20.4	107.5	54.3	104.3	55.0	273.4	129.6
Mortality rate per person year	3.3%	0%	2.8%	5.5%	2.9%	0%	2.9%	2.3%
By last follow-up visit before 02/16/07								
Number of deaths	4	0	4	3	5	0	13	3
Person years exposure	185.5	60.9	143.5	72.8	137.4	73.0	466.4	206.8
Mortality rate per person year	2.2%	0%	2.8%	4.1%	3.6%	0%	2.8%	1.5%
By 02/16/07								
Number of deaths	4	0	4	3	5	0	13	3
Person years exposure	201.4	69.3	158.3	79.2	153.4	80.1	513.2	228.6
Mortality rate per person year	2.0%	0%	2.5%	3.8%	3.3%	0%	2.5%	1.3%

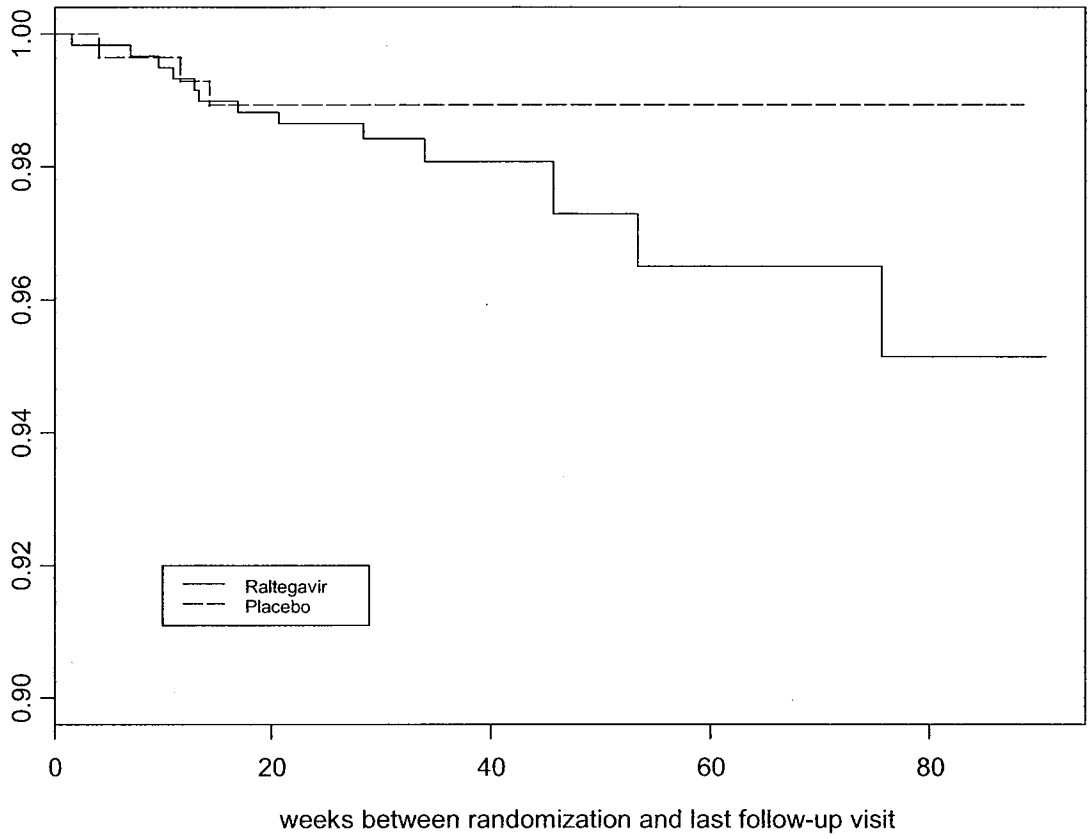
[1]The ITT analysis counts the subjects randomized as either Raltegravir or placebo.

Table 5: Studies 005, 018 and 019 – Mortality Analysis (All Treated)

	Study 005		Study 018		Study 019		Overall	
	Raltegravir (N=133)	Placebo (N=45)	Raltegravir (N=232)	Placebo (N=118)	Raltegravir (N=230)	Placebo (N=119)	Raltegravir (N=595)	Placebo (N=282)
As-treated analysis[2]								
By Week 24								
Number of deaths	2	0	3	3	3	0	8	3
Person years exposure	63.0	18.7	111.1	50.8	108.1	51.3	282.1	120.8
Mortality rate per person year	3.2%	0%	2.7%	5.9%	2.8%	0%	2.8%	2.5%
By last follow-up visit before 2/16/07								
Number of deaths	4	0	4	3	5	0	13	3
Person years exposure	223.0	23.4	156.3	60.1	150.3	60.2	529.6	143.7
Mortality rate per person year	1.8%	0%	2.6%	5.0%	3.3%	0%	2.5%	2.1%
By 2/16/07								
Number of deaths	4	0	4	3	5	0	13	3
Person years exposure	244.3	25.8	173.2	64.4	168.6	65.1	586.7	155.3
Mortality rate per person year	1.6%	0%	2.3%	4.7%	3.0%	0%	2.2%	1.9%

[2]The as-treated analyses reclassify subjects from their initially assigned treatment arm as follows: 1) a subject who was randomized to raltegravir is considered as a raltegravir subject; 2) a subject who was randomized to the placebo and continues the placebo treatment without switching to the raltegravir is considered as a placebo subjects; and 3) a subject who was randomized to the placebo and switches to receive open-label raltegravir after virologic failure is considered as two subjects – one as the placebo from the randomization to the time of switching to the open-label raltegravir, and the other as raltegravir from the time of switching to receive raltegravir to the desired ending time (i.e., Week 24, the last visit before database locked or database locked).

Figure 5: Studies 005, 018 and 019 – Survival Analysis



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4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Both applicant and the statistical reviewer carried out the subgroup analyses using the separate combined data from Studies 018 and 019, respectively. In the subgroup analyses, the applicant used OF to impute the missing data, while the statistical reviewer employed the methods displayed in Table 4.

4.1 Subgroup Analyses by Gender, Race, Age and Region

Both applicant and the statistical reviewer conducted the subgroup analyses with respect to gender, race, region and age (<= median age versus > median age) for the primary efficacy endpoint. Both applicant's and my analysis results indicated that there was no apparent treatment by the subgroup interaction. Table 15 in Appendix shows the statistical reviewer's subgroup analyses results.

4.2 Subgroup Analyses by Selected Baseline Characteristics

The applicant and the statistical reviewer performed the subgroup analyses for the primary efficacy endpoint with respect to baseline HIV RNA (<=50,000 vs. > 50,000 copies/mL; or <=100,000 vs. > 100,000 copies/mL), baseline CD4 cell count (<=50, >50 and <=200, or > 200 cells/mm^3), enfuvirtide use in OBT (no, naïve use enfuvirtide, or experienced use enfuvirtide), darunavir use in OBT (no, naïve use darunavir, or experienced use darunavir), combined uses of enfuvirtide and darunavir (naïve use enfuvirtide and darunavir, naïve use enfuvirtide and no use darunavir, no use enfuvirtide and naïve use darunavir, no use enfuvirtide or darunavir), number of active PI in OBT by phenotypic resistance (0 vs. >=1), phenotypic sensitivity score (0, 1, 2, or >=3) and genotypic sensitivity score (0, 1, 2, or >=3). No apparent treatment by subgroup interaction was observed, except that there were some subgroups with small sample size and the results were indeterminate. However, it is noticed that raltegravir efficacy compared to placebo was less impressive for treatment-naive enfuvirtide and treatment-naïve darunavir subjects and for patients with ≥3 PSS or GSS scores.

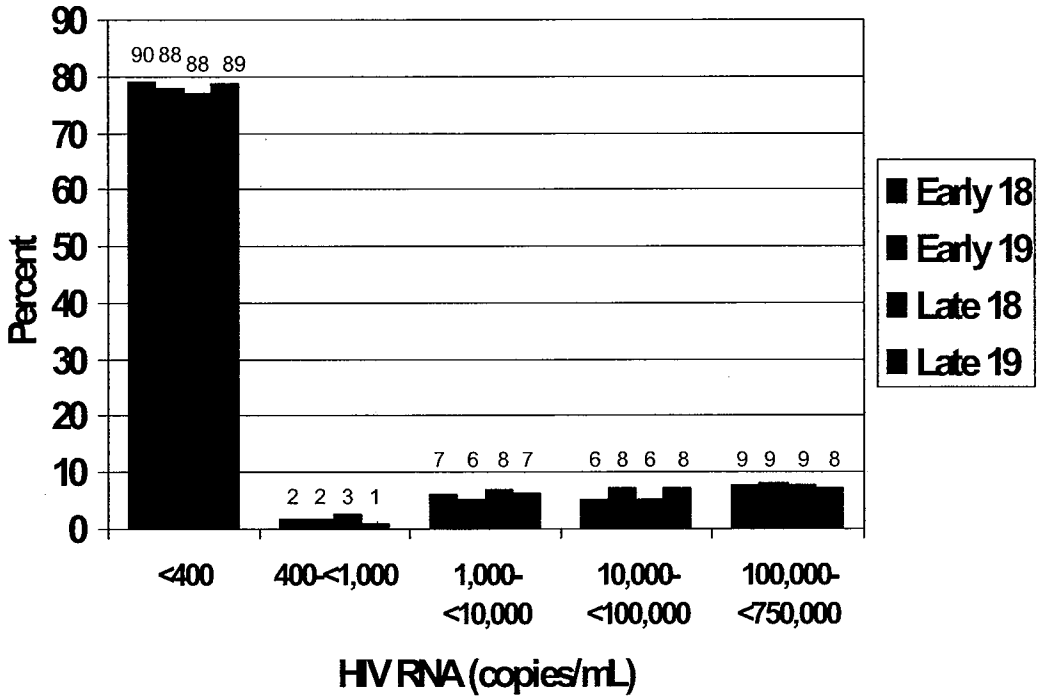
The applicant and the statistical reviewer also carried the subgroup analyses for the efficacy endpoints of percentage of patients having HIV RNA < 50 copies/mL at Week 16, percentage of patients having HIV RNA < 400 copies/mL at Week 24, and percentage of patients having HIV RNA < 50 copies/mL at Week 24. Again, the subgroup analyses did not indicate any significant treatment by subgroup interaction except for some subgroups of which the treatment effect could not be determined due to the small sample size.

Tables 16 – 19 in Appendix display the results from the statistical reviewer subgroup analyses.

4.3 Distribution of HIV RNA Data by Randomization Date and Largest Sites

Nearly identical results were also observed for the raltegravir treatment arm in patients randomized before and on or after the combined median study day of randomization for the two studies.

Figure 6: Distribution of HIV RNA Data from Phase III Studies 018 and 019 by Randomization Date for Raltegravir Treatment Group



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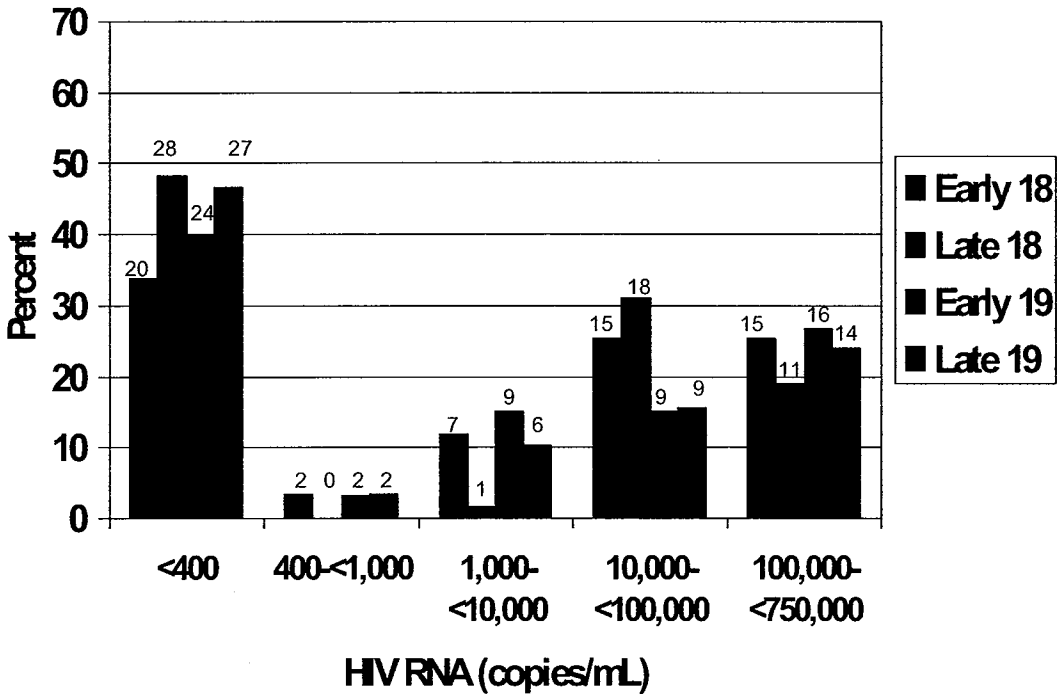
In contrast to the raltegravir treatment group, results for the primary efficacy analysis were not as similar in placebo patients randomized before and after the median study day of randomization in the two studies.

Figure 7: Distribution of HIV RNA Data from Phase III Studies 018 and 019 by Randomization Date for Placebo Treatment Group



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Within each study, treatment effects of raltegravir relative to placebo varied greatly from site to site.

Figure 8: Distribution of HIV RNA Data from Study 018 for Largest Sites (>10 Patients / Site)

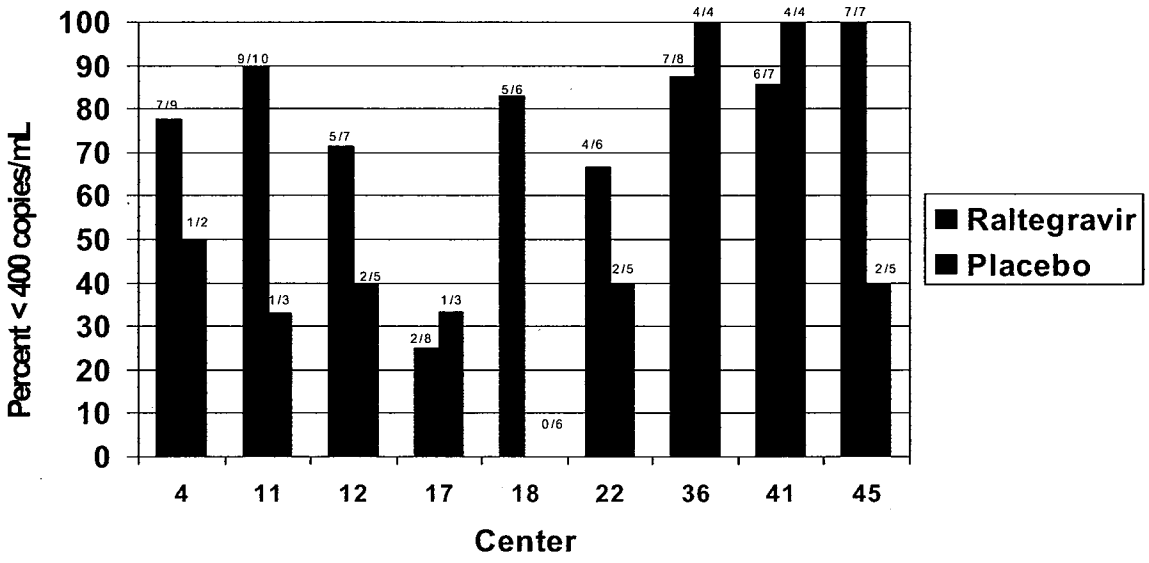
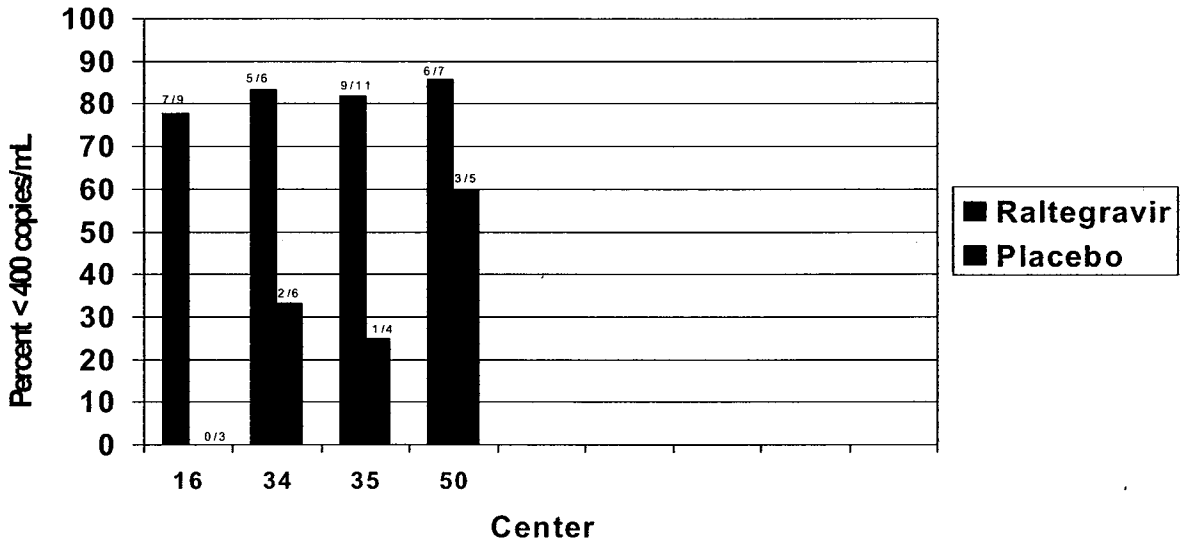


Figure 9: Distribution of HIV RNA Data from Study 019 for Largest Sites (>10 Patients / Site)



5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Overall, based on the data submitted, the following results were observed:

- In the two pivotal Phase III studies (018 and 019), approximately 78% of the patients in the raltegravir treatment group had HIV RNA viral load <400 copies/mL at Week 16 compared to 41% of the placebo patients in study 018 and 43% of the placebo patients in study 019 (where missing data were imputed assuming treatment-related discontinuations were treatment failures).

- Raltegravir efficacy compared to placebo was less impressive for treatment-naive enfuvirtide and treatment-naïve darunavir patients and for patients with ≥3 phenotypic susceptibility scores (PSS).

The following issues were raised by the statistical review team:

- Nearly identical results were observed in the raltegravir treatment group in the two pivotal phase III trials for the applicant's primary efficacy endpoint (where missing data were imputed assuming treatment-related discontinuations were treatment failures): 178/228 (78.1%) of the subjects in Study 018 and 177/226 (78.3%) of the patients in Study 019 had HIV RNA viral loads that were less than 400 copies/mL at Week 16.

- Similar trends were also apparent in the two studies for the cumulative distribution of HIV RNA data for the following categories (<50, <400, <1,000, <10,000 and <100,000 copies/mL) and for many of the secondary endpoints.

As part of the data verification process, the review team requested the copies of original source documents for HIV RNA Amplicor, HIV RNA Ultra-sensitive, and CD4 count data for selected sites in studies 018 and 019 and treatment randomization schedules that were to be sent directly to the FDA from the external vendors for studies 004, 005, 018 and 019. In addition, the FDA requested Merck's standard operating procedures for randomization schedule generation and certification from the external vendors that the randomization code documents were obtained from the original electronic file sent to the vendors from Merck prior to study initiation. A sample of treatment codes and laboratory data were compared to corresponding values in the SAS data sets and appeared to match.

To evaluate the robustness of the efficacy results of the two Phase III trials in the treatment-experienced patients, the statistical reviewer used different rules of assigning of viral load results using results from different assays (i.e., standard, ultrasensitive and dilution assays), different definitions of visit windows for measurements of HIV RNA level and CD4 counts, and different approaches to impute missing data. The statistical reviewer's results were quite similar to the applicant's. With regards to the mortality, 16 patients died in the three Phase II or III trials in the treatment-experienced patients based on the updated datasets up to the database locked on 2/16/07 (raltegravir 13 vs. placebo 3

patients). The statistical reviewer calculated the mortality rates per person-year exposure and performed survival analysis using the updated data. There was no significant difference in the mortality between raltegravir and placebo groups; however, at the same time, there were not enough deaths to rule out a difference in mortality due to the short follow-up time.

5.2 Conclusions and Recommendations

After reviewing the efficacy results based on all 16-week data and approximately 60% of the 24-week data from two pivotal Phase III trials in treatment-experienced (i.e., Studies 018 and 019) in the original submission which included the data up to database locked on 12/13/06, the statistical reviewer concluded that raltegravir 400 mg bid in combination of the optimal background therapies (OBT) had superior efficacy over the placebo in combination of OBT for the treatment of HIV treatment-experienced patients. Additionally, based on the updated data from three Phase II or III trials in treatment-experienced patients (i.e., Studies 005, 018 and 019) which included the data up to the database locked on 2/16/07, the statistical reviewer concluded that there was no significant difference in mortality between raltegravir and placebo; however, at the same time, there were not enough deaths to rule out a difference in mortality.

APPENDIX

The appendix contains the schedules of efficacy and safety assessments, the applicant's analysis results for the secondary efficacy endpoints, the reviewer's analysis results of the efficacy analyses, and the reviewer's results for the subgroup analyses.

Table 6: Studies 018 and 019 – Schedule of Efficacy and Safety Assessments during Double-Blind Treatment Phase

	Weeks (Postinitiation of Combination Therapy)										
Visit Number	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 of the protocol)	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[11]		X[11]	X[11]	X[11]	X[11]	X[11]	X[11]	X[11,6]	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 was 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.

[11] To register patients at screening.
[11] To allocate patients (Day 1) and for assignment and management of clinical supplies.

Source: Clinical Study Report for Study 018, Section 9, Table 9-1.

to be continued

Table 6: Studies 018 and 019 – Schedule of Efficacy and Safety Assessments during Double-Blind Treatment Phase (Cont.)

Weeks (Postinitiation of Combination Therapy)												
Visit Number	V30	V31	V32	V33	V34	V35	V36	V37	V38	V99	U	U
	Week 60	Fasting[a] Week 72	Week 84	Fasting[a] Week 96	Week 108	Fasting[a] Week 120	Week 132	Fasting[a] Week 144	Week 156	Fasting[a] 14-Day Posttherapy Follow-up	Virologic Failure Confirmation	Discontinuation[b]
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X
Blood and urine for safety (Appendix 1 of the protocol)	X	X	X	X	X	X	X	X	X	X		X
Pregnancy test[c]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]		
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 Population PK blood draws[e]		X		X		X		X	X		X	X[f]
Contact Interactive Voice Response System (IVRS)[g]	X	X	X	X	X	X	X	X	X			

[a] Fasting: 8 hours.
[b] For management of clinical supplies and to register discontinuation.
[c] For women of childbearing potential; serum pregnancy test (central laboratory).
[d] Not needed if obtained at virologic failure confirmation visit
[e] One sample for Population Pharmacokinetics (PK) was collected irrespective of time of dose.
[f] Limited information (mortality and participation in any other antiretroviral clinical study) was collected for patients who discontinued prior to Week 48.

Source: Clinical Study Report for Study 018, Section 9, Table 9-1.

Table 7: Studies 018 and 019 – Schedule of Efficacy and Safety Measurements during Open-Label Post Virologic Failure Treatment Phase

	Weeks (Postinitiation of Open Label Treatment Post Virologic Failure)									
Visit Number	V20	V21	V22	V23	V24	V25	V26	V27	V28	V29
	OL Day 1	OL Week 2	OL Week 4	OL Week 8	Fasting[2] OL Week 12	OL Week 16	Fasting[2] OL Week 24	OL Week 32	OL Week 40	Fasting[2] OL Week 48
12-lead ECG							X			
Physical examination		X	X	X	X	X	X	X	X	X
Blood and urine for safety (Appendix 1)	X[3]	X	X	X	X	X	X	X	X	X
Pregnancy test[1]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]
HIV RNA			X	X		X	X	X	X	X
CD4 cell count			X	X		X	X	X	X	X
Plasma for viral resistance							X			X
Population PK blood draws[5]			X	X	X	X	X	X		
Contact Interactive Voice Response System (IVRS)[6]	X[11]		X	X	X	X	X	X	X	

[1] For women of childbearing potential.
[2] Fasting; 8 hours.
[3] Collected prior to initial dose of open-label therapy. Not needed if a previous blood and urine safety tests done within 30 days.
[4] Serum pregnancy test (central laboratory).
[5] One sample for Population Pharmacokinetics (PK) was collected. At OL Weeks 12 and 24, the sample was collected pre-AM dose. At all other weeks, the samples could have been collected irrespective of time of dose.
[6] For assignment and management of clinical supplies.
[11] To register the patient in the open-label treatment option.

Source: Clinical Study Report for Study 018, Section 9, Table 9-2.

to be continued

Table 7: Studies 018 and 019 – Schedule of Efficacy and Safety Measurements during Open-Label Post Virologic Failure Treatment Phase (Cont.)

Weeks (Postinitiation of Open Label Treatment Post Virologic Failure)											
Visit Number:	V40	V41	V42	V43	V44	V45	V46	V47	V99	U	U
	Week 60	Fasting[§] Week 72	Week 84	Fasting[§] Week 96	Week 108	Fasting[§] Week 120	Week 132	Fasting[§] Final OLPVP (Total 156 Week of study therapy)	Fasting[§] 14-Day Post OL therapy Follow-up	Virologic Failure Confirmation	Discontinuation[#]
Physical examination	X	X	X	X	X	X	X	X	X		X
Blood and urine for safety (Appendix 1 of the protocol)	X	X	X	X	X	X	X	X	X		X
Pregnancy test[†]	X[†]	X[†]	X[†]	X[†]	X[†]	X[†]	X[†]	X[†]	X[†]		
HIV RNA	X	X	X	X	X	X	X	X	X	X	X
CD^4 cell count	X	X	X	X	X	X	X	X	X	X	X
Plasma for viral resistance								X		X	X[¶]
Population PK blood draws[‡]		X		X		X		X			
Contact Interactive Voice Response System (IVRS)[‖]	X	X	X	X	X	X	X	X			

† For women of childbearing potential; serum pregnancy test (central laboratory).
‡ One sample for Population Pharmacokinetics (PK) was collected irrespective of time of dose.
§ Fasting: 8 hours.
‖ For management of clinical supplies and to register discontinuation.
¶ Not needed if obtained at virologic failure confirmation visit.
# Limited information (mortality and participation in any other antiretroviral clinical study) was collected for patients who discontinued prior to Week 48.

Source: Clinical Study Report for Study 018, Section 9, Table 9-2.

Table 8: Studies 018 and 019 – Patient Demographics (All Treated)

	Study 018			Study 019			Overall		
	Raltegravir (N=232)	Placebo (N=118)	Total (N=350)	Raltegravir (N=230)	Placebo (N=119)	Total (N=349)	Raltegravir (N=462)	Placebo (N=237)	Total (N=699)
Gender – n (%)									
Male	195 (84)	103 (87)	298 (85)	210 (91)	107 (90)	317 (91)	405 (88)	210 (89)	615 (88)
Female	37 (16)	15 (13)	52 (15)	20 (9)	12 (10)	32 (9)	57 (12)	27 (11)	84 (12)
Race – n (%)									
White	175 (75)	96 (81)	271 (77)	126 (55)	77 (65)	203 (58)	301 (65)	173 (73)	474 (68)
Black	18 (8)	5 (4)	23 (7)	48 (21)	21 (18)	69 (20)	66 (14)	26 (11)	92 (13)
Asian	14 (6)	5 (4)	19 (5)	2 (1)	1 (1)	3 (1)	16 (3)	6 (3)	22 (3)
Hispanic	6 (3)	1 (1)	7 (2)	47 (20)	18 (15)	65 (19)	53 (11)	19 (8)	72 (10)
Native American	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)	1 (<1)	0 (0)	1 (<1)
Other	19 (8)	11 (9)	30 (9)	6 (3)	2 (2)	8 (2)	25 (5)	13 (5)	38 (5)
Region – n (%)									
North America	0 (0)	0 (0)	0 (0)	192 (84)	99 (83)	291 (83)	192 (42)	99 (42)	291 (42)
Central/South America	23 (10)	11 (9)	34 (10)	38 (17)	20 (17)	58 (17)	61 (13)	31 (13)	92 (13)
Asian Pacific	38 (16)	20 (17)	58 (17)	0 (0)	0 (0)	0 (0)	38 (8)	20 (8)	58 (8)
Europe	171 (74)	87 (74)	258 (74)	0 (0)	0 (0)	0 (0)	171 (37)	87 (37)	258 (37)
Age									
Mean (SD)	46 (9)	44 (8)	45 (9)	45 (9)	47 (8)	46 (8)	46 (9)	45 (8)	46 (8)
Median (min, max)	46 (16, 74)	43 (19, 64)	45 (16, 74)	45 (16, 67)	47 (17, 70)	45 (16, 70)	45 (16, 74)	45 (17, 70)	45 (16, 74)

Source: Clinical Study Report for Studies 018 and 019, Section 10, Table 10 – 4.

Table 9: Studies 018 and 019 – Selected Baseline Characteristics (All Treated)

	Study 018			Study 019			Overall		
	Raltegravir (N=232)	Placebo (N=118)	Total (N=350)	Raltegravir (N=230)	Placebo (N=119)	Total (N=349)	Raltegravir (N=462)	Placebo (N=237)	Total (N=699)
HIV RNA (copies/mL)									
Mean	40519	31828	37352	48366	47789	48168			
Median (min, max)	61750 (441, 750000)	42700 (200, 750000)	50950 (200, 750000)	56750 (200, 750000)	46700 (200, 750000)	52900 (200, 750000)	59650 (200, 750000)	45200 (200, 750000)	52500 (200, 750000)
≤ 50, 000 – n (%)	110 (47)	64 (54)	174 (50)	107 (47)	61 (51)	168 (48)	217 (47)	125 (53)	342 (49)
> 50, 000 – n (%)	122 (53)	54 (46)	176 (50)	123 (54)	58 (49)	181 (52)	245 (53)	112 (47)	357 (51)
≤ 100, 000	155 (67)	85 (72)	240 (69)	143 (62)	74 (62)	217 (62)	298 (65)	159 (67)	457 (65)
> 100, 000	77 (33)	33 (28)	110 (31)	87 (38)	45 (38)	132 (38)	164 (36)	78 (33)	242 (35)
CD4 count (cells/mm^3)									
Mean (SD)	156 (139)	153 (152)	155 (143)	146 (143)	163 (149)	152 (146)	152 (142)	160 (151)	155 (145)
Median (min, max)	140 (1, 792)	105 (3, 759)	130 (1, 792)	102 (1, 757)	132 (0, 674)	111 (0, 757)	119 (1, 792)	125 (0, 759)	121 (0, 792)
≤ 50 – n (%)	69 (30)	40 (34)	109 (31)	77 (34)	38 (32)	115 (33)	146 (32)	78 (33)	224 (32)
> 50 and ≤ 200 – n (%)	89 (38)	43 (36)	132 (38)	84 (37)	42 (35)	126 (36)	173 (37)	85 (36)	258 (37)
> 200 – n (%)	73 (32)	35 (30)	108 (31)	69 (30)	39 (33)	108 (31)	142 (31)	74 (31)	216 (31)
Missing – n (%)	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)
History of AIDs – n (%)									
Yes	217 (94)	106 (90)	323 (92)	209 (91)	110 (92)	319 (91)	426 (92)	216 (91)	642 (92)
No	15 (6)	12 (10)	27 (8)	21 (9)	9 (8)	30 (9)	36 (8)	21 (9)	57 (8)
Prior use of ART									
Year of use: Median (min, max)	11 (0, 19)	10 (1, 15)	11 (0, 19)	10 (0, 19)	10 (0, 19)	10 (0, 19)	10 (0, 19)	10 (0, 19)	10 (0, 19)
Number of use: Median (min, max)	12 (2, 19)	12 (3, 18)	12 (2, 19)	12 (0, 21)	12 (0, 22)	12 (0, 22)	12 (0, 21)	12 (0, 22)	12 (0, 19)

Source: Clinical Study Report for Studies 018 and 019, Section 10, Tables 10 – 4 and 10 – 5.

to be continued

Table 9: Studies 018 and 019 – Selected Baseline Characteristics (All Randomized) (Cont.)

	Study 018			Study 019			Overall		
	Raltegravir (N=232)	Placebo (N=118)	Total (N=350)	Raltegravir (N=230)	Placebo (N=119)	Total (N=349)	Raltegravir (N=462)	Placebo (N=237)	Total (N=699)
Hepatitis co-infection – n (%)									
No hepatitis B or C	183 (79)	91 (77)	274 (78)	202 (88)	110 (92)	312 (89)	385 (83)	201 (85)	586 (84)
Hepatitis B only	14 (6)	3 (3)	17 (5)	22 (10)	4 (3)	26 (7)	36 (8)	7 (3)	43 (6)
Hepatitis C only	31 (13)	22 (19)	53 (15)	6 (3)	5 (4)	11 (3)	37 (8)	27 (11)	64 (9)
Co-infection of Hepatitis B and C	4 (2)	2 (2)	6 (2)	0 (0)	0 (0)	0 (0)	4 (1)	2 (1)	6 (1)
Stratum – n (%)									
Enfuvirtide in OBT	88 (38)	43 (36)	131 (37)	87 (38)	46 (39)	133 (38)	175 (38)	89 (38)	264 (38)
Resistance to ≥ 2 PIs	225 (97)	112 (95)	337 (96)	222 (97)	114 (96)	336 (96)	447 (97)	226 (95)	673 (96)
Enfuvirtide use in OBT									
No	144 (62)	75 (64)	219 (63)	143 (62)	73 (61)	216 (62)	287 (62)	148 (62)	435 (62)
Yes in Enfuvirtide exp. patients	40 (17)	19 (16)	59 (17)	43 (19)	22 (19)	65 (19)	83 (18)	41 (17)	124 (18)
Yes in Enfuvirtide naïve patients	48 (21)	24 (20)	72 (21)	44 (19)	24 (20)	68 (20)	92 (20)	48 (20)	140 (20)
Darunavir use in OBT									
No	156 (67)	83 (70)	239 (68)	122 (53)	55 (46)	177 (51)	278 (60)	138 (58)	416 (60)
Yes in Darunavir exp. patients	14 (6)	5 (4)	19 (5)	4 (2)	4 (3)	8 (2)	18 (4)	9 (4)	27 (4)
Yes in Darunavir naïve patients	62 (27)	30 (25)	92 (26)	104 (45)	60 (50)	164 (47)	166 (36)	90 (38)	256 (37)
Number of active PI in OBT by phenotypic resistance test									
0	100 (43)	55 (47)	155 (44)	66 (29)	42 (35)	108 (31)	166 (36)	97 (41)	263 (38)
1 or more	123 (53)	61 (52)	184 (53)	155 (67)	76 (64)	231 (66)	278 (60)	137 (58)	415 (59)
Missing	9 (4)	2 (2)	11 (3)	9 (4)	1 (1)	10 (3)	18 (4)	3 (1)	21 (3)

Source: Clinical Study Report for Studies 018 and 019, Section 10, Tables 10 – 4 and 10 – 5.

to be continued

Table 9: Studies 018 and 019 – Selected Baseline Characteristics (All Randomized) (Cont.)

	Study 018			Study 019			Overall		
	Raltegravir (N=232)	Placebo (N=118)	Total (N=350)	Raltegravir (N=230)	Placebo (N=119)	Total (N=349)	Raltegravir (N=462)	Placebo (N=237)	Total (N=699)
Phenotypic Sensitivity Score (PSS)[1]									
Mean (SD)	1.5 (1.1)	1.5 (1.1)	1.5 (1.1)	1.6 (0.9)	1.6 (1.1)	1.6 (1.1)	1.6 (1.0)	1.6 (1.1)	1.6 (1.1)
0 – n (%)	44 (19)	21 (18)	65 (19)	23 (10)	23 (19)	46 (13)	67 (15)	44 (19)	111 (16)
1 – n (%)	67 (29)	39 (33)	106 (30)	78 (34)	32 (27)	110 (32)	145 (31)	71 (30)	216 (31)
2 – n (%)	67 (29)	33 (28)	100 (29)	75 (33)	33 (28)	108 (31)	142 (31)	66 (28)	208 (30)
3 or more – n (%)	44 (19)	21 (18)	65 (19)	41 (18)	27 (23)	68 (20)	85 (18)	48 (20)	133 (19)
Missing – n (%)	10 (4)	4 (3)	14 (4)	13 (6)	4 (3)	17 (5)	23 (5)	8 (3)	31 (4)
Genotypic Sensitivity Score (GSS)[1]									
Mean (SD)	1.2 (1.1)	1.2 (1.1)	1.2 (1.1)	1.3 (0.9)	1.2 (1)	1.2 (1.0)	1.2 (1.0)	1.2 (1.0)	1.2 (1.0)
0 – n (%)	70 (30)	34 (29)	104 (30)	45 (20)	31 (26)	76 (22)	115 (25)	65 (27)	180 (26)
1 – n (%)	76 (33)	48 (41)	124 (35)	102 (44)	48 (40)	150 (43)	178 (39)	96 (41)	274 (39)
2 – n (%)	57 (25)	22 (19)	79 (23)	54 (24)	27 (23)	81 (23)	111 (24)	49 (21)	160 (23)
3 or more – n (%)	26 (11)	13 (11)	39 (11)	25 (11)	10 (8)	35 (10)	51 (11)	23 (10)	74 (11)
Missing – n (%)	3 (1)	1 (1)	4 (1)	4 (2)	3 (3)	7 (2)	7 (2)	4 (2)	11 (2)

Source: Clinical Study Report for Studies 018 and 019, Section 10, Tables 10 – 4 and 10 – 5.

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

Table 10: Studies 018 and 019 – Applicant's Analysis Results for Key Efficacy Endpoints at Week 16 (All Treated)

Outcomes at Week 16	Study 018		Study 019		Overall	
	Raltegravir (N=232)	Placebo (N=118)	Raltegravir (N=230)	Placebo (N=119)	Raltegravir (N=462)	Placebo (N=237)
Patients with HIV RNA < 50 copies/mL – n (%)	141 (61)	39 (33)	142 (62)	43 (36)	283 (61)	82 (35)
Patients with > 1 log10 drop in HIV RNA or HIV RNA < 400 copies/mL – n (%)	197 (85)	49 (42)	190 (83)	60 (50)	387 (84)	109 (46)
Mean HIV RNA change from baseline (log10 copies/mL)	-1.9	-0.8	-1.9	-1.1	-1.9	-0.9
Mean CD4 cell count change from baseline (cells/mm^3)	83	31	85	40	84	36
Virologic failure (confirmed) – n (%)	32 (14)	63 (53)	38 (17)	57 (48)	70 (15)	120 (51)
Non responder	4 (2)	44 (37)	9 (4)	34 (29)	13 (3)	78 (33)
Rebound	28 (12)	19 (16)	29 (13)	23 (19)	57 (12)	42 (18)
Death	3 (1)	1 (1)	3 (1)	0 (0)	6 (1)	1 (<1)

Source: Clinical Study Report for Studies 018 and 019, Section 11, Tables 11 – 1.

Table 11: Studies 018 and 019 – Applicant's Analysis Results for Key Efficacy Endpoints at Week 24 (All Treated)

Outcomes at Week 24 – responders / evaluable (%)	Study 018		Study 019		Overall	
	Raltegravir (N=232)	Placebo (N=118)	Raltegravir (N=230)	Placebo (N=119)	Raltegravir (N=462)	Placebo (N=237)
Patients with Week 24 data	158/232 (68)	81/118 (69)	128/230 (56)	69/119 (58)	286/462 (62)	150/237 (63)
Patients with HIV RNA < 400 copies/mL	119/158 (75)	32/81 (40)	97/128 (76)	27/69 (39)	216/286 (76)	59/237 (39)
Patients with HIV RNA < 50 copies/mL	96/158 (61)	27/81 (33)	83/128 (65)	23/69 (33)	179/286 (63)	50/237 (33)
Patients with > 1 log10 drop in HIV RNA or HIV RNA < 400 copies/mL	128/158 (81)	35/81 (43)	103/128 (81)	30/69 (44)	231/286 (81)	65/237 (43)
Mean HIV RNA change from baseline (log10 copies/mL)	-1.8	-0.8	-2.0	-1.0	-1.9	-0.8
Mean CD4 cell count change from baseline (cells/mm^3)	86	30	93	40	89	35
Virologic failure (confirmed)	34/232 (15)	63/118 (53)	40/230 (17)	58/119 (49)	74/ (16)	121/237 (51)
Non responder	4/232 (2)	44/118 (37)	9/230 (4)	34/119 (29)	13/ (3)	78/237 (33)
Rebound	30/232 (13)	19/118 (16)	31/230 (14)	24/119 (20)	61 (13)	43/237 (18)
Death	3/232 (1)	1/118 (1)	3/230 (1)	0/119 (0)	6/462 (1)	1/237 (<1)

Source: Clinical Study Report for Studies 018 and 019, Section 11, Tables 11 – 2.
[1]The percentage is out of the patients with Week 24 data.

Table 12: Studies 018 and 019 – Reviewer's Analysis Results for Primary Efficacy Endpoint: Proportion of Patients Achieving HIV RNA < 400 copies/mL at Week 16 (All Treated)

	Study 018				Study 019			
	Responses by Treatment Group – Responders/ Evaluable (%)		Treatment Difference in Percent Response (Raltegravir – Placebo)		Responses by Treatment Group – Responders/ Evaluable (%)		Treatment Difference in Percent Response (Raltegravir – Placebo)	
	Raltegravir (N=232)	Placebo (N=118)	Odds Ratio (95% CI)	p-value	Raltegravir (N=230)	Placebo (N=119)	Odds Ratio (95% CI)	p-value
Patients with HIV RNA < 400 copies/mL	179 (77)	49 (42)	9 (5, 17)[1] 7 (4, 13)[2]	<0.001[1] <0.001[2]	180 (78)	51 (43)	9 (5, 17)[1] 9 (5, 16)[2]	<0.001[1] <0.001[2]

[1]The odds ratio and p-value were calculated using a logistic regression model adjusted for baseline HIV RNA level, enfuvirtide use in OBT with no prior exposure, active PI in OBT determined by phenotypic resistance test (not including darunavir use), darunavir use in OBT in darunavir naïve patients, and treatment group.

[2]The odds ratio and p-value were calculated using Cochran-Mantel-Haenszel adjusted for: baseline HIV RNA level (<= 50,000 copies/mL vs. > 50,000 copies/mL), enfuvirtide use in OBT in enfuvirtide naïve patients, active PI in OBT determined by phenotypic resistance test (not including darunavir use), darunavir use in OBT in darunavir naïve patients, and treatment group.

Table 13: Studies 018 and 019 – Reviewer's Analysis Results for Key Efficacy Endpoints at Week 16 (All Treated)

Outcomes at Week 16	Study 018		Study 019		Overall	
	Raltegravir (N=232)	Placebo (N=118)	Raltegravir (N=230)	Placebo (N=119)	Raltegravir (N=462)	Placebo (N=237)
Patients with HIV RNA < 50 copies/mL – n (%)	146 (63)	40 (34)	143 (62)	43 (36)	289 (63)	83 (35)
Patients with > 1 log10 drop in HIV RNA or HIV RNA < 400 copies/mL – n (%)	198 (85)	50 (42)	193 (83)	61 (51)	391 (85)	111 (47)
HIV RNA change from baseline (log10 copies/mL)						
n	232	118	230	119	462	237
Mean (SD)	-2.3 (1.1)	-1.0 (1.3)	-2.4 (1.2)	-1.3 (1.3)	-2.3 (1.2)	-1.2 (1.3)
CD4 cell count change from baseline (cells/mm^3)						
n	231	118	230	119	461	237
Mean (SD)	81 (94)	32 (73)	84 (96)	39 (74)	82 (95)	36 (74)
Virologic failure (confirmed) – n (%)						
Non responder	5 (2)	44 (37)	9 (4)	33 (28)	14 (3)	77 (32)
Rebound	29 (12)	19 (16)	29 (13)	24 (20)	58 (12)	43 (18)

Table 14: Studies 018 and 019 – Reviewer's Analysis Results for Key Efficacy Endpoints at Week 24 (All Treated)

Outcomes at Week 24 – responders / evaluable (%)	Study 018		Study 019		Overall	
	Raltegravir (N=232)	Placebo (N=118)	Raltegravir (N=230)	Placebo (N=119)	Raltegravir (N=462)	Placebo (N=237)
Patients who were randomized before 7/01/06 and had Week 24 data	158/232 (68)	81/118 (69)	128/230 (56)	69/119 (58)	286/462 (62)	150/237 (63)
Patients with HIV RNA < 400 copies/mL – n (%)	120/158 (76)	33/81 (41)	97/128 (76)	27/69 (39)	217/286 (76)	60/150 (40)
Patients with HIV RNA < 50 copies/mL – n (%)	95/158 (60)	28/81 (35)	83/128 (65)	23/69 (33)	178/286 (62)	51/150 (34)
Patients with > 1 log10 drop in HIV RNA or HIV RNA < 400 copies/mL – n (%)	129/158 (82)	38/81 (47)	104/128 (81)	30/69 (43)	233/286 (81)	68/150 (45)
HIV RNA change from baseline (log10 copies/mL)						
n	158	81	128	69	286	150
Mean (SD)	-2.2 (1.2)	-1.1 (1.3)	-2.4 (1.3)	-1.1 (1.4)	-2.3 (1.3)	-1.1 (1.3)
CD4 cell count change from baseline (cells/mm^3)						
n	158	81	128	69	286	150
Mean (SD)	83 (98)	33 (71)	92 (98)	39 (71)	87 (98)	36 (71)
Virologic failure (confirmed) – n (%)						
Non responder	5/232 (2)	44/118 (37)	9/230 (4)	33/119 (28)	14/462 (3)	77/237 (32)
Rebound	31/232 (13)	19/118 (16)	31/230 (13)	25/119 (21)	62/462 (13)	44/237 (19)

Table 15: Studies 018 and 019 – Reviewer's Results for Subgroup Analyses for Primary Efficacy Endpoint of Proportion of Patients Achieving HIV RNA < 400 copies/mL at Week 16 by Demographics (All Treated)

Responders / Evaluable (%)	Study 018			Study 019			Overall		
	Raltegravir	Placebo	Treatment Difference in Percent Response (Raltegravir – Placebo) (95% CI)	Raltegravir	Placebo	Treatment Difference in Percent Response (Raltegravir – Placebo) (95% CI)	Raltegravir	Placebo	Treatment Difference in Percent Response (Raltegravir – Placebo) (95% CI)
Gender									
Female	27/37 (73)	7/15 (47)	26 (-7, 60)	14/20 (70)	3/12 (25)	45 (7, 83)	41/57 (72)	10/27 (37)	35 (11, 59)
Male	152/195 (78)	42/103 (41)	37 (25, 50)	166/210 (79)	48/107 (45)	34 (23, 46)	318/405 (79)	90/210 (43)	36 (28, 44)
Race									
White	133/175 (76)	36/96 (38)	39 (26, 51)	107/126 (85)	35/77 (45)	39 (26, 53)	242/301 (80)	72/173 (42)	39 (30, 48)
Black	11/18 (61)	2/5 (40)	21 (-40, 82)	34/48 (71)	9/21 (43)	28 (0, 56)	45/66 (68)	11/26 (42)	26 (1, 51)
Asian	12/14 (86)	2/5 (40)	46 (-15, 100)	2/2 (100)	0/1 (0)	100 (25, 100)	14/16 (88)	2/6 (33)	54 (2, 100)
Hispanic	6/6 (100)	0/1 (0)	100 (42, 100)	31/47 (66)	6/18 (33)	33 (3, 62)	37/53 (70)	6/19 (32)	38 (10, 66)
Native American	0/0	0/0	n/a	1/1 (100)	0/0	n/a	1/1 (100)	0/0	n/a
Other	15/19 (79)	8/11 (73)	6 (-33, 45)	5/6 (83)	1/2 (50)	33 (-75, 100)	20/25 (80)	9/13 (69)	11 (-25, 46)
Region									
North America	0/0	0/0	n/a	151/192 (79)	45/99 (45)	33 (21, 45)	151/192 (79)	45/99 (45)	33 (21, 45)
Central/South America	19/23 (83)	8/11 (73)	10 (-27, 47)	29/38 (76)	6/20 (30)	46 (18, 74)	48/61 (79)	14/31 (45)	34 (11, 56)
Asian Pacific	32/38 (84)	12/20 (60)	24 (-4, 52)	0/0	0/0	n/a	32/38 (84)	12/20 (60)	24 (-4, 52)
Europe	128/171 (75)	29/87 (33)	41 (29, 54)	0/0	0/0	n/a	128/171 (74)	29/87 (33)	42 (29, 54)
Age[1]									
≤ Median Age	81/116 (70)	28/75 (37)	32 (17, 47)	96/125 (77)	22/53 (42)	35 (19, 52)	177/241 (73)	50/128 (39)	34 (24, 45)
> Median Age	98/116 (84)	21/43 (48)	36 (18, 54)	84/105 (80)	29/66 (44)	36 (21, 52)	182/221 (82)	50/109 (46)	36 (25, 48)

Note: [1]The median age for both Studies 018 and 019 was 45 years.

Table 16: Studies 018 and 019 – Reviewer's Results for Subgroup Analyses for Primary Efficacy Endpoint of Proportion of Patients Achieving HIV RNA < 400 copies/mL at Week 16 by Selected Baseline Characteristics (All Treated)

	Study 018			Study 019			Overall		
Responders / Evaluable (%)	**Raltegravir**	**Placebo**	**Treatment Difference in Percent Response (Raltegravir – Placebo) (95% CI)**	**Raltegravir**	**Placebo**	**Treatment Difference in Percent Response (Raltegravir – Placebo) (95% CI)**	**Raltegravir**	**Placebo**	**Treatment Difference in Percent Response (Raltegravir – Placebo) (95% CI)**
Baseline HIV RNA (copies/mL)									
≤ 50,000 copies/mL	100/110 (91)	35/64 (55)	36 (22, 51)	90/107 (84)	37/61 (61)	23 (8, 39)	190/217 (88)	72/125 (58)	30 (20, 40)
> 50,000 copies/mL	79/122 (65)	14/54 (26)	39 (23, 55)	90/123 (73)	14/58 (24)	49 (34, 64)	169/245 (69)	28/112 (25)	44 (33, 55)
≤ 100,000 copies/mL	136/155 (88)	42/85 (49)	38 (26, 51)	120/143 (84)	43/74 (58)	26 (12, 40)	256/298 (86)	85/159 (53)	32 (23, 41)
> 100,000 copies/mL	43/77 (56)	7/33 (21)	35 (15, 55)	60/87 (69)	8/45 (18)	51 (35, 68)	103/164 (63)	15/78 (19)	44 (31, 56)
Baseline CD4 (cells/mm^3)									
≤ 50 – n (%)	36/69 (52)	10/40 (25)	27 (7, 47)	51/77 (66)	8/38 (21)	45 (26, 64)	87/146 (60)	18/78 (23)	37 (23, 50)
> 50 and ≤ 200 – n (%)	75/89 (84)	16/43 (37)	47 (29, 65)	73/84 (87)	23/42 (55)	32 (14, 51)	148/173 (86)	39/85 (46)	40 (27, 52)
> 200 – n (%)	67/73 (92)	23/35 (66)	26 (7, 45)	56/69 (81)	20/39 (51)	30 (10, 50)	123/142 (87)	43/74 (58)	29 (15, 42)
Missing	1/1 (100)	0/0	n/a	0/0	0/0	n/a	1/1 (100)	0/0	n/a
Enfuvirtide use in OBT									
No	108/144 (75)	28/75 (37)	38 (24, 52)	108/143 (76)	25/73 (34)	41 (27, 55)	216/287 (75)	53/148 (36)	39 (30, 49)
Yes in Enfuvirtide exp. patients	26/40 (65)	4/19 (21)	44 (17, 71)	32/43 (74)	8/22 (36)	38 (11, 65)	58/83 (70)	12/41 (29)	41 (22, 60)
Yes in Enfuvirtide naïve patients	45/48 (94)	17/24 (71)	22 (0, 45)	40/44 (91)	18/24 (75)	16 (-7, 38)	85/92 (92)	35/48 (73)	19 (4, 35)
Darunavir use in OBT									
No	119/156 (76)	29/83 (35)	41 (28, 55)	84/122 (69)	13/55 (24)	45 (30, 60)	2031/278 (73)	42/138 (30)	43 (33, 52)
Yes in Darunavir exp. patients	6/14 (43)	0/5 (0)	43 (3, 82)	2/4 (50)	0/4 (0)	50 (-24, 100)	8/18 (44)	0/9 (0)	44 (13, 76)
Yes in Darunavir naïve patients	54/62 (87)	20/30 (67)	20 (0, 42)	94/104 (90)	38/60 (63)	27 (12, 42)	148/166 (89)	58/90 (64)	25 (13, 37)

to be continued

Table 16: Studies 018 and 019 – Reviewer's Results for Subgroup Analyses for Primary Efficacy Endpoint of Proportion of Patients Achieving HIV RNA < 400 copies/mL at Week 16 by Selected Baseline Characteristics (All Treated) (Cont.)

	Study 018			Study 019			Overall		
Responders / Evaluable (%)	Raltegravir	Placebo	Treatment Difference in Percent Response (Raltegravir – Placebo) (95% CI)	Raltegravir	Placebo	Treatment Difference in Percent Response (Raltegravir – Placebo) (95% CI)	Raltegravir	Placebo	Treatment Difference in Percent Response (Raltegravir – Placebo) (95% CI)
Enfuvirtide and Darunavir use in OBT									
Naïve Enfuvirtide use and naïve Darunavir use	19/20 (95)	8/9 (89)	6 (-25, 37)	24/25 (96)	12/14 (86)	10 (-15, 36)	43/45 (96)	20/23 (87)	9 (-10, 27)
Naïve Enfuvirtide use and no Darunavir use	26/28 (93)	9/15 (60)	33 (1, 65)	15/18 (83)	6/10 (60)	23 (-19, 66)	41/46 (89)	15/25 (60)	29 (5, 53)
No Enfuvirtide use and naïve Darunavir use	23/28 (82)	9/16 (56)	26 (-7, 59)	48/53 (91)	18/33 (55)	36 (15, 57)	71/81 (88)	27/49 (55)	35 (15, 50)
No Enfuvirtide use and no Darunavir use	82/109 (75)	19/55 (35)	41 (24, 57)	60/88 (68)	7/38 (18)	50 (32, 67)	142/197 (72)	26/93 (28)	44 (32, 56)

to be continued

Table 16: Studies 018 and 019 – Reviewer's Results for Subgroup Analyses for Primary Efficacy Endpoint of Proportion of Patients Achieving HIV RNA < 400 copies/mL at Week 16 by Selected Baseline Characteristics (All Treated) (Cont.)

	Study 018			Study 019			Overall		
Responders / Evaluable (%)	**Raltegravir**	**Placebo**	**Treatment Difference in Percent Response (Raltegravir – Placebo) (95% CI)**	**Raltegravir**	**Placebo**	**Treatment Difference in Percent Response (Raltegravir – Placebo) (95% CI)**	**Raltegravir**	**Placebo**	**Treatment Difference in Percent Response (Raltegravir – Placebo) (95% CI)**
Number of active PI in OBT by phenotypic resistance test									
0	70/100 (70)	9/55 (16)	54 (39, 68)	40/66 (61)	7/42 (17)	44 (26, 62)	110/166 (66)	16/97 (16)	50 (39, 61)
1 or more	102/123 (83)	39/61 (64)	19 (4, 34)	135/155 (87)	43/76 (57)	31 (17, 44)	237/278 (85)	82/137 (60)	25 (17, 35)
Missing	7/9 (78)	1/2 (50)	28 (-77, 100)	5/9 (56)	1/1 (100)	-44 (-100, 44)	12/18 (67)	2/3 (67)	0 (-77, 77)
Phenotypic Sensitivity Score (PSS)[1]									
0	25/44 (57)	1/21 (5)	52 (31, 73)	14/23 (61)	1/23 (4)	57 (31, 82)	39/67 (58)	2/44 (5)	54 (38, 69)
1	52/67 (78)	17/39 (44)	34 (14, 56)	57/78 (73)	12/32 (38)	36 (14, 57)	109/145 (75)	29/71 (41)	34 (20, 49)
2	61/67 (91)	14/33 (42)	49 (28, 69)	63/75 (84)	17/33 (52)	32 (11, 54)	124/142 (87)	31/66 (47)	40 (26, 55)
3 or more	33/44 (75)	14/21 (67)	8 (-19, 36)	37/41 (90)	18/27 (67)	24 (5, 47)	70/85 (82)	32/48 (67)	16 (-2, 33)
Missing	8/10 (80)	3/4 (75)	5 (-62, 72)	9/13 (69)	3/4 (75)	-6 (-71, 60)	17/23 (74)	6/8 (75)	-1 (-44, 42)
Genotypic Sensitivity Score (GSS)[1]									
0	40/70 (57)	4/34 (12)	45 (27, 63)	23/45 (51)	2/31 (6)	45 (25, 64)	63/115 (55)	6/65 (9)	45 (33, 58)
1	65/76 (86)	21/48 (44)	42 (24, 60)	84/102 (82)	20/48 (42)	41 (23, 58)	149/178 (84)	41/96 (43)	41 (29, 53)
2	53/57 (93)	16/22 (73)	20 (-3, 43)	47/54 (87)	21/27 (78)	9 (-12, 30)	100/111 (90)	37/49 (76)	15 (0, 29)
3 or more	18/26 (69)	8/13 (62)	7 (-30, 45)	22/25 (88)	5/10 (50)	38 (-3, 79)	40/51 (78)	13/23 (57)	21 (-4, 48)
Missing	3/3 (100)	0/1 (0)	1 (33, 100)	4/4 (100)	3/3 (100)	n/a	7/7 (100)	3/4 (75)	25 (-37, 87)

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

Table 17: Studies 018 and 019 – Reviewer's Results for Subgroup Analyses for Proportion of Patients Achieving HIV RNA < 50 copies/mL at Week 16 by Selected Baseline Characteristics (All Treated)

	Study 018			Study 019			Overall		
Responders / Evaluable (%)	**Raltegravir**	**Placebo**	**Treatment Difference in Percent Response (Raltegravir – Placebo) (95% CI)**	**Raltegravir**	**Placebo**	**Treatment Difference in Percent Response (Raltegravir – Placebo) (95% CI)**	**Raltegravir**	**Placebo**	**Treatment Difference in Percent Response (Raltegravir – Placebo) (95% CI)**
Number of active PI in OBT by phenotypic resistance test									
0	56/100 (56)	7/55 (13)	43 (29, 58)	31/66 (47)	7/42 (17)	30 (12, 49)	87/166 (52)	14/97 (14)	38 (27, 49)
1 or more	85/123 (69)	32/61 (52)	17 (0, 33)	108/155 (70)	35/76 (46)	24 (9, 38)	193/278 (69)	67/137 (49)	21 (10, 31)
Missing	5/9 (56)	1/1 (50)	6 (-100, 100)	4/9 (44)	1/1 (100)	-56 (-100, 32)	9/18 (50)	2/3 (67)	-17 (-94, 61)
Phenotypic Sensitivity Score (PSS)[1]									
0	19/44 (43)	0/21 (0)	43 (25, 61)	12/23 (52)	1/23 (4)	48 (21, 74)	31/67 (46)	1/44 (2)	44 (29, 59)
1	44/67 (66)	13/39 (33)	32 (12, 53)	40/78 (51)	9/32 (28)	23 (2, 44)	84/145 (58)	22/71 (31)	27 (12, 41)
2	47/67 (70)	11/33 (33)	37 (15, 59)	54/75 (72)	15/33 (45)	27 (5, 49)	101/142 (71)	26/66 (39)	32 (17, 47)
3 or more	30/44 (68)	13/21 (62)	6 (-22, 35)	30/41 (73)	15/27 (56)	18 (-9, 44)	60/85 (71)	28/48 (58)	12 (-6, 31)
Missing	6/10 (60)	3/4 (75)	-15 (-85, 55)	7/13 (54)	3/4 (75)	-21 (-88, 46)	13/23 (57)	6/8 (75)	-18 (-63, 26)
Genotypic Sensitivity Score (GSS)[1]									
0	31/70 (44)	2/34 (6)	38 (22, 55)	20/45 (44)	2/31 (6)	38 (18, 58)	51/115 (44)	4/65 (6)	38 (26, 50)
1	53/76 (70)	16/48 (33)	36 (18, 55)	59/102 (58)	18/48 (38)	20 (2, 39)	112/178 (63)	34/96 (35)	28 (15, 40)
2	44/57 (77)	15/22 (68)	9 (-16, 34)	40/54 (74)	16/27 (59)	15 (-10, 40)	84/111 (76)	31/49 (63)	12 (-5, 30)
3 or more	16/26 (62)	7/13 (54)	8 (-31, 46)	21/25 (84)	4/10 (40)	44 (3, 85)	37/51 (73)	11/23 (48)	25 (-2, 52)
Mising	2/3 (67)	0/1 (0)	67 (-53, 100)	3/4 (75)	3/3 (100)	-25 (-97, 47)	5/7 (71)	3/4 (75)	-4 (-77, 70)

[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.

to be continued

Table 17: Studies 018 and 019 – Reviewer's Results for Subgroup Analyses for Proportion of Patients Achieving HIV RNA < 50 copies/mL at Week 16 by Selected Baseline Characteristics (All Treated) (Cont.)

	Study 018			Study 019			Overall		
Responders / Evaluable (%)	**Raltegravir**	**Placebo**	**Treatment Difference in Percent Response (Raltegravir – Placebo) (95% CI)**	**Raltegravir**	**Placebo**	**Treatment Difference in Percent Response (Raltegravir – Placebo) (95% CI)**	**Raltegravir**	**Placebo**	**Treatment Difference in Percent Response (Raltegravir – Placebo) (95% CI)**
Darunavir use in OBT									
No	98/156 (63)	23/83 (28)	35 (22, 48)	69/122 (57)	12/55 (22)	35 (19, 50)	167/278 (60)	35/138 (25)	35 (25, 45)
Yes in Darunavir exp. patients	4/14 (29)	0/5 (0)	29 (-9, 66)	1/4 (25)	0/4 (0)	25 (-42, 92)	5/18 (28)	0/9 (0)	28 (-1, 57)
Yes in Darunavir naïve patients	44/62 (71)	17/30 (57)	14 (-9, 38)	73/104 (70)	31/60 (52)	19 (2, 35)	117/166 (70)	48/90 (53)	17 (4, 30)
Enfuvirtide use in OBT									
No	91/144 (63)	23/75 (31)	33 (18, 47)	85/143 (59)	22/73 (30)	29 (15, 44)	176/287 (61)	45/148 (30)	31 (21, 41)
Yes in Enfuvirtide exp. patients	18/40 (45)	3/19 (16)	29 (3, 56)	23/43 (53)	5/22 (27)	26 (-1, 54)	41/83 (49)	9/41 (22)	27 (9, 46)
Yes in Enfuvirtide naïve patients	37/48 (77)	14/24 (58)	19 (-7, 45)	35/44 (80)	15/24 (63)	17 (-9, 43)	72/92 (78)	29/48 (60)	18 (0, 36)
Enfuvirtide and Darunavir use in OBT									
Naïve Enfuvirtide use and naïve Darunavir use	17/20 (85)	7/9 (78)	7 (-32, 47)	22/25 (88)	9/14 (64)	24 (-10, 57)	39/45 (87)	16/23 (70)	17 (-7, 42)
Naïve Enfuvirtide use and no Darunavir use	20/28 (71)	7/15 (47)	25 (-11, 60)	13/18 (72)	6/10 (60)	12 (-32, 57)	33/46 (72)	13/25 (52)	20 (-7, 46)
No Enfuvirtide use and naïve Darunavir use	19/28 (68)	8/16 (50)	18 (-17, 53)	37/53 (70)	16/33 (48)	21 (-2, 45)	56/81 (69)	24/49 (49)	20 (1, 39)
No Enfuvirtide use and no Darunavir use	70/109 (64)	15/55 (27)	37 (21, 53)	48/88 (55)	6/38 (16)	39 (21, 56)	118/197 (60)	21/93 (23)	37 (26, 49)

Table 18: Studies 018 and 019 – Reviewer's Results for Subgroup Analyses for Proportion of Patients Achieving HIV RNA < 400 copies/mL at Week 24 by Selected Baseline Characteristics (All Treated)

Responders / Evaluable (%)	Study 018			Study 019			Overall		
	Raltegravir	Placebo	Treatment Difference in Percent Response (Raltegravir – Placebo) (95% CI)	Raltegravir	Placebo	Treatment Difference in Percent Response (Raltegravir – Placebo) (95% CI)	Raltegravir	Placebo	Treatment Difference in Percent Response (Raltegravir – Placebo) (95% CI)
Number of active PI in OBT by phenotypic resistance test									
0	44/69 (64)	8/39 (21)	43 (24, 62)	21/37 (57)	4/23 (17)	39 (14, 65)	65/106 (61)	12/62 (19)	42 (27, 57)
1 or more	71/84 (85)	24/41 (59)	26 (7, 45)	75/90 (83)	23/46 (50)	33 (15, 51)	146/174 (84)	47/87 (54)	30 (17, 43)
Missing	5/5 (100)	1/1 (100)	n/a	1/1 (100)	0/0	n/a	6/6 (100)	1/1 (100)	n/a
Phenotypic Sensitivity Score (PSS)[1]									
0	16/32 (50)	1/15 (7)	43 (17, 70)	6/12 (50)	0/11 (0)	50 (13, 87)	22/44 (50)	1/26 (4)	46 (27, 66)
1	35/43 (81)	10/26 (38)	43 (18, 68)	32/46 (70)	8/24 (33)	36 (10, 62)	67/89 (75)	18/50 (36)	39 (22, 57)
2	44/51 (86)	10/23 (43)	43 (17, 68)	38/44 (86)	5/13 (38)	48 (15, 81)	82/95 (86)	15/36 (42)	45 (25, 64)
3 or more	19/26 (73)	9/14 (64)	9 (-27, 45)	17/22 (77)	13/19 (68)	9 (-23, 41)	36/48 (75)	22/33 (67)	8 (-14, 31)
Missing	6/6 (100)	3/3 (100)	n/a	4/4 (100)	1/2 (50)	50 (-57, 100)	10/10 (100)	4/5 (80)	20 (-30, 70)
Genotypic Sensitivity Score (GSS)[1]									
0	28/48 (58)	4/23 (17)	41 (17, 65)	9/21 (43)	0/17 (0)	43 (16, 69)	37/69 (54)	4/40 (10)	44 (27, 61)
1	43/51 (84)	12/34 (35)	49 (28, 70)	51/64 (80)	11/30 (37)	43 (21, 65)	94/115 (82)	23/64 (36)	46 (31, 61)
2	34/38 (89)	10/13 (77)	13 (-18, 43)	25/29 (86)	11/14 (79)	8 (-23, 38)	49/67 (88)	21/27 (78)	10 (-10, 30)
3 or more	13/19 (68)	7/11 (64)	5 (-38, 47)	9/11 (82)	4/7 (57)	25 (-30, 80)	22/30 (73)	11/18 (61)	12 (-20, 44)
Missing	2/2 (100)	0/0	n/a	3/3 (100)	1/1 (100)	n/a	5/5 (100)	1/1 (100)	n/a

[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.

to be continued

Table 18: Studies 018 and 019 – Reviewer's Results for Subgroup Analyses for Proportion of Patients Achieving HIV RNA <400 copies/mL at Week 24 by Selected Baseline Characteristics (All Treated) (Cont.)

	Study 018			Study 019			Overall		
Responders / Evaluable (%)	**Raltegravir**	**Placebo**	**Treatment Difference in Percent Response (Raltegravir – Placebo) (95% CI)**	**Raltegravir**	**Placebo**	**Treatment Difference in Percent Response (Raltegravir – Placebo) (95% CI)**	**Raltegravir**	**Placebo**	**Treatment Difference in Percent Response (Raltegravir – Placebo) (95% CI)**
Darunavir use in OBT									
No	77/99 (78)	19/57 (33)	44 (28, 61)	47/69 (68)	5/30 (17)	51 (32, 71)	124/168 (74)	24/87 (28)	46 (34, 59)
Yes in Darunavir exp. patients	4/12 (33)	0/2 (0)	33 (-23, 89)	0/0	0/2 (0)	n/a	4/12 (33)	0/4 (0)	33 (-10, 77)
Yes in Darunavir naïve patients	39/47 (83)	14/22 (64)	19 (-7, 45)	50/59 (85)	22/37 (59)	25 (5, 46)	89/106 (84)	36/59 (61)	23 (7, 39)
Enfuvirtide use in OBT									
No	68/91 (75)	20/51 (39)	36 (18, 53)	55/76 (72)	11/41 (27)	46 (27, 64)	123/167 (74)	31/91 (34)	40 (27, 53)
Yes in Enfuvirtide exp. patients	19/30 (63)	1/14 (7)	56 (29, 83)	16/25 (64)	6/16 (38)	27 (-9, 62)	35/55 (64)	7/30 (23)	40 (18, 63)
Yes in Enfuvirtide naïve patients	33/37 (89)	12/16 (75)	14 (-14, 42)	26/27 (96)	10/12 (83)	13 (-15, 41)	59/64 (92)	22/28 (79)	13 (-6, 33)
Enfuvirtide and Darunavir use in OBT									
Naïve Enfuvirtide use and naïve Darunavir use	15/16 (94)	6/7 (86)	8 (-31, 47)	15/15 (100)	7/7 (100)	n/a	30/31 (97)	13/14 (93)	4 (-16, 24)
Naïve Enfuvirtide use and no Darunavir use	18/21 (86)	6/9 (67)	19 (-23, 61)	11/12 (92)	3/5 (60)	32 (-28, 92)	29/33 (88)	9/14 (64)	24 (-9, 56)
No Enfuvirtide use and naïve Darunavir use	15/20 (75)	7/12 (58)	17 (-24, 57)	24/28 (86)	9/20 (45)	41 (11, 70)	39/48 (81)	16/32 (50)	31 (8, 54)
No Enfuvirtide use and no Darunavir use	51/65 (78)	13/38 (34)	44 (24, 64)	31/48 (65)	2/21 (10)	55 (33, 77)	82/113 (73)	15/59 (25)	47 (32, 62)

Table 19: Studies 018 and 019 – Reviewer's Results for Subgroup Analyses for Proportion of Patients Achieving HIV RNA < 50 copies/mL at Week 24 by Selected Baseline Characteristics (All Treated)

Responders / Evaluable (%)	Study 018			Study 019			Overall		
	Raltegravir	Placebo	Treatment Difference in Percent Response (Raltegravir – Placebo) (95% CI)	Raltegravir	Placebo	Treatment Difference in Percent Response (Raltegravir – Placebo) (95% CI)	Raltegravir	Placebo	Treatment Difference in Percent Response (Raltegravir – Placebo) (95% CI)
Number of active PI in OBT by phenotypic resistance test									
0	38/69 (55)	6/39 (15)	40 (21, 58)	18/37 (49)	4/23 (17)	31 (5, 57)	56/106 (53)	10/62 (16)	37 (22, 51)
1 or more	52/84 (62)	21/41 (51)	11 (-10, 31)	64/90 (71)	19/46 (41)	30 (11, 48)	116/174 (67)	40/87 (46)	21 (7, 34)
Missing	5/5 (100)	1/1 (100)	n/a	1/1 (100)	0/0	n/a	6/6 (100)	1/1 (100)	n/a
Phenotypic Sensitivity Score (PSS)[1]									
0	13/32 (41)	1/15 (7)	34 (8, 60)	5/12 (42)	0/11 (0)	42 (5, 78)	18/44 (41)	1/26 (4)	37 (18, 56)
1	30/43 (70)	9/26 (35)	35 (9, 61)	29/46 (63)	7/24 (29)	34 (8, 60)	59/89 (66)	16/50 (32)	34 (16, 52)
2	33/51 (65)	9/23 (39)	26 (-1, 53)	33/44 (75)	4/13 (31)	44 (11, 77)	66/95 (69)	13/36 (36)	33 (13, 54)
3 or more	13/26 (50)	7/14 (50)	0 (-38, 38)	13/22 (59)	11/19 (58)	1 (-34, 36)	26/48 (54)	18/33 (55)	-0 (-25, 24)
Missing	6/6 (100)	2/3 (67)	33 (-45, 100)	3/4 (75)	1/2 (50)	25 (-94, 100)	9/10 (90)	3/5 (60)	30 (-32, 92)
Genotypic Sensitivity Score (GSS)[1]									
0	22/48 (46)	3/23 (13)	33 (10, 56)	6/21 (29)	0/17 (0)	29 (4, 53)	28/69 (41)	3/40 (8)	33 (17, 49)
1	36/51 (71)	11/34 (32)	38 (17, 61)	43/64 (67)	10/30 (33)	34 (11, 57)	79/115 (69)	21/64 (33)	36 (20, 51)
2	28/38 (74)	8/13 (62)	12 (-23, 47)	22/29 (76)	9/14 (64)	12 (-23, 46)	50/67 (75)	17/27 (63)	12 (-12, 35)
3 or more	7/19 (37)	6/11 (55)	-18 (61, 26)	9/11 (82)	3/7 (43)	39 (-16, 94)	16/30 (53)	9/18 (50)	3 (-30, 37)
Missing	2/2 (100)	0/0	n/a	3/3 (100)	1/1 (100)	n/a	5/5 (100)	1/1 (100)	n/a

[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.

to be continued

Table 19: Studies 018 and 019 – Reviewer's Results for Subgroup Analyses for Proportion of Patients Achieving HIV RNA <50 copies/mL at Week 24 by Selected Baseline Characteristics (All Treated) (Cont.)

	Study 018			Study 019			Overall		
Responders / Evaluable (%)	Raltegravir	Placebo	Treatment Difference in Percent Response (Raltegravir – Placebo) (95% CI)	Raltegravir	Placebo	Treatment Difference in Percent Response (Raltegravir – Placebo) (95% CI)	Raltegravir	Placebo	Treatment Difference in Percent Response (Raltegravir – Placebo) (95% CI)
Darunavir use in OBT									
No	64/99 (65)	15/57 (26)	38 (22, 55)	41/69 (59)	5/30 (17)	43 (23, 63)	105/168 (63)	20/87 (23)	49 (27, 52)
Yes in Darunavir exp. patients	3/12 (25)	0/2 (0)	25 (-29, 79)	0/0	0/2 (0)	n/a	3/12 (25)	0/4 (0)	25 (-16, 66)
Yes in Darunavir naïve patients	28/47 (60)	13/22 (59)	0 (-28, 29)	42/59 (71)	18/37 (49)	23 (1, 45)	70/106 (66)	31/59 (53)	14 (-3, 30)
Enfuvirtide use in OBT									
No	57/91 (63)	19/51 (37)	25 (7, 43)	44/76 (58)	8/41 (20)	38 (20, 57)	101/167 (60)	27/92 (29)	31 (18, 44)
Yes in Enfuvirtide exp. patients	12/30 (40)	0/14 (0)	40 (17, 63)	14/25 (56)	6/16 (38)	19 (-17, 54)	26/55 (47)	6/30 (20)	27 (5, 49)
Yes in Enfuvirtide naïve patients	26/37 (70)	9/16 (56)	14 (-19, 47)	25/27 (93)	9/12 (75)	18 (-15, 50)	51/64 (80)	18/28 (64)	15 (-7, 38)
Enfuvirtide and Darunavir use in OBT									
Naïve Enfuvirtide use and naïve Darunavir use	10/16 (63)	6/7 (86)	-23 (-69, 22)	14/15 (93)	6/7 (86)	8 (-32, 47)	24/31 (77)	12/14 (86)	-8 (-37, 20)
Naïve Enfuvirtide use and no Darunavir use	16/21 (76)	3/9 (33)	43 (-1, 87)	11/12 (92)	3/5 (60)	32 (-28, 92)	27/33 (82)	6/14 (43)	39 (5, 73)
No Enfuvirtide use and naïve Darunavir use	12/20 (60)	7/12 (58)	2 (-40, 44)	18/28 (64)	6/20 (30)	34 (3, 65)	30/48 (63)	13/32 (41)	22 (-3, 46)
No Enfuvirtide use and no Darunavir use	44/65 (68)	12/38 (32)	36 (15, 57)	26/48 (54)	2/21 (10)	45 (22, 67)	70/113 (62)	14/59 (24)	38 (23, 54)

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