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

Liver enzyme data submitted at the time of NDA submission were examined for hepatic abnormalities. Table 7.1.3.3.N shows the rates of AST, ALT, alkaline phosphatase and bilirubin abnormalities from the raltegravir and placebo arms of the Phase 2 and Phase 3 studies. Overall, the rates of liver enzyme elevations were similar between the raltegravir and placebo arms. A higher rate of Grade 3/4 total bilirubin was observed in the raltegravir arm. The majority of subjects with elevated total bilirubin levels had elevated indirect bilirubin (85.7%, 24/28), and all of these subjects were receiving ATV as part of the OBT. The remaining four subjects had an alternative explanation for hyperbilirubinemia: occurrence in the setting of shock for 2 subjects (AN 8204, 8325) and in the setting of transient viral hepatitis reactivation for two subjects (AN 8222, 16235).

Table 7.1.3.3.N: Grade 1 – 4 AST, ALT, Alkaline Phosphatase, Total Bilirubin Laboratory Data in Phase 2 and Phase 3 Studies, Double-Blind Treatment Period

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

Source: FDALABGD dataset for Protocols 004, 005, 018, 019

The Phase 2 and 3 data were screened for Hy's Law cases. Hy's Law is operationally defined as:

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

Six subjects met the initial laboratory screening criteria and are listed in Table 7.1.3.3.O; however, each case was confounded by either use of ATV or confounding illness. Therefore, no cases satisfied Hy's Law.

Table 7.1.3.3.O: Screening for Potential Hy's Law Cases in Phase 2 and 3 Studies: No Cases Identified

AN	Study	Raltegravir Dose	Study Day[1]	Period	↑AP	Hx HBV/HCV	OBT	Misc	Case
3877	005	200 mg	69	DB	No	No	**ATV/r**, ddI, 3TC	Day 28 bilirubin ≥2x ULN Hx elevated bilirubin, transaminases 2003; splenomegaly, steatosis 2000	No- ATV. Continued study therapy.
3891	005	200 mg	277	OLPVF	No	No	**ATV**, LPV/r, abacavir, 3TC	Unchanged OBT Hx hyperbilirubin-emia 2004	No- ATV. Continued study therapy.
8222	018	400 mg	36	DB	<Gr 1	(+)HCV	DRV/r, abacavir, TDF	BL CD4 147, Day 29 181; BL HIV RNA 413k, Day 29 0.	No – transient (+)HCV reactivation. Continued study therapy.
8325	018	400 mg	31 109	DB Post-Tx	Yes (Gr 2) Yes (Gr 2)	Hx HBV exposure	DRV/r, indinavir, 3TC, AZT	Occurred in setting of acute thyrotoxicosis on PTU (Day 26) and pneumonia (Day 102). Nl AST/ALT Day 80	No- elevated AP, concomitant illness Interrupted therapy Day 32 – 66. D/C PTU.
16235	019	400 mg	162	DB	No	(+)HBV	DRV/r, FTC, TDF	Subject stopped FTC/TDF Day 33 - 166, led to HBV reactivation. Day 162 HBV DNA 84,000,000 IU/mL.	No – HBV reactivation Stopped study therapy Day 168, resumed Day 174.
16362	019	400 mg	56	DB	No	(+) HBV	DRV/r, **ATV**, FTC, TDF	Baseline bilirubin 3.4	No – ATV, (+)HBV Continued study therapy.

Source: FDALABGD, AE, MEDHIST, CONXCLP, and CONXOBT datasets for Protocols 004, 005, 018, 019

1 If day of elevated AST/ALT and bilirubin are not the same (but within 14 days of each other), study day reflects day of elevated AST/ALT
AP = alkaline phosphatase, HX = history, Gr = grade, DB = double blind, OLPVF = open label post virologic failure, Post-Tx = post-treatment

Additional exploration of the SUR laboratory datasets identified two additional cases satisfying the laboratory screening criteria; however, neither case satisfied Hy's Law.

AN 3868 was randomized the to 600 mg twice daily raltegravir and switched to open-label on Day 224. This subject was receiving concomitant ATV and had elevated bilirubin level starting Day 14. On Day 392 the subject experienced Grade 2 AST, ALT in addition to stable Grade 2 bilirubin.

AN 8315 was HCV (+) and developed Grade 4 AST, ALT on Day 87 attributed to OBT (lamivudine, indinavir, didanosine; lopinavir/ritonavir not implicated). All antiretrovirals were held Day 91. On Day 142 lopinavir/ritonavir was restarted in addition to abacavir, lamivudine, and ATV. On Day 155, Grade 3 bilirubin occurred while the subject was off raltegravir.

Increased Creatine Kinase

An analysis was performed for elevated creatine kinase (CK) and associated musculoskeletal AEs. This analysis used the data from Phase 2 and 3 studies, limited to the double-blind treatment period. All raltegravir doses were combined as no dose-response was observed. A total of 63 subjects experienced Grade 2 - Grade 4 CK elevations, displayed in Table 7.1.3.3.P. Overall, a small increase in the rates of CK elevations in the raltegravir group (6.6%) was observed as compared to control (4.1%). There were no SAEs or study discontinuations associated with elevated CK levels.

Table 7.1.3.3.P[1]: Grade 1 – 4 Creatine Kinase Laboratory Data in Phase 2 and Phase 3 Studies, Double-Blind Treatment Period

CK Grade	Limit	Raltegravir N=755		Control N=320	
		n	%	n	%
Grade 1	3.0-5.9 x ULN	55	7.3%	17	5.3%
Grade 2	6.0–9.9 x ULN	18	2.4%	5	1.6%
Grade 3	10.0–19.9 x ULN	16	2.1%	5	1.6%
Grade 4	≥20.0 x ULN	16	2.1%	3	0.9%
All Grades		105	13.9%	30	9.4%
Grades 2-4		50	6.6%	13	4.1%

Source: FDALABGD dataset for Protocols 004, 005, 018, and 019
[1] Analysis of CK using SUR data produced similar results

The AE database for Phase 2 and 3 studies was examined for AEs associated with elevated CK, including: arthalgia, myalgia, myositis, rhabdomyolysis, musculoskeletal pain, muscle fatigue, muscle strain. The following table (Table 7.1.3.3.Q) reports the rates of elevated CK values, defined as Grade 1 or higher, and potential CK-related AEs. Of note, no AEs appeared to be

associated with Grade 1 CK levels. Reports of potentially CK-related AEs in subjects with elevations of CK were uncommon. No reported SAEs or study discontinuations were due to elevated CK levels. For the two subjects with reported myositis, both cases resolved: one was attributed to ritonavir and the other to improper ENF injection technique with associated injection site reaction.

Table 7.1.3.3.Q: Potential Clinical AEs Associated with Elevated Creatine Kinase Levels in Phase 2 and Phase 3 Studies, Double-Blind Treatment Period

Preferred Term	CK Grade	Raltegravir N=755		Control N=320	
		n	%	n	%
Myalgia					
	Grade 3	1	0.1%	0	0
	Grade 4	1	0.1%	2	0.6%
	All Grades	2	0.3%	2	0.6%
Myositis					
	Grade 2	1	0.1%	0	0
	Grade 4	1	0.1%	0	0
	All Grades	2	0.3%	0	0
Arthralgia					
	Grade 3 (All)	2	0.3%	0	0

Source: FDALABGD and AE datasets for Protocols 004, 005, 018, and 019

The majority of CK elevations in raltegravir-treated subjects were transient and resolved without study drug interruption (86%, 43/50). Seven subjects briefly interrupted therapy:

AN 138 experienced Grade 4 CK and AST in the setting of an upper respiratory tract infection and on concomitant therapy with trimethoprim/sulfamethoxazole (TMP/SMX). TMP/SMX was discontinued, all labs normalized within nine days and did not worsen after restarting ART.

AN 3256 experienced Grade 4 CK and Gr 3 AST on Day 15 associated with myositis attributed to improper ENF injection technique.

AN 3291 experienced Grade 4 CK, Grade 2 ALT, and Grade 3 AST on Day 225. Raltegravir was held Day 230-232. All symptoms resolved without worsening after raltegravir was restarted.

AN 3294 experienced Grade 4 CK on Days 282 and 289. ART were held Day 285-311. OBT consisted of d4T, ddI, 3TC. On Day 312 OBT was changed to ddI, 3TC, AZT. This subject received bovine colostrum plus egg yolk on Days 258-284. CK resolved by D296.

AN 3868 experienced Grade 3 CK on Day 91, with continued elevated CK through Day 175 and into OL. There was no change in medications (OBT ATV/r, AZT, FTC/TDF) except holding raltegravir on Day 91.

AN 6404 experienced Grade 3 CK on Day 47 temporally associated with an IM tramadol injection. This subject also experienced multiple episodes of

hypersensitivity due to variety of meds (DRV, FTC, ENF). Raltegravir held Day 38 -117 (prior to elevated CK).

AN 16240 experienced Grade 4 CK, Grade 3 AST, and Grade 1 ALT on Day 112. This subject was on concomitant fenofibrate. ART was held Day 114-127. The CK level normalized without worsening after restart.

An October 2007 update of myopathy and rhabdomyolysis cases requested by FDA reported one subject in Protocol 019 (AN 15059) originally randomized to placebo who experienced rhabdomyolysis during OLPVF. During OLPVF this subject received raltegravir plus DRV/r, delavirdine, lamivudine, saquinavir, and ENF. Concomitant medications included atorvastatin and fenofibrate. On Day 280 of OLPVF the subject was diagnosed with rhabdomyolysis and hypothyroidism. No change in ART occurred, and this subject had not yet had a follow up examination.

In the expanded access program (Protocol 023), two cases of myopathy and two cases of rhabdomyolysis have occurred outside the SUR cutoff date as reported in the October 2007 update.

Myopathy (2 cases)

AN 01522 A 46 yo man began raltegravir plus abacavir, DRV/r, FTC/TDF, and on Day 9 experienced fever, elevated lactate leading to ART discontinuation. Subsequently the subject experienced lower extremity weakness and on Day 17 was admitted; Peak CK on Day 18 was 9187 IU/L. After treatment with intravenous fluids the subject improved, and the investigator attributed the event to abacavir or viral syndrome. On Day 33 the subject restarted raltegravir plus DRV/r, FTC/TDF, and TMC-125. On Day 47 (2 wks later) the CK was 49,000 IU/L, and repeat was 4505 IU/L (Day 47 value likely lab error), The CK values normalized over the next 4 weeks while the subject continued ART therapy.

AN 00874 A 49 yo woman began raltegravir plus TMC-125, FTC/TDF, and on Day 46 experienced a subacute onset of weakness, myalgias, and shortness of breath leading to admission for myopathy with a CK of 4217 IU/L and myoglobin >1000 ng/mL. On Day 52 the subject discontinued ART, and on Day 53 the CK, myoglobin were "normal".

Rhabdomyolysis (2 cases)

AN 01584 A 40 yo man began raltegravir plus DRV/r, FTC/TDF. Concomitant medications included atorvastatin,ezetimibe, lisinopril, and rosiglitazone. On Day 32 the subject was admitted with rhabdomyolysis and acute renal failure. ART was discontinued. The subject improved and on Day 48 restarted ART. The investigator attributed acute renal failure to drug interaction between DRV/r and atorvastatin and attributed rhabdomyolysis "primarily related to atorvastatin calcium".

No # [redacted] A 42 yo man began raltegravir plus DRV/r. Concomitant medications included pravastatin. On Day 101 the

subject was admitted and diagnosed with rhabdomyolysis with a CK of approximately 15,000 IU/mL on Day 102. Pravastatin and ritonavir were discontinued, raltegravir was continued. On Day 103 the CK had improved to 3000-4000 IU/mL; however, on Day 106 the subject experienced a sudden neurologic disorder and died.

An analysis of concomitant use of HMG-CoA reductase inhibitors, fibrates, and protease inhibitors in subjects with Grade 2-4 CK elevations was performed. Ten subjects were receiving concomitant lipid lowering agents plus protease inhibitors at the time of CK elevation: 9 in the raltegravir arm and 1 in placebo.

Table 7.1.3.3.R: Concomitant Use of HMG-CoA reductase inhibitors, fibrates, and protease inhibitors in Subjects with Grade 2-4 CK elevations

AN	Protocol	Dose	Lipid Lowering Agent	Protease Inhibitor	Maximum CK Grade
3232	005	400 mg raltegravir	atorvastatin	saquinavir	Grade 2
3881	005	400 mg raltegravir	atorvastatin	atazanavir/ritonavir	Grade 2
7071	018	400 mg raltegravir	pravastatin	tipranavir/ritonavir fosamprenavir	Grade 3
7096	018	400 mg raltegravir	fenofibrate	darunavir/ritonavir	Grade 3
15048	019	400 mg raltegravir	fenofibrate	darunavir/ritonavir	Grade 2
15080	019	400 mg raltegravir	rosuvastatin fenofibrate	darunavir/ritonavir	Grade 2
16204	019	400 mg raltegravir	atorvastatin fenofibrate*	fosamprenavir/ritonavir	Grade 2
16216	019	Placebo	fenofibrate	darunavir/ritonavir	Grade 3
16240	019	400 mg raltegravir	fenofibrate	darunavir/ritonavir	Grade 4
16272	019	400 mg raltegravir	gemfibrozil	darunavir/ritonavir	Grade 3

Source: FDALABGD and CONXCLP datasets for Protocols 004, 005, 018, and 019
*Initiated on day of maximum CK

Concomitant use of a lipid-lowering agent plus a protease inhibitor in subjects with Grade 2-4 CK elevations is summarized in the following table (Table 7.1.3.3.S). In subjects with $\leq$ Grade 1 CK levels, there was 17.4% (123/705) use of these agents. In subjects with Grade 2-4 CK elevations, there was 18.0% (9/50) use of these agents. Therefore, there was no apparent association with concomitant use of lipid-lowering agents and protease inhibitors and increased CK.

Table 7.1.3.3.S: Concomitant Use of HMG-CoA reductase inhibitors, fibrates, and protease inhibitors in Subjects with Grade 2-4 CK elevations

		Grade 2-4 increased CK	
		Yes	No
Lipid Lowering agent plus Protease Inhibitor	Yes	9	123
	No	41	582

Source: FDALABGD and CONXCLP datasets for Protocols 004, 005, 018, and 019

In summary, a modest increase in Grade 2 – 4 CK elevations was observed in raltegravir arms as compared to control; however, association with clinical symptoms was balanced between the two groups. No SAEs or study discontinuations were associated with elevated CK levels in the Phase 2 and 3 studies double-blind phase. A minority of raltegravir-treated subject briefly interrupted study therapy due to elevated CK levels, but the temporal correlation with confounding factors such as ISRs and use of TMP/SMX or fibrates makes it difficult to attribute an association with raltegravir use. A total of 3 cases of rhabdomyolysis and 2 cases of myopathy have been reported in the Phase 3 and Expanded Access Programs. One subject (AN 01522) appeared to have a positive rechallenge with elevated CK levels after restarting their raltegravir-based regimen during OLPVF; however, the subject was asymptomatic and CK values normalized without interrupting study therapy.

The Applicant has agreed to include the CK laboratory data in the PI, and longer term data and safety monitoring will be collected to allow further characterization of any potential relationship between raltegravir, elevated CK levels and clinical adverse events. The isolated reports of rhabdomyolysis and myopathy warrant further consideration due to the observed CK imbalance in the Phase 2 and 3 clinical studies. Therefore, the Applicant has agreed to include the following language in the PI:

Highlights:
Creatine kinase elevations were observed in subjects who received ISENTRESS. Myopathy and rhabdomyolysis have been reported; however, the relationship of ISENTRESS to these events is not known. Use with caution in patients at increased risk of myopathy or rhabdomyolysis, such as patients receiving concomitant medications known to cause these conditions

Full Prescribing Information:
Serious Events; Regardless of Drug Relationship

Grade 2-4 creatine kinase laboratory abnormalities were observed in subjects treated with ISENTRESS (see Table 3). Myopathy and rhabdomyolysis have been reported; however, the relationship of ISENTRESS to these events is not known. Use with caution in patients at increased risk of myopathy or rhabdomyolysis, such as patients receiving concomitant medications known to cause these conditions.

Renal Events

An analysis of renal adverse experiences was performed using the SUR AE datasets for the Phase 2 and 3 studies, limiting BODY_SYS to "Renal and urinary disorders". The following table presents the distribution of "Renal and urinary disorders" among the four trials.

Table 7.1.3.3.T: Renal and Urinary Disorders in Phase 2 and Phase 3 Studies, Double-Blind Treatment Period

Protocol	Raltegravir dose					
	100 mg[1] n (%)	200 mg[2] n (%)	400 mg[3] n (%)	600 mg[4] n (%)	All doses[5] n (%)	Control[6] n (%)
004	1 (2.6%)	2 (5.0%)	1 (2.4%)	2 (5.0%)	6 (3.8%)	2 (5.3%)
005	-	1 (2.3%)	2 (4.4%)	4 (8.9%)	7 (5.3%)	2 (4.4%)
018	-	-	13 (5.6%)	-	13 (5.6%)	3 (2.5%)
019	-	-	9 (3.9%)	-	9 (3.9%)	9 (7.6%)

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

A total of 29 preferred terms were included in the "Renal and urinary disorders" category. To allow a focused analysis of renal AEs, the following preferred terms were selected: focal glomerulosclerosis, nephrolithiasis, nephropathy, nephropathy toxic, nephrotic syndrome, renal failure (acute, chronic), renal impairment, renal tubular necrosis, and urinary calculus.

A total of 22 renal AEs occurred in 18 subjects using the above definition during the double-blind treatment period. The following table (Table 7.1.3.3.U) presents the results of this analysis. No imbalance was identified between the two groups, and there was no apparent pattern to the types of renal AEs observed.

Table 7.1.3.3.U: Renal Adverse Experiences[1] in Phase 2 and Phase 3 Studies, Double-Blind Treatment Period

Preferred Term	Raltegravir[2] N=755 n (%)	Control N=320 n (%)
Renal failure[2, 3]	3 (0.4%)	3 (0.9%)
Nephropathy[4]	2 (0.3%)	1 (0.3%)
Nephrolithiasis	2 (0.3%)	4 (1.3%)
Nephrotic syndrome	2 (0.3%)	0 (0)
Focal glomerulosclerosis	2 (0.3%)	0 (0)
Renal tubular necrosis	1 (0.1%)	0 (0)
Renal impairment	1 (0.1%)	0 (0)
Urinary calculus	1 (0.1%)	0 (0)
Total	**14 (1.9%)**	**8 (2.5%)**

Source: AE (SUR Frozen File 2/16/07) datasets for Protocols 004, 005, 018 and 019.
[1]Renal Adverse Experiences were defined by one of the following preferred terms: focal glomerulosclerosis, nephrolithiasis, nephropathy, nephropathy toxic, nephrotic syndrome, renal failure (acute, chronic), renal impairment, renal tubular necrosis, and urinary calculus.
[2]Protocol 004: 1 subject in the 200 mg bid arm (urinary calculus), 1 subject in the 600 mg bid arm (nephrolithiasis); Protocol 005: 2 subjects in the 600 mg bid arm (renal failure, nephrolithiasis). All remaining renal AEs occurred in 400 mg bid raltegravir arms or control.
[3]The terms "renal failure" (N=3; 2 raltegravir, 1 control), "renal failure acute" (N=2; both control), and "renal failure chronic" (N=1; raltegravir) were combined.
[4]The terms "nephropathy" (N=2; 1 raltegravir, 1 control) and "nephropathy toxic" (N=1; raltegravir) were combined.

Five additional cases of renal AEs occurred outside the double-blind treatment phase: one in Protocol 004 in the extension phase (Day 452), one in Protocol 005 in the open-label phase (Day 549), and three in Protocols 018/019 in the open-label post virologic failure phase (Days 182, 270, 279). Of note, one of the subjects experiencing a renal AE in the OLPVF phase was originally randomized to the raltegravir arm, and a second subject experienced two prior episodes of renal AEs during the double-blind treatment period. None of the renal AEs occurring outside of the double-blind treatment period were SAEs.

Nine subjects experienced renal SAEs, all in the double-blind treatment period. A tabular listing of the renal SAEs based on the subject narratives is listed below. All subjects had plausible alternative explanations either due to use of concomitant medications such as TDF and indinavir and/or underlying disease conditions including nephrolithiasis, viral hepatitis, hypertension, and diabetes.

Table 7.1.3.3.V: Summary of Renal Serious Adverse Events in the Phase 2 and 3 Studies, Double-Blind Treatment Period

AN	Protocol	Preferred Term	Onset Day	Outcome	BL Cr[1]	Max Cr[2] (Day)	Last Cr (Day)	Notes
Raltegravir 200 mg bid								
349	004	Urinary calculus	28, 80	Recovered	0.9	1.1 (Day 28 and 77)	1.0 (Day 275)	(+)Hx nephrolithiasis
Raltegravir 400 mg bid								
7019	018	Nephrotic syndrome Focal glomerulosclerosis	208 209	Not recovered	1.0	1.1 (Day 182)	1.0 (Day 238)	(+) HCV, HTN, proteinuria.
8318	018	Nephropathy toxic Renal impairment	1 7	Recovered Recovered	1.9	1.9 (BL)	1.2 (Day 225)	(+)TDF-d/c on Day 15
8345	018	Chronic renal failure Renal tubular necrosis	129 129	Recovered Recovered	1.4	4.0[3] (Day 137)	1.3 (Day 225)	(+)HBV, HCV, history of renal insufficiency; (+) TDF- d/c on Day 138
15115	019	Renal failure	25	Not recovered	1.9	13.4 (Day 26)	11.9 (Day 40)	(+) HTN, DM. (+) TDF. Admitted with fever, confusion, diarrhea, CHF, and renal failure. D/C ART Day 26. Dx with c. diff colitis.
Raltegravir 600 mg bid								
3243	005	Renal failure	144	Death (Day 146)	0.9	0.9 (Day 113)	0.9 (Day 113)	(+) TDF. Admitted Day 142 with dyspnea, weakness, fever followed by metabolic acidosis and renal failure.
Placebo								

7024	018	Acute renal failure Nephropathy Acute renal failure	51 119 270	Recovered Not recovered-Stopped OBT Recovered	1.5	1.9 (Day 84)	1.6 (Day 291) – off drug	Started OLPVF on Day 184
15125	019	Renal failure	184	Not recovered	1.0	-[4]	-	(+)TDF. Day 174 dx endocarditis, tx vancomycin + gentamicin. Gentamicin d/c Day 184. D/C ART Day 187. Renal failure resolved Day 229, ART restarted Day 233.
16389	019	Nephrolithiasis	2	Recovered	0.9	0.9 (BL)	0.8 (Day 131)	(+)indinavir

Source: AE and LABCHEM datasets (SUR Frozen File 2/16/07) for Protocols 004, 005, 018 and 019.
[1] BL Cr = baseline creatinine
[2] Max Cr = maximum creatinine
[3] Based on conversion from recorded creatinine of 356 mmol/L to 4.0 mg/dL.
[4] The event of renal failure for subject AN 15125 occurred at the time of the frozen file, therefore, no laboratory data is available.
HTN = hypertension, HCV = hepatitis C virus, HBV= hepatitis B virus, d/c = discontinue, DM = diabetes mellitus, CHF = congestive heart failure, ART = antiretroviral therapy, dx = diagnosis, OBT = optimized background therapy, OLPVF = open label post virologic failure, tx = treated.

Overall, no imbalance of renal AEs was observed between raltegravir and control groups, and no pattern was apparent in the types of renal AEs observed. In general, other risk factors for renal AEs were present in subjects experiencing SAEs or discontinuing for renal AEs.

Cardiovascular events

An analysis was performed of cardiovascular AEs for all Phase 2 and 3 studies using the SUR AE dataset, limiting BODY_SYS to "Cardiac" and "Vascular disorders". To allow a more direct comparison among treatment arms, the following analyses of cardiovascular AEs are limited to the double-blind treatment period. A total of 70 subjects experienced 81 cardiac and/or vascular AEs during the double-blind treatment period.

Table 7.1.3.3.W: Cardiac and Vascular Disorders in Phase 2 and Phase 3 Studies, Double-Blind Treatment Period

Protocol	Raltegravir dose					
	100 mg[1] n (%)	200 mg[2] n (%)	400 mg[3] n (%)	600 mg[4] n (%)	All doses[5] n (%)	Control[6] n (%)
004	2 (5.1%)	1 (2.5%)	4 (9.8%)	2 (5.0%)	9 (5.6%)	0
005	-	5 (11.6%)	7 (15.6%)	7 (15.6%)	19 (14.3%)	4 (8.9%)
018	-	-	16 (6.9%)	-	16 (6.9%)	7 (5.9%)
019	-	-	13 (5.7%)	-	13 (5.7%)	13 (10.9%)
Total	2 (5.1%)	6 (7.2%)	40 (7.3%)	9 (10.6%)	57 (7.5%)	24 (7.5%)

Source: AE (SUR Frozen File 2/16/07) datasets for Protocols 04, 05, 018 and 019.
[1] 100 mg: Protocol 004 N=39
[2] 200 mg: Protocol 004 N=40, Protocol 005 N=43
[3] 400 mg: Protocol 004 N=41, Protocol 005 N=45, Protocol 018 N=232, Protocol 019 N=230
[4] 600 mg: Protocol 004 N=40, Protocol 005 N=45
[5] All raltegravir doses: Protocol 004 N=160, Protocol 005 N=133, Protocol 018 N=232, Protocol 019 N=230
[6] Control: Protocol 004 N=38, Protocol 005 N=45, Protocol 018 N=118, Protocol 019 N=119

The individual preferred terms are listed in the following table by treatment arm.

Table 7.1.3.3.X: Cardiac and Vascular AEs in Phase 2 and Phase 3 Studies, Double-Blind Treatment Period

Preferred Term	Raltegravir N=755 n (%)	Control N=320 n (%)
Hypertension	17 (2.3%)	4 (1.3%)
Arrhythmia[1]	9 (1.2%)	4 (1.3%)
Flushing[2]	7 (0.9%)	0
Haematoma	4 (0.5%)	3 (0.9%)
Palpitations	4 (0.5%)	0
Vascular thrombosis/ phlebitis[3]	4 (0.5%)	1 (0.3%)
Angina pectoris	2 (0.3%)	3 (0.9%)
Infarction[4]	2 (0.3%)	3 (0.9%)
Cardiac failure congestive	2 (0.3%)	0
Coronary artery disease	2 (0.3%)	1 (0.3%)
Hypotension	1 (0.1%)	2 (0.6%)
Mitral valve incompetence	1 (0.1%)	1 (0.3%)
Pericarditis	1 (0.1%)	0
Shock	1 (0.1%)	0
Cardiomyopathy	0	1 (0.3%)
Cardiovascular disorder	0	1 (0.3%)
Total	**57 (7.5%)**	**24 (7.5%)**

Source: AE (SUR Frozen File 2/16/07) datasets for Protocols 004, 005, 018 and 019.
[1] Arrhythmia is defined by the following preferred terms: arrhythmia, atrioventricular block first degree, bradycardia, bundle branch block right, sinus tachycardia, supraventricular extrasystoles, tachycardia, ventricular extrasystoles, and ventricular tachycardia

[2]Flushing is defined by the following preferred terms: flushing, hot flush, hyperaemia.
[3]Vascular thrombosis/phlebitis is defined by the following preferred terms: deep vein thrombosis, thrombophlebitis, varicophlebitis, varicose vein, venous thrombosis.
[4]Infarction is defined by the following preferred terms: infarction, myocardial infarction.

Of the 17 raltegravir-treated subjects with hypertension (HTN), 7 had a prior history and 5 had additional risk factors including: diabetes, hyperlipidemia, left ventricular hypertrophy, cardiomyopathy. Therefore, only five raltegravir-treated subjects with an AE of HTN did not have a prior history and/or risk factors (5/755 = 0.7%; Table 7.1.3.3.Y). Of those 5 remaining subjects, two had baseline BP >140/90 mmHg. Based on this analysis, a HTN safety signal associated with raltegravir is not apparent at this time.

Table 7.1.3.3.Y: Summary of Subjects with HTN and No Identified Prior History or Risk Factors, Phase 2 and 3 Studies, Double-Blind Treatment Period

AN	Age/Race/Gender	Baseline BP	HTN Onset	BP on Onset Date	F/U BP (Day)	Meds (Day)
Placebo						
8228	43/White/Male	134/96	Day 29	167/117	148/109 (57)	None
Raltegravir (dose)						
88 (100mg)	31/Hispanic/Male	110/72	Day 324	148/93	137/85 (382)	Candesartan (324)
3284 (400mg)	67/White/Male	170/90	Day 185	155/90 (Day 189)	155/85 (204)	Enalapril (185)
8291 (400mg)	62/Multi/Male	145/98	Day 70	140/87 (Day 57)	140/89 (84)	Enalapril (84)
15068 (400mg)	50/Black/Male	128/72	Day 117	140/80	120/80 (173)	None
16390 (400mg)	48/White/Male	129/88	Day 15	149/93	167/102 (31)	Lisinopril (117)

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

Thirteen (13) subjects experienced 15 cardiovascular SAEs in the double-blind treatment period: one in Protocol 005 (raltegravir) and 12 in Protocol 018/019 (six in the raltegravir, six in the placebo). A tabular listing of the cardiovascular SAEs based on the subject narratives is listed below. The majority of subjects had a history or cardiovascular disease or hyperlipidemia.

Table 7.1.3.3.Z: Summary of Cardiovascular Serious Adverse Events in the Phase 2 and 3 Studies, Double-Blind Treatment Period

AN	Protocol	Preferred Term	Onset Day	Outcome	Cardiovascular History	Hyperlipidemia History	Notes
Raltegravir 400 mg bid							
3876	005	Coronary artery disease Acute MI	209 375	Recovered Fatal	Yes	Yes	Hx obstructive cardiomyopathy
8204	018	Pericarditis Shock	71 93	Recovered Fatal	No	No	Dx with MAC Day 74, NHL Day 80
8363	018	MI Angina pectoris	128 137	Recovered Recovered	Yes	Yes	Hx ischemic cardiomyopathy
8372	018	MI	109 119	Recovered Recovered	Yes	Yes	Hx HTN and MI x 2 in 2006
16228	019	Cardiac failure congestive	221	Not recovered	Yes	No	Hx MVR, dilated cardiomyopathy
16318	019	Coronary artery disease	197	Fatal	Yes	Yes	Hx chronic cor pulmonale
16347	019	DVT	88	Recovered	Yes	Yes	Hx coronary artery disease
Placebo							
7091	018	Varicophlebitis	39	Recovered	No	No	Hx varicophlebitis and venous insufficiency
8234	018	Hypotension	71	Recovered	No	No	Occurred in setting of pseudomonal sepsis
15056	019	Coronary artery disease	187	Recovered	Yes	Yes	Hx MI 1998
15074	019	MI	68	Recovered	No	Yes	
16346	019	Infarction	221	Not recovered	No	No	Experienced cerebral infarction, occipital lobe, in setting of clostridium difficile colitis

16407	019	Mitral valve incompetence	70	Recovered	Yes	No	Hx cardiomyopathy, coronary artery disease, MVP

Source: AE (Safety Update Report Frozen File 2/16/07) and MEDHIST datasets for Protocols 004, 005, 018 and 019
MI=myocardial infarction, Hx=history, Dx= diagnosed, MAI=mycobacterium avium complex, NHL=non-Hodgkin's lymphoma, HTN = hypertension, MVR=mitral valve replacement, DVT=deep vein thrombosis, MVP=mitral valve prolapse

Seventeen additional cases of cardiac and vascular AEs occurred outside the double-blind treatment phase. Each of these events occurred in subjects with raltegravir exposure. Two events were fatal, both in Protocol 005 raltegravir-containing arms: one subject with acute myocardial infarction in the open-label phase following a diagnosis of coronary artery disease during the double-blind phase, and one subject with bradycardia, shock, and cardio-respiratory arrest in the setting of suspected sepsis in the post-treatment phase. Additionally, there was one event in Protocol 004 in the extension phase (haematoma), three events in Protocol 005 in the open-label phase (all HTN), four events in Protocol 005 in the OLPVF phase (thrombophlebitis, varicose vein, palpitations, haematoma), and five events in Protocol 018/019 in the OLPVF phase (three HTN, one tachycardia, and one angina unstable). Three subjects experienced SAEs: the two previously described fatal events, and one subject (AN 7083) originally randomized to the raltegravir arm in Protocol 018 with unstable angina on Day 158.

Overall, no imbalance was observed for cardiovascular AEs between the raltegravir and control arms, and the types of cardiovascular AEs were similar. In addition, the rates of cardiovascular AEs for both treatment arms were not unexpected in this heavily treatment-experienced HIV population.

Immune Reconstitution Syndrome

An analysis for preferred terms associated with IRS was performed for the Phase 2 and 3 studies, limited to the double-blind treatment period of the SUR. IRS was defined by the following preferred terms: IRS, herpes zoster, cytomegalovirus (CMV) infection, cryptococcal meningitis, tuberculosis, mycobacterial infection, pneumocystis jiroveci pneumonia, and progressive multifocal leukoencephalopathy. A total of 51 subjects experienced 53 potential IRS events, 42 in raltegravir-treated subjects and 11 in control, summarized in Table 7.1.3.3.AA. The majority of IRS events using this definition were due to herpes zoster, and occurred with increased frequency in the raltegravir group. The remainder of IRS events were balanced between the two groups.

Table 7.1.3.3.AA: Potential Immune Reconstitution Syndrome Events in Phase 2 and 3 Studies, Double-Blind Treatment Period

Preferred Term	Raltegravir N=755 (%)	Control N=320 (%)
Herpes zoster	29 (3.8)	6 (1.9)
CMV infection	4 (0.5)	4 (1.3)
IRS	2 (0.3)	1 (0.3)
Cryptococcal meningitis	2 (0.3)	0 (0)
Tuberculosis	2 (0.3)	0 (0)
Mycobacterial infection	1 (0.1)	0 (0)
PCP	1 (0.1)	0 (0)
PML	1 (0.1)	0 (0)
Total	42 (5.6)	11 (3.4)

Source: AE database (SUR Frozen File 2/16/07) for Protocols 004, 005, 018, 019
CMV infection = CMV chorioretinitis, CMV colitis, CMV infection, CMV viremia

Lipodystrophy

An analysis of lipodystrophy was performed in the treatment-experienced HIV population receiving the 400 mg twice daily raltegravir dose or placebo (Protocols 005, 018, 019). Lipodystrophy was defined by the following preferred terms: lipodystrophy acquired, lipoatrophy, or lipohypertrophy. A total of 15 subjects experienced 16 lipodystrophy AEs, all occurring in the double-blind period with the exception of one subject in the OLPVF treatment period. A difference in the rates of lipodystrophy events was not observed between the two treatment groups.

Table 7.1.3.3.BB: Lipodystrophy Events in the Treatment-Experienced Studies, 400 mg Twice Daily Raltegravir Dose

	Raltegravir 400 mg bid N=507		Placebo N=282	
	n	%	n	%
Subjects with any Lipodystrophy event[1]	10	2.0%	5	1.8%
Lipodystrophy acquired	7	1.4%	3	1.1%
Lipohypertrophy	3	0.6%	1	0.4%
Lipoatrophy	1	0.2%	1	0.4%

Source: AE (SUR Frozen File 2/16/07) datasets for Protocols 005, 018 and 019.
[1] Although a subject may have had two or more clinical adverse experiences, the subject is counted only once within a category. The same subject may appear in different categories.

One subject (AN 3278) experienced an SAE of lipoatrophy in Protocol 005 in the placebo arm, double-blind treatment period on Day 146 arm leading to study discontinuation on Day 181.

Body circumference measurements were collected in the Phase 2 studies, and no clinically significant changes from baseline were observed among the treatment groups at 48 weeks in Protocol 04 and at 24 weeks in Protocol 005.

Abdominal Events

Preclinical data detected gastric mucosal irritation in rodents; therefore, an analysis of abdominal events was performed for the Phase 2 and Phase 3 studies, limited to double-blind treatment period of the SUR. The definition of abdominal event included the following preferred terms: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, colitis, dyspepsia, epigastric discomfort, gastric disorder, gastric ulcer, gastritis, gastrointestinal disorder, gastrointestinal pain, and stomach discomfort. No apparent dose-response relationship was identified.

A total of 128 subjects experienced 141 abdominal AEs, 13.1% (99/755) in raltegravir-treated subjects versus 13.1% (42/320) in control. Drug-related abdominal AEs as assessed by the investigator occurred in 5.6% (42/755) of raltegravir-treated subjects versus 5.0% (16/320) in control. Four abdominal SAEs were reported, 3 in raltegravir-treated subjects (gastritis with brief interruption of study therapy; abdominal pain without an identified etiology in a subject who remained on therapy with spontaneous symptom resolution; abdominal pain occurring in the setting of a hypersensitivity event in a subject who was off raltegravir for 13 days at the time of symptom onset) and 1 in an efavirenz-treated subject.

In summary, current evaluation of available safety data does not support a causal relationship between raltegravir and abdominal AEs.

Psychiatric Events

An analysis of a potential association between raltegravir and psychiatric events was performed using the SUR AE datasets for the Phase 2 and 3 studies, limited to the double-blind treatment period. No significant dose-relationship was found, therefore, all raltegravir dose groups are combined.

An analysis for events associated with suicide was limited to the following preferred terms: depressed mood, depression, gunshot wound, intentional overdose, laceration, overdose, and suicidal ideation. A total of 44 subjects experienced 48 events including the selected preferred terms. The following table presents the preferred terms by treatment group.

Table 7.1.3.3.CC: Potential Suicide-related AEs in Phase 2 and Phase 3 studies, Double-Blind Treatment Period

Preferred Term	Raltegravir N=755	Control N=320
Depression	27 (3.6%)	10 (3.1%)
Depressed Mood	3 (0.4%)	1 (0.3%)
Intentional Overdose	2 (0.3%)	1 (0.3%)
Overdose*	1 (0.1%)	0 (0)
Suicidal Ideation	1 (0.1%)	0 (0)
Laceration	1 (0.1%)	0 (0)
Gunshot wound	0 (0)	1 (0.3%)

Source: AE (SUR Frozen File 2/16/07) datasets for Protocols 004, 005, 018 and 019.
*Overdose consisted of 1600 mg total raltegravir for 14 days before adjustment to the correct dose.

There was one fatal event of laceration: a 57 year old white man (AN 3286) with a history of affect lability was randomized to the 200 mg bid raltegravir arm in Protocol 005. OBT consisted of lopinavir/ritonavir, AZT/3TC, saquinavir, and TDF and concomitant medications included dronabinol, dipyridamole, and atorvastatin. On Day 18, the subject committed suicide via laceration.

Five additional subjects experienced SAEs: four events in raltegravir-treated subjects and one in placebo. Of the subjects receiving raltegravir, one (AN 8287) mistakenly took 1600 mg daily of raltegravir for 14 days without experiencing significant adverse events. Subject AN 398 in Protocol 004 was randomized to the 100 mg bid raltegravir arm. This subject had a history of depression and anxiety and was receiving concomitant sertraline, alprazolam, and Unisom. On Day 60, the subject experienced worsening depression and suicidal ideation secondary to relationship difficulties, and on Day 64 took an overdose of unisom. Study therapy was interrupted for four days and resumed after the subject recovered from the event. Subject AN 15100 in Protocol 019 had a history of depression and irritability and was receiving concomitant DRV/ritonavir, ENF, lamivudine, TDF, sertraline, lamotrigine, olanzapine, amitriptyline, diazepam, and zolpidem. On Day 83 the subject experienced worsened depression; however, the subject recovered and study therapy was not discontinued. Subject AN 16323 in Protocol 019 did not have a documented psychiatric history. OBT consisted of DRV/ritonavir, lamivudine, and TDF and concomitant medications included gabapentin. On Day 12 the subject was diagnosed with PML, on Day 27 the subject was diagnosed with depression. On Day 81 the subject took an overdose of nabilone and interrupted study therapy for two days before resuming therapy.

An analysis for mood-disorders was performed using the following preferred terms: adjustment disorder with depressed mood, anxiety, anxiety disorder, attention deficit hyperactivity disorder, depressed mood, depression, irritability, mental disorder, obsessive thoughts, panic attack, restlessness, and stress. A total of 71 subjects experienced 78 events using the selected preferred terms. The following table presents the preferred terms by treatment group.

Table 7.1.3.3.DD: Potential Mood Disorder-related AEs in Phase 2 and Phase 3 studies, Double-Blind Treatment Period

Preferred Term	Raltegravir N=755	Control N=320
Depression	27 (3.6%)	10 (3.1%)
Depressed mood	3 (0.4%)	1 (0.3%)
Anxiety	13 (1.7%)	6 (1.9%)
Anxiety disorder	1 (0.1%)	0 (0)
Adjustment disorder with depressed mood	2 (0.3%)	0 (0)
Irritability	4 (0.5%)	0 (0)
Stress	4 (0.5%)	0 (0)
Panic attack	2 (0.3%)	1 (0.3%)
ADHD	1 (0.1%)	0 (0)
Mental disorder	0 (0)	1 (0.3%)
Obsessive thoughts	1 (0.1%)	0 (0)
Restlessness	0 (0)	1 (0.3%)

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

There were no fatalities. One subject discontinued due to obsessive thoughts (AN 8341). This subject was a 53 year old Asian man with a history of anxiety, obsession, and paranoid state randomized to 400 mg bid raltegravir in Protocol 018. OBT consisted of AZT, ddI, and nevirapine. On Day 33 the subject experienced obsessive thoughts and discontinued from the study. Five subjects experienced SAEs: three raltegravir-treated subjects with depression previously described and two placebo subjects.

Erectile Dysfunction

An analysis of erectile dysfunction was performed to evaluation potential association with raltegravir using the SUR AE datasets for Phase 2 and 3 studies limited to the double-blind treatment period. No significant dose-relationship was found, therefore, all raltegravir dose groups are combined. The following preferred terms were selected: erectile dysfunction, libido decreased, loss of libido, ejaculation disorder. A total of 21 subjects experienced 22 AEs.

Table 7.1.3.3.EE: Erectile Dysfunction-related AEs in Phase 2 and Phase 3 studies, double-blind treatment period

Preferred Term	Raltegravir N=755	Control N=320
Erectile dysfunction	11 (1.5%)	3 (0.9%)
Libido decreased	4 (0.4%)	2 (0.6%)
Loss of libido	1 (0.1%)	0 (0)
Ejaculation disorder	0 (0)	1 (0.3%)
Total	**16 (2.1%)**	**6 (1.9%)**

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

None of the erectile dysfunction-related AEs were SAEs and none resulted in study discontinuation. One subject was receiving sildenafil pre-study, 4 subjects received drugs for treatment of ED during the double-blind treatment period, and 4 subjects received drugs for treatment of ED during open-label. Six AEs were considered possibly related to study drug: five in raltegravir-treated subjects and one in placebo.

Overall, based on review of the current data in the SUR, no association between raltegravir and erectile dysfunction is apparent.

7.1.4 Other Search Strategies

Designated Medical Events

Designated medical events were defined as: acute pancreatitis, acute respiratory failure, agranulocytosis, anaphylaxis, aplastic anemia, blindness, bone marrow depression, deafness, disseminated intravascular coagulation, hemolytic anemia, liver failure, liver necrosis, liver transplant, pancytopenia, renal failure, seizure, Stevens Johnson syndrome, sudden death, torsades de pointes, toxic epidermal necrolysis, thrombotic thrombocytopenic purpura, and ventricular fibrillation. The Phase 2 and 3 AE SUR datasets were searched for all relevant preferred terms. There were 16 designated medical events occurring in 16 subjects, 11 in the raltegravir group (aplasia, transient blindness, bone marrow toxicity, cardiorespiratory arrest, hemolytic anemia, renal failure and pancreatitis) and 5 in placebo (renal failure, pancreatitis). No events occurred in Protocol 004, five in Protocol 005 (2 in the 200 mg bid, 1 in the 400 mg bid, and 2 in the 600 mg bid groups, respectively), and 11 in Protocols 018 and 019 (6 in raltegravir and 5 in placebo). Nine of these events were classified as serious adverse events and are summarized in Table 7.1.4.A. Each of the designated medical events in raltegravir-treated subjects had a plausible etiology and does not support a causal association with raltegravir.

Table 7.1.4.A: Subjects with Serious Designated Medical Events (Phase 2 and 3 Studies, including screening, double-blind, and open label post virologic failure cohorts)

AN	Protocol	Preferred Term	Treatment Group	Period	Pertinent History	Outcome
3243	005	Cardio-respiratory Arrest	Raltegravir 600 mg bid	Post-Treatment	Suspected sepsis	Fatal
3281	005	Bone Marrow Toxicity	Raltegravir 200 mg bid	Post Virologic Failure	Due to chemotherapy for Hodgkin's Disease	Hospitalization, Recovered
3299	005	Pancreatitis acute	Raltegravir 200 mg bid	Dose-Ranging and Open-Label Optimal	(+) saquinavir, ritonavir hyperlipidemia	Hospitalization, Recovered
8241	018	Haemolytic anemia	Raltegravir 400 mg bid	Double-Blind	Hx MDS, (+) Parvovirus B19	Hospitalization, Not Recovered
8318	018	Nephropathy toxic	Raltegravir 400 mg bid	Double-Blind	(+) TDF	Hospitalization, Recovered
8345	018	Renal tubular necrosis	Raltegravir 400 mg bid	Double-Blind	Hx RI, (+) TDF, Occurred in setting of pneumococcal pneumonia	Hospitalization, Recovered
15115	019	Renal failure	Raltegravir 400 mg bid	Double-Blind	(+) TDF, Occurred in setting of dehydration, clinical clostridium difficile infection	Hospitalization, Not Recovered
15125	019	Renal failure	Placebo	Double-Blind		Hospitalization, Not Recovered
16389	019	Pancreatitis	Placebo	Double-Blind		Hospitalization, Recovered

Source: AE datasets (SUR Frozen File 2/16/07) and CSRs for Protocols 004, 005, 018, and 019
Hx=history, MDS=myelodysplastic syndrome, RI=renal insufficiency

Concomitant Atazanavir Use in OBT

ATV increases raltegravir plasma levels and therefore an analysis of AEs occurring in the subgroup of subjects receiving ATV in the OBT of the Phase 2 and 3 treatment-experienced studies. With the exception of known ATV-related effects, AEs in subjects receiving concomitant ATV were reported with similar frequency as AEs reported by all raltegravir-treated subjects (Table 7.1.4.B).

Table 7.1.4.B: Concomitant Atazanavir Use in OBT of the Phase 2 and 3 Treatment-Experienced Studies, Double-Blind Treatment Period

	Raltegravir-Treated Subjects	
Preferred Term	**OBT with ATV N=78 (%)**	**All Phase 3 and Protocol 005 N=595 (%)**
↑Bilirubin	12 (15.4)	14 (2.4)
Headache	6 (7.7)	58 (9.7)
Nausea	6 (7.7)	63 (10.6)
Cough	4 (5.1)	32 (5.4)
Diarrhea	4 (5.1)	99 (16.6)
Fatigue	4 (5.1)	48 (8.1)
Hyperbilirubinaemia	4 (5.1)	4 (0.7)
Lymphadenopathy	4 (5.1)	23 (3.9)
Nasopharyngitis	4 (5.1)	38 (6.4)
Night sweats	4 (5.1)	13 (2.2)
Ocular icterus	4 (5.1)	4 (0.7)
Vomiting	4 (5.1)	41 (6.9)

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

TDF also increases raltegravir plasma levels. An additional analysis of subjects receiving both ATV and TDF in the OBT of the Phase 2 and 3 treatment-experienced studies was performed to evaluate increased AE in this subgroup. A total of 89 subjects received ATV plus TDF (or FTC/TDF), 57 in the raltegravir group versus 32 in placebo. AEs occurring in >5% of raltegravir-treated subjects on ATV plus TDF are summarized in Table 7.1.4.C. No significant differences were identified between the two groups with the exception of ATV-associated increased bilirubin.

Table 7.1.4.C: Concomitant Atazanavir and Tenofovir Use in OBT of the Phase 2 and 3 Treatment-Experienced Studies, Double-Blind Treatment Period

	Raltegravir-Treated Subjects	
Preferred Term	**OBT with ATV and TDF N=57 (%)**	**All Phase 3 and Protocol 005 N=595 (%)**
↑Bilirubin	10 (18)	14 (2)
Nausea	7 (12)	63 (11)
Diarrhea	6 (11)	99 (17)
Headache	5 (9)	58 (10)
Night sweats	4 (7)	13 (2)

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

Adverse Events Potentially Associated with High Raltegravir Plasma Concentrations

Subjects with the highest plasma concentrations in the Phase 3 studies were examined for any potential notable AEs. As mentioned in Sections 5.1 and 5.3, high within subject variability has been observed. Because of this variability, AEs were limited to those occurring within 2 days of the elevated raltegravir level. The most frequent AEs identified were cough, lymphadenopathy and rash (Table 7.1.4.D): none were serious and none were associated with study discontinuation. Therefore, using this analysis, no temporal correlation between AEs and higher plasma concentrations was established.

Table 7.1.4.D: Adverse Events Potentially Associated with High Raltegravir Plasma Concentrations in Phase 3 studies

AE preferred term	Subjects within top 10% of plasma concentration	All raltegravir treated subjects N=462	All placebo treated subjects N=237
Cough	3	22 (4.8%)	7 (3.0%)
Lymphadenopathy	3	14 (3.0%)	6 (2.5%)
Rash	2	27 (5.8%)	6 (2.5%)

Source: Raltegravir plasma concentration analysis by Dr. Pravin Jadhav and AE datasets (SUR Frozen File 2/16/07) for Protocols 018 and 019

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

The safety population consisted of all randomized subjects who took at least one dose of study medication.

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

Adverse experiences were monitored at each study visit and reported in the case report form. Adverse experience reports contained the following details: onset date, duration, intensity, treatment required, relationship to study drug, study drug action taken, outcome, and whether the event is classified as serious. Investigators assessed if the adverse experience was definitely not, probably not, possibly, probably, or definitely related to study therapy. Drug-related adverse experiences were those the investigator assessed to be possibly, probably, or definitely related to study therapy. Clinical adverse experiences were graded by the investigator as mild, moderate, or severe intensity. Guidelines for grading the severity of laboratory abnormalities were based on the DAIDS criteria.

The Summary of Clinical Safety presented integrated safety data in three general components.

1. Phase 1 studies
2. Phase 2 studies
3. Pooled data from the raltegravir 400 mg bid cohorts in Phase 2 and Phase 3 studies of HIV treatment-experienced subjects
   Phase 2 and 3 treatment-experienced raltegravir 400 mg bid double-blind cohort – Integrated safety data from all subjects from Protocols 018 and 019 plus Protocol 005 subjects who received raltegravir 400 mg bid or placebo during the double-blind treatment phase.
   Open-label post virologic failure phase – Integrated safety data from subjects who received open-label raltegravir 400 mg bid following virologic failure in the blinded portion of Protocols 005, 018, or 019, which is limited to new events during the open-label portion of their treatment.
   Open-label extension – In Protocol 005 only, at the time of protocol amendment and extension, subjects from all treatment groups who were not virologic failures were placed on open-label raltegravir at 400 mg bid.

My integrated safety review uses the same definitions as listed above; however, it incorporates updated safety data included in the SUR with a corresponding database lock of 2/16/07. The decision to incorporate the safety data from the SUR was made to capture the most recent AE profile of raltegravir given the limited exposure in the current ongoing Phase 3 studies. Therefore, differences are observed in the numerical results generated in the AE analysis. The general trends found in this AE analysis, however, support the Applicant's findings.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The Applicant used the MedDRA dictionary of System Organ Class and Preferred Terms Version 9.1 to organize the medical terms for the various AEs provided by the investigator. Cross-check of investigator's "reported term" compared to the designated MedDRA preferred term suggests the Applicant grouped the individual investigator terms under MedDRA preferred terms appropriately. In cases where this reviewer identified MedDRA preferred terms that were inappropriate or more clinically meaningful when grouped a different way, the terms were regrouped and those changes are reflected throughout the review.

7.1.5.3 Incidence of common adverse events

The Applicant's integrated safety review included data from all subjects from Protocols 018 and 019 plus Protocol 005 subjects who received raltegravir 400 mg bid (N=507) or placebo (N=282) during the double-blind treatment phase. The AE tables in the Clinical Summary of Safety include AEs with start dates in the double-blind or OLPVF phases and those occurring within 14 days of study drug discontinuation.

7.1.5.4 Common adverse event tables

The tables that appear in this section are all AE tables derived from FDA analyses of the Phase 3 and Protocol 005 400 mg twice daily raltegravir and placebo arms and are without regard to drug causality, which is the most appropriate way to present AE data for this application in this reviewer's opinion. A higher cutoff was chosen for AEs than recommended by the Reviewer Guidance: Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review (2% versus 1%) because AEs of all types and severities are more common in this type of chronically ill, clinically advanced and treatment-experienced HIV-1 infected population as compared to the majority of study subjects.

Clinical AEs were common in study subjects, occurring in >85% of all subjects receiving either 400 mg raltegravir twice daily or placebo (Table 7.1.5.4.A). The majority of AEs were mild to moderate in intensity. The most common AEs occurring in $\geq$ 10% were diarrhea, injection site reactions (due to ENF use), nausea, and headache, and were observed with similar frequency in each treatment arm. Clinical AEs reported in raltegravir-treated subjects with $\geq$2% greater frequency over placebo include fatigue (7.9% versus 4.6%), nasopharyngitis (6.1% versus 3.9%), rash (5.3% versus 2.5%), and herpes zoster (4.1% versus 0.7%).

AEs of clinical concern or those occurring with increased frequency in raltegravir-treated subjects are characterized in greater detail in Section 7.1.3.

Table 7.1.5.4.A: Most Common Adverse Experiences by MedDRA Preferred Terms Reported in ≥2% of Subjects in Either Treatment Group Without Regard to Causality (Protocols 005, 018, 019 400 mg twice daily raltegravir and placebo arms)

	Raltegravir 400 mg bid N=507		Placebo N=282	
	n	%	n	%
Subjects with one or more AE	438 (426)	86.4% (84.0%)	247 (243)	87.5% (86.2%)
Diarrhoea	84	16.6%	55	19.5%
Injection site reaction	52	10.3%	28	9.9%
Nausea	50	9.9%	40	14.2%
Headache	49	9.7%	33	11.7%
Fatigue	**40**	**7.9%**	**13**	**4.6%**
Vomiting	35	6.9%	23	8.2%
Nasopharyngitis	**31**	**6.1%**	**11**	**3.9%**
Upper respiratory infection	27	5.3%	16	5.7%
Rash	**27**	**5.3%**	**7**	**2.5%**
Abdominal pain	26	5.1%	11	3.9%
Pyrexia	25	4.9%	29	10.3%
ALT increased	24	4.7%	5	1.8%
Cough	24	4.7%	8	2.8%
AST increased	23	4.5%	7	2.5%
Herpes zoster	**21**	**4.1%**	**2**	**0.7%**
Herpes simplex	20	3.9%	12	4.3%
Dizziness	20	3.9%	6	2.1%
Insomnia	20	3.9%	10	3.5%
Blood CPK increased	19	3.7%	3	1.1%
Blood triglycerides increased	19	3.7%	10	3.5%
Lymphadenopathy	17	3.4%	8	2.8%
Bronchitis	17	3.4%	10	3.5%
Asthenia	16	3.2%	11	3.9%
Sinusitis	16	3.2%	7	2.5%
Pain in extremity	16	3.2%	7	2.5%
Flatulence	15	3.0%	9	3.2%
Influenza	15	3.0%	5	1.8%
Blood cholesterol increased	15	3.0%	6	2.1%
Gastroenteritis	14	2.8%	5	1.8%
Arthralgia	14	2.8%	7	2.5%
Pruritus	14	2.8%	6	2.1%
Abdominal distension	13	2.6%	8	2.8%

Depression	13	2.6%	8	2.8%
Hypertension	13	2.6%	4	1.4%
Abdominal pain upper	12	2.4%	11	3.9%
Night sweats	12	2.4%	8	2.8%
Anogenital warts	11	2.2%	4	1.4%
Folliculitis	11	2.2%	2	0.7%
Pneumonia	11	2.2%	7	2.5%
Anorexia	11	2.2%	6	2.1%
Anaemia	10	2.0%	8	2.8%
Constipation	10	2.0%	1	0.4%
Blood creatinine increased	10	2.0%	5	1.8%
Back pain	10	2.0%	7	2.5%
Myalgia	10	2.0%	7	2.5%
Skin papilloma	10	2.0%	7	2.5%
Pharyngolaryngeal pain	9	1.8%	11	3.9%
Muscle spasms	8	1.6%	7	2.5%
Oral candidiasis	6	1.2%	15	5.3%
Urinary tract infection	6	1.2%	6	2.1%
Weight decreased	5	1.0%	7	2.5%
Blood phosphorous decreased	4	0.8%	6	2.1%
Neutrophil count decreased	4	0.8%	6	2.1%
Oesophageal candidiasis	3	0.6%	6	2.1%
Eczema	3	0.6%	6	2.1%

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

Package Insert

The following tables reflect adverse reaction information reported in the raltegravir package insert (Tables 7.1.5.4.B and 7.1.5.4.C). I confirmed the data reported in these tables and no discrepancies were noted between the Applicant and my analyses. The Applicant reports the total follow-up during the double-blind period for treatment-experienced subjects receiving raltegravir 400 mg twice daily or placebo in Protocols 005, 018, and 019 was 332.2 patient-years for raltegravir and 150.2 for placebo. My analysis for follow-up during this period resulted in 301.9 patient-years for raltegravir and 141.1 patient-years for placebo. Because these analyses are similar and because numerical differences are likely the result of differences in determination of study visit window, the decision was made to allow the Applicant's analysis to be reflected in the label.

Table 7.1.5.4.B: Package Insert Table 1: Percentage of Patients with the Most Commonly Reported (>10%) Adverse Reactions of All Intensities* and Regardless of Causality Occurring in Treatment-Experienced Adult Subjects

System Organ Class, Adverse Reactions	ISENTRESS 400 mg twice daily + OBT (n=507) † %	Placebo + OBT (n=282) † %
Gastrointestinal Disorders		
Diarrhea	16.6	19.5
Nausea	9.9	14.2
Nervous System Disorders		
Headache	9.7	11.7
General Disorders and Administration Site Conditions		
Pyrexia	4.9	10.3

*Intensities are defined as follows: Mild (awareness of sign or symptom, but easily tolerated); Moderate (discomfort enough to cause interference with usual activity); Severe (incapacitating with inability to work or do usual activity).
†n=total number of subjects per treatment group.

Table 7.1.5.4.C: Package Insert Table 2: Percentage of Subjects with Drug-Related* Adverse Reactions of Moderate to Severe Intensity† Occurring in ≥2% of Treatment-Experienced Adult Subjects

System Organ Class, Adverse Reactions	Randomized Studies P005, P018 and P019	
	ISENTRESS 400 mg Twice Daily + OBT (n = 507)‡ %	Placebo + OBT (n = 282)‡ %
Gastrointestinal Disorders		
Diarrhea	3.7	4.6
Nausea	2.2	3.2
Nervous System Disorders		
Headache	2.4	1.4

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

7.1.6 Less Common Adverse Events

All AEs considered clinically important or appeared to occur with greater frequency in raltegravir-treated subjects are discussed in Section 7.1.3.

Package Insert

The following text reflects less common adverse reaction information reported in the raltegravir package insert:

> Drug-related adverse reactions occurring in at least 1% but less than 2% of treatment-experienced patients (n=507) receiving ISENTRESS + OBT and of moderate (discomfort enough to cause interference with usual activity) to severe (incapacitating with inability to work or do usual activity) intensity are listed below by system organ class:
> *Gastrointestinal Disorders:* abdominal pain
> *General Disorders and Administration Site Conditions:* asthenia, fatigue
> *Nervous System Disorders:* dizziness

I confirmed this data; however, my analysis also identified lipodystrophy acquired and vomiting as adverse reactions satisfying the Applicant's definition. This information was communicated to the Applicant and they are planning to include these adverse reactions in a revised draft PI label.

7.1.7 Laboratory Findings

Evaluation of clinical laboratory findings was conducted by analyzing the proportion of HIV-1 treatment-experienced subjects in each treatment group receiving the 400 mg twice daily dose of raltegravir or placebo who experienced marked laboratory abnormalities during Protocols 005, 018, and 019. Guidelines for grading the severity of laboratory abnormalities are based on Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Experiences from December 2004.

The original NDA submission did not include grades for the laboratory data. After discussion with the Applicant, an updated laboratory table derived from the original 12/13/06 data cutoff date was submitted, and this data was used to perform most FDA laboratory analyses. Confirmatory analyses for potentially clinically important AEs used the SUR laboratory datasets. Grades were not provided by the Applicant with the SUR laboratory datasets. Therefore, in my review, I applied the DAIDS grading criteria to the laboratory results by creating appropriate formulas within the dataset; this accounts for minor differences between my analyses and the Applicant's analyses.

This integrated safety review focuses on treatment-emergent/on-treatment laboratory findings; therefore, subjects with elevated baseline laboratory parameters are excluded if no worsening occurred during the study period. In addition to evaluating marked laboratory abnormalities, mean changes from baseline for selected laboratory tests were also assessed.

7.1.7.1 Overview of laboratory testing in the development program

In Protocols 005, 018, and 019, blood samples for hematologic and chemistry safety laboratory analyses were collected at baseline and all subsequent visits (Weeks 2, 4, 8, 12, 16, 24, 32, 40,

48, and at 14 days post-therapy for those who prematurely discontinued; in addition, the Phase 3 studies also had laboratories obtained at Weeks 60, 72, 84, 96, 108, 120, 132, 144, 156, and at the 14-day post-therapy follow-up). Subjects switching to OLPVF had laboratory blood tests performed on Day 1 and at OLPVF Weeks 2, 4, 8, 16, 24, 32, 40, 48, 60, 72, 84, 96, 108, 120, 132, the final OLPVF visit (156 weeks of total study therapy), and at the 14-day post-therapy follow-up.

For the Phase 2 and Phase 3 studies, following each visit, investigators received faxed laboratory test results from the central laboratory. These laboratory results were reviewed by the investigator for potential laboratory adverse experiences. In addition to the investigator's evaluation of laboratory adverse experiences, all laboratory values outside the normal range were assessed regardless of whether they were considered by the investigator to be a laboratory adverse experience. Furthermore, sites were questioned for values that met Grade 3 or Grade 4 DAIDS criteria to determine whether these were clinically significant.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Laboratory datasets were available for the raltegravir Phase 2 and 3 development program. The laboratory data reviewed for this Clinical Review focused on that from the Phase 3 and Protocol 005 HIV-treatment experienced population where the rates of laboratory abnormalities on the 400 mg twice daily raltegravir arms were analyzed and compared to the rates of laboratory abnormalities on the placebo arms.

7.1.7.3 Standard analyses and explorations of laboratory data

This analysis of laboratory test results includes all subjects in Phase 3 and Protocol 005 400 mg twice daily raltegravir or placebo treatment arms who had both a baseline and an on-treatment or final laboratory measurement. The following table presents treatment-emergent laboratory values occurring in $\geq$2% of patients. Additional analyses of the SUR laboratory data yielded similar results. The Applicant performed their laboratory analysis using data from a central lab; however, I incorporated unscheduled supplemental laboratories into my analysis to capture all potential treatment-emergent laboratory changes. Discrepancies between the Applicant and FDA analyses occur due to differences in determination of study visit window and incorporation of the supplemental laboratory data; however, because these discrepancies were small and the derived conclusions from each analysis are similar, the decision was made to allow the Applicant's analysis to be reflected in the label.

Increased treatment-emergent laboratory values in the raltegravir group noted for creatine kinase, ALT, AST, and bilirubin are discussed in more detail in Section 7.1.3.

Table 7.1.7.3.A: Treatment-Emergent Laboratory Abnormalities Reported in ≥ 2% of HIV Treatment-Experienced Subjects in Protocols 005, 018, 019 Receiving 400 mg Twice Daily Raltegravir or Placebo, Double-Blind Treatment Period

Laboratory Parameter	Limit	Treatment Arm			
		Raltegravir N=507		Placebo N=282	
		n	%	n	%
Chemistry Laboratory Values					
Creatine kinase (IU/L)					
Grade 2	6.0-9.9 x ULN	10	2.0%	3	1.1%
Grade 3	10.0-19.9 x ULN	12	2.4%	5	1.8%
Grade 4	≥20.0 x ULN	11	2.2%	2	0.7%
Fasting (non-random) serum glucose (mg/dL)					
Grade 2	126-250	42	8.3%	17	6.1%
Grade 3	251-500	6	1.2%	4	1.4%
Grade 4	>500	0	0	0	0
Serum ALT (IU/L)					
Grade 2	2.6-5.0 x ULN	34	6.7%	22	7.8%
Grade 3	5.1-10.0 x ULN	13	2.6%	4	1.4%
Grade 4	>10.0 x ULN	2	0.4%	1	0.4%
Serum AST (IU/L)					
Grade 2	2.6-5.0 x ULN	45	8.9%	13	4.6%
Grade 3	5.1-10.0 x ULN	10	2.0%	6	2.1%
Grade 4	>10.0 x ULN	2	0.4%	1	0.4%
Serum Alkaline Phosphatase (IU/L)					
Grade 2	2.6-5.0 x ULN	9	1.8%	1	0.4%
Grade 3	5.1-10.0 x ULN	2	0.4%	3	1.1%
Grade 4	>10.0 x ULN	2	0.4%	1	0.4%
Total Serum Bilirubin (mg/dL)					
Grade 2	1.6-2.5 x ULN	28	5.5%	18	6.4%
Grade 3	2.6-5.0 x ULN	15	3.0%	7	2.5%
Grade 4	>5.0 x ULN	3	0.6%	0	0
Serum Creatinine (mg/dL)					
Grade 2	1.4-1.8 x ULN	11	2.2%	4	1.4%
Grade 3	1.9-3.4 x ULN	4	0.8%	3	1.1%
Grade 4	≥3.5 x ULN	0	0	0	0
Serum Pancreatic Amylase (IU/L)					
Grade 2	1.6-2.0 x ULN	7	1.4%	2	0.7%
Grade 3	2.1-5.0 x ULN	15	3.0%	6	2.1%
Grade 4	>5.0 x ULN	1	0.2%	0	0
Serum Lipase (IU/L)					
Grade 2	1.6-3.0 x ULN	15	3.0%	4	1.4%

Grade 3	3.1-5.0 x ULN	3	0.6%	0	0
Grade 4	>5.0 x ULN	1	0.2%	0	0
Serum Albumin (g/dL)					
Grade 2	2.0-2.9	18	3.6%	14	5.0%
Grade 3	<2.0	3	0.6%	2	0.7%
Serum Bicarbonate (mEq/L)					
Grade 2	11.0-15.9	5	1.0%	2	0.7%
Grade 3	8.0-10.9	1	0.2%	0	0
Grade 4	<8.0	0	0	0	0
Serum Calcium, high* (mg/dL)					
Grade 2	11.6-12.5	0	0	0	0
Grade 3	12.6-13.5	0	0	0	0
Grade 4	>13.5	0	0	0	0
Serum Calcium, low* (mg/dL)					
Grade 2	7.0-7.7	0	0	3	1.1%
Grade 3	6.1-6.9	0	0	1	0.4%
Grade 4	<6.1	0	0	0	0
Serum Phosphorous (mg/dL)					
Grade 2	2.0-2.4	90	17.8%	58	20.6%
Grade 3	1.0-1.9	16	3.2%	17	6.0%
Grade 4	<1.0	1	0.2%	0	0
Serum Potassium, high (mEq/L)					
Grade 2	6.1-6.5	0	0	0	0
Grade 3	6.6-7.0	1	0.2%	0	0
Grade 4	>7.0	1	0.2%	0	0
Serum Potassium, low (mEq/L)					
Grade 2	2.5-2.9	3	0.6%	2	0.7%
Grade 3	2.0-2.4	1	0.2%	0	0
Grade 4	<2.0	0	0	0	0
Serum Sodium, high (mEq/L)					
Grade 2	151-154	2	0.4%	0	0
Grade 3	155-159	0	0	0	0
Grade 4	≥160	0	0	0	0
Serum Sodium, low (mEq/L)					
Grade 2	125-129	6	1.2%	2	0.7%
Grade 3	121-124	0	0	0	0
Grade 4	≤120	0	0	1	0.4%
Lipid Laboratory Values					
Fasting Serum Cholesterol (mg/dL)**					
Grade 1	200-239	116	22.9%	50	17.7%
Grade 2	240-300	74	14.6%	36	12.8%
Grade 3	>300	23	4.5%	10	3.5%
Fasting LDL Cholesterol (mg/dL)***					

Grade 1	130-159	69	14.6%	28	10.9%
Grade 2	160-190	36	7.6%	12	4.7%
Grade 3	>190	18	3.8%	6	2.3%
Fasting Triglyceride (mg/dL)**					
Grade 2	500-750	25	4.9%	20	7.1%
Grade 3	751-1200	16	3.2%	9	3.2%
Grade 4	>1200	7	1.4%	5	1.8%
Hematologic Laboratory Values					
Absolute Neutrophil Count (10^3/microL)					
Grade 2	0.75-0.999	17	3.4%	22	7.8%
Grade 3	0.50-0.749	12	2.4%	6	2.1%
Grade 4	<0.50	5	1.0%	3	1.1%
Hemoglobin (gm/dL)					
Grade 2	7.5-8.4	5	1.0%	7	2.5%
Grade 3	6.5-7.4	4	0.8%	1	0.4%
Grade 4	<6.5	0		0	0
Platelet Count (10^3/microL)					
Grade 2	50-99.999	18	3.6%	14	5.0%
Grade 3	25-49.999	2	0.4%	1	0.4%
Grade 4	<25	4	0.8%	1	0.4%
White Blood Cell (10^3/microL)					
Grade 2	1.5-1.999	12	2.4%	9	3.2%
Grade 3	1.0-1.499	3	0.6%	7	2.5%
Grade 4	<1.0	1	0.2%	1	0.4%

Source: FDALABGD datasets for Protocols 005, 018, and 019
*Corrected for albumin
**Raltegravir arm N=506
***Raltegravir arm N=471, Placebo = 256

Grade 3-4 pancreatic amylase occurred in 3.2% of raltegravir-treated subjects versus 2.0% in placebo, and Grade 3-4 lipase occurred in 0.8% of raltegravir-treated subjects versus 0% in placebo. Five raltegravir-treated subjects experienced an SAE temporally related (within 14 days) to the time of elevated pancreatic enzymes; however, clinical pancreatitis does not appear to be directly associated with the elevations

AN 7086 experienced Grade 3 amylase/lipase while on ddI as part of OBT in the setting of gastritis.

AN 8345 experienced Grade 3 amylase in the setting of renal tubular necrosis, acute on chronic renal failure and pneumococcal pneumonia.

AN 16254 experienced Grade 3 amylase in the setting of fever, bone pain and malaise the investigator attributed to recent use of G-CSF.

AN 16279 experienced Grade 3 amylase/lipase after admission for leg cellulitis.

AN 16306 experienced Grade 4 amylase following admission for small bowel obstruction.

Lipids

A higher percentage of Grade 2-3 cholesterol and LDL laboratories were reported in raltegravir-treated subjects compared with placebo: cholesterol 19% raltegravir versus 16% placebo, LDL 11% raltegravir versus 7% placebo. In addition, there was an increased Week 24 mean change from baseline of +23 mg/dL cholesterol and +16.5 mg/dL LDL in the raltegravir group, compared with +12 mg/dL and +9 mg/dL in placebo, respectively. Triglyceride values were not increased in raltegravir-treated subjects. Despite these findings, no mean increases in total cholesterol, LDL or triglycerides were observed in raltegravir-treated subjects in the treatment-naïve Protocol 004. Lipid data from Protocol 004 is summarized in the following table (Table 7.1.7.3.B). Week 24 and 48 mean changes from baseline were lower in all raltegravir arms compared with efavirenz for cholesterol, LDL, and triglycerides.

In light of the findings from the treatment-naïve study, the increased incidence of lipid elevations in raltegravir-treated subjects may reflect confounding by receipt of multiple concomitant medications that elevate lipids, increased follow-up due to differential dropout rates and other factors.

Table 7.1.7.3.B: Change from Baseline in Serum Lipids at Week 48 in Treatment-naïve Subjects, Protocol 004

Change From Baseline in Serum Lipids at Week 48
(Cohorts I and II Combined; Combination Therapy Phase)

Treatment	N	Baseline Mean	Change From Baseline at Week 48		MK-0518 Minus EFV	
			Mean Change (SD)	95% CI	Difference[†] 95% CI	p-Value[‡]
Non-HDL-C (mg/dL)						
MK-0518 100 mg b.i.d.	39	129.3	-12.6 (33.6)	(-23.5, -1.71)	-24.8 (-38.5, -11.0)	< 0.001
MK-0518 200 mg b.i.d.	34	122.5	-5.44 (23.9)	(-13.8, 2.91)	-17.6 (-29.5, -5.75)	0.004
MK-0518 400 mg b.i.d.	40	129.8	-4.75 (25.4)	(-12.9, 3.37)	-17.0 (-28.7, -5.20)	0.005
MK-0518 600 mg b.i.d.	36	130.6	-7.03 (30.1)	(-17.2, 3.15)	-19.2 (-32.4, -6.03)	0.005
Efavirenz 600 mg q.d.	34	130.8	12.21 (25.2)	(3.42, 20.99)		
Fasting (non-random) serum HDL-C (mg/dL)						
MK-0518 100 mg b.i.d.	39	38.31	4.13 (8.87)	(1.25, 7.00)	-5.70 (-10.1, -1.26)	0.013
MK-0518 200 mg b.i.d.	34	38.44	4.32 (7.95)	(1.55, 7.10)	-5.50 (-9.87, -1.13)	0.015
MK-0518 400 mg b.i.d.	40	38.40	4.70 (8.43)	(2.00, 7.40)	-5.12 (-9.46, -0.79)	0.021
MK-0518 600 mg b.i.d.	36	36.78	6.25 (9.66)	(2.98, 9.52)	-3.57 (-8.26, 1.12)	0.133
Efavirenz 600 mg q.d.	34	36.74	9.82 (9.98)	(6.34, 13.31)		
Fasting (non-random) serum LDL-C (mg/dL)						
MK-0518 100 mg b.i.d.	37	107.2	-15.7 (26.7)	(-24.6, -6.79)	-18.7 (-30.0, -7.34)	0.002
MK-0518 200 mg b.i.d.	34	100.6	-2.56 (24.3)	(-11.0, 5.93)	-5.56 (-16.6, 5.46)	0.317
MK-0518 400 mg b.i.d.	39	103.7	-2.79 (26.6)	(-11.4, 5.82)	-5.79 (-16.9, 5.34)	0.303
MK-0518 600 mg b.i.d.	33	103.5	-8.88 (27.2)	(-18.5, 0.77)	-11.9 (-23.8, 0.04)	0.051
Efavirenz 600 mg q.d.	31	108.9	3.00 (20.1)	(-4.37, 10.37)		
Fasting (non-random) serum cholesterol (mg/dL)						
MK-0518 100 mg b.i.d.	39	167.6	-7.05 (35.1)	(-18.4, 4.33)	-27.7 (-42.6, -12.8)	< 0.001
MK-0518 200 mg b.i.d.	34	160.9	-1.12 (28.5)	(-11.1, 8.84)	-21.8 (-35.6, -7.93)	0.003
MK-0518 400 mg b.i.d.	40	168.2	-0.05 (27.0)	(-8.70, 8.60)	-20.7 (-33.7, -7.71)	0.002
MK-0518 600 mg b.i.d.	37	166.1	-0.73 (31.2)	(-11.1, 9.66)	-21.4 (-35.6, -7.22)	0.004
Efavirenz 600 mg q.d.	35	168.7	20.66 (29.1)	(10.66, 30.65)		
Fasting (non-random) serum triglyceride (mg/dL)						
MK-0518 100 mg b.i.d.	39	129.2	15.46 (93.7)	(-14.9, 45.85)	-34.0 (-94.0, 26.00)	0.261
MK-0518 200 mg b.i.d.	34	109.4	-14.0 (49.1)	(-31.1, 3.17)	-63.5 (-118, -8.42)	0.025
MK-0518 400 mg b.i.d.	40	127.2	-2.03 (85.5)	(-29.4, 25.33)	-51.5 (-110, 7.16)	0.084
MK-0518 600 mg b.i.d.	37	160.2	-5.14 (106)	(-40.6, 30.35)	-54.6 (-117, 7.93)	0.086
Efavirenz 600 mg q.d.	35	127.3	49.49 (153)	(-3.19, 102.2)		

[†] A negative value means MK-0518 is better than EFV.

[‡] Nominal p-value was calculated from t-test.

Note: MK-0518 and efavirenz (EFV) were administered with tenofovir (TFV) and lamivudine (3TC).

N = Number of patients in the treatment group.

Data Source: [16.4.2.4]

Source: Table 12-28 from Applicant MRL Clinical Study Report for Protocol 004

7.1.7.3.1 Analyses focused on measures of central tendency

An analysis of mean changes from baseline in laboratory values for hematologic and chemistry parameters was performed using the SUR LABCHEM and LABHEM datasets for Protocol 005, 018, and 019. "Baseline" was defined as Visit 2.0, "Week 16" as Visit 7.0, and "Week 24" as Visit 8.0. Therefore, this analysis does not capture data obtained outside these visit windows, nor does it capture data on subjects who switched to OLPVF.

Table 7.1.7.3.1.A summarizes the analysis of laboratory mean changes from baseline. Notably, an increased mean CK of 84.5 IU/L was observed at Week 16 in the raltegravir group compared to 4.9 IU/L in placebo. A lesser difference in increased CK was seen in the two groups at Week 24. The remaining laboratory changes from baseline were balanced between the two groups.

Table 7.1.7.3.1.A: Change from Baseline for Selected Laboratory Tests in HIV Treatment-Experienced Subjects in Protocols 005, 018, 019 Receiving 400 mg Twice Daily Raltegravir or Placebo, Double-Blind Treatment Period

	Raltegravir			Placebo		
	N	Mean BL Value	Mean Change from BL	N	Mean BL Value	Mean Change from BL
Chemistry						
AST (IU/L)						
Week 16	472	37.7	-2.5	262	38.0	-3.5
Week 24	415	38.0	-3.6	141	37.9	-4.1
ALT (IU/L)						
Week 16	487	39.0	-1.3	269	39.6	-1.8
Week 24	431	39.0	0	146	41.1	-0.8
Bilirubin (mg/dL)						
Week 16	490	0.6	+0.3	269	0.7	-0.1
Week 24	437	0.6	0	148	0.7	-0.1
Creatine kinase (IU/L)						
Week 16 (Median)*	490	153.0 (102.5)	+84.5 (+21.5)	269	147.5 (107)	+4.9 (+1.0)
Week 24 (Median)*	436	152.1 (102.5)	+28.0 (+21.0)	148	165.4 (111.5)	+20.2 (+5.5)
Creatinine (mg/dL)						
Week 16	492	0.9	+0.1	272	0.9	+0.1
Week 24	440	0.9	+0.1	150	1.0	0
Cholesterol (mg/dL)						
Week 24	432	180.0	+23.1	148	190.6	+11.6
LDL (mg/dL)						
Week 24	316	100.0	+16.5	115	107.8	+9.3
HDL (mg/dL)						
Week 24	414	35.9	+3.9	146	37.1	+0.7

Triglyceride (mg/dL)						
Week 24	432	285.5	-4.9	148	262.1	+4.8
Hematology						
WBC (10^3/microL)						
Week 16	469	4.4	+1.3	256	4.6	+0.7
Week 24	409	4.5	+1.2	141	4.8	+0.7
Hemoglobin (gm/dL)						
Week 16	469	13.5	+0.4	256	13.5	+0.1
Week 24	409	13.5	+0.5	141	13.8	+0.2
Platelet (10^3/microL)						
Week 16	444	190.2	+33.5	240	194.3	+6.4
Week 24	379	191.5	+31.8	132	197.0	+31.1
ANC (10^3/microL)						
Week 16	464	2.5	+0.7	252	2.4	+0.5
Week 24	405	2.5	+0.6	138	2.5	+0.5

Source: LABCHEM and LABHEME datasets (SUR Frozen File 2/16/07) for Protocols 005, 018, 019
*Median creatine kinase also reported
BL=baseline, WBC=white blood cell, ANC=absolute neutrophil count

7.1.7.3.2 Marked outliers and dropouts for laboratory abnormalities

Individual study subjects who developed laboratory abnormalities that were considered clinically significant were reported as AEs. Subjects who discontinued study drug because of marked laboratory abnormalities were included in the discussion of AEs resulting in study drug discontinuation presented in Section 7.1.3.2.

7.1.7.4 Additional analyses and explorations

Hepatitis co-infection

A total of 16.2% of subjects (113/699) were co-infected with HBV and/or HCV in the Phase 3 studies, 77 in the raltegravir arms and 36 in placebo. A subgroup analysis of AST, ALT, and bilirubin laboratory values was performed in this population. Subjects with hepatitis co-infection had elevated transaminases and bilirubin compared to all subjects in the Phase 3 studies; however, no discontinuations were related to increased laboratories.

Table 7.1.7.4.A[1]: Select Laboratory Data in Subjects with Hepatitis Co-infection in Phase 3 Studies, Double-Blind Treatment Period

	Raltegravir-Treated Subjects		Placebo-Treated Subjects	
Laboratory Parameter	**HBV/HCV Co-infected N=77 (%)**	**All Phase 3 N=462 (%)**	**HBV/HCV Co-infected N=36 (%)**	**All Phase 3 N=237 (%)**
Serum ALT				
Grade 2	11 (14.3)	28 (6.1)	4 (11.1)	20 (8.4)
Grade 3	6 (7.8)	16 (3.5)	1 (5.6)	4 (2.5)
Grade 4	2 (2.6)	4 (0.9)	0 (0)	3 (1.3)
Serum AST				
Grade 2	10 (13.0)	32 (6.9)	3 (8.3)	12 (5.1)
Grade 3	3 (3.9)	12 (2.6)	1 (2.8)	7 (3.0)
Grade 4	2 (2.6)	3 (0.6)	0 (0)	2 (0.8)
Total Bilirubin				
Grade 2	5 (6.5)	21 (4.5)	2 (5.6)	9 (3.8)
Grade 3	2 (2.6)	10 (2.2)	1 (2.8)	3 (1.3)
Grade 4	1 (1.3)	4 (0.9)	0 (0)	0 (0)

[1] Analysis of ALT, AST, and bilirubin in hepatitis co-infected subjects using SUR data produced similar results.
Source: FDALABGD and LABCHEM datasets for Protocols 018 and 019
Only 2 subjects with elevated alkaline phosphatase: one grade 4 in placebo, one grade 2 in raltegravir.

7.1.7.5 Special assessments

No additional special assessments were performed.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were routinely monitored in all subjects in the Phase 3 studies, and no significant differences were observed in the raltegravir arms compared with placebo.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Blood pressure, pulse, respiratory rate, temperature, and body weight were evaluated for the pivotal studies across treatment groups. No pooled analyses were performed.

7.1.8.3 Standard analyses and explorations of vital signs data

The assessment of vital signs did not identify clinically relevant differences between the treatment groups. Results of the assessments did not raise safety concerns.

7.1.8.4 Additional analyses and explorations

No additional analyses or explorations were conducted by either the Applicant or the medical reviewer.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

The potential risk of raltegravir to cause delayed ventricular repolarization in humans was investigated using several non-clinical assays. The studies included *in vivo* QT assays in dogs and an *in vitro* evaluation of the effects on human ether-a-go-go-related gene (hERG) current. Overall, the non-clinical results suggested that the risk for QT interval prolongation in humans at therapeutic concentrations is likely to be very low. In the Phase 1 program, single doses up to 1600-mg and multiple doses up to 800-mg twice daily, did not show any evidence or consistent pattern for treatment related increases in QTc interval by mean analyses of change from baseline. In the pivotal Phase 3 studies, ECGs were obtained at screening and at Week 24. No clinical relevant differences were observed among treatment groups.

A formal ECG study was performed in uninfected subjects (Protocol 024) and was reviewed by the FDA Interdisciplinary Review Team for QT Studies. The Review Team concluded the following:

A supratherapeutic dose of 1600 mg raltegravir was evaluated in this single-dose 'thorough QT study.' The mean Cmax in 12/30 (40%) subjects was 19.6 μM which is 4-fold higher than the mean steady state Cmax when 400 mg bid of the to-be-marketed formulation was administered to patients in study 004. The concentration range sufficiently covers the expected increases in raltegravir plasma concentration due to the known drug-drug interactions. For the primary analysis, the maximum mean change and upper 1-sided 95% confidence interval were -0.2 msec and 3 msec, respectively. However, drug effects on QT were only assessed for 12 hours after dosing. Some drugs (e.g., pentamidine) cause a delayed prolongation of the QT interval; i.e., at a time well after Tmax. A delayed effect of raltegravir on the QT interval at a time point later than 12 hours can not be excluded.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Not applicable as noted in Section 7.1.9.1.

7.1.9.3 Standard analyses and explorations of ECG data

Not applicable as noted in Section 7.1.9.1.

7.1.9.4 Additional analyses and explorations

Not applicable as noted in Section 7.1.9.1.

7.1.10 Immunogenicity

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

7.1.11 Human Carcinogenicity

Raltegravir was evaluated in three *in vitro* and one *in vivo* genotoxicity assays and was found not to be mutagenic or clastogenic. The carcinogenic potential of raltegravir is being evaluated in two-year carcinogenicity studies in rats and mice; as noted, studies are ongoing. Histomorphologic examination in all prematurely necropsied animals through Week 76 detected two types of carcinomas in the respiratory tract (squamous cell carcinoma and chondrosarcoma) likely due to aspiration and irritation of drug product to the respiratory tract. In mice, histomorphologic examination in all prematurely necropsied animals through Week 76 did not detect any tumors. However, dose-related increases in the incidence of squamous metaplasia were seen in nose and nasopharynx of both males and females at doses ≥ 50 mg/kg/day. These results confirm the irritability of raltegravir and suggest that rats are most sensitive to this toxicity. There is no indication of gastrointestinal irritation in clinical studies so far. There was a single carcinoma involving the vocal cord in a raltegravir-treated subject. This subject entered the study with hoarseness; the carcinoma was likely preexisting.

Discussion of malignancies in the raltegravir Phase 2 and 3 studies is presented in Section 7.1.3.

7.1.12 Special Safety Studies

With the exception of the QT study, Protocol 024, no other special safety studies were submitted with this application.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Raltegravir has no potential for drug withdrawal or abuse.

7.1.14 Human Reproduction and Pregnancy Data

Pregnancy was an exclusion criterion of the Phase 2 and 3 studies, and pregnancy was a discontinuation criterion. One pregnancy occurred during Protocol 004. The subject discontinued the study during the extension phase. The outcome of the pregnancy is unknown.

There was 1 pregnancy reported in Protocol 005 during the open-label phase. The subject underwent an elective abortion. Subsequently, the subject restarted study drug therapy including OBT. There were no pregnancies reported for subjects in Protocol 018 or Protocol 019. One subject in Protocol 019 in the raltegravir group reported that his wife became pregnant while he was taking blinded study therapy. The subject's wife had an elective abortion approximately 4 weeks after learning she was pregnant.

Based on the available data, the effects of *in utero* exposure to raltegravir are unknown.

7.1.15 Assessment of Effect on Growth

Raltegravir has only been administered to adults; therefore no clinical assessment on growth has been performed.

7.1.16 Overdose Experience

In Phase 1, 1600 mg was the highest dose of raltegravir studied. In Protocols 004 and 005, an overdose of raltegravir was defined as an excess of 2000 mg per day. No overdoses were reported in Protocols 004 and 005. Overdose criteria for Protocols 018 and 019 were defined as an excess of 1200 mg per day of raltegravir. In Protocol 018, seven subjects received more than the prescribed dose, six of these events occurred during the double-blind phase. Five subjects received the incorrect dose for one or two days. Subject AN 8287 received 1600 mg/day for 14 days, and AN 8240 received the same dose for 6 days. In Protocol 019, two subjects (AN 15016 and AN 16327) who received more than the prescribed dose of raltegravir 800 mg/day, received the incorrect dose for 1 day due to subject error. No adverse experiences were associated with the incorrect dose for either subject.

7.1.17 Postmarketing Experience

Raltegravir has not yet been approved in any country and therefore there is no postmarketing experience at this time.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Please refer to Section 7.1 for the description of studies used in the assessment of safety. A total of 902 HIV-infected subjects received at least one dose of raltegravir during the Phase 2 and Phase 3 studies at the time of the SUR: 758 subjects by initial randomization, 138 subjects by

switch from placebo to open label raltegravir after virologic failure, and 6 subjects by switch from placebo to open label raltegravir in the extension phase of Protocol 005.

7.2.1.2 Demographics

Please refer to Section 6.1.4 for description of subject baseline characteristics.

7.2.1.3 Extent of exposure (dose/duration)

The proposed dose of 400 mg twice daily was received by 41 treatment-naïve and 651 treatment-experienced subjects. A total of 507 treatment-experienced subjects have received the 400 mg twice daily raltegravir dose for at least 24 weeks during the double-blind phase, and 552 treatment-experienced subjects have received $\geq$ 400 mg twice daily raltegravir for at least 24 weeks.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

The Phase 1 studies were evaluated to support the safety assessments from the Phase 2 and 3 studies.

7.2.2.2 Postmarketing experience

As noted above, there is no post-marketing experience with raltegravir.

7.2.3 Adequacy of Overall Clinical Experience

According to the International Committee on Harmonization guidance for drugs intended for long-term treatment of non-life-threatening conditions, safety data should be collected on at least 300 to 600 patients receiving the proposed dose for six months with safety data on a total of 1,500 patients when including patients with shorter-term drug exposure. The antiretroviral guidance states the recommended safety database of 300-600 patients for 6 months was chosen to allow a reasonable chance to identify adverse events occurring at a frequency as low as 1:100. In addition, this guidance provides the regulatory definition for accelerated approval. Per 21 CFR 314.500 - 314.510, three criteria need to be addressed when considering the appropriateness of an accelerated approval: (1) the disease studied must be serious or life-threatening, (2) there must be an available surrogate that is reasonably likely to predict clinical benefit, (3) there must be demonstration of improved activity over approved drugs or activity in a population in need of additional therapeutic options. As stated in 21 CFR 314.500, accelerated approvals apply to drugs that "have been studied for their safety and efficacy in treating serious and or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of available therapy, or improved patient response over available therapy)." Shorter term reductions in HIV RNA levels

(e.g., 24 weeks) supporting an accelerated approval can be considered *surrogate endpoints* for longer, durable suppression of HIV RNA levels.

An adequate number of subjects and duration of drug exposure was obtained during the raltegravir development program to support accelerated approval. In addition, the pivotal Phase 3 studies were randomized and placebo-controlled, with use of the surrogate endpoint of HIV-1 RNA <400 copies/mL.

Few women and non-whites were assessed during the Phase 3 studies and therefore a thorough evaluation of safety and efficacy is these populations were limited. No significant differences were detected in these subgroups. Further studies in women and minorities will be the focus of a post-marketing commitment (to be negotiated).

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Appropriate pre-clinical testing was performed. Please refer to Section 3.2 and Dr. Ita Yuen's review for details of the preclinical program.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical and laboratory testing performed in the Phase 2 and 3 studies were adequate to assess safety and are summarized in Section 7.1.5.1. The evaluations occurred at baseline, Week 2, 4, 8, and then every 8 weeks through Week 48.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The metabolic, clearance, and interaction workup was adequate. Please refer to Section 5 and to Dr. Derek Zhang's review for details.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The evaluation for potential adverse events associated with raltegravir in treatment-experienced subjects was adequate given the shorter duration of exposure accepted for accelerated approval. Additional information will be available with submission of the 48 week data. As noted in Section 7.1.3, an initial imbalance in malignancies was observed in the raltegravir group; however, with longer follow-up this imbalance has diminished. A prolonged duration of observation may be necessary to detect an association of malignancy with raltegravir, and this will be addressed as a post-marketing commitment (see Section 9.3.2).

7.2.8 Assessment of Quality and Completeness of Data

The overall quality of the clinical data for conducting the safety review was acceptable, and was obtained from randomized, blinded, placebo-controlled trials. The frequency of clinical assessments was also appropriate. The original NDA submission did not include grades for the laboratory data. After discussion with the Applicant, an updated laboratory table derived from the original 12/13/06 data cutoff date was submitted, and this data was used to perform most FDA laboratory analyses. No grades were provided for the laboratory data in the SUR, and, therefore, I created formulas based on the DAIDS grading criteria to generate these grading assessments.

The proportions of study subjects who had other types of missing data were relatively small and considered acceptable. Follow-up of subjects enrolled in the pivotal studies was also acceptable with very few subjects discontinuing study for unknown reasons.

7.2.9 Additional Submissions, Including Safety Update

The Safety Update Report was submitted on June 15, 2007. The original NDA cut-off date for safety assessments was December 13, 2006, and the SUR cut-off date for safety assessments was February 16, 2007. As mentioned in Section 7.1, the SUR data was used for key safety analyses.

An update of malignancies was submitted on August 17, 2007 and contained all reported malignancies in the Phase 2 and 3 studies through July 9, 2007. The results from this report are summarized in Section 7.1.3.

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

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Potentially drug-related AEs during the Phase 2 and 3 raltegravir development program have included rash, elevated CK levels, herpes zoster, and an imbalance in malignancies that has diminished with longer follow up. Analyses of these AEs and conclusions are described in Section 7.1.3.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Protocols 018 and 019 had identical trial designs including the same eligibility criteria. Therefore, the safety data from these trials were pooled to increase the power to detect AEs potentially associated with raltegravir use. In addition, the 400 mg twice daily raltegravir and

placebo arms of Protocol 005 were pooled for many safety analyses due to inclusion of a similar treatment-experienced population. In several analyses, all doses in Protocol 005 were combined with the Phase 3 studies due to similar populations. Finally, some safety analyses pooled data from all Phase 2 and 3 studies (including the treatment-naïve Protocol 004), to capture all potential safety signals in from the Phase 2 and 3 raltegravir development program.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

In general, safety analyses of the Phase 2 dose-finding studies did not detect clinically significant dose dependent AEs. In the pivotal Phase 3 studies, only the 400 mg twice daily raltegravir dose was used to compare to placebo.

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

7.4.2.2 Explorations for time dependency for adverse findings

Time to onset analyses were performed for several safety analyses including rash, mortality, and malignancy and are reviewed in Section 7.1.3. No other formal evaluation of time dependency for adverse events was conducted.

7.4.2.3 Explorations for drug-demographic interactions

Subgroup analyses of clinical AEs by gender, race, and age did not detect significant differences between the raltegravir and placebo groups; however, as previously mentioned, the majority of enrolled subjects were white men in their 40s.

7.4.2.4 Explorations for drug-disease interactions

Subgroup analysis of hepatitis co-infected subjects detected higher liver enzymes and bilirubin in these subjects; however, no subjects discontinued the study due to these laboratory abnormalities.

7.4.2.5 Explorations for drug-drug interactions

Subgroup analysis of subjects receiving ATV in their background regimen was performed due to the potential of ATV to increase raltegravir plasma concentrations. As reviewed in Section 7.1.4, this analysis did not detect an imbalance in AEs with the exception of known ATV-associated events related to elevated bilirubin.

Please refer to Dr. Derek Zhang's review of the Phase 1 drug-drug interaction studies.

7.4.3 Causality Determination

All AEs potentially caused by raltegravir are considered in detail in Section 7.1.3.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The proposed dosing regimen for raltegravir is 400 mg twice daily in adults, taken with or without food.

8.2 Drug-Drug Interactions

Raltegravir is a UGT1A1 and P-gp substrate; therefore, raltegravir pharmacokinetics are likely to be affected by inhibitors/inducers of these enzymes/substrates. ATV increases raltegravir Cmin and AUC. Ritonavir, efavirenz, rifampicin, TPV, and TMC125 decrease raltegravir Cmin and AUC.

Raltegravir is not an inhibitor of CYP1A2, 2C8, 2C9, 2C19, 2D6, 3A4, and 2B6. Raltegravir (up to 10 μM) has no potential to induce CYP3A4. Therefore, raltegravir is considered unlikely to alter the metabolism of co-administered drugs that undergo metabolism by cytochrome P450 enzymes.

Please refer to Section 5.1 and Dr. Derek Zhang's review for further information.

8.3 Special Populations

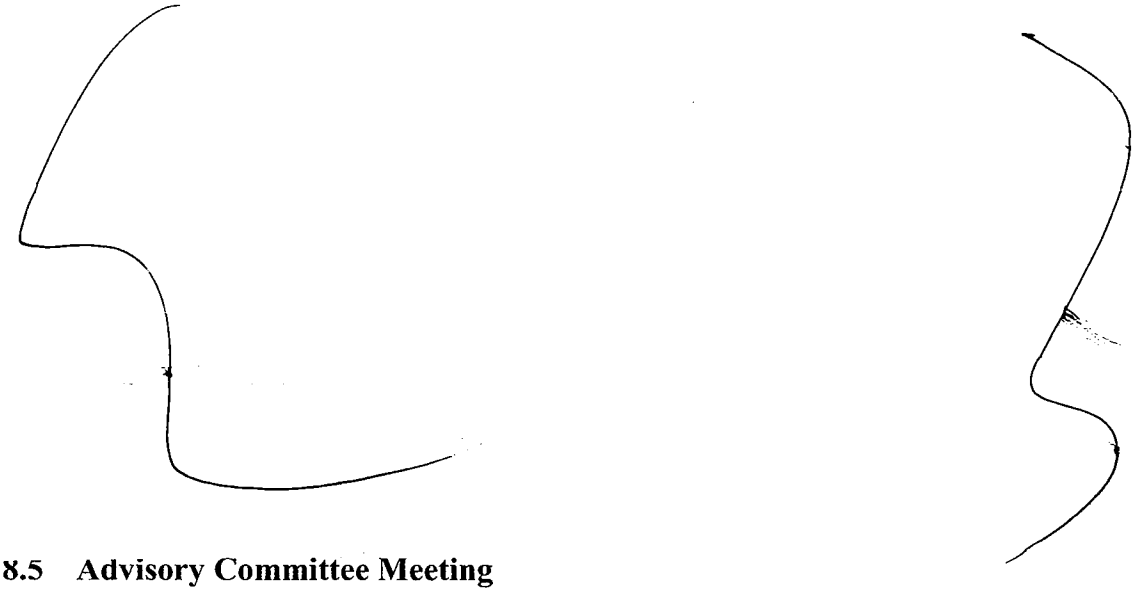
In developmental toxicity studies in rats, an increase in the incidence of supernumerary ribs relative to control was found at a dose approximately 3.4-fold higher than that anticipated with the proposed human dose. No external or visceral abnormalities and no other fetal or postnatal developmental effects were observed at this dose. In rabbits, no fetal malformations were found at the maximum raltegravir dose. No adequate studies have been performed in pregnant women. Because animal reproduction studies are not necessarily predictive of human response, raltegravir should be used during pregnancy only if the potential benefit justifies the potential risk.

No clinically important effect of moderate hepatic insufficiency on the raltegravir pharmacokinetic profile was observed in a study of subjects with Child Pugh scores of 7 to 9. No clinically important effect of severe renal insufficiency on the raltegravir pharmacokinetic profile was observed in a study of subjects with 24-hour creatinine clearance of <30 mL/min/1.73 m^2.

Insufficient numbers of subjects age 65 and older were enrolled in the clinical studies to determine whether this population responds differently from younger subjects.

8.4 Pediatrics

Discussions with the Applicant regarding the pediatric study program have been ongoing throughout raltegravir's development.



8.5 Advisory Committee Meeting

A meeting with the Antiviral Drugs Advisory Committee was held September 5, 2007. The questions posed by the FDA are in bold followed by Committee responses:

1) Do the available data support accelerated approval of raltegravir for the treatment of HIV-1 infection in combination with other antiretroviral agents in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy? If no, what additional studies are recommended?

The Committee voted unanimously that the data support accelerated approval of raltegravir for the proposed indication. Further discussion centered around the definition of "treatment-experienced". A concern was use in first-treatment failures and development of resistance if non-compliance occurred with subsequent transmission of raltegravir-resistant virus in the community. Other members supported a broad indication, possibly revising the "treatment-experienced" definition to include highly treatment-experienced patients.

2) If yes, what additional studies would you like to see undertaken as post-marketing commitments?

The Committee supported studies to characterize resistance. Additional studies include interaction studies with drugs used for tuberculosis treatment, longer studies to gather data on malignancies, and studies in women and racial minorities.

3) The applicant is proposing a Risk Management Plan for raltegravir including a routine pharmacovigilance plan, ongoing clinical trials, a pregnancy registry, and an active surveillance program. The duration of the active surveillance program is at least three years post-launch. Do you find this duration period acceptable?

The Committee supported a [redacted]

4) Please discuss the pros and cons of the following potential treatment strategies in future clinical trials used to support drug development, and more specifically, if you would like to see these studies conducted using raltegravir as post-marketing commitments.

a) Nucleoside-sparing regimens in treatment-naïve patients using either two-drug/two-class or three-drug/three-class regimens

The Committee supported this design and recommended a Phase 2 design for initial studies, possibly comparing a two-drug/two-class placebo-controlled regimen to a three-drug/three-class regimen; however, there was no recommendation for this strategy as a PMC.

b) Nucleoside-sparing regimens or three-drug/three class regimens in first treatment failure patients

The Committee discussed this population likely represents patients failing a prior once daily regimen and cautioned these patients may have difficulty complying with a multiple dose regimen. There was no recommendation for this strategy as a PMC.

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

The Committee was unable to recommend a specific strategy to increase study enrollment of women and minorities. There was general agreement that studies need to preplan enrollment of these populations up front and that these studies require a strong infrastructure.

8.6 Literature Review

Literature citations are provided in the References Section.

8.7 Postmarketing Risk Management Plan

Please refer to Section 9.3 for a detailed description of all post-marketing commitments currently being discussed with the Applicant.

8.8 Other Relevant Materials

No other materials were used during this review.

9 OVERALL ASSESSMENT

9.1 Conclusions

The superior efficacy of raltegravir over placebo in combination with an optimized background regimen was demonstrated with Week 16 results of two large double-blind randomized placebo-controlled trials, Protocols 018 and 019. Over 75% of raltegravir-treated subjects achieved an HIV-1 viral load <400 copies/mL at Week 16 versus approximately 40% of placebo-treated subjects; the treatment difference was statistically significant for each protocol. Analyses of Week 24 data, available for approximately 60% of subjects supported the Week 16 results.

Overall, raltegravir appeared to be well tolerated with few subjects discontinuing for adverse events considered potentially related to raltegravir use. No clinically significant imbalance was observed in mortality rates and AIDS defining conditions. One safety concern observed during the clinical development of raltegravir was an imbalance in the rate of malignancy between raltegravir and control subjects; however, with longer follow up the imbalance initially observed diminished. Overall, rash events were more common in raltegravir arms (7.2%) as compared to control arms (5.3%); however, no raltegravir-treated subject discontinued for rash in any Phase 2 or 3 study, no clear pattern was observed, and the majority were mild/moderate in intensity. An increase in Grade 2 – 4 CK elevations was observed in raltegravir arms as compared to control; however, association with clinical symptoms was balanced between the two groups. A total of 3 cases of rhabdomyolysis and 2 cases of myopathy have been reported in the Phase 3 and Expanded Access Programs. The Applicant has agreed to include CK laboratory data, rhabdomyolysis and myopathy in the PI, although a causal relationship with raltegravir is unclear at this time. Longer term data and safety monitoring will be collected to allow further characterization of any potential relationship between raltegravir, elevated CK levels and clinical adverse events. Finally, more raltegravir-treated subjects reported herpes zoster as compared to control subjects.

Based on review of the available safety data, the benefits of raltegravir in HIV-1 treatment-experienced subjects outweigh the currently identified risks.

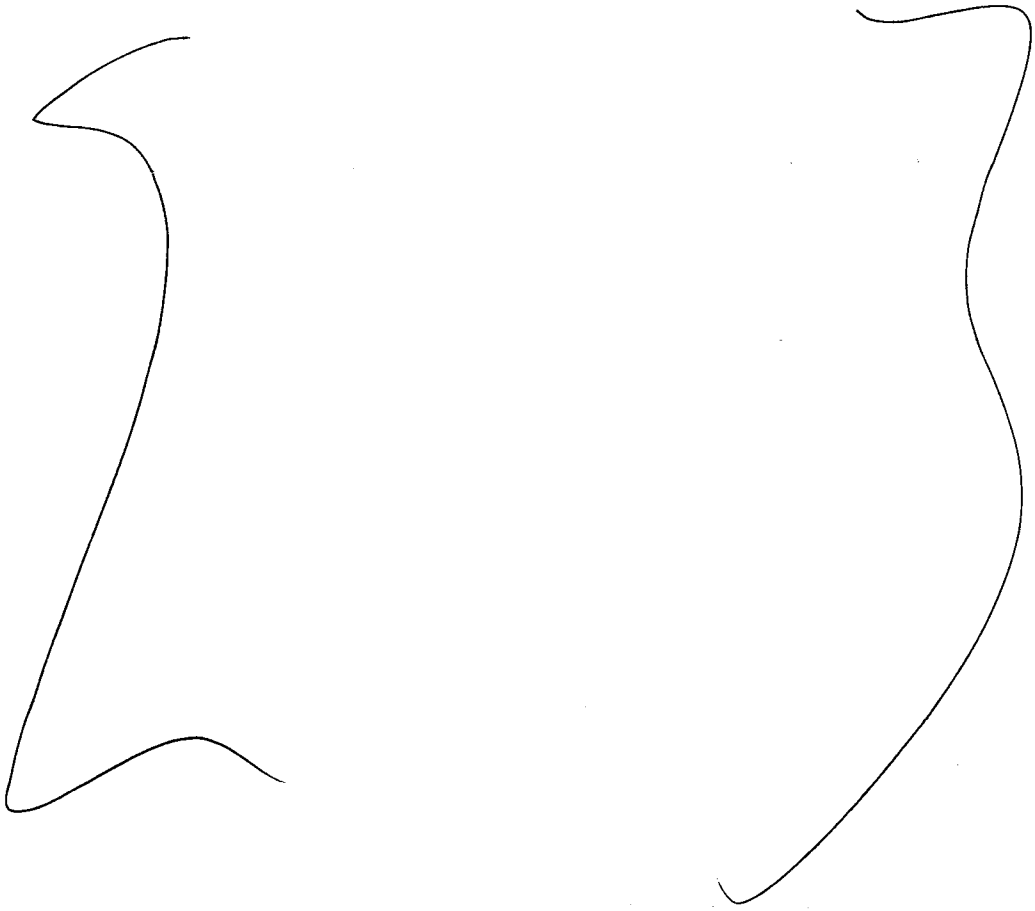
9.2 Recommendation on Regulatory Action

Accelerated approval of raltegravir is recommended for the management of HIV-1 infected treatment-experienced adults. This recommendation is based on the finding of virologic suppression in a patient population with few remaining treatment options.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

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



OSE has reviewed the proposed Active Surveillance plan, and will review the complete protocol when it is submitted by the Applicant.

9.3.2 Required Phase 4 Commitments

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

We completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.510), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text (package insert, patient package insert, immediate container label). Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

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

Please submit final printed container label that is identical to the enclosed immediate container label as soon as it is available, but no more than 30 days after it is printed. Please submit this label electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005). Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "Final Printed Container Label for approved NDA 22-145." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. We note that the following postmarketing study commitment specified in your submission dated October 8, 2007 was agreed-upon during a teleconference held on October 5, 2007. This commitment, along with the agreed-upon completion date is listed below:

1. By December 31, 2008, submit study reports for Week 48 data analyses for the ongoing Phase 3 Studies 018 and 019.

Please submit final study reports to NDA 22-145 as a supplemental application. For administrative purposes, all submissions relating to this postmarketing study commitment must be clearly designated **"Subpart H Postmarketing Study Commitment."**

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring submission of your studies in pediatric subjects from 4 weeks to 18 years of age until June 30, 2011. We are waiving submission of your studies in pediatric subjects from birth up to 4 weeks of age (neonates) because the number of neonates diagnosed with HIV-1 infection is very small; therefore, there are too few pediatric subjects to study in this age group with this disease.

Accelerated Approval PMCs

1 By December 31, 2008, submit study reports for Week 48 data analyses for the ongoing Phase 3 Studies 018 and 019.
2 Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric subjects from 2 to 18 years of age. This study will determine raltegravir exposure (pharmacokinetic profile) followed by 24 weeks of dosing. Efficacy will be based on viral load reduction through 24 weeks of dosing and safety will be monitored for a minimum of 24 weeks to support raltegravir dose selection, safety, and efficacy in this population.
Protocol Submission Date: Ongoing
Final Study Report Submission Date: June 30, 2011
3 Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric subjects from 4 weeks to 2 years of age. This study will determine raltegravir exposure (pharmacokinetic profile) followed by 24 weeks of dosing. Efficacy will be based on viral load reduction through 24 weeks of dosing and safety will be monitored for a minimum of 24 weeks to support raltegravir dose selection, safety, and efficacy in this population.
Protocol Submission Date: September 30, 2008
Final Study Report Submission Date: June 30, 2011

PMCs

1 Submit Week 96 reports and datasets for Protocols 018 and 019.
Protocol Submission Date: Completed
Week 96 Reports and Datasets Submission Date: December 31, 2009
2 Conduct a five-year follow-up for subjects in Protocols 018 and 019 focusing on safety evaluations, which should include but not be limited to assessment of mortality, malignancy, herpes zoster, creatine kinase elevations, and other adverse events.
Protocol Submission Date: May 31, 2008
Final Study Report Submission Date: December 31, 2012
3 Submit Week 48 reports and datasets for Protocol 021.
Protocol Submission Date: Completed
Week 48 Reports and Datasets Submission Date: March 31, 2009
4 Conduct a non-interventional, prospective, observational study to provide additional safety data on important clinical events. The duration of the study will be 5 years from initiation of the study; data will be reviewed on an interim basis every 6 months during the course of the study.
Protocol Submission Date: March 31, 2008
Final Study Report Submission Date: December 31, 2014
5 Complete the ongoing carcinogenicity study in mice and submit the final report.
Protocol Submission Date: Completed
Final Study Report Submission Date: July 25, 2008
6 Complete the ongoing carcinogenicity study in rats and submit the final report.

9.4 Labeling Review

The latest PI and Patient PI versions as of October 11, 2007 are attached in Section 10.2.

9.5 Comments to Applicant

Comments were provided to the Applicant throughout the review. There are no additional comments at this time.

10 APPENDICES

10.1 Review of Individual Study Reports

Information from relevant individual studies was interspersed throughout the review.

17 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical- 1

REFERENCES

DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents. October 10, 2006.

Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, 2004.

FDA Guidance for Industry "Antiretroviral Drugs Using Plasma HIV RNA Measurements – Clinical Considerations for Accelerated and Traditional Approval". October 2002.

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/s/

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10/12/2007 11:11:26 AM
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Kendall Marcus
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