Name of Sponsor/Company: Bristol-Myers Squibb	Individual Study Table Referring to the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Reyataz		
Name of Active Ingredient: Atazanavir (BMS-232632)		

SYNOPSIS

Final Clinical Study Report for Study AI424138

TITLE OF STUDY: A 96 Week Study Comparing the Antiviral Efficacy and Safety of Atazanavir/ritonavir with Lopinavir/ritonavir, Each in Combination with Fixed Dose Tenofovir-Emtricitabine in HIV-1 Infected Treatment Naive Subjects

INVESTIGATORS/STUDY CENTERS: 110/134

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 18-Nov-2005 **CLINICAL PHASE:** 3b

Data Cutoff Date: 11-Jun-2007, study on-going

OBJECTIVES:

The primary objective is to compare the proportion of subjects with HIV RNA < 50 copies/mL (c/mL) at Week 48 between the atazanavir (ATV) 300 mg QD + ritonavir (RTV) 100 mg QD + tenofovir (TDF) 300 mg QD + emtricitabine (FTC) 200 mg QD (ATV/RTV/TDF/FTC, ATV/RTV) and lopinavir (LPV)/ritonavir (RTV) 400/100 mg BID + TDF 300 mg QD + FTC 200 mg QD (LPV/RTV/TDF/FTC, LPV/RTV) treatment regimens.

Secondary objectives addressed in this report include the following

- To assess the proportion of subjects with HIV RNA < 400 c/mL at Week 48
- To assess the time to loss of virologic response (TLOVR) defined as the earliest of virologic rebound, discontinuation, never responded or never treated
- To assess the reduction of $\log_{10}$ HIV RNA from baseline through Week 48
- To assess the change in CD4 cell count from baseline through Week 48
- To assess the antiretroviral resistance profiles of subjects experiencing virologic failure
- To assess safety and tolerability of the regimens
- To assess the changes from baseline in fasting lipids over time, and the proportion of subjects with National Cholesterol Education Program (NCEP)-guided categories of fasting lipids over time
- To assess the changes from baseline in fasting glucose and insulin

Secondary objectives not addressed in this report include the following

- To assess the proportions of subjects with HIV RNA < 50 c/mL and < 400 c/mL at Week 96
- To assess the reduction of $\log_{10}$ HIV RNA from baseline through Week 96
- To assess the change in CD4 cell count from baseline through Week 96

- To evaluate the quality of life as measured by the Medical Outcomes Survey- Human Immunodeficiency Virus
- To evaluate the impact of gastro-intestinal toxicity on the quality of life as measured by the Irritable bowel syndrome-Quality of life questionnaire
- To assess trough concentrations of ATV, LPV, and RTV and to explore the correlations with efficacy and safety parameters
- To evaluate the adherence to each drug and the adherence to the regimen as measured by the Multicenter AIDS Cohort Study adherence questionnaire

METHODOLOGY:

This is a 96-week, open-label, randomized, multicenter study designed to compare the antiviral activity of ATV/RTV/TDF/FTC vs LPV/RTV/TDF/FTC in treatment-naive HIV-infected subjects who have received no prior antiretroviral treatment (or limited prior treatment as specified in the protocol) and who have a plasma HIV RNA of ≥ 5000 c/mL (Roche Amplicor®) at screening. Randomization was stratified for HIV RNA viral load (< 100,000 c/mL or ≥ 100,000 c/mL) and region.

NUMBER OF SUBJECTS (Planned and Analyzed):

Planned: 882 subjects. Analyzed: 883 randomized subjects analyzed for efficacy, 878 treated subjects analyzed for safety.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

HIV-infected, treatment-naive adults with qualifying plasma HIV RNA ≥ 5000 c/mL.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS:

ATV 150 mg capsule, 300 mg PO QD; 5G04336, 6A17818, 6B16342, 6C21904, 6H17774, 6H17778, 6H17779.

RTV 100 mg capsule, 100 mg PO QD; 5G08801, 5H00466, 5L07533, 6C15019, 6C18430.

In addition, TDF 300 mg/FTC 200 mg tablet, 300/200 mg PO QD; 5J10814, 6C12602, 6J16684.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS:

LPV 133 mg/RTV 33.3 mg, 3 133/33.3 mg capsules PO BID: 5G08451, 5G08806, 5M05245, 6C17988, 6H15539.

In addition, TDF 300 mg/FTC 200 mg tablet, 300/200 mg PO QD; 5J10814, 6C12602, 6J16684.

CRITERIA FOR EVALUATION:

Efficacy: The primary endpoint was the proportion of subjects with HIV RNA < 50 c/mL at Week 48. The secondary efficacy endpoints assessed at Week 48 were the following:

- The proportion of subjects with HIV RNA < 400 c/mL at Week 48
- Time to loss of virologic response (TLOVR) defined as the earliest of virologic rebound, discontinuation, never responded or never treated
- The reduction of $\log_{10}$ HIV RNA from baseline through Week 48

- The change in CD4 cell count from baseline through Week 48
- The antiretroviral resistance profiles of subjects experiencing virologic failure

Safety: Safety endpoints assessed at Week 48 included the following:

- Safety and tolerability of the regimens
- The changes from baseline in fasting lipids over time, and the proportion of subjects with NCEP-guided categories of fasting lipids over time
- The changes from baseline in fasting glucose and insulin over time

STATISTICAL CONSIDERATIONS:

A planned sample size of 882 subjects (441 subjects per regimen) provides 90% power to establish the non-inferiority of the ATV/RTV regimen to the LPV/RTV regimen assuming a 2-sided 95% confidence interval (CI), a lower acceptance limit of -10%, and 70% of subjects on both the ATV/RTV and the LPV/RTV regimens have been on study therapy through Week 48 with HIV RNA < 50 c/mL at Week 48. Randomization was stratified by qualifying HIV RNA level (< 100,000 c/mL; ≥ 100,000 c/mL) and region (Africa, Asia, Europe, North America and South America).

Efficacy: The primary efficacy endpoint, the proportion of subjects with HIV RNA < 50 c/mL at Week 48, is assessed with different algorithms and cohorts of randomized subjects. The principal analysis is based on the Confirmed Virologic Response (CVR) Non-Completer = Failure (NC = F) definition of response. Supportive analyses use the CVR Non-Completer = Missing (NC = M), Time to Loss of Virologic Response (TLOVR) and Virologic Response - Observed Cases (VR-OC) definitions of response.

- Principal analyses utilize CVR which defines response as confirmed HIV RNA < 50 c/mL at Week 48 for NC = F. CVR uses the TLOVR definitions of response and failure but allows for resuppression. The supportive analysis CVR (NC = M) only includes subjects with minimum follow-up (at least 42 weeks of study therapy with an HIV RNA measurement on or after 42 weeks).
- The TLOVR algorithm defines responders at Week 48 as subjects with confirmed HIV RNA < 50 c/mL through Week 48 without intervening virologic rebound or treatment discontinuation. Virologic rebound is defined as confirmed on-treatment HIV RNA ≥ 50 c/mL or last on-treatment HIV RNA ≥ 50 c/mL followed by discontinuation. Subjects are considered failures in this analysis if they experienced virologic rebound at or before Week 48, discontinued before Week 48, never responded by Week 48, never received study therapy or had missing HIV RNA at Week 48 and beyond.
- VR-OC classifies subjects who remain on study therapy as responders according to a single HIV RNA measurement < 50 c/mL closest to the planned Week 48 visit and within a pre-defined visit window. The denominator is based on subjects who remained on study therapy through Week 48 visit, ie, those who received more than 42 weeks minus 4 days of study therapy.

Treatment regimens are compared using the difference in proportions (ATV/RTV - LPV/RTV) and 95% confidence interval (CI) based on a stratified normal approximation. The ATV/RTV regimen is determined to be similar (non-inferior) to the LPV/RTV regimen if the lower confidence limit for the difference in proportions is greater than -10%.

The proportion of subjects with HIV RNA < 400 c/mL at Week 48 is assessed analogously to the primary efficacy endpoint.

The distributions of time to loss of virologic response for HIV RNA < 50 c/mL and < 400 c/mL based on TLOVR are described using Kaplan-Meier curves and life tables. Treatment regimens are compared using hazard ratios (ATV/RTV: LPV/RTV) and 95% CIs based on stratified Cox proportional hazard models.

Changes from baseline in CD4 cell counts and log10 HIV RNA changes are summarized at Week 48. Treatment regimens are compared using the difference in mean CD4 changes and 95% CI based on stratified normal approximations.

Genotypic and phenotypic resistance profiles are tabulated for subjects who met the criteria for virologic failure through Week 48 as defined by CVR (NC = F) for HIV RNA < 400 c/mL. Virologic failure includes subjects who had a virologic rebound without resuppression, never suppressed through Week 48 and on study at Week 48, or discontinued due to insufficient viral load response before Week 48.

Safety: Safety analyses tabulate the frequency of adverse events through Week 48, adverse events leading to discontinuation, and laboratory abnormalities (Grade 1 - 4, Grade 3 - 4) through Week 48 for treated subjects. Deaths and serious adverse events are tabulated for enrolled subjects without regard to onset.

Fasting lipid percent changes from baseline are summarized at Week 48. For each lipid parameter, treatment regimens are compared using the difference in mean percent changes, 95% CI and P-value based on a stratified normal approximation. Categories of fasting lipid parameters are also tabulated according to NCEP Adult Treatment Panel (ATP) III guidelines, and accepted conventions for management of dyslipidaemia and cardiovascular risk stratification based on epidemiologic data. Values are excluded after the start of serum lipid-reducing agents.

Changes from baseline in the following laboratory tests are also summarized: creatinine, estimated creatinine clearance (Cockroft-Gault formula), fasting glucose and fasting insulin.

IRIS events that developed during on treatment are tabulated. Events are identified from evidence of an opportunistic infection or inflammatory syndrome within 24 weeks after the start of study therapy or re-initiation of study therapy. In addition, subjects who never re-initiated study therapy or had onset of IRIS on or before re-initiation of study therapy must have the following: (1) □ 1 log10 decrease from baseline at last HIV RNA on or before the onset of IRIS, or (2) □ 1 log10 decrease from baseline at Week 4 HIV RNA if the onset was before Week 4.

SUMMARY OF RESULTS:

Disposition, Demographics, and Other Pertinent Baseline Characteristics: A total of 883 HIV-infected, treatment-naive subjects were randomized: 440 to the ATV/RTV treatment regimen and 443 to the LPV/RTV treatment regimen. The proportion of subjects who discontinued before the Week 48 analysis were 9% and 13% on ATV/RTV and LPV/RTV, respectively (Table 1).

Table 1: Subject Disposition - As-Randomized Subjects

	Number of Subjects (%)		
	ATV/RTV	**LPV/RTV**	**Total**
Randomized	440	443	883
Treated	438 (99)	440 (99)	878 (99)
Discontinued before Week 48	39 (9)	58 (13)	97 (11)
Adverse Event	10 (2)	14 (3)	24 (3)
Death	4 (<1)	4 (<1)	8 (<1)
Lack of Efficacy	5 (1)	8 (2)	13 (1)
Lost to Follow-up	6 (1)	6 (1)	12 (1)
Poor/non-compliance	6 (1)	9 (2)	15 (2)
Withdrew consent	4 (<1)	13 (3)	17 (2)
Additional categories[a]	4 (<1)	4 (<1)	8 (< 1)
Discontinued on or after Week 48	14 (3)	14 (3)	28 (3)
Adverse event	1 (<1)	1 (<1)	2 (<1)
Death	1 (<1)	1 (<1)	2 (<1)
Lack of Efficacy	7 (2)	1 (<1)	8 (<1)
Additional categories[b]	5 (1)	11 (2)	16 (2)
Continuing Treatment	385 (88)	368 (83)	753 (85)

[a] Includes the following categories: "other," pregnancy, no longer meets study criteria

[b] Includes the following categories: poor/not compliance, lost to follow-up, no longer meets study criteria, pregnancy, withdrew consent

Discontinuations for adverse events were 2% vs 3% before Week 48 on ATV/RTV and LPV/RTV, respectively. Three subjects were randomized to the LPV/RTV regimen but were treated with ATV/RTV. These subjects were analyzed as-randomized on LPV/RTV in all efficacy analyses but were analyzed as-treated on ATV/RTV in all safety analyses.

At baseline, the demographic characteristics were balanced (Table 2). Five subjects on each regimen received serum lipid-lowering therapy at baseline and continued taking the therapy on study. Median time on therapy was 48 weeks for both treatment regimens.

Table 2: Subject Characteristics at Baseline - As-Randomized Subjects

	ATV/RTV N = 440	LPV/RTV N = 443	Total N = 883
Age: Median (Min, Max), years	34 (19, 72)	36 (19, 71)	35 (19, 72)
Female, n (%)	138 (31)	139 (31)	277 (31)
CDC Class C AIDS, n (%)	19 (4)	24 (5)	43 (5)
HIV RNA: Median (Min, Max), $\log_{10}$ c/mL	5.01 (2.60, 5.88)	4.96 (3.32, 5.88)	4.98 (2.60, 5.88)
HIV RNA ≥ 100,000 c/mL, n (%)	225 (51)	208 (47)	433 (49)
CD4: Median (Min, Max), cells/mm^3	205 (2, 794)	204 (4, 810)	205 (2, 810)
CD4 < 50 cells/mm^3, n (%)	58 (13)	48 (11)	106 (12)
HBV positive, n (%)	24 (5)	20 (5)	44 (5)
HCV positive, n (%)	40 (9)	33 (7)	73 (8)
HBV and/or HCV positive, n (%)	61 (14)	51 (12)	112 (13)
HIV subtype B, n (%)	280 (67)	276 (65)	556 (66)

Note: Percentages are based on subjects with measurements

Efficacy Results: ATV/RTV has similar (non-inferior) antiviral efficacy compared to LPV/RTV at Week 48, as assessed by the principal analysis of the proportion of subjects with HIV RNA < 50 c/mL using confirmed virologic response (CVR) NC = F (Table 3): 78% of subjects on ATV/RTV compared to 76% on LPV/RTV (difference estimate 1.7% [95% CI, -3.8%, 7.1%]). The lower 95% confidence limit was greater than the similarity boundary of -10%. Three subjects who were randomized to LPV/RTV but were treated with ATV/RTV were all responders for LPV/RTV in the CVR analysis. The similarity of the ATV/RTV regimen to the LPV/RTV regimen was supported by the CVR (NC = M), TLOVR and VR-OC definitions of response.

The similarity of the ATV/RTV regimen to the LPV/RTV regimen was supported by CVR (NC = F and NC = M), TLOVR and VR-OC for HIV RNA < 400 c/mL at Week 48.

The regimens were comparable for the mean HIV RNA change from baseline and mean CD4 cell count change from baseline at Week 48 (Table 3).

Table 3: Efficacy Summary at Week 48 - As-Randomized Subjects

Endpoint	Responder/Evaluable (%) ATV/RTV N = 440	Responder/Evaluable (%) LPV/RTV N = 443	Difference Estimate[a] (95% CI) ATV/RTV - LPV/RTV
Primary Endpoint			
HIV RNA < 50 c/mL			
CVR (NC = F)[b]	343/440 (78)	338/443 (76)	1.7 (-3.8, 7.1)
CVR (NC = M)	343/398 (86)	338/379 (89)	-2.9 (-7.5, 1.6)
TLOVR[c]	343/440 (78)	337/443 (76)	1.9 (-3.6, 7.4)
VR-OC	335/399 (84)	333/382 (87)	-3.5 (-8.7, 1.8)
Secondary Endpoints			
HIV RNA < 400 c/mL			
CVR (NC = F)[b]	377/440 (86)	365/443 (82)	3.3 (-1.5, 8.1)
CVR (NC = M)	377/398 (95)	365/379 (96)	-1.8 (-5.1, 1.5)
TLOVR[c]	377/440 (86)	363/443 (82)	3.8 (-1.1, 8.6)
VR-OC	374/399 (94)	364/382 (95)	-1.7 (-5.2, 1.8)
CD4, mean change from baseline, cells/mm^3	203	219	-16.4 (-35.9, 3.1)
HIV RNA, mean reduction from baseline, log_{10} c/mL	-3.09	-3.13	-

[a] Difference estimates are stratified by qualifying HIV RNA and region

[b] Primary analysis

[c] Hazard ratio estimates (95% CI) are 0.93 (0.71, 1.23) and 0.78 (0.56, 1.09) for HIV RNA < 50 c/mL and < 400 c/mL, respectively

Resistance: Virologic failure includes never suppressed (HIV RNA < 400 c/mL) and on study through Week 48, rebound to HIV RNA ≥ 400 c/mL, and discontinuation due to insufficient viral load response using CVR NC = F. There were 6% patients with virologic failure through 48 weeks on ATV/RTV and LPV/RTV; of these 25/27 (93%) and 22/26 (85%) had genotypable isolates at baseline.

All baseline isolates from these virologic failure subjects had ≥ 1 International AIDS Society (IAS)-defined minor PI substitutions at baseline; the IAS-defined major PI substitutions M46I, V82A, I84V, and L90M were observed in baseline isolates of 2 subjects randomized to ATV/RTV. One of these subjects had 3 major PI substitutions, one had 2 major PI substitutions, and both had multiple minor PI substitutions with phenotypic resistance at baseline to both LPV/RTV and ATV/RTV. Both also had the M184V RT substitutions and phenotypic resistance to emtricitabine at baseline. One also had baseline phenotypic resistance to tenofovir. Three ATV/RTV patients had thymidine analogue mutations (TAMs) at baseline. No LPV/RTV patient had baseline major PI substitutions or TAMs at baseline; 1 had an M184V.

Paired baseline and on-study HIV samples through wk 48 were successfully tested for genotypic resistance from 17/27 (63%) and 15/26 (58%) of virologic failure patients on ATV/RTV and LPV/RTV, respectively. Of these, 6/17 on ATV/RTV and 2/15 on LPV/RTV had IAS-defined minor PI substitutions emerge on study.

An I50I/L substitution emerged on study in 1 of the 2 ATV/RTV patients whose baseline isolate had major PI substitutions; this patient had 2 major PI substitutions (V82A and L90M) and 6 additional minor PI substitutions associated with ATV/RTV resistance (L10I, M36I, F53L, I54V, A71V, I93L) at baseline.

The M184V substitution emerged on 3/17 ATV/RTV patients and 3/15 LPV/RTV patients, and phenotypic resistance to other NRTIs emerged in 5/18 and 5/16 ATV/RTV and LPV/RTV patients, respectively.

Phenotypic resistance to ATV/RTV or LPV/RTV did not emerge in any patient on either regimen who had a wild-type isolate at baseline. No IAS-defined major PI substitutions emerged on either regimen in patients with virologic failure, except for the single case of I50I/L described above. Phenotypic resistance to ATV/RTV did emerge in 1 patient treated with ATV/RTV; this patient had 4 baseline PI substitutions associated with ATV/RTV resistance. A further 7 minor PI substitutions associated with ATV/RTV resistance emerged on study. Phenotypic resistance to PIs other than those used in the study emerged in 4/18 and 4/16 patients treated with ATV/RTV and LPV/RTV, respectively.

Safety Results:

Deaths and Adverse Events: There were no new or unexpected safety events. Adverse events were not treatment limiting in most cases. Thirteen deaths were reported: 6 on ATV/RTV; 6 on LPV/RTV; 1 additional enrolled subject was hospitalized prior to randomization and subsequently died (Table 4). One death on LPV/RTV (case of mesenteric thrombosis) was considered "possibly related" to study drug; all others were considered "unrelated" or "not likely" related to study drug.

Serious adverse events were 12% and 10% in the ATV/RTV and LPV/RTV regimens, respectively. All SAEs were reported by < 1% subjects on either regimen with the exception of diarrhea, which was reported in 6 (1%) of subjects on LPV/RTV. Jaundice was not reported as an SAE in any subject on ATV/RTV. Few SAEs were considered related (7 possible and 5 probable) to study drug.

The incidence of adverse events leading to discontinuation of study therapy was low (2% and 3%). More subjects on ATV/RTV discontinued due to jaundice/hyperbilirubinemia (3 [<1%] subjects vs 0), while more subjects on LPV/RTV discontinued due to diarrhea (4 [<1%] vs 0). One subject on each regimen discontinued due to a renal adverse event, Fanconi syndrome on ATV/RTV and proteinuria on LPV/RTV.

Overall, the incidence of adverse events through Week 48 was high (Table 4). Bilirubin-associated disorders (all grades: ocular icterus, hyperbilirubinemia, and jaundice) were more common (≥ 5 percentage points difference) on ATV/RTV than LPV/RTV. All grades diarrhea, nausea, vomiting, and hypertriclyceridaemia were more common on LPV/RTV than ATV/RTV. The incidence of skin and subcutaneous disorders was 24% and 19%. Renal toxicity was 2% on each regimen. IRIS was 3% on each regimen.

The incidences of Grade 2 to Grade 4 related adverse events were 26% and 30%. Most Grade 2 to Grade 4 related adverse events were reported by ≤ 2% of subjects in either regimen. Hyperbilirubinemia was the only Grade 2 to Grade 4 related adverse event (6% and 0) that occurred with a higher frequency (≥ 5 percentage points difference) on the ATV/RTV than LPV/RTV regimen. Diarrhea was the only Grade 2 to Grade 4 related adverse event (2% and 11%) that occurred with a lower frequency on the ATV/RTV than LPV/RTV regimen. Grade 2 to Grade 4 related hypertriglyceridemia was < 1% and 4%.

Table 4: Summary of Adverse Events - As-Treated Subjects

	Number of Subjects (%)	
	ATV/RTV N = 441	**LPV/RTV N = 437**
Death	6 (1)	6 (1)
SAE	51 (12)	42 (10)
Adverse event leading to discontinuation	11 (2)	15 (3)
Jaundice/hyperbilirubinemia[a]	3 (< 1)	0
Diarrhea	0	4 (< 1)
Renal AE	1 (< 1)	1 (< 1)
Any adverse event through Week 48	400 (91)	399 (91)
Baseline HBV and HCV Negative	345/380 (91)	350/385 (91)
Baseline HBV and/or HCV Positive	54/60 (90)	48/51 (94)
Gastrointestinal disorders	221 (50)	317 (73)
Diarrhea	92 (21)	231 (53)
Nausea	70 (16)	101 (23)
Vomiting	28 (6)	47 (11)
Hyperbilirubinaemia, jaundice, or ocular icterus	136 (31)	5 (1)
Jaundice	69 (16)	2 (<1)
Hyperbilirubinemia[a]	49 (11)	3 (<1)
Ocular Icterus	38 (9)	0
Skin and subcutaneous tissue disorders	106 (24)	82 (19)
Metabolism and nutrition disorders	32 (7)	80 (18)
Hypertriglyceridaemia	13 (3)	37 (8)
Hyperlipidaemia	1 (< 1)	11 (3)
Renal toxicity	11 (2)	9 (2)
IRIS events	14 (3)	13 (3)

[a]Hyperbilirubinaemia also includes blood bilirubin increased, abnormal blood bilirubin, and blood bilirubin unconjugated increased from the INVESTIGATIONS system organ class.

In general, consistent results were seen for baseline HBV and/or HCV not co-infected and co-infected subjects within regimens. There were some differences within groups of anticipated adverse events. While rates of jaundice were 16% and 17%, respectively, for baseline HBV and HCV not co-infected and baseline HBV and/or HCV co-infected subjects on ATV/RTV, rates of hyperbilirubinemia were 8% and 17% respectively. For LPV/RTV-treated subjects, rates of diarrhea (52% vs 61%) and vomiting (10% vs 16%) were lower in baseline HBV and HCV not co-infected subjects. baseline HBV and HCV not co-infected subjects on both regimens had influenza reported less frequently; 4% vs 12% on ATV/RTV, and 4% vs

10% on LPV/RTV. Other adverse events with ≥ 5% difference in reported rates between baseline HBV and HCV not co-infected and baseline HBV and/or HCV co-infected subjects on LPV/RTV included rash (3% vs 8%), upper respiratory infection (8% vs 16%), pyrexia (4% vs 10%) and cough (5% vs 14%). Abdominal pain was reported less frequently among baseline HBV and HCV not co-infected than baseline HBV and/or HCV co-infected subjects on ATV/RTV (5% vs 13%).

Laboratory Test Results through Week 48

Liver Function Tests: The incidence of abnormal bilirubin was greater on ATV/RTV than LPV/RTV (Grade 1 to Grade 4: 84% and 4%; Grade 3 to Grade 4: 34% and <1%). Grade 1 to Grade 4 alanine transaminase (ALT) was 17% and 11%: for ATV/RTV and LPV/RTV, respectively; Grade 3 to Grade 4 was 2% and 1%. Grade 1 to Grade 4 aspartate transaminase (AST) was 18% and 13%: for ATV/RTV and LPV/RTV, respectively; Grade 3 to Grade 4 was 2% and < 1%.

In general, the incidence of abnormal ALT or AST was greater in subjects who were co-infected with hepatitis B or C at baseline than in those who were not co-infected when compared within each regimen.

Renal Function: Mean percent change from baseline at Week 48 in serum creatinine were ≤ 0.05 mg/dL on both regimens. Grade 3 to Grade 4 creatinine was reported as an adverse event in 1 subject on each regimen. The median percent changes from baseline in the creatinine clearance at Week 4 were -6% (quartile 1 [Q1], quartile 3 [Q3]: -14%, 3%) and -7% (Q1, Q3: -14%, 2%) on the ATV/RTV and LPV/RTV, respectively. The median percent changes at Week 48 were however -1% (Q1, Q3: -11%, 8%) and -1% (Q1, Q3: -11%, 11%) on ATV/RTV and LPV/RTV, respectively. No subjects had > 50% reduction from baseline in creatinine clearance at Week 48; 4% and 5% of subjects had >25% to ≤50% reduction in creatinine clearance at Week 48 on ATV/RTV and LPV/RTV, respectively. One subject on ATV/RTV and 3 subjects on LPV/RTV substituted alternative NRTIs for TDF/FTC through Week 48.

Fasting Lipids: Mean percent changes from baseline at Week 48 were significantly higher (P < 0.0001) on the LPV/RTV regimen than the ATV/RTV regimen for fasting total cholesterol, non-HDL cholesterol, and triglycerides (Table 5).

Table 5: Fasting Lipid Mean Percent Changes from Baseline at Week 48 - As-Treated Subjects

	ATV/RTV N = 441	LPV/RTV N = 437	Difference Estimate (95% CI) ATV/RTV - LPV/RTV
Total Cholesterol	13%	25%	-9.8% (-12.3%, -7.3%)***
LDL Cholesterol	14%	19%	-4.5% (-8.4%, -0.4%)*
HDL Cholesterol	29%	37%	-5.8% (-9.9%, -1.5%)*
Non-HDL cholesterol	8%	22%	-11.3% (-14.4%, -8.2%)***
Triglycerides	15%	52%	-24.6% (-29.6%, -19.4%)***

Difference estimates are stratified by qualifying HIV RNA and region.

Values were excluded after the start of serum lipid reduction therapy

* p < 0.05, *** p < 0.0001

More LPV/RTV subjects shifted into higher NCEP categories for total cholesterol, triglycerides and LDL cholesterol compared to ATV/RTV subjects; similarly more LPV/RTV subjects had worsening of their total-to-HDL cholesterol ratio compared to ATV/RTV subjects. More ATV/RTV than LPV/RTV subjects had worsening of their LDL-to-HDL cholesterol ratios. More subjects on LPV/RTV (8%) than ATV/RTV (2%) initiated lipid reduction therapy through 48 weeks.

Mean changes from baseline in fasting glucose levels were low (ATV/RTV: 2 mg/dL; LPV/RTV: 0 mg/dL). The mean changes from baseline in fasting insulin levels were 2.5μU/mL and 0.2 μU/mL.

CONCLUSIONS:

- ATV/RTV had similar (non-inferior) efficacy compared to LPV/RTV after 48 weeks of therapy as assessed by the primary efficacy endpoint, the proportion of subjects with HIV RNA < 50 c/mL at Week 48 using CVR (NC = F). The similarity of regimens was confirmed by supportive definitions of response CVR (NC = M), TLOVR, and VR-OC for the primary endpoint.
- The similarity of the regimens was supported by analyses of HIV RNA < 400 c/mL at Week 48.
- The regimens were comparable for time to loss of virologic response for HIV RNA < 50 c/mL and < 400 c/mL as assessed by the hazard ratio.
- Both regimens achieved ≥ 3.0 $\log_{10}$ HIV RNA reduction from baseline at Week 48.
- The regimens were comparable for CD4 cell count mean increases from baseline at Week 48.
- The virologic failure rate was low on both regimens. IAS-defined minor substitutions were present in 100% of baseline isolates of ATV/RTV and LPV/RTV virologic failure subjects. Major PI substitutions were observed at baseline in only 2 virologic failure subjects; both subjects were randomized to the ATV/RTV regimen. No subject on either regimen with a wild-type baseline isolate developed genotypic or phenotypic resistance to ATV/RTV or LPV/RTV.
- There were no new or unexpected safety events. Discontinuation rates prior to Week 48 were lower on ATV/RTV than LPV/RTV. Adverse events were not treatment limiting in most cases. Grade 2 to Grade 4 related diarrhea occurred with lower frequency on the ATV/RTV than LPV/RTV regimen. The incidences of abnormal ALT and AST were comparable between ATV/RTV and LPV/RTV, with low incidences of Grade 3 to Grade 4 abnormalities. The incidence of abnormal bilirubin was predictably higher on ATV/RTV for all grades. In general the incidence of abnormal ALT or AST was greater in subjects who were co-infected with hepatitis B and/or C than in those who were baseline HBV and HCV not co-infected when compared within each regimen. Overall there was a minimal decline in creatinine clearance on both regimens through 48 weeks. There was minimal mean change from baseline to Week 48 in serum creatinine on both regimens. Substitution of TDF/FTC for decline in renal function was < 1%.
- Mean percent changes from baseline in fasting lipids (total cholesterol, nonHDL cholesterol, triglycerides) at Week 48 were significantly higher on LPV/RTV than ATV/RTV. More LPV/RTV subjects shifted into higher NCEP categories for total cholesterol, triglycerides and LDL-cholesterol compared to ATV/RTV subjects. More subjects on LPV/RTV than ATV/RTV initiated lipid reduction therapy through 48 weeks.
- Mean changes from baseline in fasting glucose and insulin levels were low on both regimens.

DATE OF REPORT: 26-Oct-2007