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		

SYNOPSIS

Final Clinical Study Report for Study AI424131

TITLE OF STUDY: A Phase IV, Open-Label Randomized, Multicenter Trial Assessing a Reyataz-Based Substitution Approach in the Management of Lipodystrophy Syndrome. Research into Atazanavir in Lipodystrophy (The ReAL Study)

INVESTIGATORS/STUDY CENTERS: 38 centers in Europe (28), Mexico (3), Canada (1) and the USA (6)

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 08-Jul-2005 **CLINICAL PHASE:** 4

Database Cut Off Dates:

48 weeks: 10-Oct-2007

96 weeks: 26-Aug-2008

OBJECTIVES: The primary objective was to compare changes in trunk-to-limb fat ratio at Week 48 by dual energy x-ray absorptiometry (DEXA) in HIV infected subjects with lipohypertrophy, after switching to an atazanavir/ritonavir (ATV/RTV) containing regimen versus remaining on current boosted protease inhibitor (PI)-containing highly active antiretroviral therapy (HAART) regimen.

Secondary objectives in subjects who switch to an ATV/RTV containing regimen compared to those who remain on their current boosted PI-containing HAART regimen included:

- To assess changes from baseline in physical signs of lipohypertrophy.
- To assess changes from baseline in physical signs of lipoatrophy.
- To assess changes from baseline in total body fat.
- To assess changes from baseline in fasting lipid parameters.
- To assess changes from baseline in fasting glucose, insulin, and the insulin resistance index (HOMA-IR [homeostasis model assessment of insulin resistance]).
- To assess changes from baseline in physical measurements.
- To evaluate the safety of switching to an ATV/RTV containing regimen versus remaining on current PI-containing HAART regimen.
- To assess the time to confirmed virologic rebound for subjects with HIV RNA levels < 400 copies/mL (c/mL) at baseline.
- To assess changes from baseline in CD4 cell count (count/mm^3).

- To assess changes from baseline in fasting exploratory markers in particular adipocytokines and hormones (adiponectin, leptin, resistin, tumor necrosis factor [TNF]-alpha, interleukin [IL]-6, plasminogen activator inhibition [PAI-1], high sensitivity C-reactive protein [Hs-CRP], hemoglobin A1c [HbA1c] and fibrinogen).

METHODOLOGY:

In this multicenter, randomized, open-label study, subjects who were currently receiving a boosted PI-containing HAART regimen without ATV were randomized in a 2:1 ratio to a HAART regimen in which the boosted PI was replaced by boosted ATV (referred to throughout as ATV/RTV), or to their current regimen without ATV (referred to throughout as PI/RTV). Subjects were to be treated and followed for 96 weeks on their assigned regimen. Background nucleoside reverse transcriptase inhibitors (NRTIs) had to remain unchanged through the 96-week study period, unless changes were required for reasons of poor tolerability or toxicity. Blood was drawn under fasting conditions for determination of biochemical parameters of fat distribution at baseline, Weeks 4 and 12, and every 12 weeks thereafter through Week 96. DEXA and computed tomography (CT) scans were performed at baseline, Weeks 24, 48 and 96.

NUMBER OF SUBJECTS (Planned and Analyzed):

Planned: 200 subjects**,** randomized in a 2:1 ratio to switch immediately to ATV/RTV (n = 133) (switch arm) or remain on their current regimen (n = 67) (control arm). Analyzed: 201 subjects were randomized, 131 to the ATV/RTV group and 70 to the PI/RTV group; 1 subject randomized to PI/RTV was not treated.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Eligible subjects were HIV-1 infected individuals who had received a HAART regimen containing 2 NRTIs and a boosted PI for at least 12 weeks immediately prior to screening. Subjects were to have a controlled virologic response (HIV RNA level < 400 c/mL by Roche Amplicor Ultrasensitive assay) at screening and were to have been stable for at least 6 months; could not have experienced confirmed virologic failure to more than 1 prior PI-containing regimen; and could not be on a non-nucleoside reverse transcriptase inhibitor (NNRTI). Subjects were required to have fat redistribution confirmed on physical examination and defined by the presence of lipohypertrophy with or without lipoatrophy. Subjects considered to have lipohypertrophy were to have a waist-to-hip ratio (WHR) > 0.90 and waist circumference (WC) > 88.2 cm for men, and WHR > 0.90 and WC > 75.3 cm for women.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: ATV 300 mg (2 x 150-mg capsules) once daily for 96 weeks. Batch numbers: 4K3120A; 6B16342; 7C32129.

RTV 100 mg (1 x 100 mg capsule) once daily for 96 weeks. Batch Numbers.: 25541VA; 27367VA; 5C02632; 5H00466; 6A21512; 7B25420

Previous background NRTIs were to be continued unchanged through the 96-week study period. All NRTIs were sourced locally and provided to the subjects by the Investigators.

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

Previous boosted PI-containing HAART regimen was continued unchanged though the 96-week study period. Previous background NRTIs were to be continued unchanged through the 96-week study period. All study medications were sourced locally and provided to the subjects by the Investigators.

CRITERIA FOR EVALUATION:

Efficacy: Efficacy endpoints were considered secondary objectives of this study. The efficacy endpoints included:

- The time to confirmed virologic rebound for subjects with HIV RNA levels < 400 c/mL at baseline in terms of a hazard ratio.

- The mean changes from baseline in CD4 cell count (count/mm^3).

Safety: Primary endpoint: mean change from baseline in trunk-to-limb fat ratio as measured by DEXA at Week 48 (also assessed at Week 96).

Secondary endpoints included:

- The mean change from baseline in trunk-to-limb fat ratio at Week 96.
- The mean percent change from baseline in physical signs of lipohypertrophy, as assessed by changes in visceral adipose tissue (VAT) area (cm^2) by CT scans and by changes in trunk fat (kg) by DEXA.
- The mean percent change from baseline in physical signs of lipoatrophy, as assessed objectively by changes in peripheral adipose tissue (ie, limb fat [kg]) by DEXA and by changes in subcutaneous adipose tissue (SAT) area by CT scans.
- The mean percent change from baseline in total body fat by DEXA and in total adipose tissue (TAT) area by CT scans.
- The mean percent changes from baseline in fasting total cholesterol, low-density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, non-HDL cholesterol, triglycerides and apolipoprotein B (mg/dL).
- The mean changes from baseline in fasting glucose (mg/dL), insulin (uU/mL), and HOMA-IR.
- The mean change from baseline in body weight (kg), body mass index (BMI, kg/m^2), WHR and WC (cm).
- The frequency and severity of adverse events, of laboratory abnormalities, and of discontinuations for adverse events.

Other: Exploratory endpoints: mean changes from baseline in fasting adipocytokines and hormones (adiponectin, leptin, resistin, TNF-alpha, IL-6, PAI-1, Hs-CRP, HbA1c and fibrinogen).

STATISTICAL CONSIDERATIONS:
A planned sample size of 200 subjects was to be randomized in a 2:1 ratio to switch immediately to ATV/RTV (n = 133) or to remain on their current RTV-boosted PI regimen (n = 67). The sample size provided at least 80% power to demonstrate a greater mean decrease from baseline in the Week 48 trunk-to-limb fat ratio in the ATV/RTV switch regimen as compared with the PI/RTV regimen assuming:

- A 2-sided 95% confidence interval (CI)
- A difference in the Week 48 trunk-to-limb fat ratio decrease from baseline of 0.2
- A standard deviation of 0.45 in the Week 48 trunk-to-limb fat ratio decrease from baseline
- The Week 24 trunk-to-limb fat ratio was carried forward (LOCF) for subjects without a Week 48 measurement (due to missed visits, discontinuation from study therapy or technical issues)

Cohorts consisted of enrolled, randomized and treated subjects as well as treated subjects with fat pairs, and treated subjects with adipose tissue pairs:

- Enrolled subjects were those who signed an informed consent form and were assigned a Patient Identification (PID) number
- Randomized subjects were enrolled subjects who received a treatment assignment from the randomization center
- Treated subjects were randomized subjects who received at least 1 dose of study therapy
- Subjects with fat pairs were those with paired DEXA fat measurements at baseline and at or before the analysis week

- Subjects with adipose tissue pairs were those with paired CT measurements at baseline and at or before the analysis week

Efficacy: All efficacy endpoints were assessed as secondary objectives in this study.

The difference in proportions of subjects with virologic rebound (defined as 2 consecutive on-treatment HIV RNA ≥ 400 c/mL or last on-treatment HIV RNA ≥ 400 c/mL followed by discontinuation) through the analysis week was estimated with its associated 95% CI based on normal approximation.

Time to virologic rebound through the analysis week was summarized using a Kaplan-Meier curve and life table by treatment regimen. Treatment regimens were compared using a hazard ratio (ATV/RTV: PI/RTV) and 95% CI based on a Cox proportional hazards model. The time of virologic rebound was based on the time of the first HIV RNA measurement defining the rebound. Subjects without virologic rebound were censored at the time of their last HIV RNA measurement.

Difference between treatment regimens in mean change from baseline at the analysis week in CD4 cell count was estimated with its associated 95% CI based on the t-distribution.

Safety: The primary endpoint was mean change from baseline in trunk-to-limb fat ratio at Week 48. The primary analysis compared the treatment regimens using the difference in mean change from baseline in trunk-to-limb fat ratio at Week 48 with a 95% CI and P-value based on a t-test, unless the assumption of normality was not supported by the data. The ATV/RTV regimen was considered to have statistically demonstrated a greater improvement in central adiposity as compared with PI/RTV if the upper confidence limit for the between group difference (ie, ATV/RTV - PI/RTV) in mean change from baseline in trunk-to-limb fat ratio was less than 0.

In case the assumption of normality was not supported by the data, median difference (Hodges-Lehmann) and its associated non-parametric 95% CI (Moses) and P-value based on a Wilcoxon's Signed Rank test were to be calculated. These non-parametric estimates were planned to be presented only if besides a normality issue, the non-parametric and parametric estimates led to different conclusions.

Deaths, serious adverse events, adverse events (all grades, Grade 2 to 4, Grade 3 to 4; all and related to study drug), AEs leading to treatment discontinuation, Center for Disease Control (CDC) Class C AIDS Events, lipodystrophy-related AEs and laboratory abnormalities (all grades, Grade 3 to 4) were tabulated.

Deaths and serious adverse events (SAEs) were tabulated for enrolled subjects. AEs were presented by system organ class and preferred term, both in descending order of frequency on the ATV/RTV regimen.

Percentage changes from baseline through the analysis week in non-ratio DEXA scan parameters (trunk, limb and total fat), in non-ratio CT scan parameters (VAT, SAT, TAT), in fasting lipids (total cholesterol, LDL cholesterol, HDL cholesterol, non-HDL cholesterol, triglycerides and apolipoprotein B), in weight and waist were summarized using LOCF and observed cases (OC). Percent changes were calculated on the log scale and then back transformed to the original scale. Changes from baseline through the analysis week in ratio CT scan parameters (VAT-to-SAT, VAT-to-TAT), in fasting metabolic parameters (glucose, insulin and HOMA-IR), in BMI and WHR, and in fasting adipocytokines and hormones (adiponectin, resistin, TNF-alpha, IL-6, PAI-1, Hs-CRP, HbA_{1c} and fibrinogen) also were summarized using LOCF and OC. For each parameter, the difference between treatment regimens in mean percent or mean changes at the analysis week was estimated and presented the same way as for the primary endpoint (with the only difference in fasting metabolic parameters, physical measurements and fasting adipocytokines and hormones, where in case of non-normality non-parametric results were presented - regardless of whether or not the non-parametric and parametric estimates led to different conclusions).

In case the assumption of normality was not supported by the data, differences in medians and its associated non-parametric 95% CI (Moses) were presented and P-value was based on a Wilcoxon's Signed Rank test. For DEXA, CT and lipid parameters, non-parametric estimates were only presented if besides a normality issue, the non-parametric and parametric estimates led to different conclusions.

In lipid analyses, values after a change in the use of serum lipid-reducing agents while on study drug were excluded.

Categories of fasting lipid parameters were tabulated at each scheduled visit, using observed values. Categories for cholesterol and triglycerides were defined according to National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines. Cholesterol ratios followed accepted conventions for management of dyslipidaemia and cardiovascular risk stratification based on epidemiologic data.

Laboratory abnormalities (all grades; Grade 3 to Grade 4) were tabulated by baseline status (all, normal, abnormal, missing). The laboratory value with the highest toxicity grade (for a respective analyte) in the treatment period was tabulated. Subjects with at least 1 laboratory value during the treatment period were included in tabulations. Grading categories for total cholesterol were defined using NCEP ATP III guidelines, while grading categories for albumin were defined using CTCAE. Values for other laboratory tests were graded using the modified World Health Organization (WHO) criteria. Grade 1 WHO abnormalities were reset to normal if the original (unconverted) value is between the lower and upper limits of normal.

Total bilirubin levels and changes from baseline also were summarized at each scheduled visit using observed values for the treatment period.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics: A total of 219 subjects were enrolled. Of these, 201 subjects were randomized, 131 to ATV/RTV and 70 to PI/RTV (Table 1). One subject randomized to the PI/RTV group did not receive treatment. A total of 174 subjects (114, 87% ATV/RTV; 60, 86% PI/RTV) completed the study. The proportions of subjects who discontinued the study prior to Week 96 and the reasons for discontinuation were similar between the treatment regimens: ATV/RTV: 12%; PI/RTV: 13%. The most common reasons for early discontinuation in both regimens were adverse event (4% ATV/RTV; 3% PI/RTV) and subject withdrew consent (2% ATV/RTV; 6% PI/RTV).

Table 1: Subject Disposition - Randomized Subjects

	NUMBER OF SUBJECTS (%)		
	TREATMENT REGIMEN		
	ATV/RTV N = 131	PI/ PI/RTV N = 70	TOTAL N = 201
RANDOMIZED	131	70	201
NEVER TREATED	0	1 (1)	1 (<1)
TREATED	131 (100)	69 (99)	200 (100)
DISCONTINUED PRIOR TO WEEK 96 VISIT	16 (12)	9 (13)	25 (12)
ADVERSE EVENT	5 (4)	2 (3)	7 (3)
LACK OF EFFICACY	2 (2)	0	2 (<1)
LOST TO FOLLOW-UP	3 (2)	1 (1)	4 (2)
OTHER[a]	1 (<1)	1 (1)	2 (<1)
POOR/NON-COMPLIANCE	1 (<1)	1 (1)	2 (<1)
SUBJECT NO LONGER MEETS STUDY CRITERIA	2 (2)	0	2 (<1)
SUBJECT WITHDREW CONSENT	2 (2)	4 (6)	6 (3)
DISCONTINUED ON OR AFTER WEEK 96 VISIT	1 (<1)	0	1 (<1)
ADVERSE EVENT	1 (<1)	0	1 (<1)
COMPLETED STUDY	114 (87)	60 (86)	174 (87)

[a] Includes the following reasons: subject had surgical treatment of abdominal fat accumulation, and anti-retroviral medications changed by the subject's physician.

Baseline demographic and disease characteristics were similar in the 2 treatment groups (Table 2). Overall, most subjects were male (76%) and white (63%); the median age was 43 years. Baseline central adiposity, physical measurements, and cardiovascular risks were comparable between the ATV/RTV and PI/RTV groups. Drug exposure prior to screening was similar for PIs, NRTIs and NNRTIs, and the proportion of subjects exposed to d4T also was comparable. Baseline median CD4 cell count was slightly higher in the ATV/RTV than in the PI/RTV groups: 470 cells/mm^3 and 437 cells/mm^3, respectively.

Table 2: Baseline Disease Characteristics - Treated Subjects

	ATV/RTV (N = 131)	PI/RTV (N = 69)	Total (N = 200)
Age: Median (Min, Max); years	43 (23, 79)	42 (26, 65)	43 (23, 79)
Male; n (%)	96 (73)	55 (80)	151 (76)
CDC Class C AIDS, n (%)	14 (11)	9 (13)	23 (12)
HIV RNA: < 400 c/mL; n, (%)	127 (97)	69 (100)	196 (98)
CD4: Median (Min, Max), cells/mm^3	470 (90, 1919)	437 (100, 1078)	459 (90, 1919)
Waist: Median (cm)	94	95	94
BMI: Median (kg/m^2)	25.9	25.7	25.9
Waist-to-hip ratio: Median (Min, Max)	0.99 (0.78, 1.23)	0.97 (0.90, 1.18)	0.98 (0.78, 1.23)
Weeks on Prior PI therapy: Mean (SE)	207.0 (11.53)	202.6 (15.30)	205.5 (9.19)
Weeks on Prior NRTI: Mean (SE)	286.2 (17.69)	251.8 (20.33)	274.3 (13.56)
Prior use of d4T: n (%)	54 (41)	33 (48)	87 (44)
NRTI regimen included d4T: n, (%)	12 (9)	9 (13)	22 (11)
Weeks on Prior NNRTI: Mean (SE)[a]	101.5 (13.7)	97.1 (15.8)	99.8 (10.3)

[a] A total of 71 subjects (36%) had prior use of NNRTI; 43 (33%) ATV/RTV and 28 (41%) PI/RTV.

BMI = body mass index; PI = protease inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transciptase inhibitor.

Percentages are based on subjects with measurements.

Efficacy Results:

Efficacy endpoints, including analyses of virologic rebound and CD4 cell count and changes from baseline were considered secondary objectives in this study.

Rates of virologic rebound (HIV RNA ≥ 400 c/mL) through Week 48 and through Week 96 were similar between the ATV/RTV and PI/RTV regimens (Table 3). Results were consistent when virologic rebound was defined as ≥ 50 c/mL.

Table 3: Summary of Virologic Rebounds - Treated Subjects with HIV RNA < 400 c/mL or < 50 c/mL at Baseline

Time Point	Number (%) of Subjects ATV/RTV (n = 131)	Number (%) of Subjects PI/RTV (n = 69)	Difference Estimate ATV/RTV - PI/RTV (95% CI: ATV/RTV, PI/RTV)
Week 48			
HIV RNA ≥ 400 c/mL	5/127 (4)	1/69 (1)	2.5% (-2.6%, 7.5%)
HIV RNA ≥ 50 c/mL	6/117 (5)	4/64 (6)	-1.1% (-8.1%, 5.8%)
Week 96			
HIV RNA ≥ 400 c/mL	7/127 (6)	4/69 (6)	-0.3% (-7.0%, 6.5%)
HIV RNA ≥ 50 c/mL	8/117 (7)	7/64 (11)	-4.1%(-12.5%, 4.3%)

CI = confidence interval

Time to virologic rebound (HIV RNA ≥ 400/50 c/mL) was comparable between the 2 regimens at both Weeks 48 and 96 (Table 4).

Table 4: Time to Virologic Rebound Hazard Ratio (ATV/RTV: PI/RTV) - Treated Subjects with HIV RNA < 400 c/mL or < 50 c/mL at Baseline

Time Point	Hazard Ratio ATV/RTV: PI/RTV (95% CI)
Week 48	
HIV RNA ≥ 400 c/mL	2.65 (0.31, 22.68)
HIV RNA ≥ 50 c/mL	0.80 (0.23, 2.83)
Week 96	
HIV RNA ≥ 400 c/mL	1.06 (0.30, 3.72)
HIV RNA ≥ 50 c/mL	0.53 (0.19, 1.51)

CI = confidence interval

The mean change from baseline in CD4 cell count at Week 48 was 14.5 cells/mm^3 for the ATV/RTV regimen and 44.0 cells/mm^3 for the PI/RTV regimen: difference estimate: -29.5, 95% CI: -75.1, 16.1, P = 0.20 (OC). The mean change from baseline in CD4 cell count at Week 96 (OC) was 2.8 cells/mm^3 for the ATV/RTV regimen and 81.8 cells/mm^3 for the PI/RTV regimen. Although there was a statistically significant difference between the regimens (difference estimate: -79.0, 95% CI: -134.2, -23.8, P = 0.005, OC), it was not considered clinically relevant. Furthermore, the mean CD4 cell count at Week 96 was similar in the 2 regimens: 545 vs 557 cells/mm^3, respectively. The difference in change from baseline in CD4 cell counts based on time-averaged difference was -31.3 cells/mm^3, 95% CI: -59.5, -3.0 for Week 48,

and -33.5 cells/mm^3, 95% CI: -62.1, -4.8 for Week 96; the upper CI limit for both analysis weeks was greater than -50 c/mm^3, which met the criteria for similarity. The time-averaged difference analysis was the planned analysis for CD4 cell count prior to Amendment 5 to the protocol.

Genotype-phenotype samples were collected during the study for subjects who experienced confirmed virologic rebound ≥ 400 c/mL and who had a sample > 500 c/mL. However, since no baseline resistance analysis could be performed (to be eligible for screening, HIV RNA had to be < 400 c/mL), no conclusion can be made on emergent vs. pre-existing substitutions.

Safety Results:
No statistically or clinically significant difference between the ATV/RTV and PI/RTV regimens was observed in the primary endpoint, the mean change from baseline at Week 48 in trunk-to-limb fat ratio (as assessed by DEXA scan) in treated subjects with fat pairs (LOCF): 0.02 for ATV/RTV; -0.02 for PI/RTV, difference estimate: 0.03; 95% CI: -0.06, 0.12, P = 0.48 (Table 5).

Mean changes from baseline at Week 96 in trunk-to-limb fat ratio in treated subjects with fat pairs (LOCF) also were small and were similar between the ATV/RTV and PI/RTV regimens, 0.04 and 0.02, respectively; difference estimate: 0.02; 95% CI: -0.10, 0.14, P = 0.73.

Table 5: Fat Mean Changes from Baseline at Week 48 and Week 96 - Treated Subjects with Fat Pairs (LOCF)

	ATV/RTV[a]		PI/RTV[b]			
Variable	**N**	**Point Estimate[c]**	**N**	**Point Estimate[c]**	**Difference Estimate ATV/RTV - PI/RTV 95% CI (ATV/RTV, PI/RTV)**	**P-Value**
Week 48						
Trunk Fat	112	2.6%	57	-1.8%	4.4% (-1.4%, 10.6%)	0.14
Limb Fat	112	0.9%	54	-3.6%	4.6% (-1.7%, 11.4%)	0.15
Total Body Fat	112	2.1%	54	-2.2%	5.0% (0.3%, 9.7%)	0.0385
Trunk-to-Limb Fat Ratio	**112**	**0.02**	**54**	**-0.02**	**0.03 (-0.06, 0.12)**	**0.48**
Week 96						
Trunk Fat	112	1.6%	57	-3.6%	5.3% (-1.7%, 12.9%)	0.14
Limb Fat	112	-0.8%	54	-6.1%	5.7% (-2.3%, 14.4%)	0.17
Total Body Fat	112	0.6%	54	-4.9%	5.9% (-1.0%, 13.2%)	0.10
Trunk-to-Limb Fat Ratio	**112**	**0.04**	**54**	**0.02**	**0.02 (-0.10, 0.14)**	**0.73**

Subjects with fat pairs are those with paired DEXA fat measurements at baseline and at or before the analysis time point.

[a] Baseline Values - mean (standard error): Trunk Fat: 12.0 kg (0.44); Limb Fat: 7.8 kg (0.37); Total Body Fat: 20.6 kg (0.76); Trunk-to-Limb Fat Ratio: 1.76 (0.079). Median baseline value for Total Body Fat: 20.7 kg.

[b] Baseline Values - mean (standard error): Trunk Fat: 12.0 kg (0.59); Limb Fat: 8.2 kg (0.66); Total Body Fat: 21.1 kg (1.18); Trunk-to-Limb Fat Ratio: 1.75 (0.101). Median baseline value for Total Body Fat: 18.7 kg.

[c] Point estimate presented is the Hodges-Lehmann estimate (based on median) for the total body fat at Week 48, and mean change for all other parameters.

At Week 48, there was no difference between treatment groups in mean percent change from baseline in trunk fat and limb fat. However, a statistically significant difference between treatment regimens in favor of the PI/RTV regimen in mean percent change from baseline in total body fat was observed: 2.2% decrease for PI/RTV vs 2.1% increase for ATV/RTV (P = 0.04). The 2.2% mean decrease from baseline in total body fat in the PI/RTV group was associated with a mean 1.8% decrease from baseline in trunk fat and a mean 3.6% decrease from baseline in limb fat.

At Week 96, there were no differences between the 2 treatment regimens in any of the DEXA parameters. In the PI/RTV group, clinically relevant decreases in trunk fat (-0.3 kg), limb fat (-0.4 kg) and total body fat (-0.7 kg) were seen.

A post-hoc analysis showed that the percentage of subjects who had a decrease of at least 20% in limb fat was 10% in the ATV/RTV and 17% in the PI/RTV arms at Week 48, and 12% and 24%, respectively at Week 96.

No statistically significant differences in mean (percent) change from baseline in VAT, SAT, TAT, VAT-to-TAT ratio, and VAT-to-SAT ratio as assessed by CT scan were observed between the ATV/RTV and PI/RTV regimens at Week 48 or at Week 96 in treated subjects with adipose tissue pairs.

In both arms at Week 96, there was a slight decrease in SAT and a slight increase in VAT, suggesting that the TAT decrease was mainly driven by the mean percent decrease in SAT. However, the values were minimal and not clinically relevant in the ATV/RTV arm.

No clinically relevant differences in mean change from baseline in physical measurements, as assessed by body weight, body mass index, waist-to-hip ratio and waist circumference were observed between the ATV/RTV and PI/RTV regimens at Week 48 or Week 96.

The incidence of lipodystrophy-related AEs was low during the study in both treatment groups (< 1% for PI/RTV vs 4% for ATV/RTV). Acquired lipodystrophy (< 1% ATV/RTV; 3% PI/RTV) was the most frequently reported lipodystrophy-related AE.

Deaths and Adverse Events: No new or unexpected safety events were observed during the study. AEs were not treatment limiting in most cases. No deaths occurred either during the study or within 30 days of the last dose of study medication. One subject in the PI/RTV group discontinued the study because of a Grade 4, non-related squamous cell carcinoma and later died, 9 months after receiving his last dose study medication.

SAEs were reported in 8% and 7% of subjects on the ATV/RTV and PI/RTV regimens, respectively (Table 6). Most SAEs were already observed at Week 48. With the exception of hyperbilirubinemia (2%) in the ATV/RTV group, individual SAEs occurred with an incidence of ≤ 1%. Few SAEs were considered drug-related (5 probable/certain for 3 subjects for ATV/RTV; 2 probable for 1 subject for PI/RTV).

The incidence of AEs leading to discontinuation of study therapy was low (≤ 5%) in subjects on either regimen. More subjects on ATV/RTV than on PI/RTV discontinued due to jaundice/hyperbilirubinemia (3% vs 0%). Among the subjects who discontinued due to AEs, all but 2 subjects (in the ATV/RTV group) discontinued by the Week 48 analysis.

Overall, the incidence of all grades of AEs through Week 96 was high: 90% in the ATV/RTV and 83% in the PI/RTV arms (Table 6). Hyperbilirubinemia (including blood bilirubin increased, blood bilirubin abnormal, blood bilirubin unconjugated, and blood bilirubin unconjugated increased) and jaundice were more common in subjects on ATV/RTV than on PI/RTV: hyperbilirubinemia, 38% vs 4%; jaundice: 27% vs 0%. Bronchitis (11% vs 6%), influenza (8% vs 1%), pharyngitis (5% vs 0%), and ALT increased (5% vs 0%) also were more common in the ATV/RTV than in the PI/RTV group. Hypertriglyceridemia was less common in the ATV/RTV than in the PI/RTV group: 10% vs 19%, respectively. Most AEs were already observed through Week 48.

Through Week 96, related Grade 2 to Grade 4 events were reported in 47% and 17% of subjects in the ATV/RTV and PI/RTV regimens, respectively. Most of the individual Grade 2 to Grade 4 related AEs were

reported by ≤ 2% of subjects. Individual related Grade 2 to Grade 4 AEs that occurred with a higher frequency (≥ 5% difference) with the ATV/RTV than with the PI/RTV regimen were: hyperbilirubinemia (31% vs 0%), jaundice (6% vs 0%), and blood bilirubin increased (6% vs 1%). Most Grade 2 to Grade 4 events reported through Week 96 were already reported by Week 48.

Table 6: Summary of Adverse Events of Clinical Interest Through Week 96- Treated Subjects

	Number of Subjects (%)	
	ATV/RTV N = 131	**PI/RTV N = 69**
Death	0	0[a]
SAE	11 (8)	5 (7)
Adverse event leading to discontinuation	6 (5)	2 (3)
Hyperbilirubinemia	3 (2)	0
Jaundice	1 (<1)	0
Stevens Johnson Syndrome	1 (<1)	0
Drug abuse	1 (<1)	0
Renal impairment	1 (<1)	0
Hypertriglyceridemia	0	1 (1)
Squamous cell carcinoma	0	1 (1)
Any adverse events (all grades) through Week 96	118 (90)	57 (83)
Hyperbilirubinemia, jaundice, or ocular icterus	61 (47)	3 (4)
Hyperbilirubinemia[b]	50 (38)	3 (4)
Jaundice	36 (27)	0
Ocular icterus	2 (2)	0
Gastrointestinal disorders	29 (22)	16 (23)
Diarrhea	10 (8)	5 (7)
Abdominal pain	6 (5)	1 (1)
Nausea	4 (3)	2 (3)
Vomiting	2 (2)	1 (1)
Infections and Infestations	56 (43)	23 (33)
Bronchitis	14 (11)	4 (6)
Influenza	10 (8)	1 (1)
Pharyngitis	7 (5)	0
Metabolism and nutrition disorders	21 (16)	21 (30)
Hypertriglyceridemia	13 (10)	13 (19)
Hypercholesterolemia	4 (3)	2 (3)
Hyperlipidemia	2 (2)	0
Hyperglycemia	1 (<1)	2 (3)
Investigations	24 (18)	8 (12)
Alanine aminotransferase increased	6 (5)	0
Aspartate aminotransferase increased	2 (2)	0

Table 6: Summary of Adverse Events of Clinical Interest Through Week 96- Treated Subjects

	Number of Subjects (%)	
	ATV/RTV N = 131	**PI/RTV N = 69**
Skin and subcutaneous tissue disorders	18 (14)	11 (16)
Lipodystrophy acquired	1 (<1)	2 (3)
Lipoatrophy	0	1 (1)

[a] One subject ([redacted]) in the PI/RTV group died 9 months after the last dose of study drug.
Hyperbilirubinemia also includes blood bilirubin increased, blood bilirubin abnormal, blood bilirubin unconjugated and blood bilirubin unconjugated increased from the INVESTIGATIONS system organ class.

Laboratory Test Results:

Liver Function Tests: Abnormal liver function test results were common in the study, and occurred with similar frequency in the ATV/RTV and PI/RTV groups through both Week 48 and Week 96. As expected, through Week 96, the incidence of abnormal total bilirubin levels was higher in the ATV/RTV than in the PI/RTV group for both Grade 1 to Grade 4 abnormalities (95% vs 21%, respectively) and for Grade 3 to Grade 4 abnormalities (60% vs 0%, respectively). Grade 4 bilirubin levels were reported in 17% and 0% of subjects in the ATV/RTV and PI/RTV regimens, respectively. The incidence of liver function test abnormalities through Week 96 was consistent for that reported through Week 48.

Fasting Lipids: In the ATV/RTV regimen, clinically significant decreases from baseline in all atherogenic lipids were observed at Week 48 and at Week 96 for treated subjects. Mean percent decreases from baseline were significantly greater ($P < 0.01$) for the ATV/RTV regimen than for the PI/RTV regimen for total cholesterol, non-HDL cholesterol and apolipoprotein B at both Weeks 48 and 96 (Table 7).

Fewer ATV/RTV than PI/RTV subjects shifted into higher NCEP categories from baseline to Week 96 for total cholesterol (9% vs 18%), LDL cholesterol (12% vs 37%) and triglycerides (5% vs 13%). Similar results were seen at Week 48. In the ATV/RTV group, the proportion of subjects who had the worst NCEP category in total-to-HDL cholesterol ratio (ratio > 5) decreased from a baseline of 40% to 26% by Week 4, and this was maintained through Week 96. No clear trend in the PI/RTV group was observed.

No clinically significant differences between the ATV/RTV and PI/RTV regimens were observed for mean change from baseline in glucose, insulin level or HOMA-IR at Week 48 or at Week 96 in treated subjects.

Table 7: Fasting Lipid Mean Percent Changes from Baseline at Week 96 - Treated Subjects

Lipid	ATV/RTV (N = 122) Point Estimate	PI/RTV (N = 57) Point Estimate	Difference Estimate ATV/RTV - PI/RTV (95% CI)	P-Value
Week 48				
Total cholesterol	-13.0%	-1.0%	-12.1% (-16.3%, -7.6%)	<0.0001
HDL cholesterol	-6.2%	-2.6%	-3.7% (-9.4%, 2.4%)	0.22
Non-HDL cholesterol	-14.8%	-0.6%	-14.3% (-19.4%, -8.7%)	<0.0001
LDL cholesterol[a]	-10.4%	2.6%	-12.6% (-20.9%, -3.4%)	0.0086
Triglycerides	-23.8%	-11.7%	-13.7% (-25.1%, -0.6%)	0.0411
Apolipoprotein B	-7.6%	1.1%	-8.6% (-14.2%, -2.6%)	0.0061
Week 96				
Total cholesterol	-12.5%	-0.1%	-12.4% (-16.9%, -7.6%)	<0.0001
HDL cholesterol	-6.8%	-4.6%	-2.4% (-8.6%, 4.3%)	0.48
Non-HDL cholesterol	-14.0%	1.2%	-15.0% (-20.6%, -9.1%)	<0.0001
LDL cholesterol [a]	-8.4%	3.6%	-11.6% (-20.2%, -2.2%)	0.0171
Triglycerides	-25.0%	-12.2%	-14.7% (-26.5%, 0.9%)	0.0381
Apolipoprotein B	-8.3%	8.3%	-15.3% (-21.6%, -8.5%)	<0.0001

[a] N = 56 for LDL cholesterol in the PI/RTV group.

Mean (standard error) baseline values for ATV/RTV and PI/RTV, respectively: 220 (5.2) and 212 (6.4) mg/dL for total cholesterol; 48 (1.1) and 47 (1.9) mg/dL for HDL cholesterol; 119 (3.8) and 108 (4.3) mg/dL for LDL cholesterol; 285 (23.7) and 325 (34.5) mg/dL for triglycerides; 172 (5.1) and 165 (6.4) mg/dL for non-HDL cholesterol; and 97 (2.5) and 94 (2.9) mg/dL for Apolipoprotein B.

Results of the analysis of the exploratory endpoints showed that no statistically significant differences between the two regimens were observed in the change from baseline for fasting adiponectin, resistin, TNF-alpha, interleukin-6, PAI-1, hs-CRP and fibrinogen.

CONCLUSIONS:

- At Week 48 of the study, no statistically significant difference was observed in central adiposity, as assessed by the primary endpoint, change from baseline in trunk-to-limb ratio (by DEXA scan), between those HIV-infected subjects with lipohypertrophy who switched to an ATV/RTV containing regimen and those who remained on their current boosted PI regimen. Week 96 results confirmed those seen at Week 48.
- No statistically significant differences between regimens were seen for changes in physical signs of lipoatrophy at either Week 48 or Week 96, as assessed by changes in limb fat by DEXA scan and in subcutaneous adipose tissue by CT scans. However, in a post-hoc analysis, at Week 96,

more subjects in the PI/RTV than in the ATV/RTV arm had a decrease from baseline of at least 20% in limb fat.

- The regimens were comparable for changes in total body fat by DEXA scan and total adipose tissue area by CT scan after 48 weeks and after 96 weeks of study therapy.
- In the ATV/RTV regimen, there was a clinically significant decrease from baseline to Week 48 and to Week 96 in all atherogenic lipids. Statistically, significant differences between regimens in favor of ATV/RTV were observed for mean percent change from baseline in total cholesterol, LDL cholesterol (Week 48 only), non-HDL cholesterol, and apolipoprotein B.
- Mean changes from baseline in fasting glucose, insulin, and HOMA-IR were minor on both regimens at Week 48 and Week 96.
- The regimens were comparable at Week 48 and Week 96 for changes in physical measurements as assessed by body weight, body mass index, waist-to-hip ratio and waist circumference.
- No new or unexpected safety events were reported. Discontinuation rates were similar for the regimens. Adverse events were not treatment limiting in most cases. Bilirubin-associated disorders (hyperbilirubinemia and jaundice) were more common (all grades) in subjects on ATV/RTV than on the PI/RTV regimen. Consistently, the incidence of abnormal blood bilirubin was higher on ATV/RTV than for PI/RTV for all grades. Abnormal liver function test results were common in the study, and occurred with similar frequency in the two groups through both Week 48 and Week 96.
- A switch from a PI-boosted regimen to ATV/RTV maintained virologic suppression through Week 96. No statistically significant difference between regimens was observed for rates of virologic rebound ($\geq$ 400 c/mL or $\geq$ 50 c/ml) through Week 48 and Week 96, or in time to virologic rebound at Week 48 and Week 96.
- No clinically relevant differences between the ATV/RTV and PI/RTV regimens in mean change from baseline in CD4 cell count were observed at Week 48 or at Week 96.
- No clinically significant differences between the two regimens were observed in the change from baseline at either Week 48 or Week 96 for fasting adiponectin, resistin, TNF-alpha, interleukin-6, PAI-1, hs-CRP and fibrinogen.

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