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 AI424376

TITLE OF STUDY: A Multicenter, Randomized, Open-Label, Active-Controlled Pilot Study to Evaluate the Safety and Antiretroviral Activity of Unboosted Atazanavir BID Plus Raltegravir BID and Boosted Atazanavir QD in Combination with Tenofovir/Emtricitabine QD in Treatment Naive HIV-Infected Subjects

INVESTIGATORS/STUDY CENTERS: 17 sites in 3 countries

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 17-Nov-2008 **CLINICAL PHASE:** 2b

Study Completion Date: 06-May-2010

OBJECTIVES: The primary objective of this study was to determine the proportion of subjects with human immunodeficiency virus (HIV) ribonucleic acid (RNA) < 50 c/mL at Week 24 in HIV-1 infected treatment-naive subjects.

The secondary objectives of this study were:

- To determine the proportion of subjects with non-response at Week 8
- To determine the proportions of subjects with HIV RNA < 50 c/mL at Weeks 48 and 96
- To determine the proportions of subjects with HIV RNA < 400 c/mL at Weeks 24, 48, and 96
- To determine the antiretroviral activity at Weeks 24, 48, and 96 as measured by:
  - Change from baseline in CD4 (cluster of differentiation 4) cell counts
  - Emergence of genotypic substitutions and phenotypic resistance among subjects with virologic failure (HIV RNA ≤ 400 c/mL)
- To assess safety through Weeks 24, 48, and 96
  - Frequency of adverse events (AEs), serious adverse events (SAEs), discontinuations, deaths, and laboratory abnormalities
  - Changes from baseline in select laboratory test results (eg, total bilirubin, fasting lipids)
  - QRS widening, QT, and PR prolongation from electrocardiograms (ECGs) through Weeks 24, 48, and 96
- Assessment of Pharmacokinetics:
  - To estimate the population mean inhibitory quotient for atazanavir (ATV) co-administered with raltegravir (RAL) in Group 1, and for ATV boosted with ritonavir (RTV) in Group 2,

based on trough concentration and historical population mean protein-binding corrected 90% effective concentration (EC90)

- To explore correlations between trough concentrations of ATV and RAL (Group 1) and boosted ATV (Group 2) over time with efficacy and safety parameters
- To characterize the pharmacokinetic (PK) profile of ATV and RAL co-administered in a subgroup of subjects in Group 1 (area under the curve [AUC], plasma trough level [Cmin], maximum plasma concentration [Cmax])
- To estimate the individual inhibitory quotient for ATV co-administered with RAL in a subgroup of subjects in Group 1 undergoing intensive PK assessment based on trough concentrations and protein binding corrected EC_{90} at baseline
- To estimate the ATV PK when ATV was co-administered with RAL twice daily (BID) in a subgroup of subjects in Group 1 undergoing intensive PK assessment relative to when it is co-administered with RTV + tenofovir (TDF) / emtricitabine (FTC) once daily (QD) (historical control).

METHODOLOGY: This study was planned to be a 96-week, open-label, randomized, multicenter study designed to evaluate the antiviral activity of ATV+RAL and ATV+RTV plus TDF/FTC in HIV-1 infected subjects who were antiretroviral treatment-naive and who were genotypically sensitive to each component of the study regimen. Randomization was stratified by qualifying HIV RNA < 100,000 and ≥ 100,000 c/mL.

Note: After careful review of the data through Week 24, Bristol-Myers Squibb Company (BMS) and Merck jointly decided to close Study AI424376. The primary endpoint of the study had been reached, and even though efficacy of the investigational regimen of ATV 300 mg BID and RAL 400 mg BID appeared to be comparable to current standard of care for treatment-naïve subjects in this study, the overall profile of this investigational regimen did not appear to be optimal for further clinical development given its BID nature, the development of resistance to RAL, and higher rates of hyperbilirubinemia with ATV BID compared with ATV/RTV.

NUMBER OF SUBJECTS (Planned and Analyzed): Planned: 90 subjects. Analyzed: 94 randomized subjects; 93 treated subjects were evaluated for safety and efficacy.

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 300 mg capsule batch numbers: 8H32003, 9D53384, 9L47785. RAL 400 mg tablet batch numbers: 8J42679, 9B53919, and 9G46991.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: ATV 300 mg capsule batch numbers: 8H32003, 9D53384, 9D53384, 9L47785, RTV 100 mg capsule batch numbers: 9H42853, 8J37263, 8H31025, 9F46429, 8G43030. TDF/FTC 300/200 mg tablet batch numbers: 9L47796, 8H31932, and 9D52065.

CRITERIA FOR EVALUATION:

Efficacy: The primary efficacy endpoint was the proportion of subjects with HIV RNA < 50 c/mL at Week 24.

The secondary efficacy endpoints included the following:

- The proportion of subjects with non-response at Week 8
- The proportions of subjects with HIV RNA < 50 c/mL at Weeks 48 and 96
- The proportions of subjects with HIV RNA < 400 c/mL at Weeks 24, 48, and 96

- The antiretroviral activity at Weeks 24, 48, and 96 as measured by:
  - Change from baseline in CD4 cell counts
  - Emergence of genotypic substitutions and phenotypic resistance among subjects with virologic failure (HIV RNA ≥ 400 c/mL).

Safety: Safety endpoints through Weeks 24, 48, and 96 included the following:

- Frequency of AEs, SAEs, discontinuations due to AEs, deaths, and laboratory abnormalities
- Changes from baseline in select laboratory test results (eg, total bilirubin, fasting lipids)
- QRS widening, QT, and PR prolongation from ECGs through Weeks 24, 48, and 96.

Pharmacokinetics: An intensive PK assessment was conducted in a subset of subjects who received ATV/RAL 300/400 mg BID (Group 1). Serial blood samples were collected over a 12-hour period after the morning dose at Week 2 in order to assess the steady state plasma PK of ATV and RAL. Pharmacokinetic parameters were derived from plasma concentration versus time data. The PK parameters assessed for ATV and RAL included:

Cmax	Maximum observed concentration at Week 2
Tmax	Time of maximum observed concentration at Week 2
Cmin	Trough plasma concentration at 12 h post observed morning dose at Week 2
C0	Trough plasma concentration pre-morning dose
AUC(0-12h)	Area under the concentration-time curve, in 1 dosing interval from time zero to 12 hours post observed morning dose at Week 2
AUC(0-24h)	Area under the concentration-time curve to be estimated by multiplying AUC(0-12h) at Week 2 by 2
IQ	defined as Cmin at Week 2/Protein Binding Adjusted EC_{90} values for ATV derived from individual subject clinical isolates.

Trough plasma samples were collected before study drug administration at Weeks 2, 4, 8, 16, 24, and 48 in all available subjects for analysis of ATV and RAL (Group 1) and ATV and RTV (Group 2). These samples were collected approximately 12 hours after the last PM dose for Group 1: ATV and RAL (acceptable window: 10 - 14 hours) and approximately 24 hours after the last dose for Group 2: ATV and RTV (acceptable window: 20 - 28 hours).

STATISTICAL CONSIDERATIONS:

This was an estimation study. Sample size calculation was not based on power. A sample size of 90 randomized subjects (60 on ATV+RAL and 30 on ATV+RTV+TDF/FTC) provided the following exact binomial 95% confidence intervals (CIs) for various observed response rates (HIV RNA < 50 c/mL) at Week 24 (Table 1).

Table 1: Exact 95% Confidence Intervals for Observed Response Rates

Observed Response Rate	ATV+RAL n = 60	ATV+RTV n = 30
90%	(79%, 96%)	(73%, 98%)
85%	(73%, 93%)	(65%, 94%)
80%	(68%, 89%)	(61%, 92%)
75%	(62%, 85%)	(54%, 88%)
70%	(57%, 81%)	(51%, 85%)

Efficacy: The primary efficacy endpoint, the proportion of subjects with HIV RNA < 50 c/mL at Week 24, was assessed with different algorithms and cohorts of treated subjects. Response rates were tabulated by treatment regimen with exact binomial 95% CIs. The principal analysis was based on the Confirmed Virologic Response (CVR) Non-Completer = Failure (NC = F) definition of response. Supportive analyses used the CVR (NC = M) and Virologic Response - Observed Cases (VR-OC) definitions of response.

- Principal analysis utilized CVR, which is a modified intent-to-treat (mITT) method based on all treated subjects. Responders at Week 24 were subjects who achieved and maintained a confirmed response (2 consecutive on-treatment HIV RNA < 50 c/mL values) through Week 24 without intervening virologic rebound or discontinuation; or subjects who achieved resuppression (ie, a confirmed response after virologic rebound) at Week 24. Virologic rebound was defined as confirmed on-treatment HIV RNA ≥ 50 c/mL or last on-treatment HIV RNA ≥ 50 c/mL followed by discontinuation of study therapy. Non-completers (ie, those who discontinued prior to obtaining Week 24 HIV RNA) were considered failures. The supportive analysis, CVR (NC = M), excluded subjects who discontinued prior to obtaining Week 24 HIV RNA measurements.
- VR-OC was an on-treatment method based on treated subjects. It classified subjects as responders according to a single on-treatment HIV RNA measurement < 50 c/mL closest to the planned Week 24 visit and within a pre-defined visit window. The denominator was based on subjects with an on-treatment Week 24 HIV RNA measurement. Subjects with HIV RNA ≥ 50 c/mL were considered failures in this analysis.

The proportions of subjects with HIV RNA < 50 c/mL and < 400 c/mL at Week 36 were assessed analogously to the primary efficacy endpoint. Week 36 was the minimum time on study therapy for all subjects who discontinued due to BMS termination of the study. It was the furthest time point that CVR (NC=F) method was still valid. The proportions of subjects with HIV RNA < 50 c/mL and < 400 c/mL at Week 48 were assessed using VR-OC. Only subjects who were still on treatment at Week 48 were included in this analysis.

Changes from baseline in CD4 cell counts and log10 HIV RNA changes were summarized at each scheduled visit. Genotypic and phenotypic resistance profiles were tabulated for subjects who met the criteria for resistance testing.

Safety: Safety analyses tabulated the frequency of AEs (Grade 1-4, Grade 2 -4, Grade 3-4; related and regardless of relationship to study therapy), AEs leading to discontinuation, and laboratory abnormalities (Grade 1-4, Grade 3-4) for treated subjects. Deaths and SAEs were tabulated for enrolled subjects without regard to time of onset.

Fasting lipid values, changes from baseline, and percent changes from baseline were summarized over time for treated subjects using observed values and last observation carried forward (LOCF). Categories of fasting lipid parameters were also tabulated according to National Cholesterol Education Program Adult

Treatment Panel (ATP) III guidelines, and accepted conventions for management of dyslipidemia and cardiovascular risk stratification based on epidemiologic data. Values were excluded after the start of serum lipid-reducing agents.

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

Pharmacokinetics: Actual sample collection times were used for PK data analyses, and nominal sample collection times were used for generation of mean concentration-time tables and plots. All available concentration-time data from subjects who received any study medication were reported. All available derived PK parameter values were included in the PK data set and reported, but only subjects with adequate PK profiles were included in the summary statistics and statistical analysis.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics: A total of 94 HIV-infected, treatment-naive subjects were randomized (Table 2). All but 1 of the 94 randomized subjects (all 63 subjects randomized to ATV+RAL and 30 of 31 subjects randomized to ATV+RTV+TDF/FTC) were treated with ≥ 1 doses of study drug. One subject randomized to ATV+RTV+TDF/FTC withdrew consent before treatment.

As described above, the study was prematurely stopped by the sponsors. The efficacy endpoint had been met; however, the overall experimental dosing regimen was not considered optimal to support further clinical development in this subject population. Therefore, the remaining study subjects were all discontinued on or after the Week 36 visit, with the most common reason being "BMS termination/administrative reason by sponsor."

Table 2: Subject Disposition

	Number of Subjects (%)	
	ATV+RAL	**ATV+RTV+TDF/FTC**
Subject Disposition		
Randomized	63	31
Treated	63	30[a]
Discontinued	63 (100)	30 (100)
Prior to Week 24	4 (6.3)	3 (10.0)
AE	3 (4.8)	0
Withdrew consent	1 (1.6)	0
Lost to follow-up	0	1 (3.3)
No longer meet study criteria	0	2 (6.7)[b]
On or after Week 24 and prior to Week 36	8 (12.7)	0
AE	1 (1.6)	0
Lack of efficacy	6 (9.5)	0
Withdrew consent	1 (1.6)	0
On or after Week 36	51 (81.0)	27 (90.0)
Lack of efficacy	1 (1.6)	0
AE	0	1 (3.3)
Lost to follow-up	1 (1.6)	0
Poor compliance	1 (1.6)	0
No longer meet study criteria	1 (1.6)	0
Didn't come to termination visit	2 (3.2)	0

[a] One subject randomized to ATV+RTV+TDF/FTC withdrew consent before treatment.

[b] Two subjects on ATV+RTV+TDF/FTC who met the screening exclusion criteria for QRS prolongation > 120msecs were discontinued from the study.

Baseline demographic characteristics of all treated subjects were consistent between regimens (Table 3). Approximately 90% of subjects treated in this study were male, and the median age was 40 years.

Table 3: Baseline and Demographic Characteristics

	Number of Subjects (%)	
	ATV+RAL N=63	**ATV+RTV+TDF/FTC N=30**
Age (median)	40.0	40.5
Male (%)	55 (87.3)	28 (93.3)
Race		
White	54 (85.7)	23 (76.7)
Black/African American	8 (12.7)	6 (20.0)
Asian	0	1 (3.3)
Other	1 (1.6)	0
Baseline HIV RNA subtype B	54 (85.7)	23 (76.7)
Baseline HIV RNA $\log_{10}$ c/mL, mean (SE)	4.9 (0.07)	4.9 (0.12)
Baseline CD4 cells/mm^3, mean (SE)	256 (14.7)	261 (24.6)

Efficacy Results: An interim analysis was conducted to assess the non-response rate in the ATV+RAL group at Week 8. The non-response rates were 0% in the ATV+RAL group and 5% in the control group. Therefore, the stopping rule was not met, and the external review committee recommended that the study continue per the protocol. Efficacy results are summarized in Table 4.

Table 4: Efficacy Results

	Number of Subjects (%)	
	ATV+RAL	**ATV+RTV+TDF/FTC**
Efficacy at Week 24 n/N (%), 95% binomial exact CI (%)		
HIV RNA < 50 c/mL		
CVR (NC=F)	47/63 (74.6) (62.1, 84.7)	19/30 (63.3) 43.9, 80.1)
CVR (NC=M)	47/58 (81.0) (68.6, 90.1)	19/27 (70.4) (49.8, 86.2)
VR-OC	41/52 (78.8)[a] (65.3, 88.9)	19/25 (76.0)[b] (54.9, 90.6)
HIV RNA < 400 c/mL		
CVR (NC=F)	52/63 (82.5) (70.9, 90.9)	26/30 (86.7) (69.3, 96.2)
CVR (NC=M)	52/58 (89.7) (78.8, 96.1)	26/27 (96.3) (81.0, 99.9)
VR-OC	46/52 (88.5)[a] (76.6, 95.6)	24/25 (96.0)[b] (79.6, 99.9)
Mean CD4 change from baseline at Week 24 (SE)	166.0 (16.954)	127.0 (17.788)
Efficacy at Week 36 n/N (%), 95% binomial exact CI (%)		
HIV RNA < 50 c/mL		
CVR (NC=F)	43/63 (68.3) (55.3, 79.4)	22/30 (73.3) (54.1, 87.7)
CVR (NC=M)	43/51 (84.3) (71.4, 93.0)	22/27 (81.5) (61.9, 93.7)
VR-OC	42/51 (82.4) (69.1, 91.6)	19/25 (76.0) (54.9, 90.6)
HIV RNA < 400 c/mL		
CVR (NC=F)	51/63 (81.0) (69.1, 89.8)	27/30 (90.0) (73.5, 97.9)
CVR (NC=M)	51/51 (100) (93.0, 100)	27/27 (100) (87.2, 100)
VR-OC	51/51 (100) (93.0, 100)	24/25 (96.0) (79.6, 99.9)
Mean CD4 change from baseline at Week 36 (SE)	200.4 (15.950)	179.3 (23.888)

[a] Six subjects on ATV+RAL had no HIV RNA measurement within the Week 24 visit window. Five of them had HIV RNA values before and after Week 24, both < 50 c/mL. The other subject had HIV RNA values before and after Week 24, both < 400 c/mL but > 50 c/mL.

[b] Two subject on ATV+RTV+TDF/FTC had no HIV RNA measurement within Week 24 visit window. One of them had HIV RNA values before and after Week 24, both < 50 c/mL. The other subject had HIV RNA values before Week 24 < 50 c/mL and after Week 24 < 400 c/mL but > 50 c/mL.

Resistance: Through Week 24, 11 subjects on ATV+RAL vs. 8 on ATV+RTV+TDF/FTC were considered virologic failures per CVR treatment outcomes (never suppressed [confirmed HIV RNA < 50 c/mL] through Week 24 and on study at Week 24 or rebound to HIV RNA ≥ 50 c/mL without resuppression).

Ten of 11 virologic failures on ATV+RAL had baseline viral load > 100,000 c/mL. Six of 11 virologic failures on ATV+RAL had a baseline viral load > 250,000 c/mL, vs. 4 of 8 on ATV+RTV+TDF/FTC. Five of 11 virologic failures on ATV+RAL were rebounders (HIV RNA > 50 c/mL), and 6 of 11 never suppressed through Week 24. Six of 11 subjects with CVR virologic failures and 1 additional subject on ATV+RAL vs. 1 of 8 on ATV+RTV+TDF/FTC met criteria for resistance testing through Week 24. One of 7 subjects on ATV+RAL met criteria number 2 above for resistance testing because of a value at Week 6 with a wild type genotype; however, the subject resuppressed at the discontinuation visit at Week 12 and was not a CVR virologic failures at Week 24. The remaining 6 virologic failures who met criteria for resistance testing in the ATV+RAL group and 1 in the ATV+RTV+TDF/FTC group were evaluated through Week 24. In the ATV+RAL group, 4 of 6 subjects developed both RAL resistance-associated mutations (RAM) and had phenotypic resistance to RAL. One of 6 subjects had phenotypic resistance to RAL (biological cut-off > 1.5) without any genotypic evidence of RAL RAM at Week 24. One of 6 subjects did not have any RAL RAM. No subjects developed ATV resistance in the ATV+RAL group.

None of the subjects on ATV+RAL who met criteria for resistance testing or developed genotypic and/or phenotypic resistance to RAL had baseline genotypic or phenotypic resistance to any study medications.

In the ATV+RTV+TDF/FTC group, 1 of 8 subjects met criteria for resistance testing and no resistance was demonstrated to ATV/R or NRTIs. None of the subjects on ATV+RTV+TDF/FTC who met criteria for resistance testing had baseline genotypic or phenotypic resistance to any study medications.

After Week 24, 5 subjects in the ATV+RAL group and 1 subject on ATV+RTV+TDF/FTC met criteria for resistance testing. After the Week 24 primary analysis, no new subjects developed any further genotypic and/or phenotypic resistance to RAL. No subjects in either group developed ATV genotypic or phenotypic resistance throughout the study.

One subject at Week 32 was reported originally to have a major substitution (N155N/H mixture) to RAL at Week 32 but remained phenotypically sensitive to RAL. Subsequently, after further analysis, the contract reference laboratory changed the report to read "No RAL mutations detected." This subject resuppressed (HIV RNA <50 c/mL) at his discontinuation visit (Week 39).

Safety Results: There were no new or unexpected safety events. Adverse events were not treatment limiting in most cases. No subject died during the study (Table 5). The most common AEs were infections and infestations (65% and 63% on the ATV+RAL and ATV+RTV+TDF/FTC regimens, respectively), gastrointestinal disorders (38% and 47%), skin and subcutaneous tissue disorders (37% and 30%), and respiratory, thoracic and mediastinal disorders (29% and 37%).

The incidence of Grade 2-4 treatment-related AEs was 33% in each treatment group. Grade 2-4 treatment-related AEs that occurred with a higher frequency (≥ 5% difference) in the ATV+RAL group than in the ATV+RTV+TDF/FTC group were increased blood bilirubin (18% vs. 10%) and jaundice (8% vs. 0%). The only Grade 2-4 treatment-related AE that occurred with a lower frequency (≥ 5% difference) in the ATV+RAL group than in the ATV+RTV+TDF/FTC group was diarrhea (0% vs. 7%).

The overall incidence of Grade 3-4 AEs was 29% in the ATV+RAL group and 30% in the ATV+RTV+TDF/FTC group. The incidence of treatment-related Grade 3-4 AEs was 21% in the ATV+RAL group and 20% in the ATV+RTV+TDF/FTC group.

Table 5: Overall Summary of Adverse Events - Treated Subjects

	Number of Subjects (%)	
	ATV+RAL N = 63	**ATV+RTV+TDF/FTC N = 30**
At least 1 adverse event	60 (95.2)	29 (96.7)
At least 1 related adverse event	40 (63.5)	19 (63.3)
Deaths	0	0
At least 1 serious adverse event	7 (11.1)	2 (6.7)
At least 1 related serious adverse event	0	1 (3.3)
Discontinuation due to serious adverse event	1 (1.6)	0
Discontinuation due to adverse event	4 (6.3)	1 (3.3)

Laboratory Test Results:

Liver Function: Abnormal liver function test results are summarized in Table 6.

Table 6: Abnormal Liver Function Tests - Treated Subjects

	Number of Subjects (%)	
	ATV+RAL N = 63	**ATV+RTV+TDF/FTC N = 30**
ALT		
Grade 1-4	10 (15.9)	8 (26.7)
Grade 3-4	1 (1.6)	1 (3.3)
Grade 4	1 (1.6)	0
AST		
Grade 1-4	11 (17.5)	8 (26.7)
Grade 3-4	1 (1.6)	0
Grade 4	1 (1.6)	0
Total bilirubin		
Grade 1-4	62 (98.4)	28 (93.3)
Grade 3-4	43 (68.3)	19 (63.3)
Grade 4	15 (23.8)	3 (10.0)

Renal Function: Only 1 subject in each treatment group experienced a renal toxicity AE (mild renal papillary necrosis in 1 subject in the ATV+RAL group and mild hypophosphatemia in 1 subject in the ATV+RTV+TDF/FTC group). These AEs were not SAEs, did not lead to discontinuation of study drug, and were not considered related to the study drugs by the investigators.

Mean changes from baseline to Week 24 in serum creatinine were 0.062 mg/dL (n = 56) and 0.055 mg/dL (n = 24) in the ATV+RAL and ATV+RTV+TDF/FTC groups, respectively. Mean changes from baseline to Week 48 in serum creatinine were 0.030 mg/dL (n = 43) and 0.075 mg/dL (n = 25) in the ATV+RAL and ATV+RTV+TDF/FTC groups, respectively. Grade 3-4 creatinine changes were not reported as AEs in any subject.

Fasting Lipids: Grade 1-4 abnormalities in fasting total cholesterol were noted for 44% of subjects in the ATV+RAL group and 55% of subjects in the ATV+RTV+TDF/FTC group, and Grade 1-4 fasting

triglyceride abnormalities were noted for 15% and 28% of subjects in the ATV+RAL and ATV+RTV+TDF/FTC groups, respectively.

The incidence of Grade 3-4 fasting total cholesterol abnormalities was 10% in the ATV+RAL group and 13% in the ATV+RTV+TDF/FTC group. No subject had Grade 3-4 fasting triglycerides levels during this study.

Other Safety: Electrocardiogram parameters are summarized in Table 7.

Table 7: ECG Parameters

	Number of Subjects (%)	
	ATV+RAL N=63	**ATV+RTV+TDF/FTC N=30**
PR Interval (msecs)a		
< 200	55 (87.3)	25 (83.3)
200 - < 220	5 (7.9)	2 (6.7)
220 - < 240	2 (3.2)	2 (6.7)
240 - < 260	1 (1.6)	1 (3.3)
PR mean change from b/l at Week 48 using worst value in a visit window (SE)	22.1 (1.831)	12.0 (1.756)
QRS Interval (msecs)[a]		
< 100	12 (19.0)	10 (33.3)
100 - < 110	27 (42.9)	14 (46.7)
110 - < 120	20 (31.7)	2 (6.7)
120 - < 130	2 (3.2)	1 (3.3)
130 - < 140	2 (3.2)	2 (6.7)[b]
≥ 140	0	1 (3.3)[c]
QRS mean change from b/l at Week 48 using worst value in a visit window (SE)	10.2 (1.301)	5.4 (1.790)
QTc Fridericia (msecs)a		
< 400	10 (15.9)	7 (23.3)
400 - < 425	37 (58.7)	14 (46.7)
425 - < 450	15 (23.8)	7 (23.3)
450 - < 460	1 (1.6)	1 (3.3)
460 - < 470	0	1 (3.3)
QTcF mean change from b/l at Week 48 using worst value in a visit window (SE)	-1.3 (2.447)	8.2 (3.983)

[a] The longest on-treatment intervals were tabulated.

[b] Two subjects who met the screening exclusion criteria for QRS prolongation > 120 msecs were discontinued from the study.

[c] Subject had QRS interval of 141 msecs (QRS >140 msecs) measured 1 day after last dosing date.

Pharmacokinetic Results: Atazanavir PK parameters are summarized in Tables 8 and 9 for the subset of patients in Group 1 who participated in the intensive PK portion of the study.

Table 8: Summary Statistics for Atazanavir Pharmacokinetic Parameters

Treatment	Cmax (ng/mL) Geo. Mean [N] (%CV)	AUC(0-12h) (ng•h/mL) Geo. mean [N] (%CV)	AUC(0-24h)[a] (ng•h/mL) Geo. mean [N] (%CV)	Cmin (ng/mL) Geo. Mean [N] (%CV)	C0 (ng/mL) Geo. Mean [N] (%CV)
Group 1	3506.5 [13] (37)	19903.4 [13] (38)	39806.7 [13] (38)	687.1 [13] (52)	879.25 [13] (50)

Group 1 = ATV/RAL 300/400 mg BID.

[a] AUC(0-24h) estimated as 2 x AUC(0-12h).

Table 9: Other Summary Statistics for Atazanavir Pharmacokinetic Parameters

Treatment	Tmax (h) Median [N] (Min-Max)	EC_{90} (ng/mL) Geo.Mean [N] (CV)	IQ Geo.Mean [N] (CV) (Min-Max)
Group 1	3.00 [13] (2.0-4.0)	28.48 [12] (30)	23.47 [12] (48) (12.0-50.1)

Group 1 = ATV/RAL 300/400 mg BID.

The statistical analyses of ATV PK parameters for the comparison of Group 1 with historical data from Study AI424138 are summarized in Table 10. All of the 90% CIs are either entirely or nearly entirely above 1, suggesting that ATV exposures measured by Cmax, AUC(0-24h), and Cmin tend to be higher when ATV is co-administered BID with RAL BID compared to when ATV is administered as ATV/RTV 300/100 mg QD + TDF/FTC 300/200 mg QD.

Table 10: Statistical Analyses of Atazanavir Pharmacokinetic Parameters for the Comparison of Studies AI424376 (Group 1) and AI424138

Study and Comparison	Cmax (ng/mL) Adj. Geo.Mean	AUC(0-24h) (ng•h/mL) Adj. Geo.Mean	Cmin (ng/mL)[a] Adj. Geo.Mean
AI424138	2897	28605	526
AI424376 (Group 1)	3506	39807	687
AI424376 vs. AI424138	GMR (90% CI)	GMR (90% CI)	GMR (90% CI)
	1.210 (0.880,1.664)	1.392 (1.032,1.876)	1.305 (0.892,1.911)

Treatments: AI424138: ATV/RTV 300/100 mg QD + TDF/FTC 300/200 mg QD
AI424376 (Group 1): ATV/RAL 300/100 mg BID.

[a] Cmin = concentration 24 hours post-dose in AI424138 and concentration 12 hours post-evening dose in AI424376.

Raltegravir PK parameters are summarized in Tables 11 and 12 for the subset of patients in Group 1 who participated in the intensive PK portion of the study.

Table 11: Summary Statistics for Raltegravir Pharmacokinetic Parameters

Treatment	Cmax (ng/mL) Geo.Mean [N] (CV)	AUC(0-12h) (ng•h/mL) Geo.Mean [N] (CV)	AUC(0-24h)[a] (ng•h/mL) Geo.Mean [N] (CV)	Cmin (ng/mL) Geo.Mean [N] (CV)
Group 1 (N=13)	1577.0 [13] (102)	6446.4 [13] (74)	12892.7 [13] (74)	76.2 [13] (89)

Group 1: ATV/RAL 300/400 mg BID.

[a] AUC(0-24h) estimated as 2 x AUC(0-12h).

Table 12: Other Summary Statistics for Raltegravir Pharmacokinetc Parameters

Treatment	C0 (ng/mL) Geo.Mean [N] (CV)	Tmax (h) Median [N] (Min-Max)
Group 1 (N=13)	445.42 [13] (89)	2.08 [13] (0.0-8.0)

Group 1: ATV/RAL 300/400 mg BID.

Summary statistics of ATV and RAL composite trough concentration by treatment and responders, are provided in Tables 13 and 14, respectively.

Table 13: Summary Statistics for Atazanavir Composite Trough Concentrations by Treatment and Responders

Treatment	Responder	N	Composite Ctrough (ng/mL) Geo. Mean (CV) (Min - Max)
Group 1 ATV/RAL 300/400 mg BID	No	10	640.6 (39) (311 - 1130)
	Yes	48	625.8 (72) (32 - 3240)
	All Subjects	58	628.3 (69) (32 - 3240)
Group 2 ATV/RTV 300/100 mg QD + TDF/FTC 300/200 mg QD	Yes	25	750.3 (78) (192 - 3880)

Table 14: Summary Statistics for Raltegravir Composite Trough Concentration by Treatment and Responders

Treatment	Responder	N	Composite Ctrough (ng/mL) Geo.Mean (CV) (Min - Max)
Group 1 ATV/RAL 300/400 mg BID	No	10	184.4 (75) (58 - 656)
	Yes	48	250.7 (59) (35 - 779)
	All Subjects	58	237.8 (62) (35 - 779)

No association between ATV or RAL composite trough concentration and virologic failure was observed.

CONCLUSIONS:

Note: After careful review of the data through Week 24, BMS and Merck jointly decided to close Study AI424376. The primary endpoint of the study had been reached, and even though efficacy of the investigational regimen of ATV 300 mg BID and RAL 400 mg BID appeared to be comparable to current standard of care for treatment-naïve patients in this study, the overall profile of this investigational regimen did not appear to be optimal for further clinical development given its BID nature, the development of resistance to RAL, and higher rates of bilirubin-associated disorders with ATV BID compared with ATV+RTV.

- Response rates (HIV RNA < 50 c/mL) for ATV+RAL at the primary endpoint (Week 24) were consistent with the current standard of care. In addition, 37 of 45 of subjects (82%) in the ATV+RAL group and 19 of 25 subjects (76%) in the ATV+RTV+TDF/FTC group who remained on study until Week 48 had an undetectable viral load (HIV RNA < 50 c/mL) at Week 48 (using VR-OC).

- There was an imbalance in the discontinuation rate between the 2 groups through Week 36 and beyond. The high discontinuation rate in the ATV+RAL group partially explains the difference in efficacy results between the CVR NC = F and CVR NC = M analysis at the final analysis.
- There were no new or unexpected safety signals for ATV or RAL.
- Grade 4 hyperbilirubinemia rates for ATV+RAL BID were higher than observed with ATV+RTV+TDF/FTC in this study.
- PR and QRS intervals moderately increased with ATV BID as compared to boosted ATV. The ECG data overall was similar to the Week 24 primary endpoint data. No subjects met on-study ECG discontinuation criteria in either group. These findings were consistent with ATV BID studies in healthy volunteers.
- ATV exposures were higher for the ATV+RAL 300/400 mg BID group than those observed with the ATV+RTV+TDF/FTC group. Five subjects developed genotypic and/or phenotypic resistance to RAL through the Week 24 primary endpoint. One subject was found originally to have a major substitution (N155N/H mixture) to RAL at Week 32 but remained phenotypically sensitive to RAL. Subsequently, the official final report from the contracted genotyping laboratory was amended to "No RAL mutations detected." In addition, another subject, a virologic failure at Week 24, developed phenotypic resistance to RAL without any detected RAL RAMs on his genotype at Week 24 or at any other time point. After Week 24, no new subjects developed any further genotypic and/or phenotypic resistance to RAL.
- No subjects in either group developed ATV genotypic or phenotypic resistance throughout the study.
- When ATV 300 mg was co-administered with RAL 400 mg BID, ATV Cmax, AUC(0-12h), and Cmin were 3,507 ng/mL, 19,903 ng•h/mL, and 687 ng/mL, respectively. Raltegravir Cmax, AUC(0-12h), and Cmin were 1,577 ng/mL, 6,446 ng•h/mL, and 76.2 ng/mL, respectively, when co-administered.
- Atazanavir exposures (Cmax, AUC, and Cmin) appeared to be slightly higher in subjects who received ATV/RAL 300/400 mg BID relative to those subjects who received ATV/RTV 300/100 + TDF/FTC 300/200 mg QD (historical data).
- Atazanavir Cmin remained above the 10-fold mean population protein-binding adjusted EC_{90} for ATV when ATV 300 mg was co-administered with RAL 400 mg BID. In a subset of subjects treated with ATV/RAL 300/400 mg BID, the geometric mean ATV IQ was 23.5.
- Atazanavir trough concentrations after 2, 4, 8, 16, 24, and 48 weeks of treatment were similar between HIV-infected patients treated with ATV/RAL 300/400 mg BID (Group 1) and ATV/RTV 300/100 mg QD + TDF/FTC 300/200 mg QD (Group 2). There was no apparent correlation between composite trough concentrations of ATV or RAL and response to treatment.

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