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| Name of Sponsor/Company:<br>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 AI424328

**TITLE OF STUDY:** Open-Label, Multiple-Dose, Drug Interaction Study to Assess the Effect of Famotidine with or without Tenofovir on the Pharmacokinetics of Atazanavir when given with Ritonavir in HIV-Infected Subjects

**INVESTIGATORS/STUDY CENTERS:** 4 Investigators at 4 clinical sites: 3 US and 1 UK site screened subjects.

**PUBLICATIONS:** None.

**STUDY PERIOD:** Study Initiation Date: 18-Dec-2006 **CLINICAL PHASE:** 1

Study Completion Date: 15-Dec-2007

**OBJECTIVES:**

**Primary Objective:**

- To assess the effect of multiple-dose famotidine (FAM) BID on the multiple-dose pharmacokinetics (PK) of atazanavir/ritonavir (ATV/RTV) in HIV-infected subjects when FAM is administered simultaneously (without tenofovir disoproxil fumarate (TDF)) or temporally separated (with TDF).

**Secondary Objectives:**

- To assess the PK of RTV co-administered with ATV in the presence and absence of FAM
- To assess the safety and tolerability of ATV/RTV when co-administered with FAM in the presence of at least 2 NRTIs.

**METHODOLOGY:** This was an open-label, 2-cohort, 3-period, multiple-dose, sequential, multi-center study in 36 HIV-infected subjects who had been receiving a continuous antiretroviral (ARV) treatment regimen containing ATV/RTV 300/100 mg QD and ≥ 2 NRTIs (either with or without TDF) for several months, and have had documented measurements of plasma HIV RNA < 400 copies/mL prior to enrollment and less than 3 weeks prior to Day 1. Additionally, a third measurement of plasma HIV RNA was taken at Day -2. Results from this measurement were available prior to Day 11 dosing. Any subject with a result which was not < 400 copies/mL was to be immediately discontinued from the study.

Subjects who had been receiving the treatment regimen containing ATV/RTV 300/100 mg plus ≥ 2 NRTIs (dosing per USPI or SmPC) (without TDF) were enrolled into Cohort 1. Up to 18 subjects were to

complete Cohort 1. Subjects who did not complete the study were to be replaced. These subjects received the following:

- Treatment A: AM dosing of ATV/RTV 300/100 mg orally QD plus ≥ 2 NRTIs (dosing per USPI or SmPC) (without TDF) for 10 days (Days 1-10)
- Treatment B: AM dosing of ATV/RTV 300/100 mg orally QD, plus FAM 40 mg orally BID, plus ≥ 2 NRTIs (dosing per USPI or SmPC) (without TDF) for 7 days (Days 11-17) with FAM dosed simultaneously
- Treatment C: AM dosing of ATV/RTV 300/100 mg orally QD, plus FAM 20 mg orally BID, plus ≥ 2 NRTIs (dosing per USPI or SmPC) (without TDF) for 7 days (Days 18-24) with FAM dosed simultaneously

Subjects who had been receiving the treatment regimen containing ATV/RTV 300/100 mg plus TDF and ≥ 1 NRTI were enrolled into Cohort 2. Up to 18 subjects were to complete Cohort 2. Subjects who did not complete the study were to be replaced. These subjects received the following:

- Treatment D: AM dosing of ATV/RTV/TDF 300/100/300 mg orally QD plus ≥ 1 NRTI for 10 days (Days 1-10)
- Treatment E: AM dosing of ATV/RTV/TDF 300/100/300 mg orally QD, FAM 40 mg orally BID, plus ≥ 1 NRTI for 7 days (Days 11-17) with temporal separation of FAM dosing (ATV/RTV/TDF given 2 hours before AM FAM and 10 hours after PM FAM)
- Treatment F: AM dosing of ATV/RTV/TDF 300/100/300 mg orally QD, FAM 20 mg orally BID, plus ≥ 1 NRTI for 7 days (Days 18-24) with temporal separation of FAM dosing (ATV/RTV/TDF given 2 hours before AM FAM and 10 hours after PM FAM)

Study drugs (ie, ATV/RTV +/- FAM) were administered at the clinical facility on serial PK sampling days and on additional study days as required by the protocol for study related procedures. On all other study days, study drugs were administered daily by the subject. A detailed review of study medication was documented on each individual trial participant, to include drug administration and drug accountability for ATV/RTV, FAM and TDF, if applicable.

Physical examinations, vital sign measurements, 12-lead electrocardiograms (ECG), and clinical laboratory evaluations (including plasma HIV RNA and CD4 counts at study discharge) were performed at selected times throughout the study. Subjects were closely monitored for adverse events throughout the study. Approximately 275 mL of blood was drawn from each subject during the study.

**NUMBER OF SUBJECTS (Planned and Analyzed):** A total of 36 HIV-infected subjects were planned for this study (18 in each Cohort); 40 were randomized (Cohort 1 n=18, Cohort 2 n=22) and treated and 36 subjects completed the study (Cohort 1 n=17, Cohort 2 n=19).

**DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:** HIV-infected men or women, 18-65 years of age, deemed by the Investigator to have had acceptable medical history, physical examination, 12-lead ECG, clinical laboratory evaluations, and who met all subject selection criteria described in the protocol. Women of childbearing potential (WOCBP) must not have been nursing or pregnant and must have been using an acceptable method of contraception for at least 1 month before dosing. WOCBP must have had negative pregnancy test within 48 hours prior dosing to participate in the study.

**TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS:** Atazanavir was supplied by Bristol-Myers Squibb as a 150 mg capsule, batch numbers 6B10478, 6H16376, 6C14027, 6J12859 and was administered orally QD with RTV supplied by BMS as a 100 mg capsule, batch numbers 6L12095, 6G18545, 6H16378, 7C26095. The Investigator

supplied the marketed drug TDF as 300 mg tablets administered orally QD. Famotidine was supplied by BMS as a 20 mg tablet, batch numbers R5408, R5857,6K19503 administered orally BID. ATV/RTV 300/100 mg was co-administered with FAM 40 mg and 20 mg for 7 days (Treatment B and Treatment C Cohort 1) or with TDF and FAM 40 mg and 20 mg temporally separated (Treatment E and Treatment F Cohort 2) for 7 days.

**REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS:** Atazanavir was supplied by Bristol-Myers Squibb as a 150 mg capsule, batch numbers 6B10478, 6H16376, 6C14027, 6J12859 and was administered orally QD with RTV supplied by BMS as a 100 mg capsule, batch numbers 6L12095,6G18545, 6H16378, 7C26095 administered orally QD. The Investigator supplied the marketed drug TDF as 300 mg tablets administered orally QD. ATV/RTV 300/100 mg was orally administered QD for 10 days alone (Treatment A Cohort 1) or with TDF 300 mg (Treatment D Cohort 2).

**CRITERIA FOR EVALUATION:**

**Efficacy:** Not applicable.

**Safety:** Safety assessments were based on medical review of adverse event reports and the results of vital sign measurements, ECGs, physical examinations, and clinical laboratory tests. The incidence of observed adverse events was tabulated and reviewed for potential significance and clinical importance.

**Pharmacokinetics:** Steady-state PK parameters (Cmax, Tmax, Cmin, AUC(TAU), and T-HALF (RTV only)) for ATV and RTV were derived from plasma concentration versus time data.

**Pharmacodynamics:** Not applicable.

**STATISTICAL CONSIDERATIONS**:

Sample Size Determination: Although the sample size was not based on statistical power considerations, 18 evaluable subjects in each Cohort were to provide at least 85% and 92% confidence that the estimated ratios of the geometric means for ATV AUC(TAU) and Cmax, respectively, with or without FAM, would be within 10% of the true ratios. In addition, 18 evaluable subjects were to provide at least 91% confidence that the corresponding estimate for ATV Cmin would be within 20% of the true ratio. To allow for dropouts, an adequate number of subjects would be needed to meet the inclusion/exclusion criteria at screening so that 18 subjects would complete each Cohort.

These calculations were based on the assumptions that ATV AUC(TAU), Cmax and Cmin are log-normally distributed with inter-subject coefficients of variation of 34%, 28% and 60% respectively, as reported in AI424089 and that the correlation coefficient between two treatment periods was 0.6.

**Statistical Analysis:** Point estimates and 90% confidence intervals for the ratios of the geometric means for ATV and RTV Cmax, AUC(TAU) and Cmin, with and without FAM, were constructed in order to estimate:

- The effect in HIV-infected subjects of multiple-dose FAM 40 mg BID on the multiple-dose PK of ATV/RTV when dosed simultaneously (Treatment B versus Treatment A)
- The effect in HIV-infected subjects of multiple-dose FAM 20 mg BID on the multiple-dose PK of ATV/RTV when dosed simultaneously (Treatment C versus Treatment A)
- The effect in HIV-infected subjects of multiple-dose FAM 40 mg BID on the multiple-dose PK of ATV/RTV co-administered with TDF when FAM and ATV/RTV/TDF are dosed temporally separated (Treatment E versus Treatment D)
- The effect in HIV-infected subjects of multiple-dose FAM 20 mg BID on the multiple-dose PK of ATV/RTV co-administered with TDF when FAM and ATV/RTV/TDF are dosed temporally separated (Treatment F versus Treatment D)

Since differences in the distributions were anticipated between the two Cohorts, the analyses were carried out per Cohort. The estimates were generated using general linear models on log-transformed data, with treatment as a fixed effect and measurements within each subject as repeated measurements. Point estimates and 90% confidence intervals for differences at the log-scale were exponentiated to obtain estimates and confidence intervals for ratios of geometric means in the original scale. In the comparisons, ATV co-administered with RTV or ATV co-administered with RTV and TDF, were used as the reference. No adjustments were made for multiplicity.

Summary statistics were provided by treatment for all of the derived PK parameters of all analytes. Geometric means and coefficients of variation were reported for Cmax, AUC(TAU) and Cmin. Medians, minima, and maxima were reported for Tmax. Means and standard deviations were reported for half life.

**SUMMARY OF RESULTS:**

**Disposition, Demographics, and Other Pertinent Baseline Characteristics:** A total of 40 subjects were treated: 18 and 22 subjects were treated in Cohort 1 and Cohort 2, respectively; 17 subjects completed Cohort 1 and 19 subjects completed Cohort 2. For Cohort 1, 14 (78%) were males and 4 (22%) were females, with a mean (SD) age of 43(9) years. For Cohort 2, 21 (95%) were males and 1 (5%) was female, with a mean (SD) age of 40 (8) years. For Cohort 1, 9 (50%) subjects were Caucasian, 6 (33%) were black, and 3 (17%) were Other. For Cohort 2, 13 (59%) were Caucasion, 4 (18%) black, 3 (14%) Asian and 2 (9%) were Other. For Cohort 1, mean (SD) weight was 78.8 (12) kg, mean (SD) BMI was 25.6 (3.9) $kg/m^2$ and mean (SD) CD4 count was 663 (258) cells/μL. For Cohort 2, mean weight was 79.5 (10.6) kg, mean BMI was 25.0 (2.7) $kg/m^2$ and mean (SD) CD4 count was 577 (175) cells/μL.

**Efficacy Results:** Not applicable.

**Safety Results:** There were no deaths, SAEs or discontinuations due to AEs in this study.

Jaundice occurred in 1 (4.5%) subject following administration of FAM 20 mg temporally separated from ATV/RTV/TDF 300/100/300 mg (Treatment F). The most frequently reported treatment-emergent AE overall was headache observed in 12 (30%) of subjects; the most frequent occurrence in Cohort 1: 3 (16.7%) following administration of FAM 40 mg co-administered with ATV/RTV 300/100 mg (Treatment B) and in Cohort 2: 6 (27.3%) subjects following administration of ATV/RTV/TDF 300/100/300 mg alone (Treatment D). The next most frequently reported AE overall was diarrhea observed in 6 (15%) of subjects; the most frequent occurrence in Cohort 1: 2(11.1%) following administration of FAM 40 mg co-administered with ATV/RTV 300/100 mg (Treatment B) Cohort 2: 3 (13.6%) subjects following administration of FAM 40 mg temporally separated from ATV/RTV/TDF 300/100/300 mg (Treatment E). The remainder of the AEs occurred only 1 or 2 times per treatment.

Elevations in total bilirubin that were MAs occurred in 7 (17.5%) subjects: 4 subjects in Cohort 1 and 3 subjects in Cohort 2. Atazanavir is known to bind, in a predominantly competitive manner, the bilirubin glucuronidating isozyme, UGT 1A1. There is no indication from pre-clinical and clinical data collected to date that the increases in total bilirubin represented a signal for a hepatotoxic process.

There was no evidence that either ATV/RTV 300/100 mg with or without TDF 300 mg, with FAM 20 mg or 40 mg dosed simultaneously or temporally separated had any effect on ECG or vital sign measurements.

**Pharmacokinetic Results:**

**Atazanavir:**

Atazanavir pharmacokinetic parameters are summarized in Table 1.

**Table 1: Summary Statistics for ATV Pharmacokinetic Parameters**

| Pharmacokinetic Parameter | Treatment | | | | | |
|---|---|---|---|---|---|---|
| | **A:** ATV/RTV 300/100 mg QD + >=2 NRTI(s) | **B:** ATV/RTV 300/100 mg QD + FAM 40 mg BID | **C:** ATV/RTV 300/100 mg QD + FAM 20 mg BID | **D:** ATV/RTV 300/100 mg QD + TDF 300 mg QD and >=1 NRTI(s) | **E:** ATV/RTV/TDF 300/100/300 mg QD + FAM 40 mg BID | **F:** ATV/RTV/TDF 300/100/300 mg QD + FAM 20 mg BID |
| | **N =18** | **N =17** | **N =17** | **N =18** | **N =18** | **N =18** |
| Cmax (ng/mL) - Geometric Mean (CV%) | 4572 (32%) | 3592 (33%) | 3687 (33%) | 3987 (35%) | 3057 (54%) | 3130 (56%) |
| AUC(TAU) (ng•h/mL) - Geometric Mean (CV%) | 39831 (33%) | 31787 (34%) | 35322 (30%) | 36015 (41%) | 27178 (45%) | 28586 (61%) |
| Cmin[a] (ng/mL) - Geometric Mean (CV%) | 588 (61%) | 492 (49%) | 610 (51%) | 542 (62%) | 409 (64%) | 441 (91%) |
| Tmax (h) - Median (Min, Max) | 3.00(1.50,4.00) | 3.00(2.00,4.00) | 3.00(2.00,6.00) | 2.75(1.50,4.00) | 3.00(1.50,8.00) | 3.00(1.50,4.00) |

[a] Cmin defined as the 24-hour post dose concentration on serial PK sampling days

Statistical analyses of ATV pharmacokinetic parameters are presented in Table 2.

**Table 2: Statistical Analyses for ATV Pharmacokinetic Parameters**

| Pharmacokinetic Parameter | Geometric Means | | Ratios of Adjusted Geometric Means |
|---|---|---|---|
| | B | A | Point Estimate (90% CI) |
| Cmax (ng/mL) | 3529 | 4572 | 0.772 (0.674 0.884) |
| AUC(TAU) (ng•h/mL) | 30573 | 39831 | 0.768 (0.683, 0.863) |
| Cmin (ng/mL) | 468 | 588 | 0.797 (0.688 0.923) |
| | C | A | |
| Cmax (ng/mL) | 3649 | 4572 | 0.798 (0.683, 0.932) |
| AUC(TAU) (ng•h/mL) | 34626 | 39831 | 0.869 (0.748, 1.011) |
| Cmin (ng/mL) | 584 | 588 | 0.994 (0.836, 1.181) |
| | E | D | |
| Cmax (ng/mL) | 3057 | 3987 | 0.767 (0.640, 0.919) |
| AUC(TAU) (ng•h/mL) | 27178 | 36015 | 0.755 (0.644, 0.885) |
| Cmin (ng/mL) | 409 | 542 | 0.754 (0.534, 1.067) |
| | F | D | |
| Cmax (ng/mL) | 3130 | 3987 | 0.785 (0.639, 0.964) |
| AUC(TAU) (ng•h/mL) | 28586 | 36015 | 0.794 (0.655, 0.963) |
| Cmin (ng/mL) | 441 | 542 | 0.814 (0.629, 1.053) |

Treatments
A: ATV/RTV 300/100 mg QD; B: FAM 40 mg co-administered with ATV/RTV 300/100 mg;
C: FAM 20 mg co-administered with ATV/RTV 300/100 mg; D: ATV/RTV/TDF 300/100/300 mg
E: FAM 40 mg temporally separated from ATV/RTV/TDF 300/100/300 mg;
F: FAM 20 mg temporally separated from ATV/RTV/TDF 300/100/300 mg

The point estimates and confidence intervals presented in Table 2 suggest that simultaneous or temporally separated administration of FAM 40 or 20 mg BID with ATV/RTV 300/100 mg QD decrease ATV exposures when compared to the ATV/RTV 300/100 mg alone group.

**Ritonavir**

Statistical analyses of RTV pharmacokinetic parameters are presented in Table 3.

**Table 3: Statistical Analyses for RTV Pharmacokinetic Parameters**

| Pharmacokinetic Parameter | Geometric Means | | Ratios of Adjusted Geometric Means |
|---|---|---|---|
| | B | A | Point Estimate (90% CI) |
| Cmax (ng/mL) | 981 | 1052 | 0.933 (0.811, 1.072) |
| AUC(TAU) (ng•h/mL) | 6617 | 6734 | 0.983 (0.893, 1.081) |
| Cmin (ng/mL) | 45 | 41 | 1.099 (0.980, 1.234) |
| | C | A | |
| Cmax (ng/mL) | 919 | 1052 | 0.874 (0.739, 1.034) |
| AUC(TAU) (ng•h/mL) | 6460 | 6734 | 0.959 (0.842, 1.093) |
| Cmin (ng/mL) | 44 | 41 | 1.088 (0.940, 1.259) |
| | E | D | |
| Cmax (ng/mL) | 938 | 921 | 1.019 (0.899, 1.154) |
| AUC(TAU) (ng•h/mL) | 6749 | 6417 | 1.052 (0.954, 1.159) |
| Cmin (ng/mL) | 45 | 42 | 1.075 (0.779, 1.484) |
| | F | D | |
| Cmax (ng/mL) | 1073 | 921 | 1.166 (0.980, 1.386) |
| AUC(TAU) (ng•h/mL) | 6940 | 6417 | 1.081 (0.969, 1.207) |
| Cmin (ng/mL) | 44 | 42 | 1.044 (0.792, 1.376) |

Treatments
A: ATV/RTV 300/100 mg QD; B: FAM 40 mg co-administered with ATV/RTV 300/100 mg;
C: FAM 20 mg co-administered with ATV/RTV 300/100 mg; D: ATV/RTV/TDF 300/100/300 mg
E: FAM 40 mg temporally separated from ATV/RTV/TDF 300/100/300 mg;
F: FAM 20 mg temporally separated from ATV/RTV/TDF 300/100/300 mg

The point estimates and confidence intervals presented in Table 3 suggest that simultaneous or temporally separated administration of FAM 40 or 20 mg BID with ATV/RTV 300/100 mg QD have minimal effects on RTV exposures.

**Pharmacodynamic Results:** Not applicable.

**CONCLUSIONS:**

- Coadministration of FAM (40 mg BID) to HIV-infected subjects reduced the exposure of ATV by approximately 20-23%.
- In the presence of TDF, administration of FAM (40 mg BID) with ATV/RTV by temporal separation reduced the exposures of ATV by approximately 23-25% when compared to ATV/RTV/TDF without FAM.
- The lower dose of FAM (20 mg BID) had less of an impact on ATV exposures, especially Cmin.
- Ritonavir exposures were generally comparable across Treatments A through C (without TDF) and Treatments D through F (with TDF).
- ATV/RTV was safe and generally well tolerated by HIV subjects when co-administered with FAM in the presence of at least 2 NRTIs.

**DATE OF REPORT:** 09-Jul-2008