BRISTOL-MYERS SQUIBB COMPANY

Atazanavir

96-Week Clinical Study Report Addendum for Study AI424227

Phase IIIb Multicenter, Single Arm, Open-Label Pilot Study to Evaluate the Effectiveness and Safety of Maintenance with Atazanavir/ritonavir as Single Enhanced Protease Inhibitor Therapy in HIV-Infected Patients Evidencing Virologic Suppression

OREY (Only REYataz) Study

Indication:	HIV-infected patients
Phase:	3b
Study Initiation Date:	30-Jun-2006
Study Completion Date:	04-May-2009 (last patient last visit)
Report Date:	16-Nov-2009
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THIS STUDY WAS CONDUCTED IN ACCORDANCE WITH GOOD CLINICAL PRACTICE

Sponsor's Responsible Medical Officer:

[redacted]

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

Week 96 Clinical Study Report Addendum for Study AI424227

TITLE OF STUDY: Phase 3b Multicenter, Single Arm, Open-Label Pilot Study to Evaluate the Effectiveness and Safety of Maintenance with Atazanavir/ritonavir as Single Enhanced Protease Inhibitor Therapy in HIV-Infected Patients Evidencing Virologic Suppression.

INVESTIGATORS/STUDY CENTERS: This study was conducted at 8 sites in Spain.

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 30-Jun-2006 **CLINICAL PHASE:** 3b

Study Completion Date: 04-May-2009
(last patient last visit)

OBJECTIVES:

Primary: The primary objective was to establish the proportion of subjects with treatment failure (virologic rebound [HIV RNA ≥ 400 c/mL] or treatment discontinuation) at Week 48 for subjects who received atazanavir (ATV)/ ritonavir (RTV) monotherapy. It was addressed in the Week 48 Final CSR.

Secondary: Secondary objectives pertaining to Week 48 were addressed in the Week 48 Final CSR and those pertaining to Week 96 are addressed in this report. Secondary objectives evaluated in this study are listed below.

- The time to treatment failure, defined as the earlier of virologic rebound or treatment discontinuation.
- The proportion of subjects with virologic rebound (HIV RNA ≥ 400 c/mL).
- The time to virologic rebound.
- The changes in CD4 cell counts from baseline.
- The safety of maintenance treatment with ATV/RTV monotherapy.
- The incidence of resistance to ATV/RTV used as single enhanced protease inhibitor therapy.

METHODOLOGY:

Study AI424227 [OREY (Only REYataz study)] was a Phase 3b multicenter, regional, single-arm, open-label, 96-week trial in HIV-1-infected subjects who had maintained virologic suppression (HIV < 50 c/mL) for at least 24 weeks prior to study entry while on continued antiretroviral (ARV) therapy, and who never had previous virological failures while receiving any ARV therapy. Before study entry, subjects received ATV/RTV and 2 nucleoside reverse transcriptase inhibitors (NRTI; or 1 NRTI and

tenofovir [TDF]) for at least 8 weeks. Subjects must have had a HIV RNA < 50 c/mL at screening, and be free of treatment-limiting adverse events (AEs) while receiving ATV/RTV. Subjects discontinued the nucleosides and remained on a maintenance regimen with ATV/RTV monotherapy. Subjects were treated and followed on protocol until they had completed 96 weeks on the ATV/RTV monotherapy. Those subjects who prematurely discontinued study treatment prior to completion of the study, including those who changed therapy due to virologic failure, continued to be followed according to the schedule of events.

NUMBER OF SUBJECTS:

Planned: 62 treated subjects; Analyzed: 61 treated subjects.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

HIV-1 infected adults with viral suppression for at least previous 24 weeks while on continued highly active antiretroviral therapy (HAART) and who received ATV/RTV + 2 NRTIs (or 1 NRTI & TDF) for at least 8 weeks prior to study entry and who had HIV RNA < 50 c/mL at screening.

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

After successful completion of screening procedures, eligible subjects discontinued their background NRTIs and remained with maintenance ATV/RTV monotherapy (oral administration, once daily). ATV was provided as 150 mg capsules and the following batch numbers were used in the study: 5F04895, 6A17818, 6B16342, 6H17778, 7C32129, and 8D3049B. RTV was provided as 100 mg capsules and the following batch numbers were used in the study: 5E07960, 5H00466, 6C18430, 7B25420, 6H15540, and 8D32737.

CRITERIA FOR EVALUATION:

Secondary endpoints pertaining to Week 48 were addressed in the Week 48 CSR. Secondary endpoints pertaining to Week 96 are listed below and addressed in this report.

Efficacy Endpoints:

- The proportion of subjects with treatment failure, defined as virologic rebound (HIV RNA ≥ 400 c/mL) or treatment discontinuation, at Week 96
- The proportion of subjects with virologic rebound through Week 96.
- The mean changes in CD4 cell count from baseline through Week 96.
- The time to treatment failure defined as the earlier of virologic rebound or treatment discontinuation.
- The time to virologic rebound.

Safety Endpoints:

- The frequency and severity of AEs, and discontinuations due to AEs.
- The mean percent changes from baseline in fasting total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, non-HDL cholesterol, and triglycerides through Week 96.

Other Endpoints:

- The incidence and characterization of resistance among subjects with virologic failure.

STATISTICAL CONSIDERATIONS:

Sample Size and Power: A sample size of 62 subjects provides 95% confidence that the proportion of subjects with treatment failure at Week 48 can be estimated to within 10% to 30%, assuming a true rate of 20%.

Efficacy and safety analyses are based on treated subjects unless specified otherwise. In the efficacy tabulations, HIV RNA levels and CD4 cell counts are included through the last dose of study therapy (ATV/RTV monotherapy) plus 4 days. In the safety tabulations, AE and laboratory parameters are included through the last dose of study therapy plus 30 days.

Efficacy: The proportion of treated subjects with treatment failure (ie, virologic rebound or study drug discontinuation) was assessed through Week 96. Virologic rebound was defined as 2 consecutive on-treatment HIV RNA ≥ 400 c/mL or last on-treatment HIV RNA ≥ 400 c/mL followed by discontinuation of study therapy. Subjects were considered treatment failures in this analysis if they experienced virologic rebound at or before Week 96, discontinued before Week 96, or had missing HIV RNA at Week 96. The proportion with treatment failure is reported with a 95% confidence interval (CI) constructed using exact binomial methods.

Treatment outcomes at Week 96 were based on the proportion of subjects with treatment failure at or before Week 96. Time to treatment failure (measured from the start of study therapy) through Week 96 was estimated using Kaplan-Meier curve and a life table. Failure time is based on the earliest event defining failure (virologic rebound at or before Week 96, or discontinuation prior to Week 96). CD4 cell counts and changes from baseline were summarized at each scheduled visit through Week 96. Genotyping data was listed for treated subjects as provided by the laboratory. For each gene sequenced, the substitution was recorded.

Safety: Deaths, other serious adverse events (SAEs), and pregnancies were presented for enrolled subjects without regard to study period. Safety endpoints included the frequency of deaths, other SAEs, AEs leading to discontinuation, overall AEs, and laboratory abnormalities. Adverse events (related and regardless of relationship to study therapy) were presented by descending frequency of both system organ class and preferred term.

SUMMARY OF RESULTS:

Disposition, Demographics, and Other Pertinent Baseline Disease Characteristics:

The baseline demographics and disease characteristics of treated subjects are provided in Table 1.

Table 1: Demographics and Disease Characteristics at Baseline- Treated Subjects

Variable	**ATV/RTV monotherapy (N = 61)**
Median Age, Years	42
Race- White, N (%)	61 (100)
Gender, N (%)	
Male	46 (75.4)
Female	15 (24.6)
Median Duration of HIV disease, Years	6.4
HIV RNA < 50 c/mL, N (%)	60 (98.4%)
Median duration of HIV RNA < 50 c/mL, weeks	208.7
Median CD4 cell count, cells/mm^3	514

Partial dates for Date of HIV diagnosis and date of first HIV RNA less than 50 c/mL are imputed .

Of the 63 subjects enrolled, 61 were treated. Of the 61 treated subjects, 51 completed the study and 10 (16.4%) permanently discontinued the study prior to Week 96 (Table 2). Of the 51 completers, 10 subjects remained in the study but discontinued study therapy due to virologic failure prior to Week 96. In this study, those subjects who prematurely discontinue study therapy (including those with major toxicities, prohibited concomitant medications, and subjects who changed therapy due to virologic failure) continued to be followed according to the schedule of events.

Table 2: Subject Disposition (Start of Study Therapy through End of Study) - Treated Subjects in AI424227

	Number of Subjects (%) ATV/RTV monotherapy (N=61)
Treated	61 (100.0)
Discontinued prior to Week 96	10 (16.4)
Adverse Event	3 (4.9)
Subject Withdrew Consent	2 (3.3)
Pregnancy	1 (1.6)
Lost to Follow-up	2 (3.3)
Subject no Longer Meets Study Criteria	2 (3.3)
Completed Study*	51 (83.6)

* Ten additional subjects remained in the study but discontinued study therapy due to virologic failure.

Efficacy Results:

Table 3 provides the overall summary of efficacy for all treated subjects. By Week 96, 21 subjects (34.4%) were treatment failures (≥ 400 c/mL). Of these, 13 treatment failures occurred prior to Week 48 and 8 additional treatment failures occurred on or after Week 48 (2 of these discontinued study at Week 48 while being suppressed and were considered successes in the primary endpoint analysis). By Week 96, 26 subjects (43.3%) were treatment failures (≥ 50 c/mL) and of these, 20 treatment failures occurred on or prior to Week 48 and 6 additional treatment failures occurred after Week 48 through Week 96.

Table 3: Efficacy Summary Through Week 96- Treated Subjects

Endpoints	ATV/RTV monotherapy
Treatment Failure[a]	**Failure (N)/Evaluable (N) (%)**
HIV RNA ≥ 400 c/mL	21/61 (34.4)[b]
Virologic Rebound	**Rebounder (N)/Evaluable (N) (%)**
HIV RNA ≥ 400 c/mL	9/61 (14.8)[c]
CD4 Cell Counts[d]	**Values**
CD4 mean change (SE) from baseline, cells/mm^3	63 (32.9)

[a] Subjects are considered treatment failures in this analysis if they experienced virologic rebound at or before Week 96, discontinued before Week 96, or had missing HIV RNA at Week 96.

[b] Thirteen subjects experienced treatment failure prior to Week 48 and 8 additional treatment failures occurred on or after Week 48 (2 of which discontinued study at Week 48 while being suppressed and were counted as successes in the primary endpoint analysis).

[c] Seven subjects (12%) experienced virologic rebound (HIV RNA at least 400 c/mL) at or before Week 48 and 2 additional subjects (3%) after Week 48.

[d] Mean baseline CD4 value was 559 cells/mm^3.

Safety Results:

Table 4 provides the overall summary of safety for all enrolled (deaths and SAEs) and treated subjects.

Table 4: Summary of AEs of Clinical Interest - Treated Subjects

Adverse Events	Number of Subjects (%) ATV/RTV (N=61)
Death[a]	**2 (3.28)**
SAEs	**12 (19.7)**
SAEs related to study therapy	**0**
AEs leading to discontinuation	**3 (4.9)**
Any AEs through Week 96, All Grades	**46 (75.4)**
Most common AE (≥ 5%) & AEs of interest through Week 96, All Grades	
Headache	5 (8.2)
Depression	4 (6.6)
Hypercholesterolemia	7 (11.5)
Hypertriglyceridaemia	6 (9.8)
Respiratory tract infection	5 (8.2)
Tooth infection	4 (6.6)
Gastrointestinal Disorder	**6 (9.8)**
Diarrhea	2 (3.3)
Hepatobilary Disorders and Eye Disorders	
Jaundice	1 (1.6)
Ocular icterus	1 (1.6)
Hyperbilirubinaemia	1 (1.6)

[a] Death was reported in 2 subjects (1 subject with bladder carcinoma and 1 subject with bilateral pneumonia and sepsis) and both of them were not considered related to ATV/RTV monotherapy.

Laboratory Test Results through Week 96:

Through Week 96, Grade 3 to Grade 4 hematologic, pancreatic enzyme, renal function, fasting lipids, and liver function (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) abnormalities were low. Grade 3 to Grade 4 elevations in total bilirubin were observed for 44 subjects (72%) but only 2 subjects (3%) experienced both Grade 3 to Grade 4 total bilirubin and Grade 3 to Grade 4 ALT or AST

levels through Week 96. No Grade 3 to Grade 4 fasting glucose abnormalities were observed in treated subjects through Week 96. Grade 3 to 4 fasting total cholesterol abnormalities were experienced by 6 subjects (10%) and Grade 3 to 4 fasting triglycerides were experienced by 3 subjects (5%). No RT substitutions were detected in any subject.

Resistance Results: Through Week 96, 9 subjects met criteria for virologic rebound (HIV RNA at least 400 c/mL). Of these 9 subjects, 2 subjects had major International AIDS Society (IAS) PI substitutions (N88S in 1 subject and N88S and M46L in 1 subject), 4 subjects had minor PI substitutions, and 3 subjects had no PI substitutions. No RT substitutions were detected in any subject.

CONCLUSIONS:

- In HIV-1 infected subjects with viral suppression (HIV RNA < 50 c/mL) for at least 24 weeks on continued HAART and who received ATV/RTV + 2 NRTIs for at least 8 weeks prior to study entry, a switch to ATV/RTV monotherapy resulted in a treatment failure rate (HIV RNA ≥ 400 c/mL) of 21% at Week 48 (primary analysis) and 34% at Week 96. Thirteen treatment failures occurred prior to Week 48, and 8 additional treatment failures occurred on or after Week 48.
- Through Week 96, 9 subjects (15%) had a confirmed virologic rebound (HIV RNA ≥ 400 c/mL). Seven subjects (12%) experienced virologic rebound (HIV RNA at least 400 c/mL) at or before Week 48 and only 2 subjects (3%) after Week 48.
- At Week 96, slight mean CD4 increases from baseline were observed.
- Through Week 96, the safety and tolerability of ATV/RTV monotherapy were consistent with the known safety and tolerability profile of ATV/RTV.
- Through Week 96, 9 subjects met criteria for virologic rebound (HIV RNA at least 400 c/mL). Of these 9 subjects, 2 had major, 4 had minor, and 3 had no PI substitutions. No RT substitutions were detected in any subject.

DATE OF REPORT: 16-Nov-2009