BRISTOL-MYERS SQUIBB COMPANY

Atazanavir

Final Clinical Study Report 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:	Database Cut Off Dates: 48 weeks: 21-Jul-2008
Report Date:	13-Apr-2009
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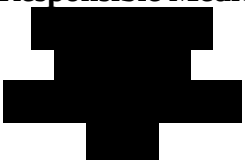
THIS STUDY WAS CONDUCTED IN ACCORDANCE WITH GOOD CLINICAL PRACTICE

Sponsor's Responsible Medical Officer:



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

SYNOPSIS

Final Clinical Study Report for Study AI424227

TITLE OF STUDY: 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

INVESTIGATORS/STUDY CENTERS: 8/8 (in Spain)

PUBLICATIONS: None

CLINICAL PHASE: 3B

STUDY PERIOD: Study Completion Date: Ongoing

Database lock for this Report: 21-Jul-2008

OBJECTIVES:

The primary objective is 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.

The secondary objectives are to evaluate the following in subjects on ATV/RTV monotherapy:

- The proportion of subjects with virologic rebound (HIV RNA ≥ 400 c/mL) at Week 48.
- The time to treatment failure, defined as the earlier of virologic rebound or treatment discontinuation.
- The time to virologic rebound.
- The changes in CD4 cell counts from baseline through Week 48.
- The safety of maintenance treatment with ATV/RTV monotherapy.
- The incidence of resistance to ATV/RTV used as single enhanced protease inhibitor (PI) therapy.

METHODOLOGY:

Study AI424227 [OREY (Only REYataz study)] is 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 entry, subjects received ATV/RTV and 2 nucleoside reverse transcriptase inhibitor (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 effects (AEs) while receiving ATV/RTV. Sixty-two subjects discontinued the nucleosides and remained on a maintenance regimen with ATV/RTV monotherapy.

Enrollment in this study was open until at least 62 subjects had received 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.

This analysis includes analyses of the primary endpoint and of all the secondary endpoints of the study at Week 48. The study is ongoing and the last patient last visit (LPLV) for this study is scheduled to be in April 2009.

NUMBER OF SUBJECTS (Planned and Analyzed):

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. Table 1 identifies the batch numbers of ATV and RTV used in the study.

Table 1: Atazanavir and Ritonavir Batch Numbers

Treatment	Formulation	Mode of Administration	Dose	Batch Numbers
ATV	capsule	oral	150 mg	5F04895, 6A17818, 6B16342, 6H17778, 7C32129
RTV	capsule	oral	100 mg	5E07960, 5H00466, 6C18430, 7B25420, 6H15540

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

None.

CRITERIA FOR EVALUATION:

Efficacy: The primary endpoint was the proportion of subjects with treatment failure, defined as virologic rebound (HIV RNA ≥ 400 c/mL) or treatment discontinuation, at Week 48.

The secondary efficacy endpoints assessed through Week 48 were the following:

- The proportion of subjects with virologic rebound through Week 48.
- The mean changes in CD4 cell count from baseline tthrough Week 48.
- The time to treatment failure defined as the earlier of virologic rebound or treatment discontinuation.
- The time to virologic rebound.

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

- 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 48.
- Other observations related to safety included lipodystrophy-related AEs and lactic acidosis syndrome (LAS).

Other: Other endpoints in this study assessed through Week 48 included the following:

- 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%. No p-values were provided.

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. The efficacy and safety listings include all available data and, data not used in tabulations is flagged.

Efficacy (Primary Endpoint): The primary efficacy analyses assessed the proportion of treated subjects with treatment failure (ie, virologic rebound or study drug discontinuation) through Week 48. 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 48, discontinued before Week 48, or had missing HIV RNA at Week 48. The proportion with treatment failure is reported with a 95% confidence interval (CI) constructed using exact binomial methods. The denominator was the number of treated subjects.

Efficacy (Key Secondary Endpoints): Treatment outcomes at Week 48 were based on the proportion of subjects with treatment failure at or before Week 48. The categories for treatment outcome were as follows: maintained suppression, virologic rebound, discontinued from study therapy, discontinued from study (including the primary reason for discontinuing study drug or not completing the study). Subjects were considered to be maintaining suppression at Week 48 if they did not have intervening virologic rebound at or before Week 48, or discontinued study therapy before Week 48. Treatment outcome was based on the first reason for failure.

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. Fasting lipid values, changes from baseline and percent changes from baseline were summarized through Week 48 using observed values. Values obtained after initiation of serum lipid-reducing agents were excluded.

SUMMARY OF RESULTS:

Disposition, Demographics, and Other Pertinent Baseline Disease Characteristics: The proportion of subjects who discontinued study before Week 48 was 8% (Table 2). Only 1 subject discontinued due to AE before Week 48.

Table 2: Subject Disposition - Treated Subjects

	Number of Subjects (%)
Treated	61 (100)
Discontinued Study Prior to Week 48	**5 (8)**
Adverse Event	1 (2)
Pregnancy	1 (2)
Lost to Follow-up	1 (2)
No Longer Meets Study Criteria	2 (3)
Discontinued Study on or after Week 48[a]	**3 (5)**
Lost to Follow-up	2 (3)
Withdrew Consent	1 (2)
Continuing On-Study	53 (87)

[a] Includes subjects who discontinued until database lock, including 2 subjects who discontinued at Week 60.

The baseline demographics and disease characteristics of treated subjects are provided in Table 3.

Table 3: Demographics and Disease Characteristics at Baseline- Treated Subjects

	ATV/RTV monotherapy (N = 61)
Variable	Descriptive Statistics
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
Median HIV RNA Plasma Level*	1.69 $\log_{10}$ c/mL
HIV RNA < 50 c/mL, N (%)	60 (98%)
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 .
*HIV RNA results reported with < 50 are included as 49 in the analysis.

Efficacy Results: Table 4 provides the overall summary of efficacy for all treated subjects. The proportion of subjects with treatment failure (HIV RNA at least 400 c/mL) through week 48 was 21%. All treatment failures occurred on or prior to Week 36.

Table 4 : Efficacy Summary Through Week 48- Treated Subjects

Endpoints	ATV/RTV monotherapy
Treatment Failure[a]	**Failure (n)/Evaluable (N) (%)**
HIV RNA ≥ 400 c/mL[b]	13/61 (21)
HIV RNA ≥ 50 c/mL	20/60[c] (33)
Virologic Rebound	**Rebounder (n)/Evaluable (N) (%)**
HIV RNA ≥ 400 c/mL	7/61 (12)
HIV RNA ≥ 50 c/mL	16/60[c] (27)
CD4 Cell Counts[d]	**Values**
CD4 mean change (SE) from baseline, cells/mm3	53 (30)

[a] Subjects are considered treatment failures in this analysis if they experienced virologic rebound at or before Week 48, discontinued before Week 48, or had missing HIV RNA at Week 48.

[b] Primary Endpoint.

[c] One subject was excluded because of baseline HIV RNA > 50 c/mL.

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

Safety Results: Table 5 provides the overall summary of safety for all enrolled (deaths and SAEs) and treated subjects.

Table 5: Summary of AEs of Clinical Interest - Treated Subjects

Adverse Events	Number of Subjects n (%) ATV/RTV (N=61)
Death[a]	**1 (2)**
SAEs	**11 (18)**
SAEs related to study therapy	**0**
AEs leading to discontinuation	**1 (2)**
Any AEs through Week 48, All Grades	**37 (61)**
Most common AEs (≥ 5%) & AEs of interest through Week 48, All Grades	
Headache	5 (8)
Gastrointestinal Disorder	**5 (8)**
Diarrhea	2 (3)
Hypercholesterolemia	4 (7)
Respiratory tract infection	4 (7)
Jaundice	1 (2)
Ocular icterus	1 (2)
Hyperbilirubinaemia	0

[a] Death in 1 subject ([redacted]) was considered unrelated to ATV/RTV monotherapy.

Deaths and Adverse Events: Among the 63 enrolled subjects, 1 subject ([redacted]) died on Study Day 172, 18 days after his last dose of study therapy. The cause of death was multiorgan failure. The subject was diagnosed of bladder cancer and his death was considered to be unrelated to the study therapy.

Serious adverse events were reported in 11(18%) subjects. Individual SAEs were reported in only 1 subject. All SAEs reported were considered to be "not related" or "not likely related" to study therapy.

Among the 61 treated subjects, 37 (61%) subjects reported AEs (all grades, through Week 48). Only 5 (8%) subjects reported AEs that were considered to be related to study therapy and 5 (8%) other subjects reported Grade 3 to Grade 4 AEs.

Laboratory Test Results through Week 48

Liver Function: Infrequent on-treatment Grade 3 to Grade 4 liver function abnormalities were observed for alanine transaminase (ALT; 2 subjects [3%]), aspartate aminotransferase (AST; 0 subjects), and alkaline phosphatase (ALP; 1 subject [2%]). Grade 3 to Grade 4 total bilirubin elevations were observed for 39 (64%) subjects.

Fasting Lipids: Few subjects had Grade 3 to Grade 4 total cholesterol (5%) or Grade 3 to Grade 4 triglyceride (2%) abnormalities through Week 48. In all aterogenic lipids, slight mean increases from baseline at Week 48 were observed.

Other Observations Related to Safety: Lipodystrophy-related AEs of all grades were reported during the treatment period through Week 48 in only 1 subject (gynaecomastia). It was not considered serious and did not lead to discontinuation.

Resistance Results: Through Week 48, 7 subjects met criteria for virologic rebound (HIV RNA at least 400 c/mL) (Table 6). Of these 7 subjects, 1 subject had a major PI substitution (N88S) as defined by International Aids Society (IAS), 4 subjects had at least 1 minor PI substitution and 2 subjects had no PI substitutions. No RT substitutions were detected in any subject. Most of these virologic rebounds occurred on or prior to Week 24.

Table 6: Genotype Substitutions for Virologic Rebounds (HIV-RNA ≥ 400 c/mL) through Week 48

Outcome	Number of Subjects/Evaluable
	ATV/RTV N = 61
Virologic Rebounds (HIV-RNA ≥ 400 c/mL)	7/61
Baseline Genotype	NA
Genotype at Virologic Rebounds ≥ 400 c/mL	7/7
IAS-USA-defined major PI substitutions[a]	1[b]/7
RT (Reverse Transcriptase) substitutions	
TAMS	0/7
M184V	0/7

[a] International Aids Society (IAS)-USA-defined major PI substitutions are V32I, L33F, M46I/L, I47V, G48V, I50L/V, I54M/L, I76V, I82A/F/T/S, I84V, N88S, and L90M.

[b] Substitution N88S was detected in one subject at Week 48. One additional subject who rebounded after Week 48 showed N88S and M46L major PI substitutions.

NA: not assessable

CONCLUSIONS:

- In HIV-1 infected subjects, with viral suppression (HIV RNA < 50 c/mL) for at least previous 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). All treatment failures occurred on or prior to Week 36.
- Treatment outcomes at Week 48 showed that 79% and 67% of the treated subjects maintained viral suppression below 400 c/mL and 50 c/mL, respectively.
- Through Week 48, 7 (12%) subjects had a confirmed virologic rebound (HIV RNA ≥ 400 c/mL): 1 subject had a major PI substitution (N88S) and 4 subjects had at least 1 minor PI substitution. Of these 7, most occurred on or prior to Week 24. One subject who rebounded after Week 48 showed both N88S and M46L major PI substitutions. No RT substitutions were detected in any subject.
- At Week 48, slight mean CD4 increases from baseline were observed.
- Through Week 48, the safety and tolerability of ATV/RTV monotherapy were consistent with the known safety and tolerability profile of ATV/RTV.

DATE OF REPORT: 13-Apr-2009