SYNOPSIS

TITLE OF STUDY: Atazanavir (BMS-232632) for HIV-Infected Individuals: An Early Access Program

INVESTIGATORS: Multicenter (see Appendix 4A for a Description of Investigators)

STUDY CENTERS: Multicenter (see Appendix 4A for a list of study centers)

PUBLICATIONS:

STUDY PERIOD: Date first subject enrolled: 07-Feb-2002 (Authorization for Temporary Utilization [ATU] Nominative)
17-May-2002 (Protocol AI424900)

Date of last subject visit: 31-Mar-2004 (ATU Nominative)
22-Apr-2005 (Protocol AI424900)

CLINICAL PHASE: 3B

OBJECTIVES:

Primary objective:
• To make atazanavir (ATV) available to human immunodeficiency virus (HIV)-infected subjects who had evidenced virologic failure with available antiretroviral (ARV) treatment options and who were unable to construct an alternative effective treatment regimen using currently available ARV agents due to virologic failure, drug intolerance, or adherence issues.

Secondary objective:
• To collect safety information on the use of ATV in this ARV-experienced population.

METHODOLOGY:
Protocol AI424900 was an open-label, multicenter, noncomparative early access program (EAP) to provide ATV to HIV-infected, treatment-experienced subjects who had failed ARV therapy and who were unable to construct an alternative effective treatment regimen using other available ARV agents due to prior virologic failure, drug intolerance, and/or adherence issues, or who otherwise met eligibility requirements. The Authorization for Temporary Utilization (ATU) Nominative was a temporary premarketing authorization program whereby investigators submitted a request form to the French Health Authority (FHA) on a named-patient basis. If a request was deemed acceptable, the release of ATV was authorized by the FHA.

The selection of ARV therapy was determined by the subject’s medical provider. In the original protocol, subjects received ATV 400 mg, administered once daily (QD) with food, in combination with 2 or more additional ARV agents. Based on accumulating evidence from other ongoing ATV clinical studies, amendments were subsequently made to the protocol that changed the dose of ATV to 300 mg QD if concomitant ARV medications included any 1 of the following: 1) Norvir® (ritonavir [RTV]) 100 mg QD (per Amendment 3); 2) RTV 100 mg plus Sustiva® (efavirenz [EFV]) 600 mg QD (per Amendment 3); or 3) RTV 100 mg plus Viread® (tenofovir disoproxil fumarate [TDF]) 300 mg QD (per Amendment 5). The subject’s HIV strain should have been susceptible to at least 1 of the ARV agents; susceptibility was determined based on the subject’s ARV history in conjunction with results of genotypic/phenotypic ARV resistance testing, if available. Subjects continued to receive ATV until 1 of the following occurred: the subject experienced a treatment-limiting toxicity; the subject voluntarily withdrew, died, or became lost to follow-up; the subject or the physician determined that the subject was no longer receiving any benefit from ATV therapy; or until termination of the study by the sponsor.

NUMBER OF SUBJECTS:
A total of 9924 subjects were enrolled: 9626 into Protocol AI424900 (including 4284 in The Americas cohort and 5342 in the Europe cohort) and 298 into the ATU Nominative. 8100 subjects received treatment in Protocol AI424900 and 233 in the ATU Nominative.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:
Subjects with a limited ability to construct a safe and effective ARV regimen from available agents based on the 2001 International Acquired Immunodeficiency Syndrome (AIDS) Society Treatment Guidelines were eligible for the EAP and ATU. The key eligibility criterion was treatment failure defined as ARV resistance, metabolic abnormalities (e.g., hypercholesterolemia, hypertriglyceridemia), or other intolerance or adherence problems and where a subject was unable to construct an alternate effective highly active antiretroviral therapy (HAART) regimen using other available ARV agents.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:
Reyataz® (atazanavir) was provided by Bristol-Myers Squibb (BMS) as both 200 mg and 150 mg capsules. Batch numbers for atazanavir 200 mg capsules were: MCD49; MCM175; MED71; MFE204; MFE205; MFE206; MKM358; MKM359; and MLA22. Batch numbers for atazanavir 150 mg capsules were: MBA105; MBA106; MED72; MFD75; and MKE271.

DURATION OF TREATMENT:
In Protocol AI424900, ATV was provided until the withdrawal of the subject, termination of the program by the sponsor, or until ATV became otherwise available to the subject. The first subject was enrolled into the ATU Nominative on 07-Feb-2002 and into Protocol AI424900 on 17-May-2002. The last subject visit date occurred on 31-Mar-2004 in the ATU Nominative and on 22-Apr-2005 in Protocol AI424900. In Protocol AI424900, 8100 subjects were treated with ATV. The median time on study drug was 26.1 weeks in Protocol AI424900. 72.5% of treated subjects in Protocol AI424900 and 84.5% of treated subjects in the ATU Nominative completed the study and transitioned to commercial sources of ATV.

CRITERIA FOR EVALUATION:
The only protocol-required laboratory testing after screening was alanine aminotransferase (ALT) and direct and total bilirubin. These tests were required at study entry, Week 4, Week 12, and every 12 weeks thereafter. All other testing was voluntary.

Safety:
The primary safety outcome for this EAP was the frequency and severity of adverse events (AEs) and serious adverse events (SAEs), both clinical and laboratory. Secondary safety outcomes were as follows: the change from study entry in serum levels of total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides (TG), and glucose over time; and the frequency of premature study therapy discontinuation.

The ATU Nominative program only required the French investigators to report SAEs.

Efficacy:
Efficacy was not a prespecified study objective. Routine measurements of HIV ribonucleic acid (RNA) and absolute CD4 cell counts were recommended to be performed every 8 to 12 weeks in accordance with current standards of HIV care. The following efficacy outcomes were considered to be exploratory and were evaluated based on receipt of adequate data: the change in HIV RNA over time (expressed as log_{10} c/mL); the proportion of subjects with ≥ 1.0 log_{10} c/mL decrease from study entry in HIV RNA or undetectable HIV RNA (< 400 c/mL); the proportion of subjects with undetectable HIV RNA (< 400 c/mL and < 50 c/mL); and the change in CD4 cell counts from study entry.

The ATU Nominative program did not require any efficacy data to be collected; therefore, the reporting of HIV RNA levels and absolute CD4 cell counts was done by the French investigators on a voluntary basis. Available data were analyzed.
STATISTICAL METHODS:
Analyses provided descriptive assessments by treatment regimen: unboosted ATV; “boosted ATV” (ATV + RTV, or ATV + Kaletra [LPV/RTV]); and total (unboosted ATV + boosted ATV). Boosted ATV was defined as subjects who received either RTV or Kaletra at any time during the study. No comparisons of treatment regimens were conducted.
Categorical variables were tabulated with counts and proportions. Continuous variables were summarized with univariate statistics.
Analyses were based on 4 cohorts. There were 3 cohorts which represented distinct geographic regions: “The Americas” (United States, Puerto Rico, Canada, and Latin America), “Europe” (all European countries except France; including 1 subject from Australia), and the “ATU Nominative” (French named-patient initiative). The fourth cohort was The All EAP cohort, hereafter referred to as the EAP cohort, which consisted of The Americas and Europe cohorts combined. The same analyses were performed for all 4 cohorts.
The efficacy data set included all treated subjects. HIV RNA levels and CD4 cell counts were included through 4 days after the last visit date.
The safety data set except those for SAEs and deaths prior to dosing included treated subjects; the exceptions noted were based on enrolled subjects. Adverse events and laboratory measurements were included through 60 days after the last visit date.

STUDY POPULATION:
Subjects in Protocol AI424900 were predominantly male (77.6%) and had a median age of 42 years. Subjects were moderately immunosuppressed. In Protocol AI424900 the baseline median HIV RNA level and CD4 cell count for treated subjects were 4.11 log₁₀c/mL and 258.0 cells/mm³ respectively. In the ATU Nominative the baseline median HIV RNA level was 3.96 log₁₀c/mL and the baseline median CD4 cell count was 268.0 cells/mm³. A history of CDC AIDS events was reported by 35.4% of treated subjects in Protocol AI424900. The study population was heavily pretreated; for the protocol AI424900 and ATU Nominative populations 93.0% and 70% respectively reported a history of exposure to PIs; 80.1% and 24.5% respectively reported a history of exposure to NNRTIs; and 99.5% and 82% reported a history of exposure to NRTIs.

SAFETY RESULTS:
• Clinical AEs (all grades) regardless of relationship to study therapy were reported in 29.2% of treated subjects in the EAP cohort. Clinical AEs were reported in 29.7% of ATV-treated subjects and 28.6% of ATV/RTV-treated subjects. The majority of all clinical AEs were mild or moderate (Grade 1 to 2). No specific Grade 3 to 4 events were reported in > 1.0% of treated subjects. Grade 3 to 4 events occurred in 9.3% of subjects receiving the ATV regimen and 7.7% of subjects receiving the ATV/RTV regimen.
• The clinical AEs of any grade that were reported in the EAP were consistent with expectations for ATV-based and ATV/RTV-based ARV regimens. Common clinical AEs reported were diarrhea (3.2% overall), nausea (3.1%), rash (2.7%), and vomiting (1.9%).
• Jaundice occurred in 1.7% of treated subjects overall (1.3% ATV and 2.1% ATV/RTV) in the EAP cohort. In addition, icterus/jaundice sclera was reported in 0.8% of treated subjects overall (0.5% ATV and 1.1% ATV/RTV).
• Serious AEs that developed on study were reported in 8.6% of treated subjects in the EAP cohort. Serious AEs were reported in 9.4% of ATV-treated subjects and 7.7% of ATV/RTV-treated subjects. The most commonly reported SAE for treated subjects was pneumonia (1.4% overall; 1.6% ATV and 1.1% ATV/RTV). All other SAEs occurred in < 1.0% of treated subjects in the EAP cohort.
Adverse events that led to discontinuation from study were reported in 7.0% of treated subjects in the EAP cohort (6.9% ATV and 7.2% ATV/RTV). The most common AEs leading to discontinuation for treated subjects were hyperbilirubinemia (0.7% overall; 0.4% ATV and 1.1% ATV/RTV) and rash (0.6% overall; 0.8% ATV and 0.4% ATV/RTV). Bilirubin increased and jaundice were each reported in 0.5% of subjects (0.4% ATV and 0.6% ATV/RTV). All other AEs leading to discontinuation were reported in ≤ 0.4% of treated subjects in the EAP cohort.

Overall, a total of 187 (1.9%) enrolled subjects in the EAP cohort died, including 134 subjects on the ATV regimen and 53 subjects on the ATV/RTV regimen. The analysis of deaths included both enrolled subjects who had death reported on the study termination page of the CRF and subjects who had an AE leading to death. The frequency of death was 2.5% in the ATV regimen and 1.2% in the ATV/RTV regimen. The majority of deaths were AIDS-related or associated with opportunistic infections and/or carcinomas associated with HIV disease progression. Of the 187 subjects who died, the most common AE resulting in death was AIDS (31/187, 16.6%), followed by pneumonia (18/187, 9.6%) and sepsis (17/187, 9.1%).

Clinical Laboratory Evaluations:

The majority of post-study entry liver function test abnormalities were Grade 1 to 2. By Week 4, the overall median total bilirubin value for all subjects in the EAP cohort increased to 1.37 mg/dL (1.20 mg/dL ATV and 1.62 mg/dL ATV/RTV). Not unexpectedly, subjects with AEs of jaundice or scleral icterus had higher total bilirubin values than subjects in the overall All EAP population.

The overall beneficial changes seen in metabolic parameters were as expected for ATV-based ARV regimens. There were greater reductions in total cholesterol, LDL cholesterol, and triglycerides in subjects taking ATV-based ARV regimens than in those taking ATV/RTV-based regimens. No clinically relevant changes in glucose were observed throughout the study.

Efficacy Results:

In the EAP cohort, the mean reduction at Week 24 in HIV RNA for subjects with HIV RNA > 400 c/mL at study entry was 1.2 log10 c/mL for the ATV regimen and 1.5 log10 c/mL for the ATV/RTV regimen. The mean reduction at Week 48 was 1.5 log10 c/mL for both regimens.

Of the 8100 treated subjects in the EAP cohort, 7474 had HIV RNA data recorded at the initiation of study therapy; of these, 2311 (30.9%) and 1336 (17.9%) had HIV RNA < 400 c/mL and < 50 c/mL, respectively. At Week 24, the proportions of treated subjects in the EAP cohort with HIV RNA < 400 c/mL and < 50 c/mL were 64.7% and 41.9%, respectively. Response rates at Week 48 were 69.4% and 52.5% for subjects with HIV RNA < 400 c/mL and < 50 c/mL, respectively. Response rates for the ATV/RTV regimen were greater than for the ATV regimen at Week 24 (59% vs 70%) but not at Week 48 (70.7% vs 68.2%). This finding may reflect that subjects who were initially on an ATV regimen who did not achieve good virologic response likely switched to ATV/RTV after Amendments 3 and 5 were incorporated into the study. This would have had the likely effect of improving response rates for the ATV regimen and lowering the response rates for the ATV/RTV regimen at Week 48 and thereafter.

As noted previously, of the 7474 treated subjects in the EAP cohort in whom HIV RNA data was recorded at the initiation of study therapy, 2311 (30.9%) had HIV RNA < 400 c/mL. By Week 24, 67.7% of these 7474 subjects had achieved either a ≤ 1.0 log10 c/mL decrease from their HIV RNA level at study entry or had an undetectable HIV RNA (< 400 c/mL). The proportion of subjects achieving this combined endpoint at Week 48 was 74.0%.

The median CD4 cell count at study entry for treated subjects in the EAP cohort was 258.0 cells/ mm³ (238.5 cells/mm³ for the ATV regimen and 277.0 cells/mm³ for the ATV/RTV regimen). The mean increases for subjects on the ATV regimen were 42.7 cells/ mm³ and 55.9 cells/ mm³ at Weeks 24 and 48, respectively. The mean increases for subjects on the ATV/RTV regimen were 48.3 cells/ mm³ and 63.9 cells/ mm³ at Weeks 24 and 48, respectively.
The number of subjects with available data in the ATU Nominative was considered too small to indicate clinically meaningful results.

CONCLUSIONS:

- Protocol AI424900 and the ATU Nominative provided early access to 9924 HIV-1 infected subjects worldwide who had limited options for a safe and effective ARV regimen.
- The efficacy of ATV- and ATV/RTV-based ARV regimens in treatment-experienced subjects was consistent with expectations based on previous studies.
- No new areas of safety concern were identified during the study.

REPORT DATE: 19-Jan-2006