Population Pharmacodynamic (PD) Assessment of the Safety and Antiretroviral Activity of Atazanavir (BMS-232632)

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ABSTRACT

Background: Atazanavir (BMS-232632), currently in Phase III development, is a well-tolerated, once-daily protease inhibitor (PI) which does not appear to elevate cholesterol or triglyceride blood levels and has a favorable resistance profile in vitro. Using a population pharmacokinetic (PK) model developed previously, PK/PD analyses were performed on interim Phase II data to assist in dose selection.

Methods: Sparse PK sampling was performed at weeks 2, 4, 12, 24, and 48 during a randomized Phase II study. Patients received 200, 400, or 500 mg once daily for 2 weeks as monotherapy, then combined with stavudine (d4T) and didanosine (ddI) thereafter. The PK model was a 2-compartment mixture model allowing for 2 populations of absorption rate constant and volume of the central compartment. Bayesian parameter estimates were utilized to predict individual values for the area under the plasma concentration-time curve (AUC) as the exposure measure. Plasma HIV RNA and bilirubin (bili) levels were obtained at baseline and after 2 weeks. Logistic regression analyses were performed evaluating AUC as a predictor of failure to achieve a 1.5 log decrease in HIV RNA or probability of bili elevation >2.5 mg/dL.

Results: Fifty-six patients had PK, HIV RNA and bili data. Logistic regression identified AUC as a significant predictor of failure to achieve 1.5 log reduction in HIV RNA (P=0.0164), where failure to respond was more likely in patients with lower AUC values. Conversely, the probability of bili elevation >2.5 mg/dL was greater in patients with higher AUC values (P=0.0002). In dose comparisons, the mean/median steady state AUC (ng•hr/mL) values for 400 mg versus 500 mg were 23.5/23.1 and 36.4/31.7, respectively. The associated probabilities of achieving the HIV RNA reduction at these doses were 0.78/0.77 and 0.9/0.86, whereas the probabilities for bili elevation were 0.171/0.168 and 0.338/0.269, respectively.

Conclusions: The 400-mg once-daily dose of atazanavir provides an effective reduction of HIV RNA and minimizes the probability of hyperbilirubinemia. Overall, these results support selection of the 400-mg dose for Phase III evaluation.

INTRODUCTION

- Optimal antiretroviral therapy for HIV-infected patients involves potent combinations of antiretroviral agents that are well tolerated and facilitate patient adherence. Highly active antiretroviral therapy (HAART) with 2 nucleoside analogs and a protease inhibitor (PI) is a current standard of care in developed countries
- Atazanavir (BMS-232632), currently in Phase III development, is a safe, well-tolerated and effective once-daily PI with a superior lipid profile. Atazanavir does not appear to elevate total cholesterol, fasting LDL cholesterol or fasting triglyceride blood levels compared with prompt, marked and sustained elevations with current PIs
- Atazanavir is one of a new class of azapeptide PIs, and atazanavir has a favorable resistance profile in vitro. This agent has demonstrated in vitro activity against HIV-1 isolates and in clinical trials rapidly and durably suppresses HIV RNA and increases CD4
- The PK profile of atazanavir obtained in Phase I dose-escalation studies supports once-daily dosing. Atazanavir has been well tolerated in healthy subjects, although the clinical laboratory abnormality of isolated elevations of (primarily unconjugated) serum bilirubin levels has been noted
- The present investigation was conducted to evaluate therapeutic and safety-response relationships with atazanavir at 3 dose levels. AUC was used as an exposure measure, and HIV RNA and bilirubin levels were used as response measures. The results were expected to support a Phase III dose selection

METHODS

Study Design

- In this 48-week Phase II study, patients were randomized to receive oral atazanavir 200, 400, or 500 mg once daily as monotherapy for 2 weeks before d4T and ddI were added for an additional 46 weeks. A 2-week course of monotherapy with atazanavir was selected, as there was little risk of HIV resistance occurring in this time frame
  - Doses of atazanavir and ddI were administered at least 1 hour apart
  - Initial doses were adjusted based on viral loads and bilirubin levels
- Randomization was stratified by plasma HIV RNA levels: <30,000 copies/mL and ≥30,000 copies/mL
- Sampling
  - Two samples were obtained at week 2 (predose and at least 3 hours after the preceding dose)
  - One sample was obtained at weeks 4, 12, 24, and 48 (at least 3 hours after the preceding dose)

Pharmacokinetic Analyses

- PK model
  - Developed using data from fasted subjects in a Phase I dose-escalation study
  - Two-compartment mixture model allowing for 2 populations of absorption rate constant and volume of the central compartment using NONMEM
- Bayesian parameter estimates from this PK model were used to predict steady state Cp–time profiles for each Phase II patient

Pharmacodynamic Analyses

- AUC_{0-24}
  - Calculated using the trapezoidal rule on the predicted concentration-time profile
- Plasma HIV-RNA levels
  - Obtained at baseline and at 2 weeks
  - Magnitude and durability of the reduction in terms of the change from baseline, expressed in $\log_{10}$
- Bilirubin levels
  - Obtained at baseline and at 2 weeks
- Logistic regression analyses with stepwise selection were used to evaluate the probability of a log drop in HIV RNA versus AUC and the probability of a bilirubin level elevation above 2.5 mg/dL (lower bound of grade 3 lab toxicity) versus AUC. The 1.5-log decline in HIV RNA copies from baseline was selected, as that value was greater than the mean change in HIV RNA from baseline for both indinavir and ritonavir monotherapies[1,2]
- An α=0.05 (1 degree of freedom) was used to define statistical significance for the addition of a single parameter, and an α=0.01 (1 degree of freedom) was used for the deletion of a single parameter

RESULTS

Data

- A total of 56 Phase II patients had PI exposure, HIV RNA, and bilirubin data
- All PK data available at the time of the interim analyses were used to generate the steady state AUCs
- Since the data were unlocked, it was assumed that all patients were fasted and that patients received all doses for the entire trial

Pharmacokinetic Modeling

Table 1. Parameter Estimates From the Phase I PK Model Used for Bayesian Prediction of the Phase II Patients

	Final Parameter Estimate		Magnitude of Interindividual Variability (% CV)	
Parameter	Final Estimate	% SEM	Final Estimate	% SEM
CL–200 mg (L/hr)	36.7	18.8	28.35	35.9
CL–400 & 600 mg (L/hr)	25.2	7.2		
Vc–Group 1 (L)	187	16.5		
Vc–Group 2 (L)	109	16.9		
Q (L/hr)	6.08	19.2		
Vp (L)	39.1	27.1		
Ka–Group 1 (1/hr)	1.45	24.2		
Ka–Group 2 (1/hr)	6.48	50.5		
Abs. lag time (hr)	0.470	1.4		
Prob. Group 1	0.477	23.1		
Residual variability (% CV)	38.86	12.8		
Min. value of the objective function	3626.564			

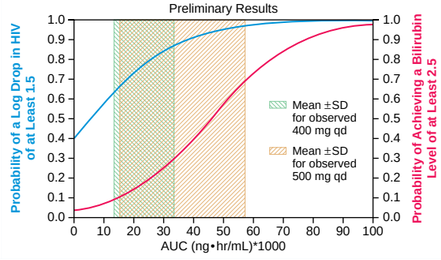
Pharmacodynamic and Safety Analyses

Table 2. Logistic Regression Analyses of Predictors of Failure

Daily Dose	AUC [ng-hr/mL*1000] (mean/median steady state)	HIV RNA Drop (mean/median probability)	Bilirubin Elevation (mean/median probability)
200 mg	6.82/5.41	0.52/0.49	0.06/0.06
400 mg	23.5/23.1	0.78/0.77	0.171/0.168
500 mg	36.4/31.7	0.90/0.86	0.338/0.269

- Patients with lower AUC values were less likely to achieve a 1.5-log reduction in HIV RNA (p=0.0164).
- Patients with higher AUC values were more likely to have bilirubin elevations >2.5 mg/dL (p=0.0002).

Figure 3. Logistic Regression Probability Curves Overlayed



- If this evaluation were performed in fed patients, at each dose level the AUC range would be shifted higher and the variability would be decreased

Figure 1. Line Plot of the Measured Concentration (ng/mL) Versus Time Since Last Dose and the Bayesian (Individual) Predicted Concentration Versus Time Since Last Dose Overlayed, Stratified by ID, Mixture Model Group, and Dose for Two Selected Phase I Subjects

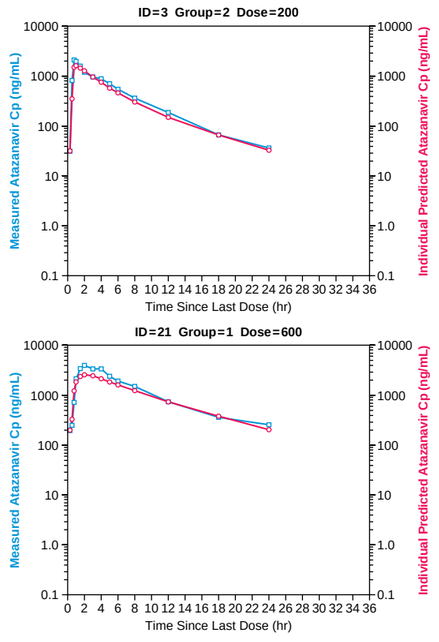
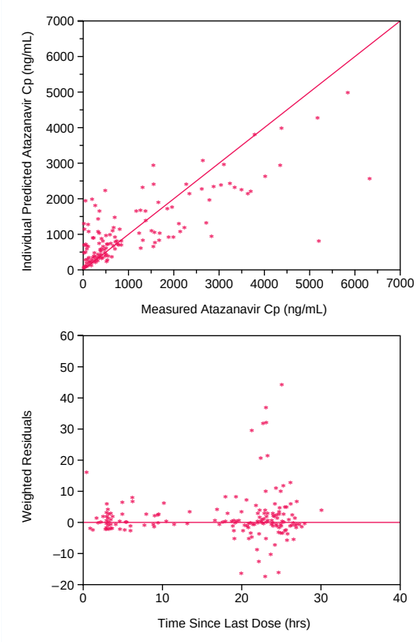


Figure 2. Scatterplot of the Bayesian (Individual) Predicted Cp Versus Measured Cp and Scatterplot of Weighted Residuals Versus Time Since Last Dose for the Phase II Data



CONCLUSIONS

- Based on this, the 400-mg once-daily dose of atazanavir provides an effective reduction of HIV RNA and minimizes the probability of hyperbilirubinemia
- With atazanavir treatment once daily, the likelihood of a patient achieving a 1.5-log drop in HIV RNA copies is greater at the 400-mg and 500-mg dose levels
- The risk of a bilirubin elevation >2.5 mg/dL is greatest at the 500-mg dose level
- AUC was shown to be a significant predictor of virologic failure and bilirubin elevation
- Overall, these findings support selection of the 400-mg dose of atazanavir once daily for Phase III evaluation

REFERENCES

1. Physicians' Desk Reference, 55th Edition. Ritonavir package insert. Montvale, NJ: Medical Economics Company; 2001;472–478.
2. Physicians' Desk Reference, 55th Edition. Indinavir package insert. Montvale, NJ: Medical Economics Company; 2001;1904–1909.