Population Pharmacodynamic Assessment of Atazanavir Exposure, Uridine Diphosphate-Glucuronosyl Transferase (UGT) 1A1 Genotype and Safety in Healthy Subjects

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ABSTRACT

Background: Atazanavir (BMS-232632) is a potent HIV-protease inhibitor with a favorable resistance profile *in vitro*. Dose-related elevations of total bilirubin (primarily unconjugated) have been observed with atazanavir, and are attributed to inhibition of UGT 1A1, which glucuronidates unconjugated bilirubin. Total bilirubin levels observed secondary to isoform inhibition by atazanavir are not considered clinically toxic. The two principal alleles in the promoter region of the UGT 1A1 gene are designated "6" and "7." The 7/7 genotype is synonymous with Gilbert's syndrome.

Objective: Assess the relationship between total bilirubin, atazanavir exposure and UGT 1A1 genotype in healthy subjects.

Methods: Oral atazanavir at 200-800 mg QD or 100-200 BID was evaluated in 6 Phase I studies. Total bilirubin was measured at selected times up to 21 days. Genotyping quantified the "6" and "7" allelic forms. Steady-state pharmacokinetic profiles were obtained to estimate the 24-hour area under the concentration-time curve (AUC) as the exposure measure. Total bilirubin and AUC within the genotype groups were assessed with non-parametric tests. Logistic regression analyses evaluated AUC and genotype as predictors of total bilirubin elevation > 2.5 mg/dL.

Results: Of 202 subjects with total bilirubin data, 156 had genotypes and 138 also had atazanavir PK data. Total bilirubin levels plateaued approximately 3-4 days after the first dose in subjects with genotypes 6/6 and 6/7, but continued to increase at a slower rate for genotype 7/7 subjects. This group had significantly higher median total bilirubin levels than the 6/6 or 6/7 groups (3.4 mg/dL versus 1.2 and 1.6 mg/dL, respectively). No significant relationship between AUC and UGT genotype was found. Genotype was identified as a significant predictor of higher probability of total bilirubin elevation > 2.5 mg/dL (p=0.0001). The probability was higher in subjects with higher AUC values (p=0.0001).

Conclusions: Overall, total bilirubin elevation after atazanavir dosing is more likely in subjects with the UGT1A1 genotype 7/7 or with higher atazanavir AUC values.

INTRODUCTION

- Atazanavir is a potent, safe, well-tolerated azapeptide protease inhibitor in Phase III clinical development. Four hundred milligrams once-daily, administered as 2 capsules, rapidly and durably supress HIV RNA.
  - ATV has a distinct resistance profile
  - Resistance (I50L) uncommonly observed; associated with increased *in vitro* sensitivity to other protease inhibitors
- Atazanavir has been well tolerated in healthy subjects, although the clinical laboratory abnormality of dose-related elevations of (primarily unconjugated) serum bilirubin has been observed.

INTRODUCTION (cont'd)

- *In vitro* investigation has demonstrated that the mechanism of the bilirubin elevation is a primarily competitive inhibition of the UGT 1A1 isoform by atazanavir. Because of the inhibition of the isoform (producing a pseudo-Gilbert's syndrome), there is less UGT isozyme available to glucuronidate bilirubin, thus causing an elevation of unconjugated bilirubin.
- The likelihood of bilirubin elevation may also be related to individual genotype. Two principal allelic forms have been described for the promoter region of the UGT gene (hereafter 6 and 7). The presence of two "7" alleles results in reduced expression of the gene and is synonymous with Gilbert's syndrome.
- These analyses describe the relationship between total bilirubin, UGT genotype, and atazanavir exposure in Phase I subjects.

OBJECTIVE

- To assess the time course of serum bilirubin levels after initiation of atazanvir for subjects with UGT genotypes 6/6, 6/7, and 7/7.
- To assess the relationship between total bilirubin, atazanavir exposure, and UGT genotype.
- To statistically evaluate the above relationship for bilirubin elevations greater than 2.5 and 5.0 mg/dL at treatment durations of 5,6, or 7 days.

METHODS

Study Design and Data

- Oral atazanavir was evaluated in six Phase I studies of healthy male subjects.

Table 1: Summary of Data

Protocol/ Treatment Duration (days)	Dosing Regimen	Study Day Bilirubin Measured in Trend Analysis	PK Profile/Bilirubin Measurement Day in Exposure Analysis	Meal Status When Drug Administered
AI424-002/ 14	200 mg QD 400 mg QD 600 mg QD 800 mg QD 100 mg BID 200 mg BID	Screening, 3, 5, 7, 9, 11, 13, 16, and 21 and possibly more frequently than once-daily	7/7	Fasted
AI424-016/ 6	400 mg QD	Screening, 2, 4, 5	6/5	Fed
AI424-021/ 14	400 mg QD	Screening, 7, 14	7/7	Fed
AI424-028/ 6	200 mg QD 400 mg QD	Screening, 1, 2, 4, 6	6/6	Fed
AI424-039/ 14	400 mg QD	Screening, 1, 14	----	Fed
AI424-040/ 5	200 mg QD 400 mg QD 800 mg QD	Screening, 5	5/5	Fed

- UGT genotyping quantified "6" and "7" allelic forms in the promoter region of the UGT 1A1 gene.

METHODS (cont'd)

Trend Analysis

- Evaluation of total bilirubin versus time, stratified by dose and genotype, for bilirubin levels obtained during atazanvir monotherapy
- Evaluation of total bilirubin versus estimated AUC_{0-24}, stratified by genotype

Pharmacodynamic Analyses

- AUC_{0-24} calculated using the trapezoidal rule on the predicted concentration-time profile
- Kruskal-Wallis tests were performed to evaluate differences in total bilirubin or atazanavir exposure among the three genotype groups. Pair-wise comparisons of total bilirubin and AUC_{0-24} by genotype were performed using the Wilcoxon Rank Sum test to further detect differences (p-value ≤ 0.0016).
- Statisitical analyses were performed for data from Days 5, 6, and 7 combined. Only data from subjects administered once-daily regimens were included.
- Logistic regression analyses with backward elimination were performed to evaluate AUC and genotype as predictors of bilirubin elevation ≥ 2.5 (lower bound of grade 3 lab toxicity) and 5 mg/dL (dose reduction to next lowest atazanavir dose at this elevation). Level of significance for backward selection was 0.05.
- Goodness-of-fit of the final model assessed by evaluation of graphic displays and the Hosmer-Lemeshow statistic.

RESULTS

- Of 202 subjects with total bilirubin data, 156 had genotypes and 138 also had atazanavir PK data.

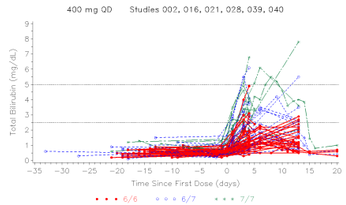
Table 2: Subject Demographic Characteristics

Demographic Characteristic		All Subjects (n = 156)
Age (years)	Mean (SD)	31.97 (8.44)
Weight (kg)	Mean (SD)	77.73 (10.53)
Height (cm)	Mean (SD)	176.20 (7.49)
Gender	Female, n (%)	24 (15.4 %)
	Male, n (%)	132 (84.6 %)
Race	White, n (%)	127 (81.4 %)
	Black, n (%)	24 (15.4 %)
	Asian/Pacific Islander, n (%)	3 (1.9 %)
	Hispanic/Latino, n (%)	2 (1.3 %)
Dose (mg)	100 mg BID, n (%)	6 (3.8 %)
	200 mg BID, n (%)	5 (3.2 %)
	200 mg QD, n (%)	18 (11.5 %)
	400 mg QD, n (%)	96 (61.5 %)
	500 mg QD, n (%)	6 (3.8 %)
	600 mg QD, n (%)	12 (7.7 %)
	800 mg QD, n (%)	13 (8.3 %)

RESULTS (cont'd)

Trend Analysis

Figure 1: Total Bilirubin vs. Time Since First Dose (400 mg QD)



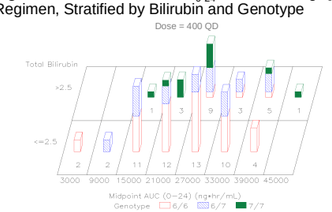
- The same pattern of reversible changes in total bilirubin was observed at all dose levels.

Table 3: Summary Statistics for $AUC_{(0-24)}$ (ng*hr/mL) on Study Day 5 (Study 040), Study Day 6 (Studies 016 and 028), and Study Day 7 (Studies 002 and 021)

Dose Regimen	Number of Subjects	Mean (SD) $AUC_{(0-24)}$	$AUC_{(0-24)}$ Range[b]
100 mg BID	6	4512.8 (2274.0)	1848.6-8031.2
200 mg BID	5	19251.1 (9799.9)	10108.8-34107.2
200 mg QD	17	7468.4 (3673.1)	1961.6-18051.5
400 mg QD	79	25725.4 (9191.4)	4075.6-46987.1
500 mg QD[a]	6	14556.2 (9803.5)	2847.6-28406.1
600 mg QD[a]	12	24269.8 (18080.0)	2353.3-73217.6
800 mg QD	13	61127.0 (30209.0)	6986.9-113981.8

[a] All subjects from AI424-002 (fasted).
[b] Range = Minimum-Maximum

Figure 2: Block Chart of AUC_{0-24} for the 400 mg QD Dosing Regimen, Stratified by Bilirubin and Genotype



Pharmacodynamic Analysis

- No relationship was evident between AUC_{0-24} and UGT genotype, suggesting that UGT genotype does not significantly influence the pharmacokinetics of atazanavir.
- Total bilirubin was significantly higher in the genotype 7/7 group compared to genotype 6/6 and 6/7 (p-value = 0.0001 and 0.0006, respectively).

RESULTS (cont'd)

Pharmacodynamic Analysis (cont'd)

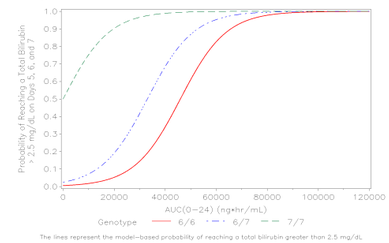
- The percentage of subjects with total bilirubin > 2.5 mg/dL was 12.9% (8/62) in the 6/6 genotype group, 34.7% (17/49) with genotype 6/7, and 84.6% (11/13) with genotype 7/7.

Table 4: Logistic Regression Analysis Results for AUC_{0-24} Model Evaluating Probability of Total Bilirubin Greater Than 2.5 mg/dL on Days 5, 6, and 7

Parameter	Estimate	Standard Error	p-value	Odds Ratio	95% CI
AUC_{0-24} ng*hr/mL	0.000111	0.0256	0.0001	1.117	(1.063,1.175)
Genotype 6/6	-5.1009	0.9105	0.0001	0.006	(0.001,0.036)
Genotype 6/7	-3.6679	0.7873	0.0001	0.026	(0.005,0.119)

- Logistic regression analysis evaluating bilirubin elevation > 5.0 mg/dL could not be performed due to the small number of subjects with this level of elevation.

Figure 3: Model-Based Predicted Probability of Total Bilirubin Elevation Greater Than 2.5 mg/dL on Days 5, 6, and 7 versus AUC_{0-24} Stratified by Genotype



SUMMARY

- UGT genotype does not significantly influence the pharmacokinetics of atazanavir.
- The likelihood of bilirubin elevation > 2.5 mg/dL was significantly greater throughout the ranges of AUC_{0-24} for subjects with genotype 7/7 compared to subjects with genotypes 6/6 and 6/7 after 5-7 treatment days.
- With increasing AUC_{0-24}, the proportion of subjects with total bilirubin > 2.5 mg/dL increases, regardless of genotype.