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Study Initiation Date:	13-Feb-2006
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EFFECT OF A HIGH-FAT OR A LIGHT MEAL RELATIVE TO FASTING CONDITIONS ON THE PHARMACOKINETICS OF ATAZANAVIR WHEN ADMINISTERED WITH RITONAVIR IN HEALTHY SUBJECTS

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FINAL REPORT SYNOPSIS

TITLE OF STUDY: Effect of a High Fat or a Light Meal Relative to Fasting Conditions on the Pharmacokinetics of Atazanavir When Administered With Ritonavir in Healthy Subjects

INVESTIGATORS: [redacted]

STUDY CENTERS:

PUBLICATIONS: None

STUDY PERIOD: Date first subject enrolled: 13-Feb-2006

Date last subject completed: 16-May-2006

CLINICAL PHASE: 1

OBJECTIVES:

Primary Objective: To assess, in healthy subjects, the effect of a light or high fat meal on the single dose pharmacokinetics (PK) of atazanavir (ATV) 300 mg, when administered in combination with ritonavir (RTV) 100 mg.

Secondary Objectives:

- To assess, in healthy subjects, the effect of a light or high fat meal on the PK of a single dose of RTV 100 mg, when administered in combination with ATV 300 mg
- To assess, in healthy subjects, the safety of a single dose of ATV 300 mg when administered in combination with RTV 100 mg, with or without food

METHODOLOGY: This was an open-label, randomized, three-period, three-treatment, crossover study in healthy subjects. Subjects underwent screening evaluations to determine eligibility within 21 days prior to first study dose. Subjects were admitted to the clinical facility the evening prior to dosing (Day -1) for each period. Prior to Period 1, 42 subjects were randomized to receive 1 of 6 sequences of 3 treatments including: **Treatment A**, a single oral dose of ATV 300 mg (2 x 150 mg capsules) with RTV 100 mg (1 x 100 mg capsule) in a fasted condition, **Treatment B**, a single oral dose of ATV 300 mg with RTV 100 mg after consuming a standard light breakfast and **Treatment C**, a single oral dose of ATV 300 mg with RTV 100 mg after consuming a standard high fat breakfast. There was a $\geq$ 7 day washout period between each dose. For each treatment period, subjects were confined to the clinical facility until at least 72 hours post-dose. Blood samples were collected for PK analysis up to 72 hours post-dose. Physical examinations, vital sign measurements, 12-lead electrocardiograms (ECG), and clinical laboratory evaluations were performed at selected times throughout the study. Subjects were closely monitored for adverse events (AEs) throughout the study. Approximately 260 mL of blood was drawn from each subject during the study.

NUMBER OF SUBJECTS: A total of 60 subjects were enrolled and 42 were treated in this study. Thirty-nine (39) subjects completed the study. Twenty-eight (28) males and 14 females were randomized and treated. Mean (SD) age and body mass index (BMI) were 31 (7) years and 23.9 (3) kg/m^2,

respectively. Race designation of these subjects were 31 Caucasian (74%), 6 Black (14%), 1 Asian (2%), and 4 Other (10%). Races designated as "Other" included Latino (1), Brazilian (2), and Mixed (1).

MAIN CRITERIA FOR INCLUSION: Eligible subjects included men and women (including WOCBP who had been using an adequate method of contraception 1 month prior to, throughout, and for 1 month after study completion and who had not used a prohibited contraceptive method within 3 months of dose) within 18 to 50 years of age, with a BMI of 18-30 kg/m^2, inclusive.

TEST PRODUCT, DOSAGE FORM AND MODE OF ADMINISTRATION, BATCH NUMBERS: Atazanivir 300 mg (2 X 150 mg capsule) for oral use, Product Identification Number 232632-R150-057-0, Product Batch Number 5F03857, Label Batch Number 5F02658. Ritonavir 100 mg (1 X 100 mg capsule) for oral use, Product Batch Number 5E07960, Label Batch Number 27367VA, 5F02691. ATV/RTV was dosed orally with either a light or high fat meal.

DURATION OF TREATMENT: Each subject received 3 single-daily doses of ATV/RTV as randomized for a duration of treatment of 3 days.

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

Atazanivir 300 mg (2 X 150 mg capsule) for oral use, Product Identification Number 232632-R150-057-0, Product Batch Number 5F03857, Label Batch Number 5F02658. Ritonavir 100 mg (1 X 100 mg capsule) for oral use, Product Batch Number 5E07960, Label Batch Number 27367VA, 5F02691. ATV/RTV was dosed orally fasting.

CRITERIA FOR EVALUATION:

Pharmacokinetic Measures:

For all subjects, the following pharmacokinetic parameters were determined for ATV and RTV:

- Cmax: Maximum observed concentration on Day 1 of each period
- Tmax: Time to reach Cmax on Day 1 of each period
- AUC(0-T): Area under the plasma concentration-time curve from zero to the last time of the last quantifiable concentration
- AUC(INF): Area under the plasma concentration-time curve from time zero extrapolated to infinite time
- T-HALF: Terminal elimination half-life
- C24: Concentration 24 hours after a single dose; a surrogate for Cmin, the steady-state concentration 24 hours after multiple dosing

Pharmacodynamic Measures: Not applicable.

Safety Measures: Safety assessments were based on medical review of AE reports and the results of vital sign measurements, ECGs, physical examinations, and clinical laboratory tests. The incidence of AEs were tabulated and reviewed for potential significance and clinical importance for treatments of ATV/RTV.

STATISTICAL METHODS:

Sample Size: If food had no effect on the PK of ATV in the ATV/RTV regimen, then 36 completed subjects would provide at least 90% power to conclude absence of effect on each of AUC(INF) and Cmax of ATV. If the actual effect was a 10% increase, the power would be reduced to 59% for AUC(INF). To allow for dropouts, 42 subjects were randomized to the study.

Statistical Analysis:

Safety Data: All recorded adverse events were listed and tabulated by preferred term, system organ class, and treatment. Vital signs and clinical laboratory test results were listed and summarized by treatment sequence. Any significant physical examination findings and clinical laboratory results were listed. ECG recordings were evaluated by the Investigator and abnormalities, if present, were listed.

Pharmacokinetic Data: To assess the effect of food on the PK of ATV in the ATV/RTV regimen, general linear model analyses were performed on log(Cmax), log[AUC(0-T)], and log[AUC(INF)] of ATV. The factors in the analyses were treatment, period, and sequence as fixed effects and subject nested within sequence as a random effect. The ATV/RTV regimen under fasting conditions was used as the reference. Point estimates and 90% confidence intervals for differences on the log scale were exponentiated to obtain estimates for ratios of geometric means on the original scale. Similar analyses were performed to assess the effect of food on the PK of RTV in the ATV/RTV regimen. No adjustments were made for multiplicity. Though not specified in the protocol, similar analyses were carried out for ATV C24 (the 24 hour post-dose concentration).

Summary statistics were provided by treatment for all of the PK parameters of each of the analytes. Geometric means and coefficients of variation were reported for Cmax, AUC(0-T), and AUC(INF). Medians, minima, and maxima were reported for Tmax. Means and standard deviations were reported for all other PK parameters. Though not specified in the protocol, geometric means and coefficients of variation were reported for ATV C24 (the 24 hour post-dose concentration).

Pharmacodynamic Data: Not applicable.

PHARMACOKINETIC RESULTS:

The adjusted geometric means and their ratios with 90% confidence intervals for ATV PK parameters are presented below:

Statistical Analyses for ATV Pharmacokinetic Parameters

Pharmacokinetic Parameter	Adjusted Geometric Means		Ratios of Adjusted Geometric Means Point Estimate (90% CI)
	A: ATV/RTV 300/100 mg fasted	B: ATV/RTV 300/100 mg Light Meal	
Cmax (ng/mL)	2386	3335	1.3976 (1.1740, 1.6637)
AUC(INF) (ng•h/mL)	22148	29507	1.3323 (1.1696, 1.5175)
AUC(0-T) (ng•h/mL)	21937	29356	1.3382 (1.1729, 1.5267)
C24 (ng/mL)	270	377	1.3954 (1.2414, 1.5685)
	A: ATV/RTV 300/100 mg fasted	**C: ATV/RTV 300/100 mg High Fat Meal**	
Cmax (ng/mL)	2386	2120	0.8883 (0.7478, 1.0553)
AUC(INF) (ng•h/mL)	22148	22430	1.0127 (0.8904, 1.1519)
AUC(0-T) (ng•h/mL)	21937	22261	1.0147 (0.8907, 1.1561)
C24 (ng/mL)	270	358	1.3258 (1.1809, 1.4885)

A light meal increased ATV Cmax, AUC(INF), and C24 by on average 40%, 33%, and 40%, respectively, compared to when ATV was administered under fasted conditions. With a high fat meal, ATV Cmax was estimated to be within 12% of fasted values, AUC (INF) and AUC(0-T) were unchanged, and C24 on average was increased by 33%. Tmax increased to 5h (range:1.5-10h) with a high fat meal as compared to that with either a light meal (2.5h, 1.5-6h) or fasting (2h, 1-5h).

The adjusted geometric means and their ratios with 90% confidence intervals for RTV PK parameters are presented below:

Statistical Analyses for RTV Pharmacokinetic Parameters

Pharmacokinetic Parameter	Adjusted Geometric Means		Ratios of Adjusted Geometric Means Point Estimate (90% CI)
	A: ATV/RTV 300/100 mg fasted	B: ATV/RTV 300/100 mg Light Meal	
Cmax (ng/mL)	1151	1261	1.0959 (0.9478, 1.2673)
AUC(INF) (ng•h/mL)	6531	7370	1.1286 (1.0149, 1.2550)
AUC(0-T) (ng•h/mL)	6464	7313	1.1314 (1.0159, 1.2600)
	A: ATV/RTV 300/100 mg fasted	C: ATV/RTV 300/100 mg High Fat Meal	
Cmax (ng/mL)	1151	868	0.7544 (0.6535, 0.8709)
AUC(INF) (ng•h/mL)	6531	5908	0.9046 (0.8144, 1.0049)
AUC(0-T) (ng•h/mL)	6464	5846	0.9043 (0.8129, 1.0061)

A light meal increased RTV Cmax and AUC(INF) by on average 10% and 13%, respectively, and a high fat meal decreased RTV Cmax and AUC(INF) by on average 25% and 10%, respectively compared to when administered under fasted conditions.

PHARMACODYNAMIC RESULTS: Not applicable.

SAFETY AND TOLERABILITY RESULTS: There were no deaths or discontinuations due to AEs during the study. A total of 28 AEs were reported in 14 of the 42 (33%) treated subjects. No notable differences existed in the frequency of AEs observed while the subjects were in a fed (light or high fat) versus a fasted state.

The most frequently reported treatment emergent AE in this study was headache which was reported in 9 (21%) subjects. The only other AEs occurring in more than 1 subject were nausea and diarrhea which were each noted in 2 subjects.

Incidence of laboratory abnormalities (hematology, chemistry, and urinalysis) were generally infrequent, of low grade of severity, and were not related to the fasted/fed state of dosing. Additionally, vital signs, ECG recordings , and physical exam results were unaffected by fasted/fed state of dosing.

CONCLUSIONS:

- Relative to fasting conditions, a light meal increased ATV exposures following ATV/RTV; Cmax and C24 were increased by approximately 40% and AUC by approximately 33%.
- ATV Cmax with a high fat meal was estimated to be within 12% of fasting values. AUC was unchanged relative to fasting conditions. C24 was increased by approximately 33% due to delayed absorption - median Tmax was increased from 2.0 to 5.0 h.
- In the presence of RTV, the coefficient of variation (CV) of ATV exposures under fasting conditions was approximately 45- 49%. Under fed conditions, the CV decreased to approximately 35- 37%.
- When given with either a light or high fat meal, RTV AUC was minimally affected (on average within 13% of fasting). Absorption was delayed when administered with food.
- ATV/RTV was generally safe and well tolerated.
- Coadministration of ATV and RTV with food optimizes ATV bioavailability.

DATE OF REPORT: 11-Apr-2007