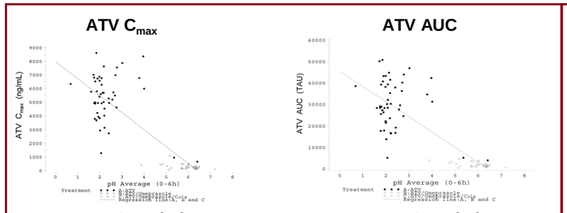
RESULTS (Cont'd)

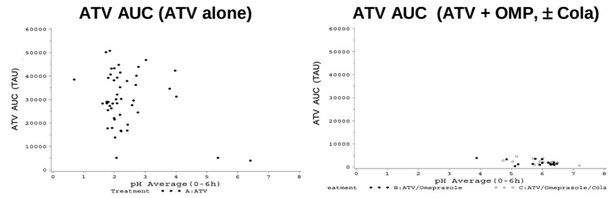
Figure 7: Regression Plots of ATV C_{max} and AUC versus pH Average (0-6h) for ATV alone, and ATV + OMP ± Cola



Pearson Correlation Coefficient =-0.84

Pearson Correlation Coefficient =-0.82

Figure 8: Scatter Plots of ATV AUC versus pH Average (0-6h) for ATV alone, and ATV + OMP ± Cola



Pearson Correlation Coefficient =-0.31

Pearson Correlation Coefficient =-0.47

- When data from the three treatments (ATV alone, ATV + OMP, ATV + OMP + cola) were analyzed together, a good correlation between ATV C_{max} and AUC vs pH was obtained
- At physiologic intra-gastric pH, a weak correlation was obtained for ATV alone
- Similarly, a weak correlation for ATV and OMP was noted as the pH data were clustered around pH values of 5-6.5

Safety

- No deaths, serious adverse events, or discontinuation from study due to AEs were reported in this study
- A total of 28 treatment-emergent clinical AEs were reported in 20 (41.7%) of the subjects; all were mild in intensity with the majority resolving prior to study discharge
- Jaundice was the most commonly reported AE occurring in 10 (20.8%) subjects. Other AEs with ≥ 3% frequency included headache in 8 (16.7%) subjects, dizziness in 2 (4.2%) subjects and abdominal pain in 2 (4.2%) subjects
- Grade 3 and 4 elevations in total bilirubin was observed in 13 (27.1%) and 3 (6.3%) of subjects, respectively. Upon discharge and any captured follow-ups, total bilirubin levels were noted to return to baseline or show a trend toward return to baseline

Table 4: Safety Results

Deaths - subjects (%)	0 (0)
Discontinuation due to AEs - subjects (%)	0 (0)
Serious AEs - subjects (%)	0 (0)
Most Frequent AEs (≥ 3%) - subjects (%)	
Jaundice	10 (20.8)
Headache	8 (16.7)
Dizziness	2 (4.2)
Abdominal Pain	2 (4.2)
Grade 3-4 Laboratory Abnormalities – subjects (%)	
Total Bilirubin	16 (33.3)

Summary/Discussion

- Administration of OMP 40 mg with ATV 400 mg both with and without cola decreased ATV AUC, C_{max} and C_{min} (> 93%) considerably compared with ATV 400 mg alone
- Administration of OMP 40 mg with ATV/RTV 300/100 mg decreased ATV AUC by 50% and C_{max} by 73% relative to ATV at 400 mg alone. ATV C_{min} was increased by 23%
- When given in a single dose as a probe drug, OMP AUC and C_{max} were increased by 45% and 24% respectively during ATV 400 mg QD dosing
- Due to the dependence of the metabolism of OMP on the CYP2C19 pathway, inhibition of CYP2C19 causes substantial increases in OMP exposure
  - The relative importance of CYP2C19 and CYP3A4 pathways for OMP metabolism has been demonstrated in previous interaction studies
    - Co-administration of fluconazole, a potent CYP2C19 inhibitor but weak CYP3A4 inhibitor, increased OMP AUC (0-10 h) by 6-fold[2]
    - Co-administration of ketoconazole, a potent CYP3A4 inhibitor increased the OMP AUC (0-6 h) by approximately 36%[3]
    - On this basis, the increased AUC of OMP seen in the current study is likely due to inhibition of CYP3A4-mediated metabolism rather than by a clinically significant inhibition of CYP2C19-mediated metabolism by ATV

CONCLUSIONS

- Given the substantial decreases observed in ATV exposures, ATV and OMP should not be co-administered in the regimens employed in this study
- A modest increase in OMP AUC relative to a single-dose OMP comparison suggests that ATV does not appreciably inhibit CYP2C19 *in vivo*
- Intra-gastric pH was well correlated with AUC and C_{max} values for ATV (r = -0.82 and -0.84, respectively) in the presence of OMP. However, only a weak correlation was noted at physiologic intra-gastric pH (r ≤ -0.3)

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Pharmacokinetic Interaction Between Atazanavir and Omeprazole in Healthy Subjects

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BACKGROUND

- Atazanavir (ATV) is a potent, well-tolerated, once-daily, HIV protease inhibitor (PI) extensively studied in naïve and experienced patients
- ATV exhibits pH-dependent solubility, previous data have indicated that ATV bioavailability is sensitive to gastric pH
- ATV is a moderate inhibitor of CYP2C19 in vitro (Ki value of approximately 9 µM)
- Omeprazole (OMP), a proton pump inhibitor (PPI), is primarily metabolized by CYP2C19, suppresses acid secretion and increases gastric pH
- In a separate study, co-administration of OMP 40 mg QD with ATV/ritonavir (ATV/RTV) 300/100 mg QD decreased ATV exposures by 72-78% relative to ATV/RTV 300/100 mg alone[1]
- Due to an anticipated reduction in ATV exposures with concomitant administration of acid suppressing agents, this drug interaction study was designed to evaluate the effect of OMP on the PK of ATV and the effect of ATV on the PK of OMP, a CYP2C19 probe. In addition, attempts were made to investigate strategies to mitigate any observed effects

OBJECTIVES

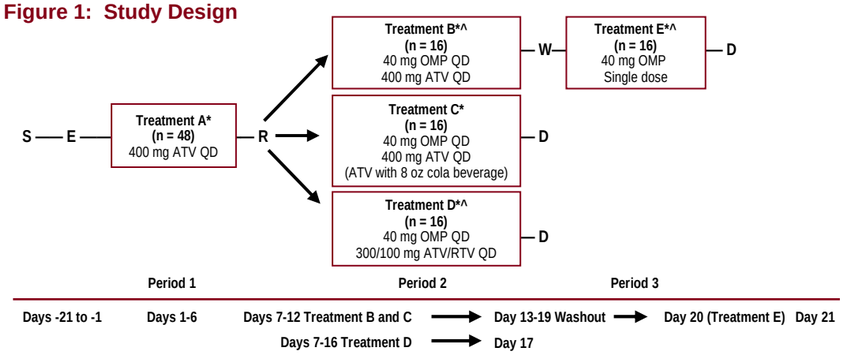
- Primary
  - To assess the comparability of the steady-state PK of ATV 400 mg with 8 oz of cola and ATV/RTV 300/100 mg, both co-administered with OMP relative to ATV 400 mg alone in healthy subjects
- Secondary
  - To assess the effect of
    - OMP on the PK of ATV
    - ATV on the PK of OMP (CYP2C19 probe)
    - Intra-gastric pH on the PK of ATV
- Safety and tolerability of ATV when concomitantly administered with OMP

METHODS

- Randomized, open-label, multiple-dose drug interaction study in 48 healthy adults
- All subjects received ATV 400 mg QD for 6 days (Treatment A) and were then randomized into three treatment groups (Figure 1):
  - ATV 400 mg QD + OMP 40 mg QD for 6 days (Treatment B)
  - ATV 400 mg QD + OMP 40 mg QD + 8 oz. cola for 6 days (Treatment C)
  - ATV/RTV 300/100 mg QD + OMP 40 mg QD for 10 days (Treatment D)

  ATV or ATV/RTV were administered with a light meal; OMP was administered fasted 2 hours before all treatments except as noted below
- For CYP2C19 probe analysis, subjects in Treatment B received:
  - ATV 400 mg, 2 hours before OMP 40 mg (first day of dosing only), and
  - Single-dose of OMP 40 mg following a washout (Treatment E)

Figure 1: Study Design



S = Screening (within 21 days of Day 1)
E = Enrollment
R = Randomization (Day 7)
D = Study Discharge
W = 7-day Washout (Day 13 through Day 19)

* Each dose of OMP was administered on an empty stomach 2 hours prior to ATV or ATV/RTV in the AM (except day 7 Treatment B). Each dose of ATV or ATV/RTV were administered 5 minutes following consumption of a light meal.

^ To assess the effect of ATV on CYP2C19-medicated metabolism, OMP was given 2 hours after ATV administration on Day 7 for subjects in Treatment B as well as by itself on Day 20 to subjects in Treatment E. Day 20 OMP was dosed 2 hours after a light meal.

METHODS (Cont'd)

Pharmacokinetics

- ATV and RTV
  - Intensive PK samples were evaluated on Days 6 (ATV), 7 and 12 (ATV, OMP), 16 (ATV, RTV, OMP) and 20 (OMP)
  - PK parameters: C_{max}, T_{max}, C_{min}, AUC(TAU), T-Half
  - ATV and RTV measured by LC/MS/MS: LLQ = 5 ng/mL
  - OMP measured by LC/MS/MS: LLQ = 1 ng/mL
- Intra-gastric pH monitoring
  - Performed at baseline and on intensive PK evaluation days for ATV
    - Intra-gastric pH probe - position verified by a manometer
    - pH measurements evaluated every 10 seconds from which 15-minute averages were calculated
    - pH average over 0-6 h were computed by pH AUC(0-6)/6
- Statistics
  - To assess the effect of OMP on the PK of ATV at steady-state, general linear model analyses with treatment as fixed effect and measurements within each subject as repeated measures grouped by sequence, were performed on the log(C_{max}), log(AUC(TAU)) and log(C_{min}) of ATV
  - To assess the effect of ATV on the PK of single-dose OMP, the same general linear model analyses were performed on the log(C_{max}) and log(AUC(INF)) of OMP
  - 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

Demographics

Table 1: Subject Demographics

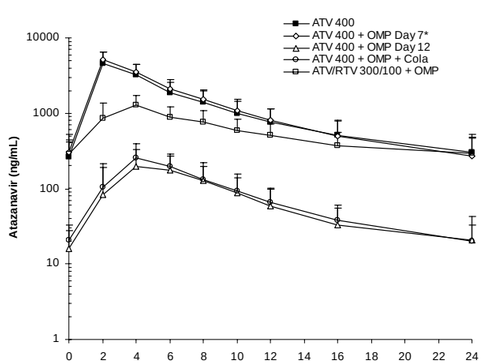
	Treatment A+B+E (n = 16)	Treatment A+C (n = 16)	Treatment A+D (n = 16)	All Subjects (n = 48)
Age (years)				
Mean (SD)	35 (11)	33 (9)	36 (5)	35 (8)
Range	19-49	20-46	26-44	19-49
Gender, n (%)				
Male	14 (88)	12 (75)	14 (88)	40 (83)
Female	2 (13)	4 (25)	2 (13)	8 (17)
Race, n (%)				
Caucasian	9 (56)	10 (63)	3 (19)	22 (46)
Black	7 (44)	4 (25)	12 (75)	23 (48)
Asian	0	1 (6)	0	1 (2)
Other	0	1 (6)	1 (6)	2 (4)

Treatments: A = ATV 400 mg QD; B = ATV 400 mg QD + OMP 40 mg QD; C = ATV 400 mg QD + OMP 40 mg QD + 8 oz. cola; D = ATV/RTV 300/100 mg QD + OMP 40 mg QD; E = OMP 40 mg single dose

RESULTS

Evaluation of Steady-State ATV

Figure 2: Mean (SD) Plasma Concentration-Time Profiles of ATV



*On day 7 ATV 400 mg was given 2 hours prior to OMP 40 mg

Table 2: Summary of Statistical Analyses of ATV PK Relative to ATV at 400 mg Alone

PK Parameter	Treatment	Geometric Means (CV%)	Ratios of Adjusted Geometric Means vs Control Pt. Estimate (90% CI)
C_{max} (ng/mL)	ATV + OMP	215 (54)	0.04 (0.04, 0.05)
	ATV + OMP + Cola	271 (72)	0.06 (0.04, 0.07)
	ATV/RTV + OMP	1293 (34)	0.27 (0.23, 0.33)
AUC(TAU) (ng•h/mL)	ATV + OMP	1504 (61)	0.06 (0.05, 0.07)
	ATV + OMP + Cola	1855 (53)	0.07 (0.05, 0.09)
	ATV/RTV + OMP	12648 (39)	0.50 (0.42, 0.60)
C_{min} (ng/mL)	ATV + OMP	10.4 (123)	0.05 (0.03, 0.07)
	ATV + OMP + Cola	14.6 (72)	0.05 (0.04, 0.07)
	ATV/RTV + OMP	240.4 (59)	1.23 (1.00, 1.52)

Control arm = ATV 400 mg; ATV + OMP = ATV 400 mg QD + OMP 40 mg QD; ATV + OMP + Cola = ATV 400 mg QD + OMP 40 mg QD + Cola 8 oz, ATV/RTV + OMP = ATV/RTV 300/100 mg QD + OMP 40 mg QD

RESULTS (Cont'd)

- A substantial reduction in ATV exposures was noted on OMP administration with and without cola, relative to ATV at 400 mg alone. When ATV/RTV at 300/100 mg was added to the regimen, AUC and C_{max} were 50% and 73% lower, respectively, and C_{min} was 23% higher compared to ATV at 400 mg alone
- T_{max} was 2.0 h for the control arm and ranged from 3.0-5.0 h across treatments
- Mean T-Half for ATV was 8.1 for the control arm and ranged from 5.2 – 6.1 for treatments with ATV 400 mg. Due to insufficient sampling time, T-Half could not be estimated reliably over 24 hours in the presence of RTV

Evaluation of Steady-State OMP

Figure 3: Mean (SD) Plasma Concentration-Time Profiles of OMP at Steady State

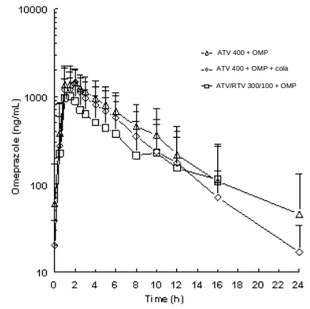
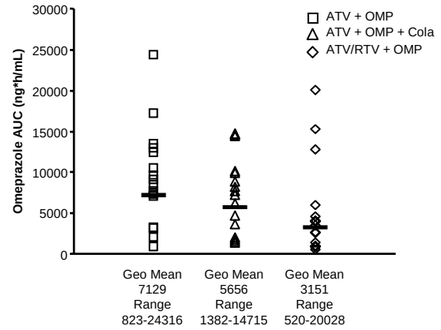


Figure 4: Individual AUC(TAU) Values for OMP at Steady State



- Individual exposures of OMP overlapped across treatments and were generally comparable to historical values
- Geometric means ranged from 1061-1661 ng/mL for OMP C_{max} and 3151-7129 ng•h/mL for OMP AUC(TAU)
- The median T_{max} for OMP ranged from 1.5-1.8 h and the mean T-Half for OMP ranged from 1.8-2.7 h

Evaluation of Single-Dose OMP CYP2C19 Probe Analysis

Figure 5: Comparison of Individual AUC(INF) Single Dose OMP Values Between OMP + ATV vs OMP Alone

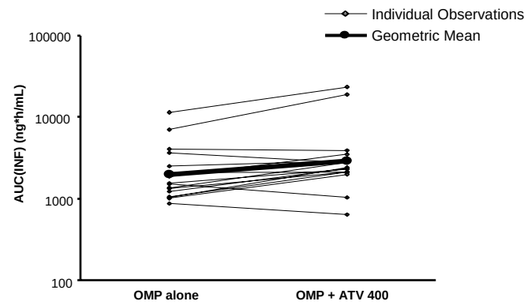


Table 3: Geometric Means, Point Estimates and 90% CI for Single-Dose OMP PK Parameters

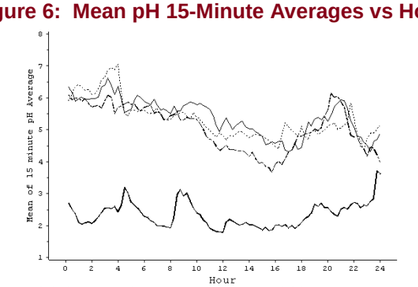
PK Parameter	Geometric Means (CV%)		Ratios of Adjusted Geometric Means Pt. Estimate (90% CI)
	ATV + OMP (Day 7)	OMP (Day 20)	
AUC(INF)(ng•h/mL)	2883 (139)	1985 (103)	1.45 (1.20, 1.76)
C_{max} (ng/mL)	1150 (38)	929 (45)	1.24 (1.04, 1.47)

ATV + OMP = ATV 400 mg QD + OMP 40 mg QD; OMP = OMP 40 mg QD

- Following a single dose of OMP, ATV increased OMP C_{max} and AUC by 24% and 45%, respectively. ATV concentrations on Day 7 were adequate to make this assessment as ATV was administered before the first dose of OMP
- The median T_{max} for OMP was 1.5 h for both treatments
- OMP T-Half ranged from 1.4-1.9 h

Intra-gastric pH analysis

Figure 6: Mean pH 15-Minute Averages vs Hour by Treatment



- As shown in Figure 6, co-administration of OMP substantially increased intra-gastric pH as compared to ATV alone
- pH average 0-6h was 2.36 in the presence of ATV alone and ranged from 5.58-5.93 with the addition of OMP in all treatments