**RESULTS** (Cont'd)

When data from the three treatments (ATV alone, ATV + OMP, ATV + OMP + cola) were analyzed together, a good correlation between ATV Cmin and AUC vs pH was obtained.

At physiological 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.

### Pharmacokinetic Interaction Between Atazanavir and Omeprazole in Healthy Subjects

**BACKGROUND**

**ATV** exhibits pH-dependent solubility, previous data have indicated that **ATV** bioavailability is sensitive to gastric pH. The *in vitro* IC50 of CYP3A4 for **ATV** is 9 µM.

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.

**OMP** is a proton pump inhibitor (PPI), primarily metabolized by CYP2C9, suppresses acid secretion and increases gastric pH. In this study, co-administration of **OMP** 40 mg QD with **ATV/ritonavir (ATV/RTV)** 300/100 mg QD did not affect **ATV** exposures.

**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** (CYP2C9 probe)

**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): (Treatment B) **ATV** 400 mg QD + **OMP** 40 mg QD 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.

**CONCLUSIONS**

- **SUMMARY**
  - **All subjects received ATV** 400 mg QD for 6 days (Treatment A) and were then randomized into three treatment groups (Figure 1):
  - **Treatment B**
    - **ATV** 400 mg QD + **OMP** 40 mg QD
  - **Treatment C**
    - **ATV/RTV** 300/100 mg QD + **OMP** 40 mg QD

- **SINGLE DOSE** of **OMP** 40 mg following a washout period (Treatment E)

**REFERENCES**


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**RESULTS** (Cont'd)

**Pharmacokinetics**

- A substantial reduction in ATV exposures was noted on OMP administration with and without cola, relative to ATV at 400 mg alone.
- ATV and RTV measured by LC/MS/MS: LLQ = 5 ng/mL
- OMP measured by LC/MS/MS: LLQ = 1 ng/mL

**Method**

- ATV and RTV at 300/100 mg was added to the regimen, AUC and Cmax were 50% and 73% lower, respectively, and Cmin was 23%–higher compared to ATV at 400 mg alone
- Tmax 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

**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(Cmax), log(AUC(TAU)) and log(Cmin) 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(Cmax) 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

**Evaluation of Steady-State OMP**

- Individual exposures of OMP overlapped across treatments and were generally comparable to historical values
- Mean T-half for OMP ranged from 1.5-1.6 h and the mean T-1/2 for OMP ranged from 1.8-2.7 h

**Evaluation of Single-Dose OMP CYP2C19 Probe Analysis**

- Ratios of Adjusted Geometric Means vs OMP Alone

**Evaluation of Intra-gastric pH**

- 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

**RESULTS** (Cont’d)

**Evaluation of Steady-State ATV**

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

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

**Table 1: Subject Demographics**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n (n=16)</th>
<th>n (n=16)</th>
<th>n (n=16)</th>
<th>n (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
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<td>33 (9)</td>
<td>36 (5)</td>
<td>35 (9)</td>
</tr>
<tr>
<td>Gender</td>
<td>19-49</td>
<td>20-46</td>
<td>26-44</td>
<td>19-42</td>
</tr>
<tr>
<td>Race</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td>14 (48)</td>
<td>12 (75)</td>
<td>14 (48)</td>
<td>11 (68)</td>
</tr>
<tr>
<td></td>
<td>2 (13)</td>
<td>24 (36)</td>
<td>2 (13)</td>
<td>8 (57)</td>
</tr>
</tbody>
</table>

**Demographics**

<table>
<thead>
<tr>
<th>Gender (%)</th>
<th>Age (years)</th>
<th>Race (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>14 (88)</td>
<td>9 (56)</td>
</tr>
<tr>
<td>Female</td>
<td>2 (13)</td>
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</tr>
<tr>
<td></td>
<td>2 (13)</td>
<td>24 (36)</td>
</tr>
</tbody>
</table>

**Intra-gastric pH analysis**

**Figure 6: Mean 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