ATV is a potent, safe and effective once-daily (QD) azapeptide protease inhibitor, recently approved in the US, that does not result in clinically relevant elevations in serum lipids.

Methods: A double-blind, randomized, placebo-controlled, 3 period/treatment crossover study was conducted in 72 healthy subjects who received placebo, 400 mg or 800 mg ATV QD for 6 days with a light meal. An objective of the study was to delineate the steady-state (Day 6) PK profile of ATV through 72 h post-dose.

Results: ATV was rapidly absorbed with peak plasma concentrations occurring at 2.5 h. Steady-state was achieved by Day 6 with a mean T-HALF of 6.7 h. A greater than dose-proportional increase in exposures (AUC) was noted, with an inter-subject variability of about 30% for both doses. ATV plasma concentrations (mean ± S.D.; range) ng/mL following the 400 mg dose were noted to be 378 ± 271; (37-1225) at 24 h, 134 ± 129; (8-523) at 36 h, 49 ± 8; (1-29) at 72 h.

Conclusion: ATV concentrations were readily detectable in plasma for 72 hours beyond last dose. Mean viral concentrations, expressed as an IC50 value (adjusted for protein binding), of about 5 ng/mL have been noted in a Phase II study of treatment-naive patients. A dose of 400 mg QD of ATV in healthy subjects generally provided concentrations which substantially exceeded the aforementioned mean IC50 value beyond the once-dosing interval.

### R E S U L T S

#### Summary statistics for ATV Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>ATV at 400 mg (n = 65)</th>
<th>ATV at 800 mg (n = 66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>13400 ± 3400</td>
<td>11902 ± 2700</td>
</tr>
<tr>
<td>Geometric Mean (C.V.%)</td>
<td>13102 (34)</td>
<td>93423 (27)</td>
</tr>
<tr>
<td>AUC(TAU) (ng·h/mL)</td>
<td>1000 ± 800</td>
<td>1000 ± 400</td>
</tr>
<tr>
<td>Median (Max. Min.)</td>
<td>134 (72-273)</td>
<td>93423 (53)</td>
</tr>
<tr>
<td>T-HALF (h)</td>
<td>100 ± 50</td>
<td>72 (24-249)</td>
</tr>
<tr>
<td>Cmax (Mean ± S.D.)</td>
<td>13400 ± 271 (72%)</td>
<td>11902 ± 1373 (53%)</td>
</tr>
<tr>
<td>Cmax (Mean ± S.D.; range)</td>
<td>13102 (34)</td>
<td>93423 (27)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>134 (72-273)</td>
<td>93423 (53)</td>
</tr>
<tr>
<td>Protein-Adjusted EC90 (C.V.%)</td>
<td>288 (72)</td>
<td>1373 (53)</td>
</tr>
</tbody>
</table>

ATV was detectable in the plasma at 72 h beyond the last dose

Cmin values > median protein-adjusted EC90 (14 ng/mL)
- For 100% of subjects at 24 h
- For 91% of subjects at 36 h
- For 55% of subjects at 48 h
- For 30% of subjects at 60 h
- For 13% of subjects at 72 h

The PK cushion was 1.5 fold greater than the median protein-adjusted EC90 at 48 h
- Mean Cmin at 48 h (20 ng/mL) > Median protein-adjusted EC90 (14 ng/mL)

### C O N C L U S I O N S

- 400 mg QD of ATV provided a PK cushion over the protein-adjusted EC90 of 14 ng/mL for several hours beyond the once-daily dosing interval
- Full patient compliance is required for optimal anti-retroviral suppression
  - Plasma concentrations in all subjects were above the target protein-adjusted EC90 for the entire dosing interval of 24 h
- A missed dose is to be taken as soon as possible. If the missed dose is within 6 hours of the next dose, the missed dose should not be taken, instead the next dose should be taken at the regular time interval

---

**Characterization of the Steady-State Pharmacokinetic (PK) Profile of Atazanavir (ATV) Beyond the 24-hour Dosing Interval**


Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton NJ USA

**A B S T R A C T**

**R A T I O N A L E**

- HIV is a constantly replicating virus
- Viral suppression has been linked to circulating plasma concentrations of anti-retroviral agents together with the underlying sensitivity of the virus, defined by EC90 values
- Knowledge of the impact of missed doses of ATV and assessment of ATV plasma concentrations above the protein-adjusted median EC90 beyond the once-dosing interval is warranted

**M E T H O D S**

- Double-blind, randomized, placebo-controlled, 3 period/treatment crossover study in 72 healthy subjects
- Treatments
  - Placebo, 400 mg or 800 mg ATV QD for 6 days with a light meal
  - Washout: 14 d between treatments
- Pharmacokinetics
  - Blood samples collected for up to 72 h post dose in Period 1 only & for up to 24 h post dose in Periods 2 & 3
  - Predose samples collected on Days 2 and 4 of each period
- Statistics
  - Summary statistics for each of the pharmacokinetic parameters of ATV were tabulated by treatment

**B A C K G R O U N D**

- ATV is a potent, safe and well-tolerated azapeptide protease inhibitor (PI) that has been recently approved in the US
- ATV, administered as 2 capsules once-daily at a dose of 400 mg, rapidly and durably suppresses HIV RNA
- ATV does not result in clinically relevant elevations in serum lipids, unlike other protease inhibitors
- ATV resistance is characterized by a signature I50L mutation that has been noted in all treatment naive patients who develop resistance to ATV
- Overall ATV resistance is uncommonly observed
- I50L is associated with increased in vitro susceptibility to other PIs