Abstract # 845

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

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ABSTRACT

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; (8-502) at 36 h, 49 ± 60; (2-202) at 48 h, and 7 ± 8; (1-29) at 72 h.

Conclusion: ATV concentrations were readily detectable in plasma for 72 hours beyond last dose. Mean viral sensitivities, expressed as an IC_{50} 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 IC_{50} value beyond the once-daily dosing interval.

BACKGROUND

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 naïve patients who develop resistance to ATV
  - Overall ATV resistance is uncommonly observed
  - I50L is associated with increased *in vitro* susceptibility to other PIs

RATIONALE

- 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 EC_{90} values
- Knowledge of the impact of missed doses of ATV and assessment of ATV plasma concentrations above the protein-adjusted median EC_{90} beyond the once-daily dosing interval is warranted

OBJECTIVES

- A secondary objective of the study was to examine the PK profile of ATV through 72 h post-dose following multiple doses of ATV to steady-state

METHODS

Study design:

- 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 d 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

RESULTS

- Rapid absorption, Tmax = 2.5 h
- Greater than dose proportional increase in exposure (AUC)
  - An increase in dose of 1:2 produced an increase of 1:2.7 in exposure
- ATV concentrations at 24 h substantially > protein-adjusted EC_{90}
  - Cmin, Mean (C.V.%) at 24 h;
    - 400 mg = 288 ng/mL (72%); 800 mg = 1373 ng/mL (53%)
  - Median (range) protein-adjusted EC_{90} = 14 (2.4 - 40.6) ng/mL
  - Cmin >> protein-adjusted EC_{90} → Substantial PK cushion at 24 h
- T-half ~ 6 - 7 h
- Inter-subject variability ~ 30%

RESULTS

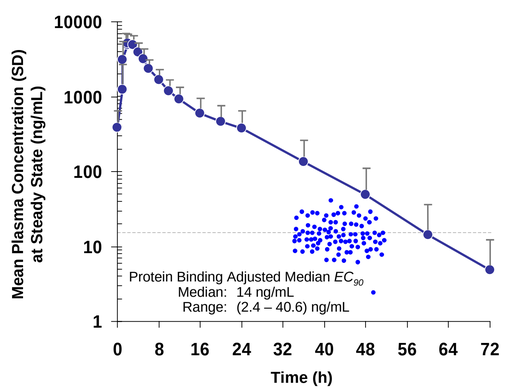
Summary statistics for ATV Pharmacokinetic Parameters

Pharmacokinetic Parameter	Treatment: ATV at 400 mg (n = 65)	Treatment: ATV at 800 mg (n = 66)
Cmax (ng/mL) Geometric Mean (C.V.%)	5500 (34)	11102 (27)
AUC(TAU) (ng·h/mL)[a] Geometric Mean (C.V.%)	33097 (36)	90432 (29)
Tmax (h) Median (Min, Max)	2.50 (1.5, 5.0)	2.50 (1.0, 4.0)
T-HALF (h)[b] Mean (S.D.)	6.27 (1.41)	7.25 (1.99)
Cmin (ng/mL)[c] Geometric Mean (C.V. %)	288 (72)	1373 (53)

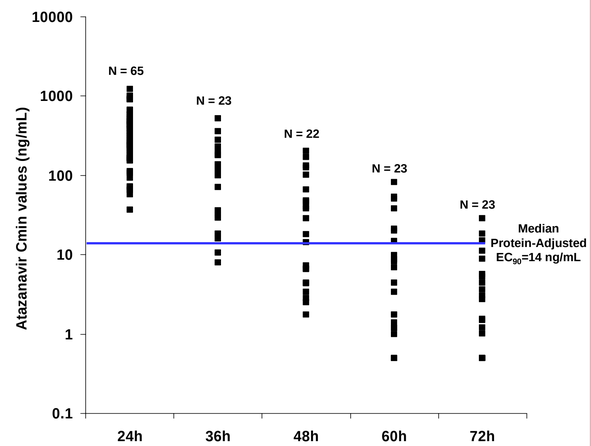
[a] TAU = 24 h
[b] For Period 1 only, with 72 hours of sampling (n = 24 for 400 mg; n = 23 for 800 mg)
[c] Day 7 only

- ATV was detectable in the plasma at 72 h beyond the last dose
- Cmin values > median protein-adjusted EC_{90} (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 EC_{90} at 48 h
  - Mean Cmin at 48 h (20 ng/mL) > Median protein-adjusted EC_{90}(14 ng/mL)

Mean (S.D.) Steady State Concentration Time Profile for Atazanavir Following 400 mg QD Dosing for 6 Days



Trough (Cmin) Concentrations Following 400 mg ATV QD for 6 d



	24h	36h	48h	60h	72h
Geomean (ng/mL)	288	76	20	5	2
Range (ng/mL)	(37-1225)	(8-523)	(2-202)	(0.5-82)	(0.5-29)
% of subjects above median protein-adjusted EC_{90}	100%	91%	55%	30%	13%

CONCLUSIONS

- 400 mg QD of ATV provided a PK cushion over the protein-adjusted EC_{90} 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 EC_{90} 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