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Pharmacokinetic Boosting of Atazanavir with the Pharmacoenhancer GS-9350 versus Ritonavir

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Introduction

- GS-9350 is a specific, potent, mechanism-based inhibitor of human cytochrome P450 3A (CYP3A) enzymes without antiviral activity
- GS-9350 increases (boosts) plasma exposures of the CYP3A4 probe midazolam and the HIV integrase inhibitor elvitegravir comparably to ritonavir (RTV)[1]
- Boosted-atazanavir (ATV) is an HIV protease inhibitor preferred for first line treatment of patients in HIV treatment guidelines

Background

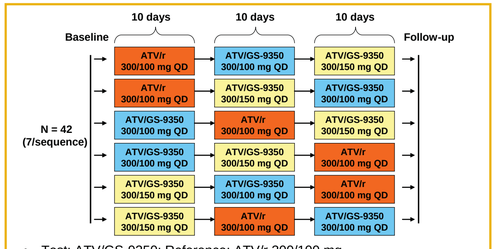
- ATV is a substrate and inhibitor of CYP3A4 and is coadministered with RTV, a CYP3A4 inhibitor, (ATV/r) to achieve high trough concentrations
- ATV-associated adverse effects include hyperbilirubinemia due to UGT1A1 inhibition and modest PR interval prolongation
- RTV-associated safety and tolerability issues include hyperlipidemia, gastrointestinal disorders, and risk for developing cardiac conduction abnormalities[2-4]
- GS-9350 may offer an alternative to RTV to boost ATV with the potential for reduced adverse biochemical effects

Objectives

- To evaluate the pharmacokinetics of ATV when coadministered with GS-9350 or RTV
- To evaluate the safety of administration of ATV in combination with GS-9350 or RTV

Methods

Figure 1. Study Design



- Test: ATV/GS-9350; Reference: ATV/r 300/100 mg
- PK on Day 10 of each period; 4-day washout between periods

Methods (cont'd)

- All treatments administered with a standard meal (~ 400 kcal, 13 g fat)
- Plasma PK sampling performed over 24 hours; ATV, GS-9350, and RTV levels determined using validated LC/MS/MS assays
- PK parameters estimated via non-compartmental methods using WinNonlin™ 5.2 (Pharsight Corporation, Mountain View, CA, USA)
- ANOVA and 90% confidence interval bounds for equivalence about the geometric mean ratio (Test:Reference) were 80 to 125% for ATV C_{max}, AUC_{tau}, and C_{tau}
- Descriptive PK for GS-9350 and RTV
- Adverse event (AE) monitoring, clinical laboratory and ECG evaluations performed throughout study

Results

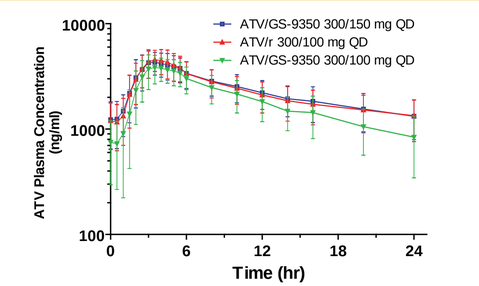
Demographics

- 42 healthy subjects enrolled
  - 28 males, 14 females
  - Mean age: 28 yrs (range: 18 – 45)
  - Ethnicity: 28 White, 10 Black, 3 Asian, 1 Native American

Disposition

- 33 completed study
- 9 discontinuations
  - 2 withdrew consent
  - 2 Investigator's discretion
  - 5 due to AEs

Figure 2. ATV Plasma Concentration-Time Profile (mean ± SD)



Results (cont'd)

Table 1. Plasma Pharmacokinetic Parameters of ATV Following ATV/r 300/100 mg and ATV/GS-9350 300/150 mg Dosing

ATV PK	ATV/GS-9350 300/150 mg (N = 34)	ATV/r 300/100 mg (N = 36)	GMR (90% CI)
AUC_{tau} (ng•h/mL)	55,900 (28.2)	55,200 (27.6)	**101 (94.5, 108)**
C_{max} (ng/mL)	4880 (24.9)	5270 (23.6)	**92.3 (85.1, 100)**
C_{tau} (ng/mL)	1330 (42.7)	1340 (40.8)	**97.6 (88.1, 108)**
$T_{½}$ (h)	16.7 (11.7, 20.4)	15.7 (13.6, 21.1)	NA
T_{max} (h)	3.0 (2.5, 3.5)	3.0 (2.5, 3.5)	NA

Data expressed as arithmetic mean (%CV) or *median (Q1,Q3)
GMR: Geometric Mean Ratio; CI: Confidence Interval; NA : Not applicable

Table 2. Plasma Pharmacokinetic Parameters of ATV Following ATV/r 300/100 mg and ATV/GS-9350 300/100 mg Dosing

ATV PK	ATV/GS-9350 300/100 mg (N = 35)	ATV/r 300/100 mg (N = 36)	GMR (90% CI)
AUC_{tau} (ng•h/mL)	45,100 (30.9)	55,200 (27.6)	81.2 (76.0, 86.7)
C_{max} (ng/mL)	4420 (21.4)	5270 (23.6)	84.2 (77.7, 91.2)
C_{tau} (ng/mL)	837 (58.8)	1340 (40.8)	57.4 (51.9, 63.5)
$T_{½}$ (h)	9.7 (7.1, 12.9)	15.7 (13.6, 21.1)	NA
T_{max} (h)	3.5 (3.0, 4.0)	3.0 (2.5, 3.5)	NA

Data expressed as arithmetic mean (%CV) or *median (Q1,Q3)
GMR: Geometric Mean Ratio; CI: Confidence Interval; NA : Not applicable

Table 3. Plasma Pharmacokinetic Parameters of RTV and GS-9350 Following ATV/r and ATV/GS-9350 Dosing

	RTV	GS-9350	
PK Parameter	ATV/r 300/100 mg (N = 37)	ATV/GS-9350 300/150 mg (N = 35)	ATV/GS-9350 300/100 mg (N = 38)
AUC_{tau} (ng•h/mL)	11,900 (32.6)	11,300 (24.4)	5960 (23.3)
C_{max} (ng/mL)	2050 (28.5)	1380 (19.3)	849 (18.1)
C_{tau} (ng/mL)	74.4 (58.8)	61.6 (93.5)	21.7 (95.9)
$T_{½}$ (h)	5.3 (4.4, 6.1)	4.4 (3.5, 4.9)	4.1 (3.5, 4.6)
T_{max} (h)	5.0 (4.5, 5.0)	3.0 (2.5, 3.5)	3.0 (2.5, 3.5)

Data expressed as arithmetic mean (%CV) or *median (Q1,Q3)

Pharmacokinetics

- Bioequivalent ATV exposures between ATV/GS-9350 300/150 mg and ATV/r 300/100 mg
  - Comparable $T_{1/2}$ and T_{max} for these ATV treatments
- ATV/GS-9350 300/100 mg provided lower ATV exposures
- GS-9350 exposure increased greater than dose-proportional between 100 mg and 150 mg doses
- RTV pharmacokinetics comparable to historical data[5]

Safety: Adverse Events (AEs)

- No Grade 3/4 AEs, serious AEs
- Discontinuations due to AEs (moderate (Grade 2) severity)
  - ATV/r: 2 (1 each for anemia, parasthesia)
  - ATV/GS-9350: rash (n = 2 at 100 mg, n = 1 at 150 mg GS-9350)
    - Resolved upon study drug discontinuation
- ATV/r and ATV/GS-9350 dosing generally well tolerated
  - Similar incidence of AEs across GS-9350 vs RTV treatments
  - Most frequent AEs: headache, ocular icterus, jaundice, contact dermatitis
  - AEs were mild or moderate and resolved on treatment

Safety: Laboratory Abnormalities

Liver: Table 4. Total Bilirubin

Treatment	Change from baseline (mean ± SD); mg/dL	Grade 3	Grade 4
ATV/GS-9350 300/100 mg	3.1 ± 1.9	30.0%	12.5%
ATV/GS-9350 300/150 mg	4.1 ± 1.5	57.9%	5.3%
ATV/r 300/100 mg	4.2 ± 1.7	52.6%	10.5%

  - Total bilirubin returned to baseline levels upon washout (~0.5 mg/dL)
- No changes in ALT, AST, GGT

ECG

- No clinically relevant changes in QTcF, QRS intervals
- No difference in PR interval changes for ATV/GS-9350 vs ATV/r ($p > 0.05$)
  - Maximum change from baseline (mean ± SD)
    - ATV/GS-9350 300/100 mg: 19.2 ± 16.2 msec
    - ATV/GS-9350 300/150 mg: 22.3 ± 17.2 msec
    - ATV/r 300/100 mg: 15.9 ± 12.6 msec
    - Historical data - ATV/r 300/100 mg: 20 ± 42 msec[6]; ATV 400 mg: 24 ± 15 msec[7]
  - Three subjects had Grade 1 PR interval prolongation during all three treatments

Conclusions

- **ATV/GS-9350 300/150 mg provides bioequivalent ATV exposures to ATV/r**
- **ATV/GS-9350 administration is safe and well tolerated**
- **The pharmacoenhancer GS-9350 may be a suitable alternative to RTV for boosting of ATV**
- **A fully enrolled Phase II clinical trial comparing ATV/GS-9350 300/150 mg versus ATV/r 300/100 mg, each in combination with emtricitabine/tenofovir disoproxil fumarate, in treatment-naive HIV patients is ongoing**

References

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