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Pharmacokinetics and Safety of Twice Daily Atazanavir 300 mg and Raltegravir 400 mg in Healthy Subjects

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BACKGROUND

- Atazanavir (ATV) is a potent inhibitor of HIV-1 protease. When boosted with ritonavir (RTV) 100 mg and combined with other antiretrovirals (ARV), ATV 300 mg once daily (QD) has been demonstrated to be highly effective and well-tolerated in both ARV naïve and experienced patients
- Raltegravir (RAL) belongs to a novel class of ARV that potently and selectively inhibits HIV-1 integrase. RAL in combination with other ARVs is indicated for the treatment of HIV-1 infection in treatment-experienced adult patients
- Twice daily (BID) ATV allows for increased ATV exposure without the need for RTV
- ATV 300 mg BID given with RAL 400 mg BID is being explored as a RTV and nucleoside-sparing treatment strategy
- Both ATV and RAL are individually well-tolerated, with low rates of GI intolerance and minimal impact on lipids. Thus, this combination may produce minimal gastrointestinal (GI) and lipid effects
- ATV is a reversible inhibitor of UGT 1A1 (K_i ~ 1.9 μM), the dominant isoform that catalyzes the glucuronidation of RAL. In previously conducted healthy subject studies, as expected, coadministration of RAL with ATV 400 mg QD or ATV/RTV 300/100 mg QD resulted in a modest increase in RAL exposure[1]
- RAL has been shown to have no electrocardiogram (ECG) interval effects inclusive of PR, QRS and QTc at a supratherapeutic dose of 800 mg[2]
- With respect to ECG effects for ATV BID, observed in a previous study in which the PK and safety of ATV doses from 200 to 400 mg BID were investigated:[3]
  - The mean PR and QRS effects at doses of ATV 200, 300 and 400 mg BID were shown to be dose- and concentration-related: PR changes were similar to or slightly higher than those observed historically from ATV/RTV 300/100 mg QD
  - QRS interval increased by a mean of approximately 10 msec at a dose of 300 mg BID; in 17/18 subjects maximum QRS was < 120 msec. In one subject, QRS was between 120 and 130 msec; increases from baseline were < 25% in all 18 subjects
  - ATV given 200 - 400 mg BID did not prolong the QTc (corrected by Fridericia)

OBJECTIVES

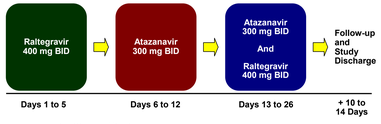
- To assess the two-way PK interaction when ATV 300 mg BID is coadministered with RAL 400 mg BID
- To assess the ECG effects of 300 mg ATV BID over 21 days, given with or without RAL 400 mg BID
- To assess the safety and tolerability of the coadministration of ATV 300 mg BID with RAL 400 mg BID

METHODS

Study Design

- Open-label, sequential, multiple-dose study in 22 healthy HIV-negative subjects, aged 18 to 45, inclusive, with no clinically relevant abnormalities on ECG. Excluding subjects with PR interval >200 msec, QTc interval >450 msec, and QRS interval >100 msec

Figure 1: Study Design



Subjects are screened and enrolled within 21 days of Day 1
Subjects returned for a follow-up visit and discharge 10 to 14 days after Day 26
Study drug was administered within 5 minutes of completing a light meal

Pharmacokinetics

- Blood (plasma) samples for ATV and RAL were collected for 12 hours (h) post-morning (AM) doses on Days 5, 12, and 26
- Steady state PK parameters were derived by non-compartmental analysis using the validated computer program Kinetica™: Cmax, Tmax, Cmin (concentration 12 h postdose), C0 (concentration pre-dose), and AUC(0-12h).
- Samples assayed via LC/MS/MS with standard curve ranging from
  - ATV: 10-10,000 ng/mL, with between-run %CV ≤3.33 and within-run %CV ≤4.73
  - RAL: 2-1,000 ng/mL, with between-run %CV ≤8.1and within-run %CV ≤1.5

Safety

- Based on medical review of adverse event reports (AEs), vital signs, ECGs, physical exam findings, and lab results
- Safety lab profiles were obtained at Screening, Days -1, 5, 12, 26 and at Discharge
- Serial time-matched ECGs were obtained at 0, 2 and 6 h post-AM dose on Days -1, 1, 5, 6, 8, 10, 12, 13, 15, 19, 22, and 26

Statistics

- Point estimates and 90% confidence intervals (CIs) for ratios of geometric means for RAL and ATV Cmax, AUC(0-12h), C0, and Cmin when coadministered compared to when dosed alone were constructed using general linear models
- All recorded AEs, significant physical examination findings, vital sign measurements, clinical laboratory test results, and ECG recordings were listed and summarized by treatment

RESULTS

- Twenty-two (22) subjects were treated in this study, with 19 subjects completing the study
- Three (3) subjects discontinued due to an AE following administration of ATV 300 mg + RAL 400 mg BID. Additional details are provided in the safety section

Table 1: Summary of Demography Characteristics

Age, years	
Mean (SD)	32 (8)
Range	22 – 45
Gender, N (%)	
Male	16 (73%)
Female	6 (27%)

Race, N (%)	
White	10 (45%)
Black	10 (45%)
Asian	1 (5%)
Other	1 (5%)

Weight, kg	
Mean (SD)	77.3 (13.3)
Range	54.1 102.0
BMI, kg/m²	
Mean (SD)	26.6 (2.5)
Range	22.2 – 30.3

RESULTS

Pharmacokinetics of Atazanavir:

Figure 2: Mean (SD) Plasma Concentration-Time Profiles for Atazanavir

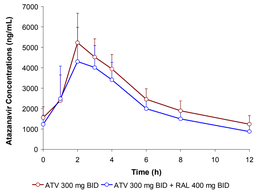


Figure 3: Individual Atazanavir Cmin following Atazanavir 300 mg BID alone and with Raltegravir 400 mg BID, Overlaid with 10 x EC_{90} Atazanavir for wild type HIV

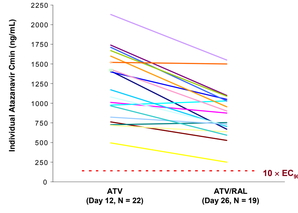


Table 2: Summaries and Statistical Analyses for Atazanavir Pharmacokinetic Parameters

Pharmacokinetic Parameter	Treatment: ATV BID Day 12 (N=22)	Treatment: ATV+RAL BID Day 26 (N=19)	Ratios of Adjusted Geometric Means (ATV+RAL/ATV BID) Point Estimate (90% CI)
Cmax (ng/mL) – Geometric Mean (%CV) Range	5434 (19) (3150 – 7690)	4817 (21) (2780 – 6290)	0.887 (0.835, 0.941)
AUC(0-12) (ng•h/mL) – Geometric Mean (%CV) Range	30906 (21) (19539 – 45957)	25579 (25) (12065 – 39179)	0.830 (0.777, 0.886)
Cmin (ng/mL) – Geometric Mean (%CV) Range	1166 (34) (495 – 2130)	817 (36) (250 – 1550)	0.710 (0.647, 0.779)
C0 (ng/mL) – Geometric Mean (%CV) Range	1468 (34) (668 – 2810)	1148 (37) (469 – 2160)	0.779 (0.716, 0.846)
Tmax (h) – Median (Min, Max)	2.0 (2.0, 4.0)	2.0 (1.0, 4.0)	–

- Following combined administration of ATV and RAL, ATV Cmax and AUC were reduced by approximately 10 – 20%, likely due to a decrease in bioavailability
- ATV Cmin were approximately 30% lower following coadministration, compared to ATV 300 mg BID alone
  - Despite the reduction, all individual Cmin values on Day 26 were well above the 10-fold population mean protein binding adjusted EC90 against wild type HIV (140 ng/ml; EC_{90} = 14 ng/mL). The lowest ATV Cmin was 250 ng/mL
- The ATV AUC(0-24h) [calculated as 2 x AUC(0-12h) = 61812 ng•h/mL)] and Cmin after ATV 300 mg BID alone appeared to be similar to historical values[4] after ATV/RTV 300/100 mg QD [60454 ng•h/mL for AUC and 1236 ng/mL for Cmin (concentrations at 24 h)], but moderately lower upon the addition of RAL
  - Exposures from ATV 300 mg BID were higher than those previously observed in healthy subjects following the same treatment (ATV 300 mg BID) in a previous healthy volunteer study (46451 ng•h/mL for AUC (0-24h) and 705 ng/mL for Cmin).[3] Neither study includes a within study ATV/RTV comparator treatment arm

Figure 4: Mean (SD) Plasma Concentration-Time Profiles for Raltegravir

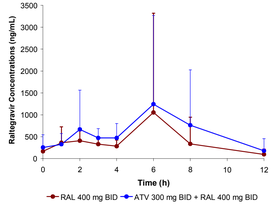


Figure 5: Individual Raltegravir AUC following Raltegravir 400 mg BID alone and with Atazanavir 300 mg BID

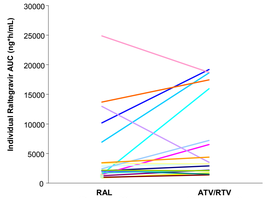


Table 3: Summary and Statistical Analyses for Raltegravir Pharmacokinetic Parameters

Pharmacokinetic Parameter	Treatment: RAL BID Day 5 (N=22)	Treatment: ATV+RAL BID Day 26 (N=19)	Ratios of Adjusted Geometric Mean (ATV+RAL/RAL) Point Estimate (90% CI)
Cmax (ng/mL) – Geometric Mean (%CV) Range	634 (169) (252 – 9429)	952 (120) (254 – 6296)	1.394 (0.990 – 1.964)
AUC(0-12h) (ng•h/mL) – Geometric Mean (%CV) Range	2728 (129) (890 – 24871)	4539 (98) (1394 – 19186)	1.536 (1.135 – 2.081)
Cmin (ng/mL) – Geometric Mean (%CV) Range	60.2 (128) (14.5 – 566)	97.8 (154) (30.4 – 1219)	1.479 (1.083 – 2.020)
C0 (ng/mL) – Geometric Mean (%CV) Range	135 (70) (41.0 – 523)	158 (114) (33.1 – 1266)	1.134 (0.782 – 1.645)
Tmax (h) – Median (Min, Max)	3.0 (1.0, 6.0)	4.0 (2.0, 8.0)	–

- Consistent with the known PK characteristics of RAL, there was considerable inter-individual variability associated with RAL exposure parameters both following its administration alone and in combination with ATV
- Compared to RAL 400 mg BID alone, the geometric means for RAL Cmax, AUC(0-12h), and Cmin were increased by 39%, 54%, and 48%, respectively, albeit with wide 90% CI following coadministration with ATV 300 mg BID; a similar trend was previously observed when RAL was coadministered with ATV 400 mg QD or with ATV/RTV 300/100 mg QD [1]

Safety

Table 4: Safety Results

	Treatment: RAL BID N = 22	Treatment: ATV BID N = 22	Treatment: ATV + RAL BID N = 22
Total number of AEs	8	21	22
Subjects - N (%)	7 (31.8%)	15 (68.2%)	13 (59.1%)
Most Frequent AEs - N (%)			
Jaundice	0	10 (45.5%)	6 (27.3%)
Headache	4 (18.2%)	1 (4.5%)	1 (4.5%)

- All AEs were mild to moderate in intensity
- The incidence of AEs was similar when ATV BID was administered alone or with RAL
- Three (3) subjects discontinued due to an AE following administration of ATV 300 mg + RAL 400 mg BID
  - One subject had an asymptomatic ECG abnormality of occasional PVC that began on Day 19 which continued in the absence of study drug, and ultimately was considered an AE unlikely to be related to study drug. No other ECG abnormalities noted in other subjects during the study were considered clinically relevant by the Investigator
  - One subject had a generalized rash that began on Day 14 which was considered mild and certainly related to study drug by the Investigator
  - One subject had a generalized rash that began on Day 15 which was considered mild and probably related to study drug by the Investigator

Table 5: Total Bilirubin Abnormalities

	Treatments in AI424352: RAL 400 BID N=22	ATV 300 BID N=22	ATV + RAL BID N=20*
Subjects with Increased Total Bilirubin - N (%)	0	22 (100)	17(77.3)**
Total Bilirubin (mg/dL)			
Mean (SD)	0.43 (0.15)	4.48 (2.15)	3.63 (2.55)
Range (mg/dL)	0.20 - 0.70	1.30 - 10.00	0.30 - 12.40
Grading Abnormalities - N (%)			
Grade 1: 1.1-1.5xULN	0	1 (4.5)	0
Grade 2: 1.6 - 2.5xULN	0	5 (22.7)	5 (22.7)
Grade 3: 2.6 - 5.0xULN	0	7 (31.8)	6 (27.3)
Grade 4: >5.0xULN	0	9 (40.9)	6 (27.3)

*Two subjects discontinued prior to labs.
**Three subjects were within normal limits

- As expected, increases in bilirubin levels were associated with ATV exposure. Results suggest that there is no additional influence of RAL on ATV associated hyperbilirubinemia
- Compared to historical data after ATV/RTV 300/100 mg QD (mean of 5.32 mg/dl across healthy subject studies), the incidence of hyperbilirubinemia appeared to be comparable after ATV 300 mg BID alone or in the presence of RAL 400 mg BID

Table 6: Summaries of ECG intervals at 2 Hours Postdose and Change from Baseline

ECG Intervals	Baseline (Day -1)	Absolute Value: RAL 400 BID (Day 5)	Absolute Value: ATV 300 BID (Day 12)	Absolute Value: ATV+RAL BID (Day 26)	Change from Baseline: RAL 400 BID (Day 5)	Change from Baseline: ATV 300 BID (Day 12)	Change from Baseline: ATV+RAL BID (Day 26)
N	22	22	22	19	22	22	19
PR (msec) Mean (SD) Range	153 (17) 122 – 183	153 (16) 120 – 186	191 (21) 160 – 224	184 (21) 154 – 223	-0.1 (10) -20 – 22	37 (13) 17 – 63	31 (11) 12 – 54
QRS (msec) Mean (SD) Range	88 (8.0) 72 – 101	88.0 (8.0) 72 – 105	99 (8.3) 79 – 116	99 (8.3) 85 – 117	0.0 (5.2) -10 – 10	11 (7.4) 2 – 25	11 (7.1) -2 – 25
QTcF (msec) Mean (SD) Range	407 (15) 368 – 440	402 (14) 377 – 439	398 (14) 375 – 430	394 (13) 367 – 417	-4.2 (13) -40 – 27	-8.8 (12) -26 – 18	-11 (13) -39 – 20

Figure 6: Mean (SE) Change from Baseline in PR Interval (msec) versus Study Day

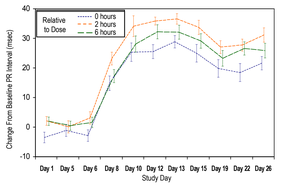


Figure 7: Individual PR Interval (msec) at 2 Hours Postdose versus Study Day

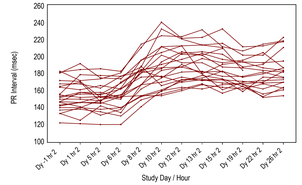


Figure 8: Mean (SE) Change from Baseline in QRS Interval (msec) versus Study Day

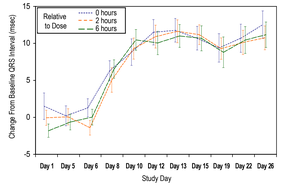
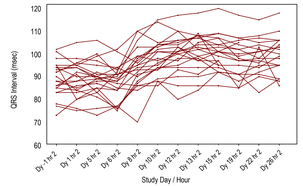


Figure 9: Individual QRS Interval (msec) at 2 Hours Postdose versus Study Day



RESULTS

- No ECG PR, QRS, or QT interval changes were observed with RAL alone
- The prolongation of PR interval appeared to be more pronounced at 2 h post dose, whereas the QRS effect was similar at all 3 time points, suggesting that QRS changes may be less associated with ATV Cmax relative to PR changes
- Mean QRS and PR intervals were increased with ATV alone, and remained elevated, but relatively stable throughout coadministration with RAL; RAL did not appear to affect ATV-associated PR or QRS changes
- Compared to historical data after ATV/RTV 300/100 mg QD, the prolongation of PR intervals were comparable to or slightly higher. Note that minimal QRS interval widening (mean of ≤ 3 msec) has been observed historically for ATV 300/100 mg QD
- Mean QTcF did not increase across the study; No individual change in QTcF exceeded 30 msec

CONCLUSIONS

- Compared to ATV 300 mg BID alone, ATV adjusted geometric mean Cmax, AUC and Cmin were 11%, 17% and 29% lower, respectively, upon coadministration with RAL; all of the individual ATV Cmin values were greater than the 10-fold protein binding adjusted EC90 for ATV against wild type HIV
- RAL exposures were increased by approximately 40 – 55% when coadministered with ATV 300 mg BID; a similar trend was previously observed when RAL was concomitantly administered with ATV 400 mg QD and ATV/RTV 300/100 mg QD
- ATV BID and RAL BID alone and when coadministered were generally safe and well-tolerated
- RAL coadministration did not appear to affect ATV-associated hyperbilirubinemia
- Mean QRS and PR interval increases were observed with ATV alone and remained elevated throughout coadministration with RAL; RAL did not appear to affect ATV-associated PR or QRS changes
  - The clinical relevance of QRS interval increases with ATV BID is unclear and is being investigated further in an HIV-infected patient pilot safety and efficacy study

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