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Atazanavir/Cobicistat Fixed-Dose Combination is Bioequivalent to the Separate Agents

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INTRODUCTION

Background

- The once-daily protease inhibitor atazanavir (ATV) boosted with low-dose ritonavir (RTV) and combined with other antiretrovirals is approved for the treatment of HIV-1 infection[1]
- Cobicistat (COBI):
  - Developed as an alternative pharmacoenhancer to RTV
  - Potent, mechanism-based inhibitor of CYP3A with no antiretroviral activity
  - Greater CYP inhibition specificity and less induction liability
  - Comparable efficacy and safety in a 48-week Phase III trial of ATV 300 mg + COBI 150 mg relative to ATV 300 mg + RTV 100 mg (85% vs 87% virologic suppression, respectively)[2]
  - To reduce pill burden, a fixed-dose combination (FDC) of ATV/COBI 300/150 mg was developed
- Because ATV is recommended to be taken with food, which enhances ATV bioavailability and reduces pharmacokinetic (PK) variability, the objectives of our study were as follows:

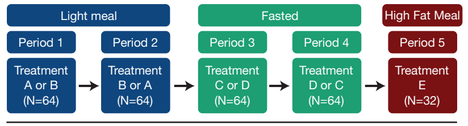
Objectives

- Primary: Demonstrate bioequivalence of ATV in the FDC to ATV capsule + COBI tablet administered with a light meal
- Secondary:
  - Assess the relative bioavailability of ATV in the FDC compared to ATV capsule + COBI tablet under fasted conditions
  - Assess the relative bioavailability of COBI in the FDC compared to ATV capsule + COBI tablet administered with a light meal and under fasted conditions
  - Assess the food effect of a light meal and a high fat meal on the PK of ATV in the FDC
  - Assess the safety and tolerability of single doses of the FDC and single doses of the single agents coadministered

METHODS

Study design

- This was an open-label, single-dose, 5-period (7-day washout between each period), 5-treatment, crossover study in healthy subjects randomized equally to one of eight treatment sequences (ABCDE, ABDCE, BACDE, BADCE, ABCD, ABDC, BACD or BADC)



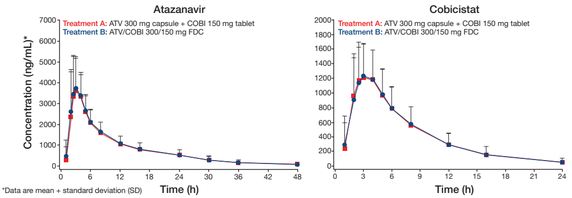
  - Treatment A: ATV 300 mg capsule + COBI 150 mg tablet with a light meal
  - Treatment B: ATV/COBI 300/150 mg FDC with a light meal
  - Treatment C: ATV 300 mg capsule + COBI 150 mg tablet fasted
  - Treatment D: ATV/COBI 300/150 mg FDC fasted
  - Treatment E: ATV/COBI 300/150 mg FDC with a high fat meal

Pharmacokinetic and statistical analysis

- Pharmacokinetic parameters of ATV and COBI, C_{max}, $AUC_{0\text{-}T}$, AUC_{INF}, C_{24}, were derived from plasma concentration versus time data
- For the primary objective, complete data from 56 subjects would provide approximately 95% power for ATV C_{max} and AUC_{INF} if the true ratios (FDC vs single agents) were 0.95
- Linear mixed-effects models with natural logarithms of ATV or COBI as response and with treatment, period and sequence as fixed effects and subject(sequence) as a random effect was used for assessment of bioequivalence and relative bioavailability
- For assessment of food effect, a simpler linear mixed-effects model was used with natural logarithms of ATV as response and with treatment as fixed effect and subject(sequence) as a random effect
- Point estimates and 90% confidence intervals (CI) for differences on the log scale were exponentiated to obtain estimates of geometric mean ratio (GMR) on the original scale
- Bioequivalence was concluded if the adjusted GMR 90% CIs fell within 0.80 to 1.25 for PK parameters

RESULTS – BIOEQUIVALENCE (WITH LIGHT MEAL)

ATV and COBI PK profiles – FDC vs Single Agents with a Light Meal



*Data are mean + standard deviation (SD)

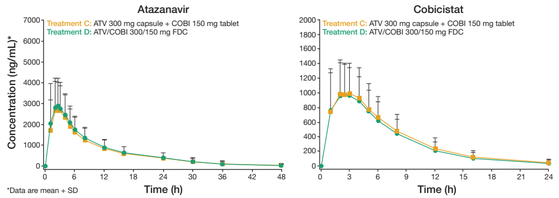
PK parameters	Adjusted Geometric Mean		Adjusted Geometric Mean Ratio
	ATV + COBI (Treatment A)	ATV/COBI FDC (Treatment B)	GMR (90% CI) [B vs A]
n	63*	62*†	
Atazanavir (light meal)			
C_{max} (ng/mL)	3822	4101	1.073 (1.012, 1.137)
AUC_{INF} (ng•h/mL)	33475	35623	1.064 (1.011, 1.120)
$AUC_{0\text{-}T}$ (ng•h/mL)	32723	34848	1.065 (1.012, 1.120)
C_{24} (ng/mL)	416	450	1.084 (1.014, 1.158)
Cobicistat (light meal)			
C_{max} (ng/mL)	1320	1351	1.023 (0.991, 1.057)
AUC_{INF} (ng•h/mL)	9053	9225	1.019 (0.982, 1.058)
$AUC_{0\text{-}T}$ (ng•h/mL)	8745	8912	1.019 (0.983, 1.057)

*One subject excluded as accidentally given both Treatments A and B simultaneously.
†One subject excluded as vomited shortly after receiving Treatment B.

- All ATV PK parameter adjusted GMR 90% CIs fell within the predefined limits indicating bioequivalence of the FDC to ATV 300 mg and COBI 150 mg coadministered individually
- Although not prespecified, COBI in the FDC also met the criteria for bioequivalence to coadministration of the individual agents

RESULTS – BIOAVAILABILITY (FASTED)

ATV and COBI PK profiles – FDC vs Single Agents under Fasted Conditions



*Data are mean + SD

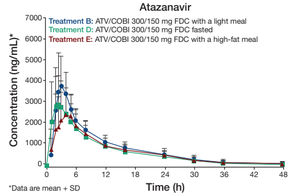
PK parameters	Adjusted Geometric Mean		Adjusted Geometric Mean Ratio
	ATV + COBI (Treatment C)	ATV/COBI FDC (Treatment D)	GMR (90% CI) [D vs C]
n	63*	63*	
Atazanavir (fasted)			
C_{max} (ng/mL)	2588	2942	1.137 (1.000, 1.292)
AUC_{INF} (ng•h/mL)	25532	28341	1.110 (0.991, 1.244)
$AUC_{0\text{-}T}$ (ng•h/mL)	25004	27841	1.113 (0.993, 1.248)
C_{24} (ng/mL)	294	337	1.144 (1.006, 1.300)
Cobicistat (fasted)			
C_{max} (ng/mL)	952	1033	1.085 (0.925, 1.273)
AUC_{INF} (ng•h/mL)	7582	7398	0.976 (0.886, 1.075)
$AUC_{0\text{-}T}$ (ng•h/mL)	6534	7199	1.102 (0.929, 1.307)

*One subject withdrew consent 3 days following the completion of Treatment B.

- The bioavailability of ATV administered as an FDC was similar to ATV + COBI administered as individual components when given under fasted conditions
- The adjusted GMR 90% CIs for ATV $AUC_{0\text{-}T}$ and AUC_{INF} and COBI AUC_{INF} were completely contained within the (0.80, 1.25) range

RESULTS – BIOAVAILABILITY (FOOD EFFECT)

ATV PK profile – ATV/COBI FDC with a Light Meal vs Fasted vs with a High Fat Meal



*Data are mean + SD

Atazanavir PK	Geometric Mean			Adjusted Geometric Mean Ratio (90% CI)		
	Light Meal (Treatment B)	Fasted (Treatment D)	High Fat Meal (Treatment E)	Light Meal vs Fasted [B vs D]	High Fat Meal vs Fasted [E vs D]	High Fat Meal vs Light Meal [E vs B]
n	62*†	63‡	30§			
C_{max} (ng/mL)	4104	2941	2545	1.423 (1.273, 1.590)	0.862 (0.701, 1.059)	0.643 (0.545, 0.759)
AUC_{INF} (ng•h/mL)	35673	28378	26510	1.280 (1.171, 1.398)	0.956 (0.810, 1.128)	0.749 (0.658, 0.852)
$AUC_{0\text{-}T}$ (ng•h/mL)	34905	27875	25873	1.275 (1.166, 1.393)	0.950 (0.804, 1.122)	0.746 (0.655, 0.849)
C_{24} (ng/mL)	449	337	398	1.349 (1.215, 1.498)	1.231 (1.023, 1.483)	0.912 (0.789, 1.054)

*One subject excluded as accidentally given both Treatments A and B simultaneously. †One subject excluded as vomited shortly after receiving Treatment B. ‡One subject withdrew consent 3 days following the completion of Treatment B. §One subject discontinued prior to receiving Treatment E due to poor/noncompliance.

RESULTS – BIOAVAILABILITY (FOOD EFFECT)

- When the FDC tablet was administered with a light meal (Treatment B) compared to under fasted conditions (Treatment D), the AUCs of ATV were increased by approximately 28% and C_{max} was increased by 42%; in addition, C_{24} was increased by 35%
- However, the AUCs of ATV with high fat meal (Treatment E) were not significantly affected compared to fasted conditions (Treatment D), but C_{max} decreased by 14% while C_{24} increased by 23%
- When comparing the high fat meal (Treatment E) versus the light meal (Treatment B), ATV AUCs and C_{max} with a high fat meal were decreased by 25% and 36%, respectively; however, ATV C_{24} was similar when FDC was administered with either a light meal or a high fat meal

RESULTS – SAFETY AND TOLERABILITY

- No deaths, serious adverse events, or discontinuations due to adverse events (AEs)
  - One subject received a duplicate dose of study drugs on study Day 1, no AEs reported
  - One subject withdrew consent on study Day 10
- Overall, the most common AEs (≥5%) were dizziness, abdominal discomfort, musculoskeletal chest pain, and nasopharyngitis; all were mild to moderate
- Laboratory marked abnormalities in two or more subjects included:
  - Total bilirubin; not unexpectedly with ATV, five subjects (7.8%) treated per protocol had elevations (1.2–2.1 × upper limit of normal)
  - Creatine kinase (n=2, 3.1%)
  - Low leukocytes (n=4, 6.3%)
  - Low neutrophils (n=5, 7.8%)
  - Urine red blood cells (n=2, 3.1%) and white blood cells (n=7, 10.9%)
  - All resolved or were determined to be not clinically significant at study discharge
- No clinically significant trends in ECG parameters, vital signs, or physical exam findings were noted

CONCLUSIONS

- ATV administered in an FDC tablet containing 300 mg ATV and 150 mg COBI is bioequivalent to coadministration of the individual components when given with a light meal
- Although not prespecified, COBI in the FDC also met the criteria for bioequivalence to coadministration of the individual components when given with a light meal
- Under fasted conditions, the bioavailability of ATV and COBI in the FDC is comparable to that following coadministration of the individual components
  - Although the study was not powered to assess bioequivalence under fasted conditions, results demonstrate that the FDC performs similarly to the ATV capsule and COBI tablet
- A light meal increased ATV AUCs, C_{max} and C_{24} relative to fasted conditions. A high fat meal yielded an ATV C_{24} similar to that of a light meal suggesting that, consistent with the current dosing recommendations for ATV, the ATV/COBI FDC should be administered with food
- Single doses of 300 mg ATV and 150 mg COBI were well tolerated either as an FDC or as single agents

ACKNOWLEDGEMENTS

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