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APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	206353
Original Submission Date	4 Apr 2014
Submission Type	505(b)(1), standard review
SDN	1, 4
Brand Name	EVOTAZ (proposed)
Generic Name	Atazanavir (ATV)/cobicistat (cobi) fixed-dose combination
Office of Clinical Pharmacology (OCP) Review Team	Leslie Chinn, Ph.D., Islam R. Younis, Ph.D.
OCP Division	DCP4
OND Division	Division of Antiviral Products
Applicant	Bristol-Myers Squibb Co.
Strength and Formulation	Atazanavir (b) (4) 300 mg plus cobicistat 150 mg fixed-dose combination (FDC) oral IR tablet
Proposed Dosing Regimen	One tablet once daily with food
Proposed Indication	Treatment of HIV-1 infection, in combination with other antiretroviral agents, in adults
Referenced Applications	NDA 21567 (atazanavir, REYATAZ®), NDA 203094 (cobicistat, TYBOST®), IND 117131 (ATV/cobi FDC)

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1. EXECUTIVE SUMMARY

Atazanavir (ATV, marketed in the US as Reyataz®) is an inhibitor of human immunodeficiency virus type 1 (HIV-1) protease that interferes with viral polyprotein processing, thereby preventing the formation of mature virions. It was approved in the US for the treatment of HIV-1 infection as a component of a combination antiretroviral treatment regimen in 2003; the prescribing information was updated in 2004 to include a dosage regimen including the HIV-1 protease inhibitor ritonavir (RTV), a potent CYP3A inhibitor that increases systemic ATV exposures upon coadministration.

Cobicistat (cobi, marketed in the US as Tybost®) is a structural RTV analogue that lacks anti-HIV-1 activity. It was approved in the US as a CYP3A inhibitor indicated to increases systemic exposures of ATV or the HIV-1 protease inhibitor darunavir in combination with other antiretroviral agents in the treatment of HIV-1 infection in 2014.

The Applicant is seeking approval of the current NDA based on the results from the bioequivalence study AI424511, in which the pharmacokinetics of ATV and cobi coadministered as single agents (Reyataz® and Tybost®) were compared to the pharmacokinetics of ATV and cobi following administration of the ATV/cobi fixed-dose combination (FDC) tablet.

1.1 BACKGROUND

The option of taking a fixed-dose combination tablet in place of two or more components of an antiretroviral regimen is appealing to patients with a chronic medical condition such as HIV-1 infection. Through the reduced pill burden, FDC tablets may increase patient adherence with the potential for improved efficacy and decreased development of resistance.

For these reasons, the Applicant undertook development of the current ATV/cobi FDC. Per the Applicant, (b) (4) (b) (4) thus resulting in the current dosage form, a film-coated tablet containing the approved dosages of ATV coadministered with cobi in adults (i.e. ATV 300 mg plus cobi 150 mg).

The safety and efficacy of ATV coadministered with cobi were compared to ATV coadministered with RTV, both in combination with tenofovir disoproxil fumarate and emtricitabine FDC (Truvada®), in a Phase 3 study in which 692 HIV-1 infected treatment-naïve patients were enrolled (GS-US-216-114). The efficacy of the cobicistat-containing regimen was non-inferior to the efficacy of the regimen containing RTV (the difference in the percentage of subjects who achieved HIV-1 RNA less than 50 copies/mL at Week 48 between the ATV/cobi and ATV/rtv treatment arms was -2.2%, with 95% CI of -7.4 to 3%; please refer to the Clinical Review of NDA 203094). The findings in treatment-naïve patients were determined to be extrapolatable to treatment-experienced patients because the approved regimens are the same in both populations (ATV 300 mg plus RTV 100 mg QD) and because ATV exposures following coadministration with RTV 100 mg or cobi 150 mg are expected to be similar (please refer to the Clinical Pharmacology Review of NDA 203094).

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To support the current Application, the Applicant conducted Study AI424511 in order to evaluate the pharmacokinetics of ATV and cobi when administered as single agents or the FDC in the fed and fasted states. According to the Reyataz® prescribing information, administration of ATV with food increases bioavailability; therefore, ATV should be taken with food. The Applicant therefore identified the assessment of the bioavailability of ATV and cobi exposures provided by the FDC relative to the single agents following a light meal (e.g. 336 kcal, 5.1 g fat, 9.3 g protein) as the primary objective (and calculated statistical power for this objective), with relative bioavailability assessed under fasted conditions as a secondary objective. In pre-NDA correspondence (IND 117131 pre-NDA meeting minutes, 20 Dec 2013), the Division had the following comment for the Applicant:

> …Since the proposed product is intended to be administered under fed conditions only, the Agency may consider the BE results under fed conditions. This requires information on the effect of high fat meal on the BA of your proposed product. Therefore, the acceptability of the study design (e.g. under light fat meal) as the basis for approval of your proposed product will be determined once the results of the effect of high fat content on the BA of your proposed product are submitted and reviewed. In addition, the results of the fasted BE study and its relevance on regulatory decision making will be a review issue.

As stated in pre-NDA communications with the Applicant, the acceptability of the evaluation of relative bioavailability under fed conditions as the basis for approval will be discussed in this review. In addition, the findings of the relative bioavailability study AI424511 will be summarized in the current review.

1.2 Summary of Clinical Pharmacology Findings

Study AI424511 was a randomized crossover study intended to assess the relative bioavailability of single doses of ATV 300 mg and cobi 150 mg when administered together as single agents compared to a single dose of the ATV/cobi 300/150 mg FDC under fasted or fed (following a light meal) administration in 64 healthy volunteers. In addition, the effect of food (light meal and high-fat meal [1038 kcal, 59 g fat, 37 g protein]) on the pharmacokinetics of ATV and cobi were evaluated. The study schema of AI424511 is displayed in Figure 1. Please refer to the individual study review (Section 3.1) for additional details about the study design and results.

Figure 1. Study AI424511 schema (source: adapted from CSR Appendix 1.1)

Period 1		Period 2		Period 3		Period 4		Period 5
Day 1	7-Day Washout	**Day 8**	7-Day Washout	**Day 15**	7-Day Washout	**Day 22**	7-Day Washout	**Day 29**
A		B		C		D		E
B		A		D		C		

Treatment A: ATV 300 mg capsule plus cobi 150 mg tablet (light meal)
Treatment B: ATV/cobi 300/150 mg FDC tablet (light meal)
Treatment C: ATV 300 mg capsule plus cobi 150 mg tablet (fasted)
Treatment D: ATV/cobi 300/150 mg FDC tablet (fasted)
Treatment E: ATV/cobi 300/150 mg FDC tablet (high-fat meal)

Statistical analyses of ATV and cobi PK parameters following administration of the ATV/cobi FDC compared to the ATV capsule plus the cobi tablet under fed (light meal) or fasted

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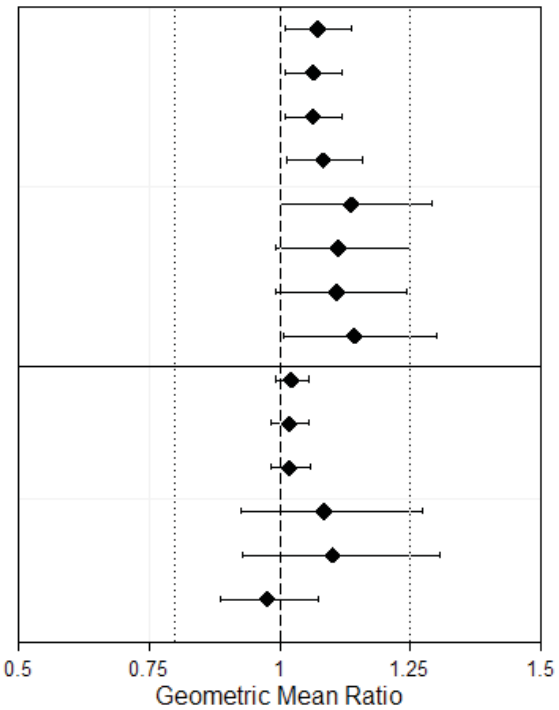
conditions are displayed in Figure 2. Administration of the FDC with a light meal resulted in similar exposures of both ATV and cobi compared to administration of the single agents (90% CI for ATV C_{max}, AUC_t, and C_{24} and for cobi C_{max} and AUC_t within the predefined no-effect bounds of 80-125%). Under fasted conditions, the FDC provided slightly higher exposures of both ATV and cobi compared to the single agents (90% CI for ATV C_{max}, AUC_t, and C_{24} and for cobi C_{max} and AUC_t ranging from 93-131%).

Figure 2. Statistical comparisons of key atazanavir and cobicistat pharmacokinetic parameters following administration of the ATV/cobi 300/150 mg FDC relative to coadministration of ATV 300 mg plus cobi 150 mg under fed conditions (source: Reviewer's analysis of CSR Tables 9.2.1.1-2, 9.2.1.2-2, 9.2.2.1-2, 9.2.2.2-2)

Analyte	Meal	Parameter	GMR
ATV	Light meal	Cmax	1.073
		AUC24	1.065
		AUCinf	1.064
		C24	1.084
	Fasted	Cmax	1.137
		AUC24	1.113
		AUCinf	1.11
		C24	1.144
Cobi	Light meal	Cmax	1.023
		AUC24	1.019
		AUCinf	1.019
	Fasted	Cmax	1.085
		AUC24	1.102
		AUCinf	0.976



Statistical analyses of ATV and cobi PK parameters following administration of the ATV/cobi FDC under fed (light meal or high-fat meal) conditions compared to fasted conditions are displayed in Figure 3. In general, administration of the ATV/cobi FDC with a light meal provided higher systemic exposures compared to fasted administration (90% CI for ATV and cobi C_{max}, AUC_t, and AUC_{inf} ranging from 114-159%), while administration of the FDC with a high-fat meal resulted in systemic ATV exposures that were slightly lower (90% CI for ATV C_{max}, AUC_t, and AUC_{inf} ranging from 70-113%) and systemic cobi exposures that were similar to those observed following administration of the FDC in the fasted state (90% CI for cobi C_{max}, AUC_t, and AUC_{inf} within the predefined no-effect bounds of 80-125%). The reason for the larger increase in ATV exposures following a light meal compared to a high-fat meal is unknown, but the food effect is consistent between the ATV/cobi FDC and the ATV capsule with or without RTV (coadministration with a light meal resulted in a larger increase in ATV

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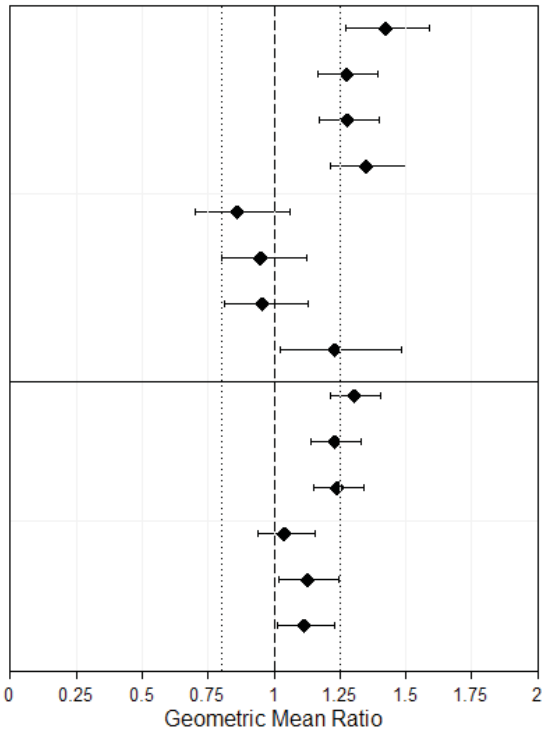
exposures than a high-fat meal when compared to fasted administration). Overall, administration of the ATV/cobi FDC with food, regardless of fat content, resulted in slightly higher ATV trough concentrations (approximately 23-35% increase in ATV C_{24}) compared to administration of the FDC in the fasted state.

Figure 3. Statistical comparisons of key atazanavir and cobicistat pharmacokinetic parameters following administration of the ATV/cobi 300/150 mg FDC under fed conditions relative to administration of the FDC under fasted conditions (source: Reviewer's analysis of CSR Tables 9.2.1.3-3, 9.2.1.3-3, 9.2.2.3-2, 9.2.2.3-3)

Analyte	Meal	Parameter	GMR
ATV	Light meal	Cmax	1.423
		AUC24	1.275
		AUCinf	1.28
		C24	1.349
	High-fat meal	Cmax	0.862
		AUC24	0.95
		AUCinf	0.956
		C24	1.231
Cobi	Light meal	Cmax	1.305
		AUC24	1.232
		AUCinf	1.24
	High-fat meal	Cmax	1.04
		AUC24	1.127
		AUCinf	1.116



One of the primary issues discussed in preNDA communications and addressed during the review process was the appropriateness of using the comparison of relative ATV bioavailability of the ATV/cobi FDC to the single agents under fed conditions (following a light meal) as the primary endpoint, rather than the comparison of relative bioavailability under fasted conditions as is recommended in the FDA's Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products (March 2003). The Applicant designed Study AI424511 to evaluate exposures of ATV and cobi following a light meal because ATV is administered under fed conditions (refer to the Reyataz® prescribing information). The study was powered based on the interindividual variability in ATV exposures observed following fed administration; fasted administration results in a higher degree interindividual variability and would therefore have required additional subjects to be enrolled in the study.

This Reviewer agrees with the Applicant that it is reasonable to assess the relative bioavailability of the ATV/cobi FDC to the ATV capsule plus the cobi tablet under fed conditions as ATV is

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administered with food in clinical practice. Therefore, although the FDC was technically not bioequivalent under fasted conditions (i.e. 90% CI for ATV C_{max}, AUC_{inf}, and AUC_t were not within 80-125%), demonstration of bioequivalence of the ATV/cobi FDC to the ATV capsule plus the cobi tablet administered following a light meal is sufficient to establish that ATV exposures are comparable between the FDC and the single agents. In addition, the deviations from bioequivalence under fasted conditions were slight, indicating that, if a patient were to mistakenly take the ATV/cobi under fasted conditions, no clinically relevant consequences would be anticipated under normal circumstances as exposures would be within the range evaluated in previous clinical studies using ATV. It should be noted that cobi exposures followed a similar pattern (bioequivalent following a light meal but not under fasted conditions), although the relative bioavailability of cobi was considered a secondary endpoint as it does not have antiviral activity.

Overall, the results of Study AI424511 support that administration of the ATV/cobi 300/150 mg oral FDC tablet and coadministration of ATV 300 mg plus cobi 150 mg provide similar exposures when administered with a light meal. Based on the higher ATV trough concentrations (the clinically relevant parameter for efficacy) observed following fed administration compared to fasted administration, as well as the fact that bioequivalence was established under fed conditions, this Reviewer concurs with the Applicant that the ATV/cobi FDC should be administered with food.

While inspections of the clinical and bioanalytical sites for Study AI424511 were requested, the Office of Scientific Investigations determined that inspections were not necessary because both the clinical and bioanalytical sites had been inspected recently and no issues were noted.

1.3 RECOMMENDATIONS

The Office of Clinical Pharmacology (OCP) review team finds this application acceptable and recommends approval of the atazanavir/cobicistat 300/150 mg FDC tablet for the treatment of HIV-1 infection, in combination with other antiretroviral agents, in adults. In addition, the OCP review team also recommends the labeling changes described in Section 2 of this review.

1.4 POST-MARKETING COMMITMENTS OR REQUIREMENTS

There were no clinical pharmacology PMCs or PMRs at the time of completion of this review.

2. LABELING RECOMMENDATIONS

The following section describes labeling recommendations made by the Clinical Pharmacology review team based on our interpretation of the review issues at the time this review was filed. Internal labeling discussions are ongoing and negotiations with the Applicant are in progress; recommendations described in this section are subject to change.

Substantive clinical pharmacology changes were made to the label as follows:

- Table 5 containing clinical recommendations regarding drug-drug interactions was updated to (b) (4) drugs for which no dose adjustment was needed; these drugs were added to the list of non-interacting drugs under the table

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- Contraindications and clinical recommendations regarding drug-drug interactions were checked for consistency with the Tybost® prescribing information, the darunavir/cobicistat FDC (NDA 205395) that is currently under review, and the approved prescribing information for the concomitantly administered drug; lurasidone for all patients and colchicine for patients with renal or hepatic impairment were added to the list of contraindicated drugs for consistency with the lurasidone and colchicine prescribing information, respectively

(b) (4)

3. APPENDICES

3.1 REVIEW OF STUDY AI424511

A Randomized, 5-Period, Crossover Study in Healthy Subjects to Assess the Bioequivalence of Atazanavir when Coadministered with Cobicistat as a Fixed Dose Combination Relative to the Single Agents Following a Light Meal, the Relative Bioavailability of Atazanavir when Coadministered with Cobicistat as a Fixed Dose Combination Relative to the Single Agents Under Fasted Conditions, and the Effect of Food on the Bioavailability of Atazanavir in the Fixed Dose Combination

Trial Period
25 Apr to 20 Jun 2012
Final report date: 22 Nov 2013

Trial Site
PPD Development, Inc., Austin, Texas, USA

Trial Rationale
Atazanavir (ATV, REYATAZ®) is an HIV-1 protease inhibitor (PI) approved in combination with other antiretroviral agents for the treatment of HIV-1 infection. Cobicistat (COBI) is a potent and specific CYP3A inhibitor with no antiretroviral activity. Cobicistat is currently available in a fixed-dose combination (FDC) tablet with elvitegravir, tenofovir DF, and emtricitabine as a complete regimen for the treatment of HIV-1 infection in treatment-naïve individuals (STRIBILD®); NDA 203094 for COBI as a pharmacoenhancer of atazanavir (based on a Phase 3 trial) or darunavir (based on exposure-matching) is currently under review by the FDA. An FDC containing ATV 300 mg and COBI 150 mg is being developed to reduce pill burden and improve adherence, with a proposed indication for the treatment of HIV-1 infection in combination with other antiretroviral agents. The primary goal of this study was to evaluate the bioavailability of ATV and COBI from the FDC relative to the single agents under both fasting conditions and after a light meal.

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Trial Objectives

The primary objective of the trial was to:

- assess the relative bioavailability of ATV in an FDC of ATV/COBI 300/150 mg as compared to a 300 mg ATV capsule coadministered with a 150 mg COBI tablet when administered with a light meal

The secondary objectives of the trial were to:

- assess the relative bioavailability of ATV in an FDC of ATV/COBI 300/150 mg as compared to a 300 mg ATV capsule coadministered with a 150 mg COBI tablet when administered under fasted conditions
- assess the relative bioavailability of COBI administered as an FDC of ATV/COBI 300/150 mg as compared to COBI 150 mg tablet coadministered with ATV 300 mg capsule as individual components with a light meal and under fasted conditions
- assess the effect of a light meal and a high fat meal on the PK of ATV and COBI when administered as an FDC (ATV/COBI 300/150 mg
- assess the safety and tolerability after a single dose of an FDC of ATV/COBI 300/150 mg as well as after a single dose of 300 mg ATV capsule coadministered with a 150 mg COBI tablet as individual components

Trial Design

This was an open-label, single-dose, five-period, randomized crossover study with five treatments:

Treatment A ATV 300 mg capsule + COBI 150 mg tablet (following a light meal)
Treatment B ATV/COBI 300/150 mg FDC tablet (following a light meal)
Treatment C ATV 300 mg capsule + COBI 150 mg tablet (fasted)
Treatment D ATV/COBI 300/150 mg FDC tablet (fasted)
Treatment E ATV/COBI 300/150 mg FDC tablet (following a high fat meal)

Subjects were randomized to one of eight treatment sequences (ABCDE, ABDCE, BACDE, BADCE, ABCD, ABDC, BACD, or BADC). Treatment periods were separated by seven-day washouts. Subjects were confined to the clinic from Day -1 until the day of discharge (Days 24 or 31, depending on randomization). The study schema is shown in Figure 1.

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Figure 1. Study schema

Days -21 to -1	Period 1[a] and Period 2			Wash-out up to Day 14	Periods 3 and 4[b],			Wash-out up to Day 28	Period 5[c],	
	Day 1	Wash-out up to Day 7	Day 8		Day 15	Wash-out up to Day 21	Day 22		Day 29	Day 31
S & E[d]	Treatment A or B		Treatment B or A		Treatment C or D		Treatment D or C		Treatment E	Discharge

Source: Appendix 1.1

[a] Approximately 64 subjects will be randomized prior to Day 1 dosing

[b] Approximately 32 subjects will be discharged at the end of Period 4 (Day 24) based on the assigned treatment sequence

[c] Remaining approximately 32 subjects will be discharged at the end of Period 5 (Day 31) based on the assigned treatment sequence

[d] Screening and Enrollment

Rationale for Dose Selection

The approved dose of ATV is 300 mg in combination with RTV 100 mg QD with food. A Phase 1 study showed that ATV exposures following administration of 300 mg QD were bioequivalent when administered with RTV 100 mg QD or COBI 150 mg QD. Therefore, ATV 300 mg and COBI 150 mg were the doses evaluated in this study.

Drug Administration

Study drugs were administered in the morning following a 10 h fast and within 5 min of completion of a standardized meal (when applicable).

Investigational Product

ATV/COBI 300/150 mg FDC tablets (Lot 3D75067) and COBI 150 mg tablets (Lot 3B75616) were supplied by the Sponsor. ATV 300 mg capsules were commercially available (Lot 2H60813).

Key Inclusion and Exclusion Criteria

Subjects were healthy nonsmoking males and females between 18 and 49 years of age with a BMI of 18 to 32 kg/m^2 with no clinically significant findings. Females of childbearing potential were willing to use an effective method of birth control (condom, diaphragm, cervical cap, vaginal sponge, spermicide, IUD, tubal ligation, vasectomized partner) for at least four weeks before dosing and had a negative pregnancy test within 24 h prior to study drug administration. Potential subjects were excluded if they were pregnant or lactating. Exclusion criteria also included any acute or chronic clinically significant medical condition, evidence of organ dysfunction, or any clinically significant deviation from normal in physical examination, vital signs, ECG, or clinical laboratory tests.

Concomitant Medications

Concomitant medications, including prescription drugs, over-the-counter drugs including acid controllers, hormonal contraceptives (oral, injectable, or implantable, within 3 months of the

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study), herbal remedies, and nutritional supplements and vitamins, were prohibited during the study.

Sample Collection

Blood was collected to assess ATV or COBI concentrations in plasma predose and 1, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24 h postdose as well as 30, 36, and 48 h postdose for ATV in K_2EDTA blood collection tubes.

Analytical Plan

Pharmacokinetic data

$C_{max,}$ C_{24}, and t_{max} were recorded from observed data. AUC_t was calculated by log and linear trapezoidal summations. The slopes of the terminal phases (λ) were determined by log-linear regression of at least three data points and were used to estimate terminal half-life. AUC_{inf} was also estimated. A linear mixed effect model with treatment, period, and sequence as fixed effects and subject as a random effect was fitted to the log-transformed PK parameters $C_{max,}$ $AUC_{t,}$ and AUC_{inf} and two-sided 90% CI for GMR was compared against the prespecified bounds 0.8-1.25. Descriptive statistics were calculated for other pharmacokinetic parameters.

Trial Results

Bioanalytical methods

Concentrations of ATV (BMS-232632) and COBI in plasma samples were measured simultaneously by LC-MS/MS by [redacted] (b) (4); Method TNJM12160.00). Analysis was performed between 12 Jun and 23 Jul 2013. The maximum storage sample time was 70 days, which is within the validated long-term frozen stability duration of 106 days in plasma. The calibration standards ranged from 5-5000 ng/mL and the quality control (QC) concentrations were 15, 200, 2000, and 4000 ng/mL for both analytes. All inter-assay accuracy and precision estimates were within the acceptable range (data not shown).

Trial population

A total of 64 subjects were enrolled in the study, two of whom discontinued (one due to noncompliance [did not consume entire predose meal] and one withdrew consent due to personal reasons). A summary of subject demographics is displayed in Table 1.

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Table 1. Demographic summary (source: CSR Table 5.3.1-1)

Characteristics	All Subjects (n=64)
Age, years	
Mean (SD)	32.5 (7.4)
Range	18-48
Gender, n (%)	
Male	40 (62.5)
Female	24 (37.5)
Race, n (%)	
White	29 (45.3)
Black	33 (51.6)
Asian	2 (3.1)
BMI, kg/m^2	
Mean (SD)	26.5 (2.9)
Range	18.5-32.1

Source: Tables S.3.1 and S.3.2

Assessment of plasma atazanavir pharmacokinetics following a light meal

The mean atazanavir concentration-time profiles following a single dose of the ATV/COBI 300/150 mg FDC oral tablet or ATV 300 mg capsule plus COBI 150 mg tablet to healthy subjects following a light meal are displayed in Figure 2. ATV exposures were similar between formulations following administration after a light meal, with geometric mean ratios near 1 and 90% CI for C_{max}, AUC_t, AUC_{inf}, and C_{24} contained entirely within 0.8-1.25 (Table 2).

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Figure 2. Mean ± SD atazanavir plasma concentration-time profiles by treatment (A: ATV + COBI, B: ATV/COBI FDC) under fed (light meal) conditions (semi-log scale; source: CSR Figure 9.2.1.1-1)

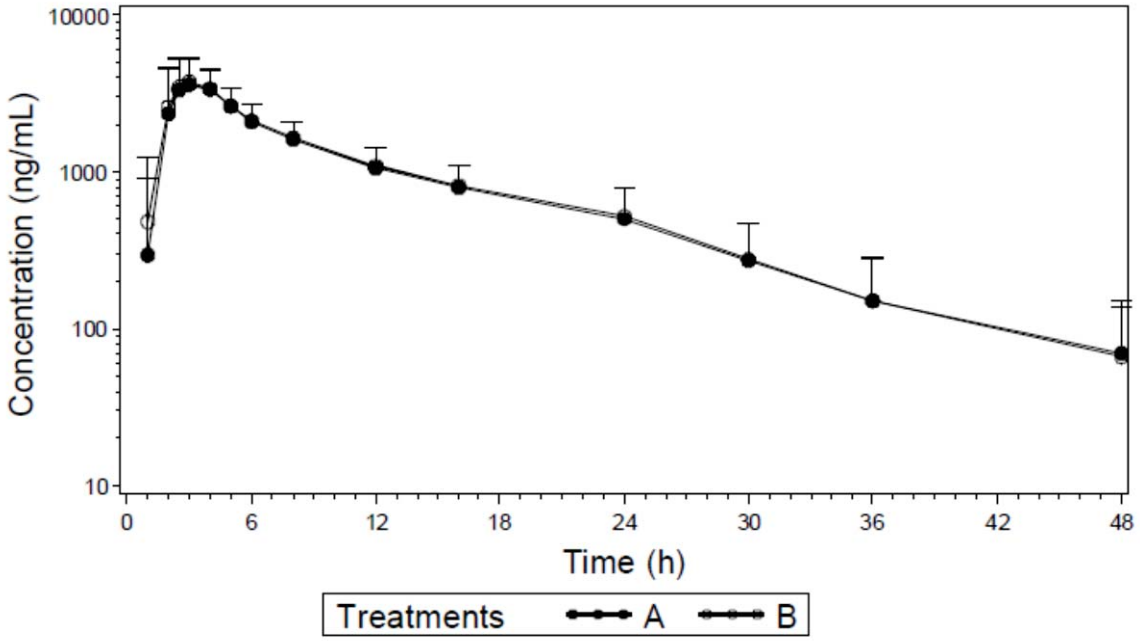

Table 2. Key atazanavir pharmacokinetic parameters and statistical comparisons between treatments (A: ATV + COBI, B: ATV/COBI FDC) under fed (light meal) conditions (source: Study Report Table 9.2.1.1-2)

TREATMENT AND COMPARISON	CMAX (ng/mL) Adj.GEO.MEAN[a]	AUC(0-T) (ng•h/mL) Adj.GEO.MEAN[a]	AUC(INF) (ng•h/mL) Adj.GEO.MEAN[a]	C24 (ng/mL) Adj.GEO.MEAN[a]
A	3821.887	32723.14	33474.57	415.606
B	4101.017	34848.27	35622.54	450.365
	GMR(90% CI)	GMR(90% CI)	GMR(90% CI)	GMR(90% CI)
B vs A	1.073(1.012,1.137)	1.065(1.012,1.120)	1.064(1.011,1.120)	1.084(1.014,1.158)

[a] Derived from linear mixed model with treatment, period and sequence as fixed effects and subject(sequence) as a random effect based on the data of Treatment A and Treatment B only

Treatment Codes: A = ATV 300mg cap+150mg COBI tab light meal, B = ATV 300mg/150mg COBI-FDC tab light meal, C = ATV 300mg cap+150mg COBI tab fasted, D = ATV 300mg/150mg COBI-FDC tab fasted,

E = ATV 300mg/150mg COBI-FDC tab high fat meal

PROGRAM SOURCE:/gbs/prod/clin/programs/ai/424/511/csr01/rpt/crossover_MIX-Atazanavir-AB.sas

Source: Tables S.8.2.4.1A, S.8.2.4.2A, S.8.2.4.3A and S.8.2.4.4A

Assessment of plasma atazanavir pharmacokinetics following fasted administration

The mean atazanavir concentration-time profiles following a single dose of the ATV/COBI 300/150 mg FDC oral tablet or ATV 300 mg capsule plus COBI 150 mg tablet to healthy subjects following fasted administration are displayed in Figure 3. ATV overall systemic exposures were similar between formulations following administration in the fasted state, with

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geometric mean ratios near 1 and 90% CI for AUC_t and AUC_{inf} contained entirely within 0.8-1.25, while the upper bound of the 90% CI for the GMRs for ATV C_{max} and C_{24} were slightly above 1.25 (1.29 and 1.30, respectively; Table 3). For both formulations, t_{max} was more variable following fasted administration compared to fed (range: 1.0-8.0 and 1.0-6.0 h for the FDC and the single agents in the fasted state compared to 2.0-5.6 and 2.0-4.1 h for the FDC and the single agents in the fed state).

Figure 3. Mean ± SD atazanavir plasma concentration-time profiles by treatment (C: ATV + COBI, D: ATV/COBI FDC) under fasted conditions (semi-log scale; source: CSR Figure 9.2.1.2-1)

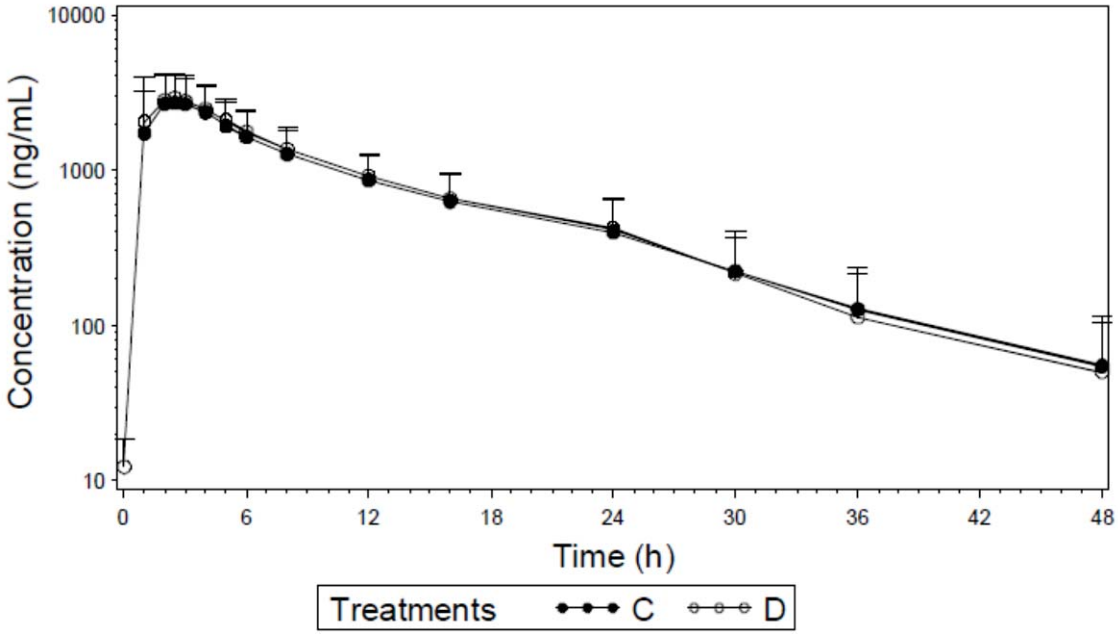


Table 3. Key atazanavir pharmacokinetic parameters and statistical comparisons between treatments (C: ATV + COBI, D: ATV/COBI FDC) under fed (light meal) conditions (source: Study Report Table 9.2.1.2-2)

TREATMENT AND COMPARISON	CMAX (ng/mL) Adj.GEO.MEAN[a]	AUC(0-T) (ng•h/mL) Adj.GEO.MEAN[a]	AUC(INF) (ng•h/mL) Adj.GEO.MEAN[a]	C24 (ng/mL) Adj.GEO.MEAN[a]
C	2587.993	25004.12	25531.53	294.310
D	2941.715	27841.20	28341.13	336.594
	GMR(90% CI)	GMR(90% CI)	GMR(90% CI)	GMR(90% CI)
D vs C	1.137(1.000,1.292)	1.113(0.993,1.248)	1.110(0.991,1.244)	1.144(1.006,1.300)

[a] Derived from linear mixed model with treatment, period and sequence as fixed effects and subject(sequence) as a random effect based on the data of Treatment C and Treatment D only

Treatment Codes: A = ATV 300mg cap+150mg COBI tab light meal, B = ATV 300mg/150mg COBI-FDC tab light meal, C = ATV 300mg cap+150mg COBI tab fasted, D = ATV 300mg/150mg COBI-FDC tab fasted, E = ATV 300mg/150mg COBI-FDC tab high fat meal

PROGRAM SOURCE:/gbs/prod/clin/programs/ai/424/511/csr01/rpt/crossover_MIX-Atazanavir-CD.sas

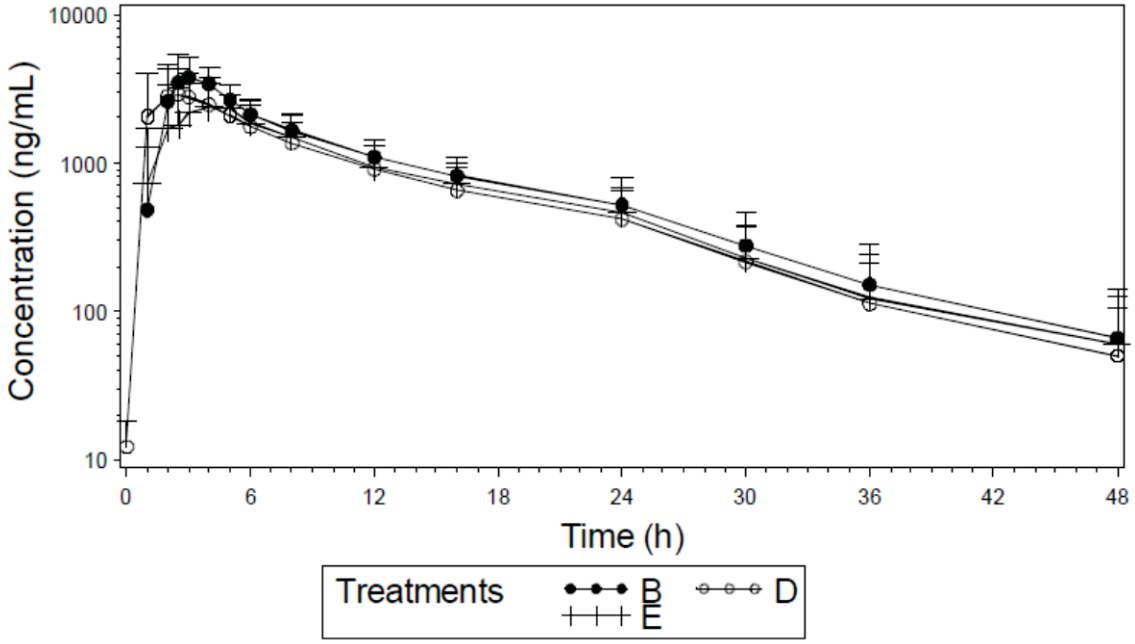
Source: Tables S.8.2.4.1B, S.8.2.4.2B, S.8.2.4.3B and S.8.2.4.4B

Reference ID: 3678805

Assessment of the effect of food on atazanavir plasma pharmacokinetics after FDC administration

The mean atazanavir concentration-time profiles following a single dose of the ATV/COBI 300/150 mg FDC oral tablet in the fed (light meal or high-fat meal) and fasted states is displayed in Figure 4 and PK parameters for ATV are listed in Table 4. As expected, ATV half-life was unaffected by food; however, the rate and extent of absorption (t_{max} and C_{max}, respectively) were susceptible to a food effect, with FDC administration with a light meal resulting in higher C_{max} and a less variable t_{max} compared to administration with a high-fat meal or fasted administration. Compared to fasting exposures, mean ATV AUC values were unaffected by a high-fat meal but were increased by approximately 28% by a light meal and mean ATV C_{max} values were decreased by 14% by a high-fat meal and increased by 42% by a low-fat meal (Table 5).

Figure 4. Mean ± SD atazanavir plasma concentration-time profiles by treatment (B: light meal, D: fasted, E: high fat meal) following administration of the ATV/COBI FDC (semi-log scale; source: CSR Figure 9.2.1.3-1)



Reference ID: 3678805

Table 4. Key atazanavir pharmacokinetic parameters by treatment (B: light meal, D: fasted, E: high fat meal) following administration of the ATV/COBI FDC (source: Study Report Table 9.2.1.3-1)

	Treatment		
	B	**D**	**E**
Cmax (ng/mL)			
Geo.Mean [N]	4104 [62]	2941 [63]	2545 [30]
(%CV)	(32)	(44)	(43)
Tmax (h)			
Median [N]	2.50 [62]	2.00 [63]	3.54 [30]
(Min-Max)	(2.00 - 4.05)	(1.00-6.00)	(2.00-8.02)
AUC(0-T) (ng•h/mL)			
Geo. Mean [N]	34905 [62]	27875 [63]	25873 [30]
(%CV)	(31)	(41)	(40)
AUC(INF) (ng•h/mL)			
Geo. Mean [N]	35673 [62]	28378 [63]	26510 [30]
(%CV)	(32)	(42)	(40)
C24 (ng/mL)			
Geo. Mean [N]	449 [62]	337 [63]	398 [30]
(%CV)	(52)	(56)	(45)
T-HALF (h)			
Mean [N]	7.50 [62]	7.21 [63]	7.14 [30]
(SD)	(2.60)	(2.28)	(2.99)

Source: Table S.8.2.3.1
Treatment: A = ATV 300mg cap+150mg COBI tab light meal, B = ATV 300mg/150mg COBI-FDC tab light meal, C = ATV 300mg cap+150mg COBI tab fasted, D = ATV 300mg/150mg COBI-FDC tab fasted, E = ATV 300mg/150mg COBI-FDC tab high fat meal.
Program Source: /gbs/prod/clin/programs/ai/424/511/csr01/rpt/rt-pki-xvr-01-3-v01.sas

Reference ID: 3678805

Table 5. Statistical analysis of food effect on atazanavir pharmacokinetic parameters by treatment (B: light meal, D: fasted, E: high fat meal) following administration of the ATV/COBI FDC (source: Clinical Pharmacology Summary)

Treatment and Comparison	Cmax (ng/mL) Adjusted Geometric Mean	AUC(0-T) (ng.h/mL) Adjusted Geometric Mean	AUC(INF) (ng.h/mL) Adjusted Geometric Mean	C24 (ng/mL) Adjusted Geometric Mean
Effect of Light Meal Relative to Fasted Conditions				
B (FDC with a light meal)	4113.98	35017.10	35786.90	451.09
D (FDC fasted)	2891.87	27473.54	27967.56	334.34
	GMR(90% CI)	GMR(90% CI)	GMR(90% CI)	GMR(90% CI)
B vs. D	1.423(1.273,1.590)	1.275(1.166,1.393)	1.280(1.171,1.398)	1.349(1.215,1.498)
Effect of a High Fat Meal Relative to Fasted Conditions				
D (FDC fasted)	2954.08	27243.98	27736.41	322.96
E (FDC with a high fat meal)	2545.20	25873.37	26510.19	397.69
	GMR(90% CI)	GMR(90% CI)	GMR(90% CI)	GMR(90% CI)
E vs D	0.862(0.701,1.059)	0.950(0.804,1.122)	0.956(0.810,1.128)	1.231(1.023,1.483)
Effect of a High Fat Meal Relative to a Light Meal				
B (FDC with a light meal)	3912.31	34278.62	35023.26	433.62
E (FDC with a high fat meal)	2516.17	25572.97	26221.38	395.46
	GMR(90% CI)	GMR(90% CI)	GMR(90% CI)	GMR(90% CI)
E vs B	0.643(0.545,0.759)	0.746(0.655,0.849)	0.749(0.658,0.852)	0.912(0.789,1.054)

Source: Tables 9.2.1.3-2, 9.2.1.3-3, and 9.2.1.3-4 of the AI424511 final study report[6]

Assessment of plasma cobicistat pharmacokinetics following a light meal

The mean cobicistat concentration-time profiles following a single dose of the ATV/COBI 300/150 mg FDC oral tablet or ATV 300 mg capsule plus COBI 150 mg tablet to healthy subjects following a light meal are displayed in Figure 5. COBI exposures were similar between formulations following administration after a light meal, with geometric mean ratios near 1 and 90% CI for C_{max}, AUC_t, and AUC_{inf} contained entirely within 0.8-1.25 (Table 6).

Reference ID: 3678805

Figure 5. Mean ± SD cobicistat plasma concentration-time profiles by treatment (A: ATV + COBI, B: ATV/COBI FDC) under fed (light meal) conditions (semi-log scale; source: CSR Figure 9.2.2.1-2)

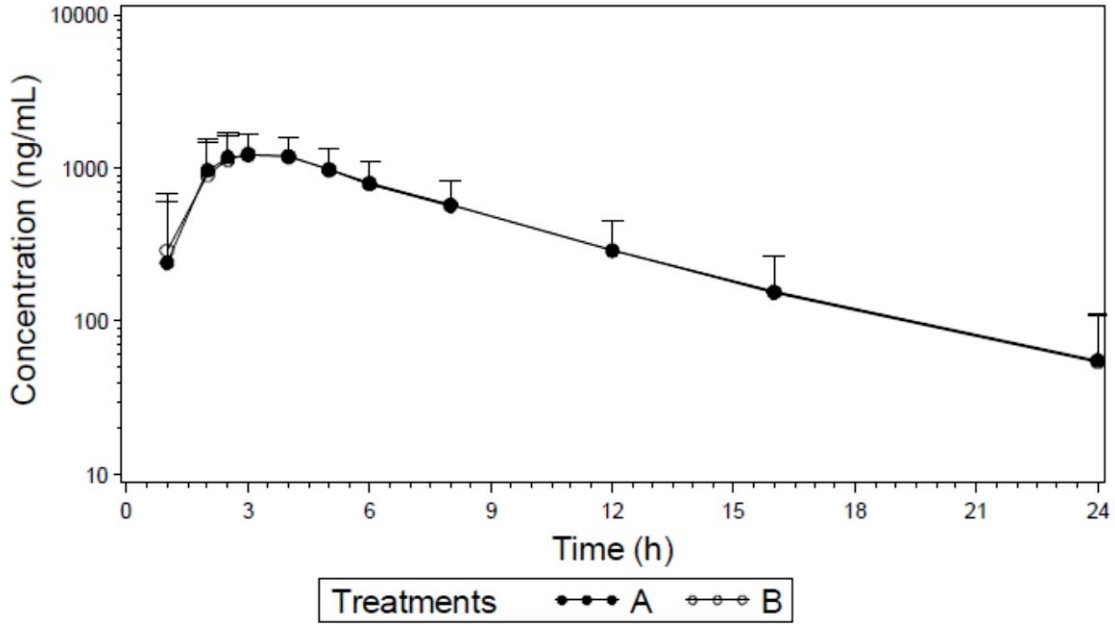


Table 6. Key cobicistat pharmacokinetic parameters and statistical comparisons between treatments (A: ATV + COBI, B: ATV/COBI FDC) under fed (light meal) conditions (source: Study Report Table 9.2.2.1-2)

TREATMENT AND COMPARISON	CMAX (ng/mL) Adj.GEO.MEAN[a]	AUC(0-T) (ng•h/mL) Adj.GEO.MEAN[a]	AUC(INF) (ng•h/mL) Adj.GEO.MEAN[a]
A	1320.324	8745.302	9053.001
B	1351.323	8912.257	9224.634
	GMR(90% CI)	GMR(90% CI)	GMR(90% CI)
B vs A	1.023(0.991,1.057)	1.019(0.983,1.057)	1.019(0.982,1.058)

[a] Derived from linear mixed model with treatment, period and sequence as fixed effects and subject(sequence) as a random effect based on the data of Treatment A and Treatment B only

PROGRAM SOURCE:/gbs/prod/clin/programs/ai/424/511/csr01/rpt/crossover_MIX-Cobi-AB.sas

Source: Tables S.8.2.4.5A, S.8.2.4.6A, and S.8.2.4.7A

Treatment Codes: A = ATV 300mg cap+150mg COBI tab light meal, B = ATV 300mg/150mg COBI-FDC tab light meal, C = ATV 300mg cap+150mg COBI tab fasted, D = ATV 300mg/150mg COBI-FDC tab fasted, E = ATV 300mg/150mg COBI-FDC tab high fat meal

Assessment of plasma cobicistat pharmacokinetics following fasted administration

The mean cobicistat concentration-time profiles following a single dose of the ATV/COBI 300/150 mg FDC oral tablet or ATV 300 mg capsule plus COBI 150 mg tablet to healthy subjects following fasted administration are displayed in Figure 6. Mean COBI AUC_{inf} values were comparable between formulations following administration in the fasted state, with geometric mean ratios near 1 and 90% CI contained entirely within 0.8-1.25. However, mean COBI C_{max} and AUC_{tau} values were slightly higher for the single agents compared to the FDC, with geometric mean ratios near 1.1 and upper bounds of the 90% CI near 1.3 (Table 7). For both formulations, t_{max} occurred slightly earlier following fasted administration compared to fed

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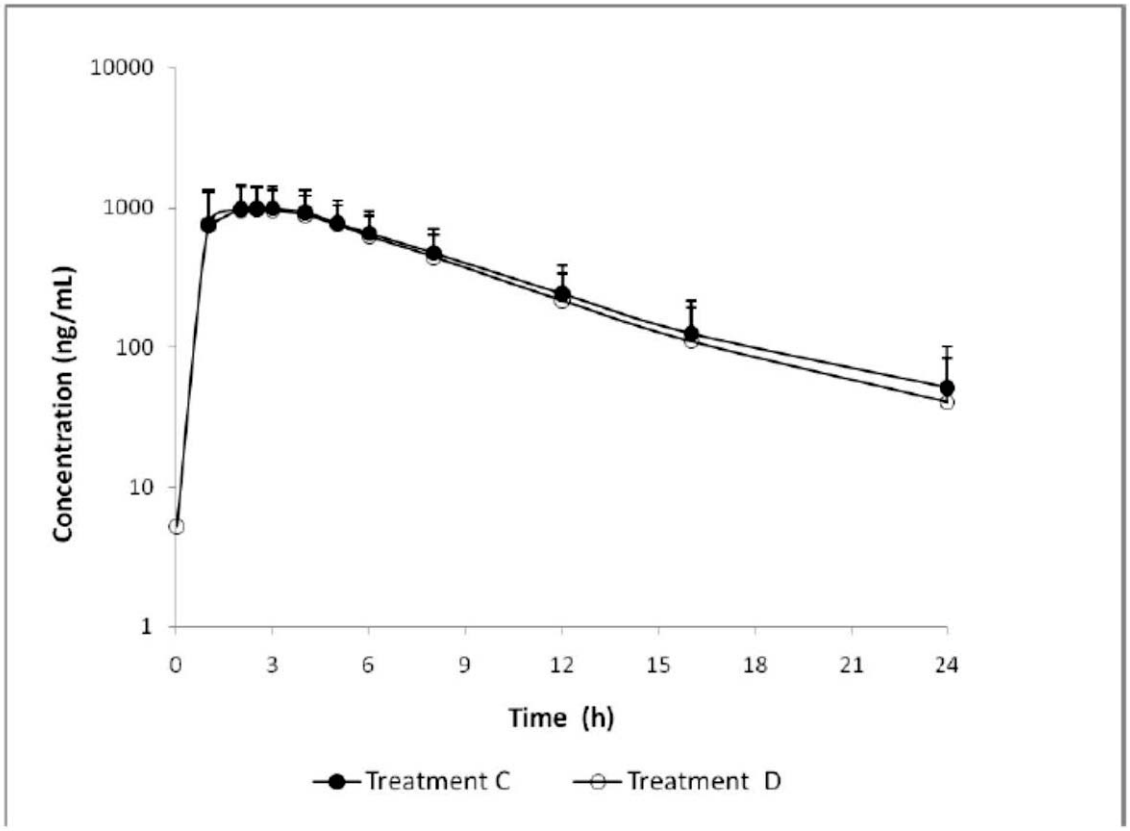
(median: 2.52 and 2.52 h for the FDC and the single agents in the fasted state compared to 2.00 and 2.00 h for the FDC and the single agents in the fed state), although the ranges were unchanged.

Figure 6. Mean ± SD cobicistat plasma concentration-time profiles by treatment (C: ATV + COBI, D: ATV/COBI FDC) under fasted conditions (semi-log scale; source: CSR Figure 9.2.2.2-1)



Treatment Codes:C = ATV + COBI fasted; D = FDC fasted
Data Source: eToolbox\BMS-232632\AI452511\GENERIC_PK_1_2_2.0006

Reference ID: 3678805

Table 7. Key cobicistat pharmacokinetic parameters and statistical comparisons between treatments (C: ATV + COBI, D: ATV/COBI FDC) under fed (light meal) conditions (source: Study Report Table 9.2.2.2-2)

TREATMENT AND COMPARISON	CMAX (ng/mL) Adj.GEO.MEAN[a]	AUC(0-T) (ng•h/mL) Adj.GEO.MEAN[a]	AUC(INF) (ng•h/mL) Adj.GEO.MEAN[a]
C	952.165	6533.615	7581.826
D	1032.980	7198.855	7398.160
	GMR(90% CI)	GMR(90% CI)	GMR(90% CI)
D vs C	1.085(0.925,1.273)	1.102(0.929,1.307)	0.976(0.886,1.075)

[a] Derived from linear mixed model with treatment, period and sequence as fixed effects and subject(sequence) as a random effect based on the data of Treatment C and Treatment D only

Treatment Codes: A = ATV 300mg cap+150mg COBI tab light meal, B = ATV 300mg/150mg COBI-FDC tab light meal, C = ATV 300mg cap+150mg COBI tab fasted, D = ATV 300mg/150mg COBI-FDC tab fasted, E = ATV 300mg/150mg COBI-FDC tab high fat meal

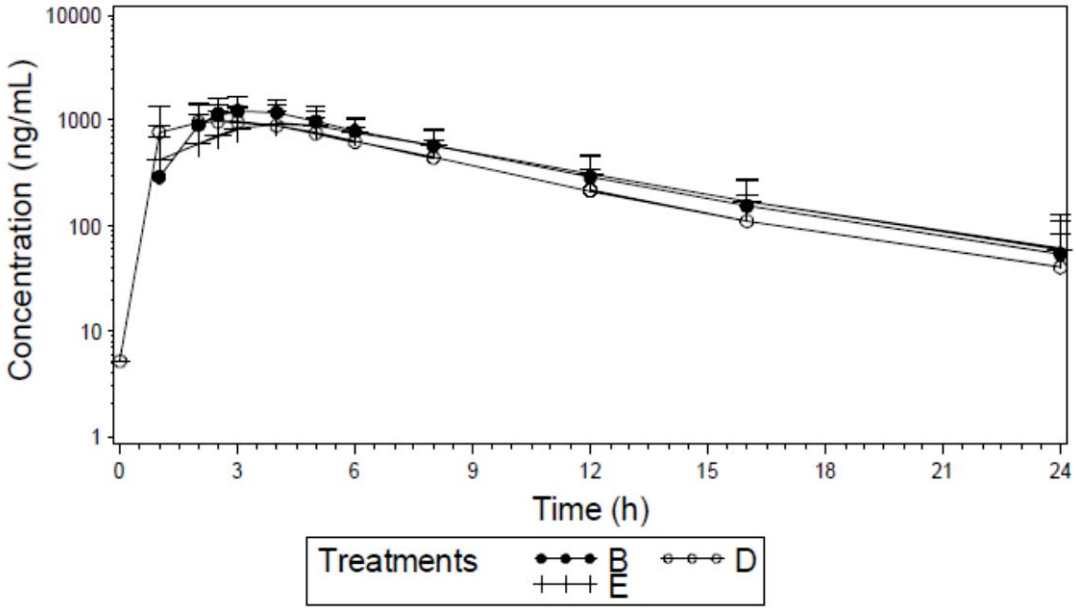
PROGRAM SOURCE: gbs/prod/clin/programs/ai/424/511/csr01/rpt/crossover_MIX-Cobi-CD.sas

Source: Tables S.8.2.4.5B, S.8.2.4.6B and S.8.2.4.7B

Assessment of the effect of food on cobicistat plasma pharmacokinetics after FDC administration

The mean cobicistat concentration-time profiles following a single dose of the ATV/COBI 300/150 mg FDC oral tablet in the fed (light meal or high-fat meal) and fasted states is displayed in Figure 7 and PK parameters for COBI are listed in Table 8. FDC administration with a light meal resulted in a slightly higher C_{max} and AUC values compared to administration with a high-fat meal or fasted administration (Table 9).

Figure 7. Mean ± SD cobicistat plasma concentration-time profiles by treatment (B: light meal, D: fasted, E: high fat meal) following administration of the ATV/COBI FDC (semi-log scale; source: CSR Figure 9.2.1.3-1)



Reference ID: 3678805

Table 8. Key cobicistat pharmacokinetic parameters by treatment (B: light meal, D: fasted, E: high fat meal) following administration of the ATV/COBI FDC (source: Study Report Table 9.2.1.3-1)

	Treatment		
	B	**D**	**E**
Cmax (ng/mL)			
Geo.Mean [N]	1348 [62]	1033 [63]	1060 [30]
(%CV)	(29)	(38)	(32)
Tmax (h)			
Median [N]	2.52 [62]	2.00 [63]	4.00 [30]
(Min-Max)	(1.00 - 5.00)	(1.00-5.00)	(1.00-12.0)
AUC(0-T) (ng•h/mL)			
Geo. Mean [N]	8866 [62]	7204 [63]	7916 [30]
(%CV)	(38)	(44)	(39)
AUC(INF) (ng•h/mL)			
Geo. Mean [N]	9178 [62]	7408 [63]	8298 [28]
(%CV)	(41)	(46)	(39)
T-HALF (h)			
Mean [N]	4.33 [62]	4.09 [63]	4.27 [28]
(SD)	(1.42)	(1.20)	(1.39)

Source: Table S.8.2.3.2
Treatment: A = ATV 300mg cap+150mg COBI tab light meal, B = ATV 300mg/150mg COBI-FDC tab light meal, C = ATV 300mg cap+150mg COBI tab fasted, D = ATV 300mg/150mg COBI-FDC tab fasted, E = ATV 300mg/150mg COBI-FDC tab high fat meal.
Program Source: gbs/prod/clin/programs/ai/424/511/csr01/rpt/rt-pki-xvr-01-6-v01.sas

Reference ID: 3678805

Table 9. Statistical analysis of food effect on cobicistat pharmacokinetic parameters by treatment (B: light meal, D: fasted, E: high fat meal) following administration of the ATV/COBI FDC (source: Clinical Pharmacology Summary)

Treatment and Comparison	Cmax (ng/mL) Adjusted Geometric Mean	AUC(0-T) (ng.h/mL) Adjusted Geometric Mean	AUC(INF) (ng.h/mL) Adjusted Geometric Mean
Effect of Light Meal Relative to Fasted Conditions			
B (FDC with a light meal)	1345.12	8864.07	9173.49
D (FDC fasted)	1030.51	7193.21	7395.91
	GMR(90% CI)	GMR(90% CI)	GMR(90% CI)
B vs. D	1.305(1.215,1.402)	1.232(1.141,1.331)	1.240(1.148,1.340)
Effect of a High Fat Meal Relative to Fasted Conditions			
D (FDC fasted)	1018.97	7025.68	7434.10
E (FDC with a high fat meal)	1059.53	7915.71	8297.66
	GMR(90% CI)	GMR(90% CI)	GMR(90% CI)
E vs D	1.040(0.937,1.154)	1.127(1.017,1.248)	1.116(1.012,1.231)
Effect of a High Fat Meal Relative to a Light Meal			
B (FDC with a light meal)	1345.99	8861.044	9146.980
E (FDC with a high fat meal)	1055.91	7884.836	8273.117
	GMR(90% CI)	GMR(90% CI)	GMR(90% CI)
E vs B	0.784(0.717,0.858)	0.890(0.825,0.960)	0.904(0.836,0.978)

Source: Tables 9.2.2.3-2, 9.2.2.3-3, and 9.2.2.3-4 of the AI424511 final study report[6]

Results of safety analysis

There were adverse events reported in four subjects that were categorized by the study investigator as related to study treatment (moderate vomiting [Treatment A]; mild headache [Treatment C]; moderate vomiting, mild nausea, dizziness and light-headedness [Treatment B] and mild vomiting and headache [Treatment C]; mild light-headedness and abdominal pain [Treatment A]). No subjects discontinued study drug due to adverse events and no serious adverse events or deaths occurred during the study.

Trial Summary

In this study, the pharmacokinetics of atazanavir and cobicistat following a single dose of the ATV/cobi 300/150 mg FDC oral tablet administered after a light meal or in the fasted state were evaluated in healthy subjects. Administration of the FDC with a light meal resulted in similar exposures of both ATV and cobi compared to administration of the single agents (90% CI for ATV C_{max}, AUC_t, and C_{24} and for cobi C_{max} and AUC_t within 80-125%). Under fasted conditions, the FDC provided slightly higher exposures of both ATV and cobi compared to the single agents (90% CI for ATV C_{max}, AUC_t, and C_{24} and for cobi C_{max} and AUC_t ranging from 93-131%). In general, administration with food resulted in delayed absorption of ATV and cobi and slightly higher ATV trough concentrations (approximately 23-35% increase in ATV C_{24}).

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Overall, the results of this study support the administration of the ATV/cobi 300/150 mg oral FDC tablet with food.

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/s/

LESLIE W CHINN
12/29/2014

ISLAM R YOUNIS
12/29/2014

BIOPHARMACEUTICS REVIEW

Office of New Drug Quality Assessment

Application No.:	NDA 206353	**Reviewer:** Minerva Hughes	
Submission Date:	4 April 2014		
Division:	DAVP	**Team Leader:** Angelica Dorantes	
		Acting Supervisor: Paul Seo	
Sponsor:	Birstol-Myers Squibb	**Secondary Reviewer:** Elsbeth Chikhale	
Trade Name:	Evotaz	**Date Assigned:**	4 April 2014
		Primary Review: **PDUFA Date:**	31 December 2014 4 February 2015
Generic Name:	Atazanavir/Cobicistat	**Date of Review:**	15 December 2014
Indication:	HIV	**Type of Submission:** **505(b)(1) Original NDA**	
Dosage Form/Strengths	Fixed Dose Combination Tablet (300 mg/150 mg)		
Route of Administration	Oral		

Biopharmaceutics Review Focus:

- Dissolution method and acceptance criteria
- Drug product development and dissolution quality risks

SYNOPSIS – SUMMARY OF IMPORTANT BIOPHARMACEUTICS FINDINGS

General

NDA 206353 was submitted under Section 505(b) of the FDC Act for the use of atazanavir (ATV) and cobicistat (COBI) in the treatment of the human immunodeficiency virus (HIV). ATV is an azapeptide protease inhibitor of HIV-1 that has been approved for the treatment of HIV infection (in combination with other antiretroviral [ARV] agents). In treatment-naive patients, the current recommended dose of ATV is 300 mg with ritonavir (RTV) 100 mg once daily (QD) with food or ATV 400 mg QD (without RTV) with food. In treatment-experienced patients, the current dosing recommendations are ATV 300 mg with RTV 100 mg QD with food. Cobicistat (COBI) is a structural analogue of RTV, has no ARV activity, and has been shown to be a more specific mechanism-based cytochrome P450 (CYP) 3A4 inhibitor than RTV in vitro. The proposed new drug product is a fixed dose combination (FDC) tablet comprised of ATV 300 mg and COBI 150 mg.

Bioequivalence Study

Per the agreements made between ONDQA and OCP management, the bioequivalence study in this NDA will be reviewed entirely by OCP. Biopharmaceutics will evaluate the proposed dissolution method and acceptance criteria.

Dissolution Testing

The following dissolution method and acceptance criteria are acceptable for product quality control.

Dissolution Method - ATV/COBI	
Apparatus	USP 2
Medium	0.05 M Citrate Buffer (pH 2.8), 1000 mL
Agitation speed	75 rpm
Temperature	37 °C
Sampling Times	Varies
Analytical Method	HPLC
Acceptance Criterion	ATV - Q = (b) (4) % in 30 min COBI – Q = (b) (4) % in 15 min

QUALITY RISK ASSESSMENT

Reference is made to the Product Quality review by Dr. George Lunn for a comprehensive quality risk assessment. From the biopharmaceutics perspective, (b) (4) should appropriately account for dissolution effects as these parameters have a noted potential for affecting product dissolution. Given the physicochemical properties of ATV in particular, dissolution is expected to highly influence overall bioavailability and thus, maximal therapeutic benefit.

CONSULTS

None.

PHASE 4 COMMITMENTS

None.

RECOMMENDATION

From the perspective of Biopharmaceutics, NDA 206353 for Evotaz (atazanavir/cobicistat) is recommended for approval.

Signature Block

Minerva A. Hughes -S
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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000389946, cn=Minerva A. Hughes -S
Date: 2014.12.15 14:26:49 -05'00'

Minerva Hughes, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Elsbeth G. Chikhale -S
Digitally signed by Elsbeth G. Chikhale -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300136142, cn=Elsbeth G. Chikhale -S
Date: 2014.12.15 14:38:32 -05'00'

Elsbeth Chikhale, Ph.D.
Biopharmaceutics Team Leader (Acting)
Office of New Drug Quality Assessment

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BIOPHARMACEUTICS REVIEW

1 GENERAL ATTRIBUTES

1.1 *What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility) and formulation of the drug product?*

The proposed drug product is a fixed dose combination (FDC) tablet comprised of the active ingredients atazanavir (ATV), 300 mg as the free base (drug substance = sulfate salt), and cobicistat (COBI), 150 mg, formulated as an immediate release, (b) (4), film-coated tablet. The qualitative and quantitative formulation is presented below.

Table 2.3.P.1-2: Composition of ATV/COBI FCT

Component	Quality Standard	Function	Quantity per Tablet (mg)	
			(%w/w)	(mg)
(b) (4)				
Atazanavir Sulfate[a]	In-house[b]	Active	(b) (4)	341.70
Stearic Acid	NF	(b) (4)		
Microcrystalline Cellulose[c]	NF, Ph.Eur.			
Sodium Starch Glycolate	NF, Ph.Eur.			
Crospovidone	NF, Ph.Eur.			
Hydroxypropyl Cellulose	NF, Ph.Eur.			
Magnesium Stearate	NF, Ph.Eur.			
(b) (4)	USP, Ph.Eur.			
(b) (4)				
Cobicistat on silicon dioxide[e]	In-house[f]			
(b) (4)				
Total Tablet Weight (film-coated tablets)				**1081.50**

(footnotes excluded)

The atazanavir sulfate drug substance is manufactured as a white to pale yellow crystalline powder using a commercial process that consistently (b) (4) The drug substance is relatively non hygroscopic and is

slightly soluble in water (4-5 mg/mL, free base equivalent). The drug substance used to manufacture the FDC tablets is the same as that used for the approved Reyataz (atazanavir) Capsules, and reference is made to NDA 21567 for drug substance CMC information.

The cobicistat drug substance is manufactured as an [redacted] (b) (4) and is relatively hygroscopic. Similar to atazanivir, cobicistat exhibits pH dependent solubility with >40 mg/mL observed at pHs ≤1.9. Cobicistat, however, is used in the FDC formulation [redacted] (b) (4) Drug solubility is reduced when measured from a [redacted] (b) (4). Reference is made to Gilead Sciences' (Gilead) DMF #25188 for CMC information regarding the COBI on silicon dioxide drug substance.

1.2 ***What are the proposed mechanism(s) of action and therapeutic indication(s)?***

Atazanavir is an azapeptide human immunodeficiency virus-type 1 (HIV-1) protease inhibitor. Atazanavir capsules (150, 200, and 300 mg), in combination with low-dose ritonavir (RTV) as a pharmacokinetic (PK) enhancer, has been approved for the treatment of HIV-1-infected adults and pediatric patients ≥ 6 years of age in the United States (Reyataz – NDA 21567) , European Union (EU), Canada, and many other countries globally.

Cobicistat, an inhibitor of cytochrome P-450 (CYP) 3A enzymes, was developed by Gilead for use as a PK enhancer of antiretroviral agents, including the protease inhibitor ATV. Cobicistat is a structural analogue of RTV, has no antiretroviral activity, and in vitro, has been shown to be a more specific mechanism-based CYP3A inhibitor than RTV. Reference is made to the COBI NDA, NDA 203094 for COBI specific data.

The proposed FDC tablet (ATV/COBI) is indicated for the treatment of HIV-1 infection.

1.3 ***What are the proposed dosage(s) and route(s) of administration?***

The proposed FDC tablet is intended for oral administration. The recommended dose in adults is one tablet daily (ATV 300 mg and COBI 150 mg), taken orally with food.

1.4 ***Is there any information on BCS classification? What claim does the applicant make based on BCS classification? What data are available to support this claim?***

A BCS class II classification is reported for both the atazanavir and cobicistat drug substances. The application includes drug substance solubility data, but incomplete information on permeability, or a clear reference to previously submitted data, to support the proposed designation. However, the BCS II classification is not associated with any requests for regulatory flexibility and additional information is not needed to support NDA approval.

2 GENERAL BIOPHARMACEUTICS (IN VIVO)

2.1 CLINICAL STUDIES

2.1.1 What are the design features of the biopharmaceutics studies used to support the proposed to-be-marketed formulation? Summary of individual study reviews provided.

Reference is made to the ATV NDA for clinical data on the ATV component. Reference is also made to the COBI NDA for clinical data on COBI and the use of COBI in combination with ATV, administered as single entities.

A single bioequivalence study was completed to support approval of the proposed FDC tablet under this NDA, as agreed upon with FDA (pre-NDA meeting minutes dated 20 December 2013). Study AI424511 was an open-label, single-dose, 5-period, 5-treatment, randomized crossover study in healthy subjects. The primary objective of the study was to demonstrate the bioequivalence of ATV in an FDC tablet of ATV/COBI 300/150 mg compared to a 300 mg ATV capsule co-administered with a 150 mg COBI tablet when given with a light meal. Secondary objectives of the study were to assess:

- the bioavailability of ATV when co-administered with COBI as a FDC tablet relative to the single agents under fasted conditions
- the bioavailability of COBI when co-administered with ATV as a FDC tablet relative to the single agents following a light meal and under fasted conditions
- the effects of food (light and high fat meal) on the PK of ATV and COBI in the FDC tablet
- the safety and tolerability after a single dose of the FDC tablet as well as a single dose of the individual agents co-administered.

It was agreed between Biopharmaceutics and the Office of Clinical Pharmacology that the submitted bioequivalence study will be entirely reviewed by the Office of Clinical Pharmacology. See the Clinical Pharmacology review for details.

2.1.2 If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?

See the Clinical Pharmacology review.

2.1.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

See the Clinical Pharmacology review.

2.2 BIOANALYTICAL METHOD SECTION

2.2.1 How are the active moieties and/or metabolites identified and measured in the plasma in the biopharmaceutics studies?

See the Clinical Pharmacology review.

2.2.2 What bioanalytical methods are used to assess concentrations?

See the Clinical Pharmacology review.

2.2.2.1 What is the range of the standard curve? How does it relate to the requirements for the clinical studies? What curve fitting techniques are used? What are the lower and upper limits of quantification (LLOQ/ULOQ, and assay validation parameter: accuracy, precision, selectivity, sample stability, etc.?

See the Clinical Pharmacology review.

2.2.2.2 What is the QC sample plan?

See the Clinical Pharmacology review.

2.2.2.3 Are the Inspection reports of the BE study acceptable?

See the Clinical Pharmacology review.

3 GENERAL BIOPHARMACEUTICS (IN VITRO)

3.1 DISSOLUTION INFORMATION

3.2 DISSOLUTION METHOD

3.2.1 What is the proposed dissolution method?

A single dissolution method is proposed for testing both drug substances.

Table 3.2.P.2.2.4-1: Dissolution Method Parameters

USP Apparatus	Agitation Speed	Media Volume	Medium	Temperature
2 (Paddles)	75 rpm	1000 mL	0.05M Citrate Buffer (pH 2.8)	37°C

Profile sampling is done at 10, 15, 30, 45, and 60 minutes.

3.2.2 What data are provided to support the adequacy of the proposed dissolution method (e.g. medium, apparatus selection, etc.)?

Medium

(b) (4)

[redacted]

(b) (4)

Citrate buffer at pH 2.8 provided the most optimal results for both actives and was selected as optimal.

Apparatus/Hydrodynamics

- The Applicant evaluated the suitability of both USP Apparatus 2 ([redacted] (b) (4) 75 rpm) and USP Apparatus [redacted] (b) (4) using the proposed dissolution medium. [redacted] (b) (4) Thus, a USP Apparatus 2 with a paddle speed of 75 rpm was selected.

Other Method Parameters

- Sample filtration (0.45 µm) is used prior to analysis.

.Medium Volume

- A volume of 900 - 1000 mL is the standard medium used with a USP 2 apparatus; 1000 mL was selected.

Medium Temperature

- A temperature of 37ºC is the standard temperature used for testing oral tablets and was selected.

3.2.3 What data are available to support the discriminating power of the method?

The discriminating ability of the proposed dissolution method for the ATV component was evaluated by comparing the dissolution profiles of batches manufactured under various manufacturing conditions. [redacted] (b) (4) An overall summary of the Applicant's findings is presented below.

Table 3.2.P.2.2.4-8: Impact of Manufacturing Variables and Material Attributes on Dissolution of ATV/COBI FCT at pH 2.8, Apparatus 2 at 75 rpm

Manufacturing Variable or Material Attributes	Variation Range	Impact on Dissolution	
		ATV	COBI
[redacted] (b) (4)			

(b) (4)

The proposed method has been used throughout clinical development.

3.2.4 *What information is available to support the robustness (e.g. linearity, accuracy, etc.) of the dissolution methodology?*

Reference is made to the Chemistry (Quality) Review for full details on the analytical method validation. Per discussions with the Review Chemist Dr. George Lunn, the analytical method validation is acceptable for the proposed dissolution method.

Method Summary

- A single isocratic HPLC-based method was developed for dissolution sample analysis. The drug substance peaks are appropriately resolved to permit a single analytical method. The method was validated with respect to specificity, linearity, repeatability, filter compatibility, accuracy, precision, reproducibility, solution stability, and robustness for the following ranges.

Validated Operating Ranges of the Method

(b) (4)

3.2.5 Is the proposed dissolution method biorelavant? What data are available to support this claim?

No. The proposed method is not biorelavant.

3.2.6 Is the proposed method acceptable? If not, what are the deficiencies?

Yes, the proposed dissolution method is acceptable. The potential for small pH changes in the dissolution medium to influence the ATV dissolution profile, and possibly the method's long-term performance, is a risk for the proposed method; however, absent a finding of method validation issues, it is presumed a manageable risk for product testing. An alternative pH medium within the narrow working pH range would likely run into similar issues. In addition, reasonable efforts were made to select testing conditions that provide a working balance between the duration of testing (IR formulation), the physicochemical properties of the drug substances, and the importance of detecting process changes. (b) (4)

3.3 ACCEPTANCE CRITERIA

3.3.1 What are the proposed dissolution acceptance criteria for this product?

The proposed dissolution acceptance criteria are summarized below.

Atazanavir: Q = (b) (4)% at 30 minutes

Cobicistat: Q = (b) (4)% at 15 minutes

3.3.2 What data are available to support the criteria?

<u>Atazanavir</u>

Batch analysis data from 10 batches were used in the analysis: 3 investigational stability, 3 registration stability, and 4 commercial-scale batches. Registration batch 2J3499 was used in the pivotal BE study.

Per the Applicant's analysis, the mean dissolution at 30 minutes across all batches is (b) (4) at release. Twelve months of stability data are included in the file to support a proposed 24 month shelf life, and the projected dissolution at 24 months was estimated as (b) (4)% (lower 95% confidence bound at (b) (4)%). The per batch dissolution stability trend data are illustrated below for only the three registration stability lots.

(b) (4)

Reviewer's Note: There were no apparent trends in the dissolution data under long-term or accelerated conditions from the Biopharmaceutics perspective.

Cobisistat

Based on the release data (10 batches), the mean dissolution at 15 minutes was (b) (4)%. The projected dissolution after 24 months of storage at 15 minutes is (b) (4)% with a lower confidence bound of (b) (4)%. The per batch dissolution stability trend data are illustrated below for only the three registration stability lots.

(b) (4)

Reviewer's Note: There were no apparent trends in the dissolution data under long-term or accelerated conditions from the Biopharmaceutics perspective.

3.3.3 Is the setting of the dissolution acceptance criteria based on data from clinical and registration batches?

Yes. The clinical lot is one of the three registration lots, and all registration lots were included in setting acceptance criteria.

3.3.4 Are mean (n =12) dissolution profile data used for the setting of the acceptance criteria?

Yes, the registration lot dissolution data (release) included 12 samples. It is noted that the commercial batch release data are also based on 12 samples.

3.3.5 Are the acceptance criteria acceptable? If not, what are the recommended criteria?

The proposed acceptance criterion for COBI of Q = (b)(4)% at 15 minutes is acceptable.

(b) (4)

An information request was submitted on November 19, 2014, requesting that the Applicant change the ATV dissolution acceptance criterion from Q= (b)(4)% in 30 minutes to Q= (b)(4)% in 30 minutes. The Applicant accepted FDA's recommended changes and the NDA was amended on December 9, 2014 to include a revised ATV acceptance criterion of Q = (b)(4)% at 30 minutes.

4 DISSOLUTION APPLICATIONS

4.1 FORMULATION CHANGES

4.1.1 Is the to-be-marketed formulation the same as the formulation used in the pivotal clinical or bioequivalence studies? If not, is dissolution used to bridge the data?

The composition and manufacturing process of ATV/COBI FDC used in the ATV/COBI bioequivalence study is the same as proposed for the commercial drug product.

4.1.2 Is the finished tablet scored? Do the dissolution data comparing the split versus whole tablet support tablet splitting?

The finished tablet is not scored.

4.2 BIOWAIVERS

4.2.1 Is there a waiver request for in vivo BA or BE data (Biowaiver)? If yes, what is/are the purpose/s of the biowaiver request/s? What data support the biowaiver request/s? Is the biowaiver request acceptable?

No.

4.3 IVIVC APPLICATION

4.3.1 Is there any IVIVR or IVIVC information submitted? What is the regulatory application of the IVIVR/IVIVC in the submission? What data are provided to support the acceptability of the IVIVR or IVIVC model?

No.

4.4 SURROGATES IN LIEU OF DISSOLUTION

4.4.1 Are there any manufacturing parameters (e.g. disintegration, drug substance particle size, etc.) being proposed as surrogates in lieu of dissolution testing? What data are available to support the approval of the proposed surrogate test?

No.

4.5 DISSOLUTION AND QBD

4.5.1 Does the application contain QbD elements? If yes, is dissolution identified as a CQA for defining design space?

There are no QbD elements (i.e., design space) for review.

4.5.2 Was dissolution included in the DoE? What raw materials and process variables are identified as having an impact on dissolution? What is the risk assessment been performed to evaluate the criticality of dissolution?

(b) (4)

Critical steps in the process and controls are appended to this review.

The (b) (4) also has an impact on product dissolution, as indicated in Section 3.2.3 of this review, and controls are defined to mitigate future dissolution quality risks. Reference is made to the Product Quality review by Dr. George Lunn for a complete evaluation of the manufacturing controls and process risk assessment and a final recommendation on the acceptability of proposed controls.

From the biopharmaceutics perspective, (b) (4) appear to have the highest potential for affecting dissolution and should be reviewed closely. Overall, there is an appreciable risk of dissolution limiting effects on bioavailability for products formulated with ATV (salt or free base) given its physicochemical properties.

4.5.3 What biopharmaceutics information is available to support the clinical relevance of the proposed design space?

Not applicable.

4.5.4 Is there any dissolution model information submitted as part of QbD implementation? What is the regulatory application of the dissolution model in the submission? What data are provided to support the acceptability of the dissolution model?

Not applicable.

5 LABELING

As per the current MOU, the Office of Clinical Pharmacology is the lead for addressing Biopharmaceutics issues in the labeling. Any labeling comment considerations that may have developed during the review have been communicated to the Clinical Team and are not captured in this review.

6 INFORMATION REQUESTS DURING THE REVIEW

The following information requests were issued during the NDA review cycle. Responses are incorporated into the QBR above. There are no outstanding review issues.

November 19, 2014

1. *Based on the dissolution performance of your clinical batch, development, and registration lots, with consideration of the likely process ranges at commercial scale, we do not consider your proposed ATV acceptance criterion of Q=* (b)(4)*% at 30 minutes optimal for product quality control. We recommend an acceptance criterion of Q =* (b)(4)*% at 30 minutes for ATV. Nevertheless, it must be recognized that some batches may require Stage 2 and, occasionally, Stage 3 testing.*

   Provide a revised drug product specification table reflecting this change with a commitment to amend protocols, as needed, before utilization.

SUPPLEMENTAL TABLES AND FIGURES

Dissolution Method Development

Table 3.2.P.2.2.4-6: Effect of Media pH on ATV/COBI FCT[1] Dissolution at Paddle Speed of 75 rpm [2]

(b) (4)

[redacted]

Controls of Critical Steps and Intermediates

Table 3.2.P.3.4-1: Process Controls for the Manufacture of ATV/COBI FCT

Process Step	Target	Acceptance range	Linked to

(b) (4)