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APPLICATION NUMBER:

203094Orig1s000
203094Orig2s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 203094	Original Submission Date: June 27, 2012
SDN: 42 (Original 1)	Resubmission Date: March 28, 2014 (Original 1)
SDN: 45 (Original 2)	Resubmission Date: April 3, 2014 (Original 2)
Brand Name	Tybost
Generic Name	Cobicistat
Reviewer	Stanley Au, Pharm.D., BCPS
Clinical Pharmacology Team Leader	Shirley Seo, Ph.D.
OCP Division	Division of Clinical Pharmacology 4
OND Division	Division of Antiviral Products
Applicant	Gilead Sciences
Proposed U.S commercially marketed strength and formulation	150 mg tablets
Proposed dosage regimens	Cobicistat 150 mg once daily coadministered with: 1) atazanavir 300 mg once daily (treatment naïve or treatment experienced patients) OR 2) darunavir 800 mg once daily (treatment naïve patients or treatment experienced patients with no darunavir resistance associated substitutions)
Proposed Indication for the Application	Cobicistat: None Cobicistat coadministered with atazanavir or darunavir: Treatment of HIV-1 infection in treatment naïve or treatment-experienced patients
Review Type(s)	505 (b)(1) New Drug Application, Class 2 resubmission

1 Executive Summary

The applicant, Gilead Sciences, resubmitted a 505(b)(1) NDA subsequent to two Complete Response (CR) letters, designated as Original 1 and Original 2, that were issued by the Division of Antiviral Products on April 26, 2013. The Original 1 indication was for cobicistat 150 mg once daily coadministered with atazanavir 300 mg once daily and the Original 2 indication was for cobicistat 150 mg once daily coadministered with darunavir 800 mg once daily.

For the Original 1 indication, the CR letter was issued because of deficiencies that were identified by the Office of Manufacturing and Product Quality during an inspection of Gilead's manufacturing facility in Foster City, CA.

For the Original 2 indication, the CR letter was issued because of deficiencies that were identified by the Office of Manufacturing and Product Quality during an inspection of Gilead's manufacturing facility and deficiencies that were identified by the Office of Scientific Investigations during an inspection of (b) (4)). These bioanalytical laboratories were involved in the analysis of darunavir or cobicistat plasma samples. The resubmission provides links to prior submissions where information relevant to addressing the form 483 observations was provided by the applicant. The information is discussed below.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the information in this NDA resubmission and the information provided supports the approval of the application.

2 Trial specific information

GS-US-216-115 trial

A) Form 483 observations for the GS-US-216-115 trial

(b) (4)

Overall, the submitted long term stability data for darunavir in combination with cobicistat adequately addresses the 483 observation.

(b) (4)

(b) (4)

Based on the results of the applicant's updated pharmacokinetic analysis (see section B) (b) (4), the revised results adequately addresses the 483 observation.

(b) (4)

Based on the results of the applicant's updated pharmacokinetic analysis (see section B) (b) (4), the revised results adequately addresses the 483 observation.

B) Applicant's revised statistical analysis for GS-US-216-115

Based on the results of the revised statistical analysis for GS-US-216-115, excluding the recommended darunavur concentration data did not result in any changes to the conclusions for the trial.

Table 1-Applicant's original and revised darunavir statistical analysis for GS-US-216-115 excluding selected darunavir concentration data outlined in Table 2

DRV PK Parameter	Mean (%CV) DRV/co	Mean (%CV) DRV/r	GLSM Ratio (%)	90% CI
Reported in Original CSR				
DRV/co versus DRV/r	[redacted]			(b) (4)
AUC_{tau} (ng·h/mL)				
C_{max} (ng/mL)				
C_{0h} (ng/mL)				
Reanalysis including Criteria A-C*				
DRV/co versus DRV/r	n = 29	n = 29	—	—
AUC_{tau} (ng·h/mL)	79224.6 (31.2)	78463.2 (34.5)	101.45	(96.76, 106.36)
C_{max} (ng/mL)	7564.5 (21.3)	7341.7 (20.2)	102.83	(99.66, 106.10)
C_{0h} (ng/mL)	2355.2 (52.0)	2425.1 (35.0)	89.66	(80.10, 100.37)

Clinical pharmacology review note: criteria A-C include excluding the selected darunavir concentration data that are discussed and noted above),

Table 2-Applicant revisions to the darunavir concentration data for the updated statistical analysis for GS-US-216-115

Subject	Concentration data excluded
1020	All concentration data
1021	Sample 4875805: Day 24, 3.5 hours postdose
1022	All concentration data (including sample 4875825: Day 10, 3.5 hours postdose)
1030	Sample 4876103: Day 10, 2.5 hours postdose Sample 4876106: Day 10, 4 hours postdose

Subject	Revised data
1021	Day 10 and day 24 concentration data revised to include data from [redacted] (b) (4)

GS-US-216-116 trial

A) Form 483 observations for the GS-US-216-116 trial

1) Failure to report all aspects of study conduct pertinent to bioanalytical studies.

(b) (4)

(b) (4)

Based on the results of the applicant's updated pharmacokinetic analysis (see section B) that excluded cobicstat concentration data from (b) (4), the revised results adequately addresses the 483 observation.

B) Applicant's revised statistical analysis for GS-US-216-116

Based on the results of the revised statistical analysis for GS-US-216-116, excluding the recommended cobicistat data from (b) (4) with the predose sample from subject (b) (4), treatment A, period 1 set to either "zero" or "missing" did not result in any changes to the conclusions for the trial.

Table 3-Applicant's original and revised cobicistat statistical analysis for GS-US-216-116 excluding selected cobicistat concentration data outlined in Table 5

COBI PK Parameter	Mean (%CV)		GLSM Ratio (%)	90% CI
	COBI Formulation 2	COBI Formulation 1		
Reported in Original CSR				
COBI Formulation 2 versus COBI Formulation 1	n = 35	n = 35	—	—
AUC_{tau} (ng·h/mL)	12,429.5 (30.6)	12,577.3 (28.5)	98.21	(94.61, 101.94)
C_{max} (ng/mL)	1597.6 (21.7)	1578.5 (22.0)	101.27	(97.47, 105.21)
C_{tau} (ng/mL)	82.5 (81.9)	80.0 (69.9)	96.31	(87.12, 106.47)
Reanalysis				
COBI Formulation 2 versus COBI Formulation 1	n = 33	n = 33	—	—
AUC_{tau} (ng·h/mL)	12154.3 (29.6)	12289.0 (27.6)	98.31	(94.48,102.29)
C_{max} (ng/mL)	1573.3 (21.1)	1562.5 (22.0)	100.87	(96.88,105.02)
C_{tau} (ng/mL)	77.7 (81.1)	75.9 (71.2)	96.46	(86.75,107.26)

Table 4-Comparison of the revised cobicistat statistical analysis for GS-US-216-116 with the predose sample from subject (b) (4), treatment A, period 1 set to values of "zero" or "missing"

COBI PK Parameter	Mean (%CV)		GLSM Ratio (%)	90% CI
	COBI Formulation 2	COBI Formulation 1		
Reanalysis with Pre-dose sample assigned as BLQ (i.e., zero)				
COBI Formulation 2 versus COBI Formulation 1	n = 33	n = 33	—	—
AUC_{tau} (ng·h/mL)	12154.3 (29.6)	12289.0 (27.6)	98.31	(94.48,102.29)
C_{max} (ng/mL)	1573.3 (21.1)	1562.5 (22.0)	100.87	(96.88,105.02)
C_{tau} (ng/mL)	77.7 (81.1)	75.9 (71.2)	96.46	(86.75,107.26)
Reanalysis with Pre-dose sample assigned as missing (i.e., excluded)				
COBI Formulation 2 versus COBI Formulation 1	n = 33	n = 33	—	—
AUC_{tau} (ng·h/mL)	12155.7 (29.6)	12289.0 (27.6)	98.32	(94.49,102.30)
C_{max} (ng/mL)	1573.3 (21.1)	1562.5 (22.0)	100.87	(96.88,105.02)
C_{tau} (ng/mL)	77.7 (81.1)	75.9 (71.2)	96.46	(86.75,107.26)

*Data from Subjects (b) (4) excluded in the reanalyzed data

Table 5-Applicant revisions to the cobicistat concentration data for the updated statistical analysis for GS-US-216-116

Subject	Concentration data excluded
(b) (4)	All concentration data from (b) (4)
	All concentration data from (b) (4)

Subject	Revised data
(b) (4)	Treatment A, period 1 predose value changed to zero

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STANLEY AU
08/20/2014

SHIRLEY K SEO
08/21/2014

ADDENDUM TO THE OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 203094	Submission Date: June 27, 2012
Brand Name	Tybost
Generic Name	Cobicistat
Reviewer	Stanley Au, Pharm.D., BCPS
Pharmacometrics Reviewer	Jeff Florian, Ph.D.
Pharmacometrics Team Leader	Yaning Wang, Ph.D.
Clinical Pharmacology Team Leader	Shirley Seo, Ph.D.
OCP Division	Division of Clinical Pharmacology 4
OND Division	Division of Antiviral Products
Applicant	Gilead Sciences
Proposed U.S commercially marketed strength and formulation	150 mg tablets
Proposed dosage regimens	Cobicistat 150 mg once daily coadministered with: 1) atazanavir 300 mg once daily (treatment naïve or treatment experienced patients) OR 2) darunavir 800 mg once daily (treatment naïve patients or treatment experienced patients with no darunavir resistance associated substitutions) (b) (4)
Proposed Indication for the Application	Cobicistat: None Cobicistat coadministered with atazanavir, darunavir (b) (4): Treatment of HIV-1 infection in treatment naïve or treatment-experienced patients
Review Type(s)	505 (b)(1) New Drug Application, standard review

This addendum to the Clinical Pharmacology review provides updates on relevant review issues subsequent to the finalization of the Clinical Pharmacology review for NDA 203094.

The information that is discussed in the addendum includes the following:

-Based on the form 483 observation that was issued (b) (4) (b) (4) (b) (4) the clinical pharmacology information submitted in the cobicistat NDA does not support the approval of the application for the use of cobicistat in combination with darunavir. The applicant was requested to remove information related to the use of cobicistat in combination with darunavir from the proposed cobicistat U.S prescribing information because the requested long-term stability data will not be available by the Prescription Drug Fee User Act (PDUFA) goal date for the cobicistat NDA.
- The clinical pharmacology trials proposed as postmarketing requirements have been finalized (see section A below).

A) Postmarketing Commitments or Requirements

The Clinical Pharmacology review team proposes that the applicant conduct the drug-drug interaction trials listed below as postmarketing requirements. The proposed PMRs for cobicistat coadministered with darunavir will not be included in the decision letter for the use of cobicistat in combination with atazanavir. The justification for the proposed postmarketing trials is discussed in the original Clinical Pharmacology review for NDA 203094.

Postmarketing trials for cobicistat coadministered with atazanavir

1) A clinical trial in healthy subjects evaluating the effect of cobicistat coadministered with atazanavir at steady state on the pharmacokinetics of atorvastatin.
2 A clinical trial in healthy subjects evaluating the effect of cobicistat coadministered with atazanavir at steady state on the pharmacokinetics of rosuvastatin.
3 A clinical trial in healthy subjects evaluating the effect of cobicistat coadministered with atazanavir at steady state on the pharmacokinetics of the estrogen and progestin components of a combined oral contraceptive.

Postmarketing trials for cobicistat coadministered with darunavir

1) A clinical trial in healthy subjects evaluating the effect of cobicistat coadministered with darunavir at steady state on the pharmacokinetics of atorvastatin.
2) A clinical trial in healthy subjects evaluating the effect of cobicistat coadministered with darunavir at steady state on the pharmacokinetics of rosuvastatin.
3 A clinical trial in healthy subjects evaluating the effect of cobicistat coadministered with darunavir at steady state on the pharmacokinetics of the estrogen and progestin components of a combined oral contraceptive.

The rationale for evaluating two different HMG-CoA reductase inhibitors (stains) is that

different pathways are involved in the disposition of rosuvastatin and atorvastatin. Rosuvastatin is a transporter substrate of both OATP1B1 and the breast cancer resistance protein (BCRP) and atorvastatin is metabolized by CYP3A and an OATP1B1 transporter substrate. While the currently available information from NDAs with cobicistat information or from the FDA's February 2012 draft drug interaction guidance document indicates that both ritonavir and cobicistat can inhibit CYP3A and OATP1B1 and cobicistat inhibits BCRP, it is not known whether the magnitude or direction of change in statin exposure when atazanavir or darunavir is coadministered with ritonavir versus cobicistat is similar.

B) Office of Scientific Investigations (OSI) Inspections of the GS-US-216-115 and GS-US-216-116 trials

Inspections conducted at the bioanalytical laboratories

At the time the original Clinical Pharmacology review for NDA 203094 was finalized, OSI's recommendations for addressing the form 483 observations for both trials were pending. The form 483 observations that were issued to the bioanalytical laboratories that analyzed darunavir and cobicistat plasma samples for the GS-US-216-115 and GS-US-216-116 trials, respectively, were included in the original Clinical Pharmacology review for NDA 203094, however for completeness they are also listed below.

GS-US-216-115 trial-form 483 observations issued to (b) (4)

(b) (4)

GS-US-216-116 trial-form 483 observations issued to (b) (4)

(b) (4)

For the GS-US-216-115 trial, the form 483 observations outlined in items 1, 2, and 3 requires further follow up with Gilead.

(b) (4)

For the GS-US-216-116 trial, the form 483 observation outlined in item 3 requires further follow up with Gilead. (b) (4)

(b) (4)

Inspections conducted at the clinical site

For the GS-US-216-115 trial, one form 483 observation was issued to Comprehensive Clinical Development because the clinical site did not prepare or maintain accurate case histories. The examples citied included randomization times that occurred after dosing, lack of documentation regarding the date when urine samples were collected and missing information for the "QC'd by" portion of urine collection records. However, the OSI report states that the issue does not impact the trial results.

For the GS-US-216-116 trial, there were no form 483 observations that were issued to SeaView Research. Two verbal observations were noted in the establishment inspection report:

(b) (4)

C) Labeling Recommendations

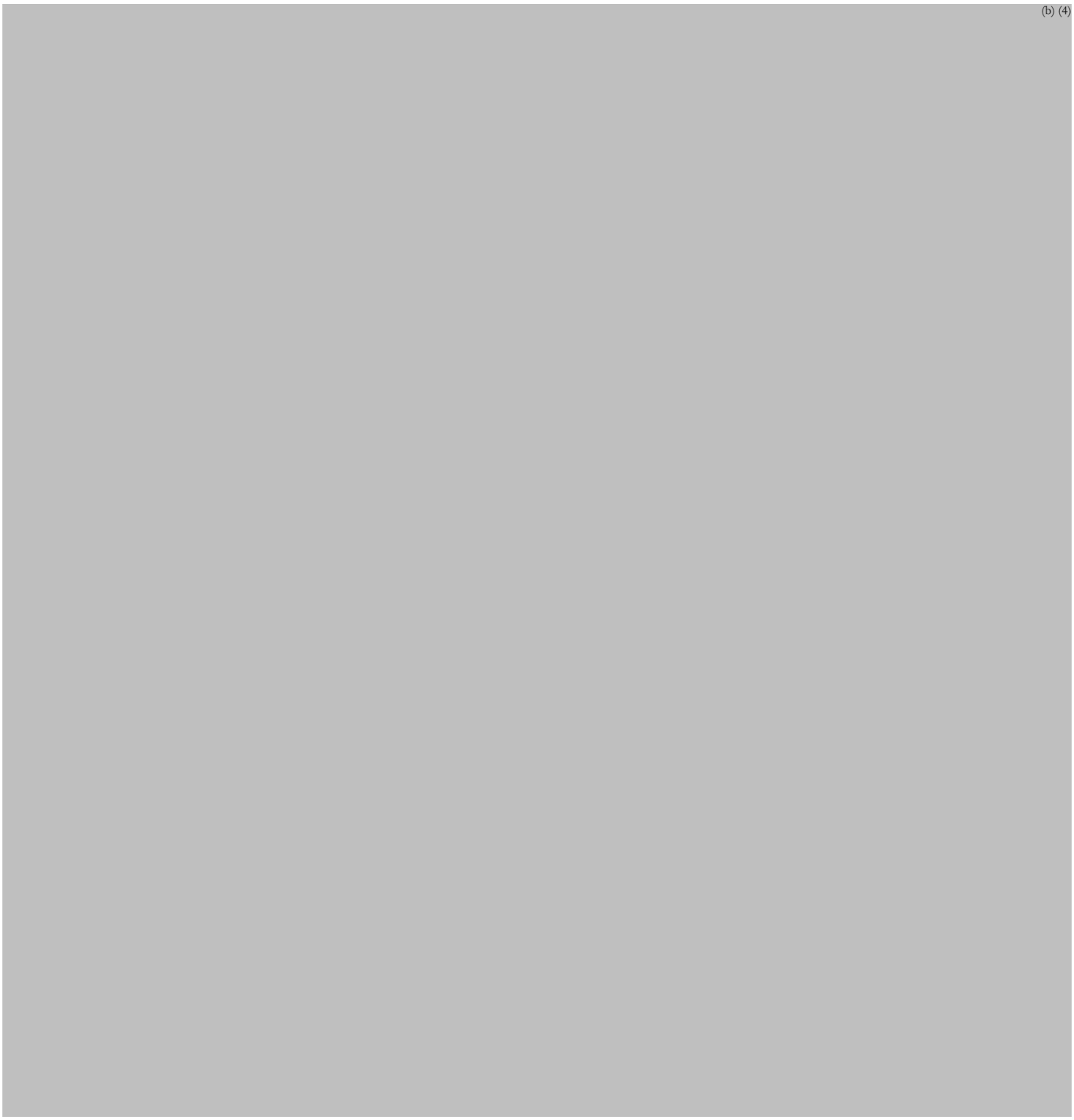
The final labeling for sections 7 and 12 that excludes information related to the use of cobicistat in combination with darunavir is displayed below.

7 DRUG INTERACTIONS

See also Dosage and Administration (2), Contraindications (4), Warnings and Precautions (5.3, 5.4), and Clinical Pharmacology (12.3).

(b) (4)

12 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page



D) Conclusions

The updates for relevant review issues subsequent to the finalization of the Clinical Pharmacology review for NDA 203094 that are discussed in the addendum do not affect the recommendation that the cobicistat NDA supports the approval of the application for the use of cobicistat in combination with atazanavir. However, based on the form 483 observation that was issued (b) (4) regarding the absence of the long term stability data for darunavir combined with cobicistat in the same plasma matrix, the clinical pharmacology information submitted in the cobicistat NDA does not support the

approval of the application for the use of cobicistat in combination with darunavir. The applicant was requested to remove information related to the use of cobicistat in combination with darunavir from the proposed cobicistat U.S prescribing information because the requested long-term stability data will not be available by the Prescription Drug Fee User Act (PDUFA) goal date for the cobicistat NDA.

Appendix 1-DCP4 Division Director's Concurrence on PMRs

APPEARS THIS WAY ON ORIGINAL

Au, Stanley

From: Lazor, John A
Sent: Tuesday, April 02, 2013 11:27 AM
To: Au, Stanley
Cc: Seo, Shirley
Subject: RE: Cobi NDA-PMRs

Concur

From: Au, Stanley
Sent: Monday, April 01, 2013 2:09 PM
To: Lazor, John A
Cc: Seo, Shirley
Subject: Cobi NDA-PMRs

Hi John:

As discussed, please review the finalized list of PMRs for the cobi NDA and provide comments or concurrence.

Stanley Au, Pharm.D., BCPS
Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 4
10903 New Hampshire Ave
Building 51, Room 2141
Silver Spring, MD 20993
FDA/CDER/OTS/OCP/DCP4
(301)796-3988
<< File: Cobi PMCs PMRs 040113 for fax.doc >>

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STANLEY AU
04/19/2013

SHIRLEY K SEO
04/19/2013

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 203094	Submission Date: June 27, 2012
Brand Name	Tybost
Generic Name	Cobicistat
Reviewer	Stanley Au, Pharm.D., BCPS
Pharmacometrics Reviewer	Jeff Florian, Ph.D.
Pharmacometrics Team Leader	Yaning Wang, Ph.D.
Clinical Pharmacology Team Leader	Shirley Seo, Ph.D.
OCP Division	Division of Clinical Pharmacology 4
OND Division	Division of Antiviral Products
Applicant	Gilead Sciences
Proposed U.S commercially marketed strength and formulation	150 mg tablets
Proposed dosage regimens	Cobicistat 150 mg once daily coadministered with: 1) atazanavir 300 mg once daily (treatment naïve or treatment experienced patients) OR 2) darunavir 800 mg once daily (treatment naïve patients or treatment experienced patients with no darunavir resistance associated substitutions) (b) (4)
Proposed Indication for the Application	Cobicistat: None Cobicistat coadministered with atazanavir, darunavir (b) (4): Treatment of HIV-1 infection in treatment naïve or treatment-experienced patients
Review Type(s)	505 (b)(1) New Drug Application, standard review

Table of Contents

1 Executive Summary

This review summarizes the clinical pharmacology information for a New Drug Application (NDA) for cobicistat. Cobicistat is designed specifically to increase the systemic concentrations of medications that are substrates of the cytochrome P450 3A (CYP3A) enzyme system. A therapeutic indication has not been demonstrated for cobicistat when administered by itself. The cobicistat NDA includes trials evaluating the use of cobicistat in combination with atazanavir or darunavir for the treatment of HIV-1 infection. (b) (4) In August 2012, cobicistat was approved for marketing in the United States as part of a fixed dose combination (FDC) tablet [Stribild®] for the treatment of HIV-1 infection in treatment naïve patients. The fixed dose combination tablet consists of cobicistat combined with elvitegravir, an integrase strand transfer inhibitor, and two nucleoside or nucleotide reverse transcriptase inhibitors, tenofovir and emtricitabine. Please refer to the clinical pharmacology review for the elvitegravir/cobicistat/emtricitabine/tenofovir fixed dose combination tablet NDA (NDA 203100) for the following information: a) cobicistat clinical pharmacology information, and b) exposure-safety analyses for cobicistat.

The following dosage regimens and treatment populations for concomitant use of cobicistat 150 mg once daily with either darunavir, atazanavir (b) (4) are proposed: a) atazanavir 300 mg once daily (treatment naïve or treatment experienced patients), b) darunavir 800 mg once daily (treatment naïve patients or treatment experienced patients with no darunavir resistance associated substitutions) (b) (4) (b) (4)

The proposed indication for the use of darunavir coadministered with cobicistat is based

on a multiple dosing trial (GS- US-216-115) in healthy subjects that evaluated the relative bioavailability of darunavir coadministered with cobicistat to darunavir coadministered with ritonavir.

The proposed U.S. commercial formulation of cobicistat was not evaluated in any of the trials evaluating the use of darunavir coadministered with cobicistat that were included in the original submission for the NDA. Subsequently, as supportive information, a Phase 3 trial (GS-US-216-130) evaluating the use of darunavir coadministered with the proposed U.S. commercial formulation of cobicistat was submitted. Only the pharmacokinetic data for darunavir and cobicistat from this trial were reviewed. The efficacy and safety data were not evaluated as part of the cobicistat NDA review.

A Phase 3 trial (GS-US-216-114) in HIV-1 infected, treatment naïve subjects evaluating concomitant use of atazanavir with cobicistat compared to atazanavir with ritonavir, both in combination with a background regimen of tenofovir and emtricitabine administered as fixed dose combination tablets, was conducted to support the proposed indication for the use of atazanavir coadministered with cobicistat. A multiple dosing trial (GS-US-216-110) in healthy subjects comparing the relative bioavailability of atazanavir coadministered with cobicistat to atazanavir coadministered with ritonavir was also conducted.

(b) (4)

1.1 Recommendation

The clinical pharmacology information submitted in the NDA supports the approval of the application for the following indications: a) use of cobicistat in combination with atazanavir, and b) use of cobicistat in combination with darunavir (pending the recommendations from of the Office of Scientific Investigations [OSI] for the GS-US-216-115 and GS-US-216-116 trials). (b) (4)

(b) (4)

(b) (4)

1.2 Postmarketing Commitments or Requirements

At the time the review was finalized, discussions were still ongoing regarding the proposed postmarketing commitments or requirements. The concomitant medications that were selected for the postmarketing trials are frequently administered in the HIV-1 infected population. Additionally, obtaining the drug-drug interaction information is important for deriving appropriate dosing recommendations that account for potential

safety or efficacy issues. The recommendations on concomitant use with certain HMG-CoA reductase inhibitor that are not contraindicated or oral contraceptives can not be extrapolated from the existing recommendation in the atazanavir or darunavir U.S. prescribing information because the interactions are due to complex or unknown drug-drug interaction mechanisms of interaction.

The potential postmarketing trials for cobicistat coadministered with atazanavir or darunavir include the following objectives:

a) Potential changes in oral contraceptive exposure (estrogen and progestin components) when combined with oral contraceptives.
b) Potential changes in HMG-CoA reductase inhibitor exposure when combined with certain HMG-CoA reductase inhibitors. The specific HMG-CoA reductase inhibitors were still being determined at the time the review was finalized.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

1.3.1 Formulation issues

Three different cobicistat formulations were evaluated in various clinical trials. Information on the composition of the three different formulations is displayed in Table 1. The relative bioavailability of cobicistat formulation 1 and formulation 2 were evaluated in the GS-US-216-116 trial that was reviewed in a previous NDA submission (see the Clinical Pharmacology review for NDA 203100), but a relative bioavailability trial was not conducted evaluating cobicistat formulation 2 and formulation 3. Formulation 3 is the proposed U.S. commercial formulation of cobicistat.

The Phase 3 trial (GS-US-216-114) in HIV-1 infected subjects evaluating concomitant use of atazanavir with cobicistat compared to atazanavir with ritonavir was conducted with the proposed U.S. commercial formulation of cobicistat. However, both relative bioavailability trials (GS-US-216-110 and GS-US-216-115) in healthy subjects comparing darunavir or atazanavir coadministered with cobicistat to darunavir or atazanavir coadministered with ritonavir were conducted with cobicistat formulation 1.

Table 1-Composition of cobicistat formulations, 150 mg tablet strength

Ingredient for Tablet Core	Amount (%w/w)		
Clinical Phase	Phase 1/2	BE Study	Phase 3
	Formulation 1	Formulation 2	Formulation 3
(b) (4)			
Cobicistat			
(b) (4)			
(b) (4) Silicon Dioxide			
Microcrystalline Cellulose			
Croscarmellose Sodium			
(b) (4)			
Magnesium Stearate			
(b) (4)			
Total core weight (mg)			
Film-coating			
(b) (4)			
Total tablet weight			

(b) (4)

The differences in the composition of formulation 2 compared to formulation 3 were discussed with the Biopharmaceutics and Product Quality reviewers within the Office of New Drug Quality Assessment (ONDQA). Based on the internal discussions, it was concluded that an additional relative bioavailability trial comparing formulation 2 to formulation 3 was not necessary. The decision was made by ONDQA with the concurrence of the Office of Clinical Pharmacology using a risk based assessment and the nature of the formulation changes provides supporting evidence for the decision. The following factors were used in supporting the rationale (please also see the Biopharmaceutics review):

a) The cobicistat dissolution method is discriminating.
b) The changes in the cobicistat formulation are not anticipated to affect dissolution or solubility but may impact disintegration. In vivo, the area under the curve (AUC) is not expected to be affected but the C_{max} may be altered (e.g. increased). However, no safety issues are anticipated with an increased cobicistat C_{max}.
c) Not all excipients are created equal. (b) (4)

(b) (4)

For cobicistat coadministered with atazanavir, a Phase 3 trial was conducted and subsequently, the results of the GS-US-216-110 relative bioavailability trial are not critical for approval of the indication. In contrast, for cobicistat coadministered with darunavir, the results of the GS-US-216-115 relative bioavailability trial are critical for approval of the indication. Therefore, the following information was used to link the results of the GS-US-216-115 trial to the proposed U.S. commercial formulation of cobicistat:

a) The 90% confidence intervals for the cobicistat $AUC_{(0\text{-}24h)}$, C_{max}, and C_{24h} geometric least squares means ratios were within 80% to 125% in comparing cobicistat formulation 2 to cobicistat formulation 1 in the GS-US-216-116 trial.
b) Based on an internal FDA assessment, an additional relative bioavailability trial comparing formulation 2 to formulation 3 was not necessary, as discussed above.
c) Additional supportive pharmacokinetic data for darunavir from the Phase 3 trial (GS-US-216-130) was reviewed. The GS-US-216-130 trial was conducted with the proposed U.S. commercial formulation of cobicistat coadministered with darunavir.

The FDA Office of Scientific Investigations (OSI) was requested to inspect the clinical trial sites and the relevant bioanalytical laboratories for the GS-US-216-115 and GS-US-216-116 trials. The inspection findings for the clinical trial site for the GS-US-216-115 trial are pending at the time the Clinical Pharmacology review was finalized and for the bioanalytical laboratory (b) (4) that analyzed darunavir plasma samples the following 483 observations were issued:

a) The long term stability of darunavir in combination with cobicistat was not evaluated.

(b) (4)

For the GS-US-216-116 trial, no 483 observations were issued for the clinical trial site; however 483 observations were issued for the bioanalytical laboratory (b) (4) that analyzed cobicistat plasma samples. The following 483 observations were issued:

(b) (4)

OSI's recommendations for addressing the 483 observations for both the trials are pending at the time the Clinical Pharmacology review was finalized.

Overall, if either the OSI inspection results or the resolution of any inspection observations are satisfactory for the GS-US-216-115 and GS-US-216-116 trials, there are no outstanding deficiencies for the cobicistat formulation issue.

1.3.2 Exposure-response (efficacy) analysis

Atazanavir exposure-response analysis

For cobicistat coadministered with atazanavir, information from the Phase 3 trial (GS-US-216-114) in HIV-1 infected subjects and supportive information from the multiple dosing trial (GS-US-216-110) in healthy subjects comparing the relative bioavailability of atazanavir coadministered with cobicistat to atazanavir coadministered with ritonavir were reviewed. In the GS-US-216-110 trial, the 90% confidence intervals for atazanavir $AUC_{(0\text{-}24h)}$, C_{max}, and C_{24h} geometric least squares means ratios were within 80% to 125% when comparing the proposed dosage regimen of cobicistat 150 mg coadministered with atazanavir 300 mg once daily to ritonavir 100 mg coadministered with atazanavir 300 mg once daily (see Table 2). A graphical analysis of the atazanavir exposure-response relationship when coadministered with cobicistat based on exposure and efficacy data from the GS-US-216-114 trial was not conducted. However, in the GS-US-216-114 trial, using snapshot analysis, the percentage of HIV-1 infected, treatment naive subjects that achieved the primary endpoint of HIV-1 RNA less than 50 copies/mL at week 48 was 85.2% in HIV-1 infected subjects that received cobicistat 150 mg coadministered with atazanavir 300 mg once daily compared to 87.4% in HIV-1 infected subjects that received ritonavir 100 mg coadministered with atazanavir 300 mg once daily. The percentage difference and the 95.2% confidence interval were -2.2% (-7.4% to 3%), with the lower limit of the confidence interval not exceeding the non inferiority margin of -12%. Therefore, the exposure-response relationship for cobicistat 150 mg coadministered with atazanavir 300 mg once daily is expected to be similar to ritonavir 100 mg coadministered with atazanavir 300 mg once daily,

While HIV-1 infected, treatment experienced subjects were not specifically evaluated in the GS-US-216-114 trial, an indication for cobicistat coadministered with atazanavir in treatment experienced subjects is supported using the following rationale: a) the recommended dosage regimen for HIV-1 infected, treatment experienced adult patients is atazanavir 300 mg coadministered with ritonavir 100 mg once daily, b) the similarity in atazanavir exposures with a 300 mg dose when combined with either ritonavir 100 mg or cobicistat 150 mg once daily in the GS-US-216-110 trial in healthy subjects and in the GS-US 216-114 trial where noninferiority was demonstrated for cobicistat coadministered with atazanavir in treatment naïve subjects, and c) an expectation that atazanavir exposures when coadministered with ritonavir or cobicistat would be similar regardless of the HIV-1 infected treatment population (naïve or experienced).

Table 2-Comparison of atazanavir pharmacokinetic data with cobicistat 150 mg coadministered with 300 mg atazanavir once daily (test arm) compared to ritonavir 100 mg coadministered with 300 mg atazanavir once daily (reference arm)

Atazanavir PK Parameter	Geometric Least Squares Means		Geometric Least Squares Mean Ratio (%)	90% Confidence Interval
	Test Treatment	Reference Treatment		
Atazanavir/GS-9350 300/150 mg (test) versus Atazanavir/r 300/100 mg (reference)				
n	34	36		
AUC_{tau} (ng•h/mL)	53,272.76	52,772.91	100.95	94.47, 107.87
C_{max} (ng/mL)	4701.26	5094.52	92.28	85.13, 100.03
C_{tau} (ng/mL)	1190.42	1220.18	97.56	88.14, 107.99

Darunavir exposure-response analysis

For cobicistat coadministered with darunavir, information was reviewed from the following sources: a) the multiple dosing trial (GS-US-216-115) in healthy subjects comparing the relative bioavailability of darunavir coadministered with cobicistat to darunavir coadministered with ritonavir and b) supportive information from the Phase 3 trial (GS-US-216-130) evaluating the use of darunavir coadministered with the proposed U.S. commercial formulation of cobicistat were reviewed. When comparing the proposed dosage regimen of cobicistat 150 mg coadministered with darunavir 800 mg once daily to ritonavir 100 mg coadministered with darunavir 800 mg once daily, the 90% confidence intervals for the darunavir $AUC_{(0\text{-}24h)}$, C_{max}, and C_{0h} geometric least squares means ratios were within 80% to 125% but the darunavir C_{24h} was not within 80% to 125%. The darunavir C_{24h} geometric least squares mean was decreased by 31% and the 90% confidence interval was not within 80%-125% (see Table 3). The cause of the difference in the C_{24h} value was attributed to an increase in darunavir concentrations between 20 hours and 24 hours that occurred most frequently when ritonavir was coadministered with darunavir on Day 24 (additional information is included in the Pharmacometrics review [section 4]).

Table 3-Comparison of darunavir pharmacokinetic data with cobicistat 150 mg coadministered with 800 mg darunavir once daily (test arm) compared to ritonavir 100 mg coadministered with 800 mg darunavir once daily (reference arm)

DRV Plasma PK Parameters	Geometric Least-Squares Means		Geometric Least-Squares Means Ratio (%) of Test/Reference (Treatment A/Treatment B) (90% CI)
	Test Treatment Treatment A DRV 800 mg + GS-9350 150 mg (N=31)	Reference Treatment Treatment B DRV 800 mg + RTV 100 mg (N=31)	
AUC_{tau} (ng·h/mL)	77,390.28	76,036.36	101.78 (97.40, 106.36)
C_{max} (ng/mL)	7538.12	7292.95	103.36 (100.34, 106.48)
C_{tau} (ng/mL)	1056.59	1521.83	69.43 (59.02, 81.68)
C_{0h} (ng/mL)	2089.67	2337.65	89.39 (80.36, 99.44)

DRV, darunavir; CI, confidence interval; PK, pharmacokinetic

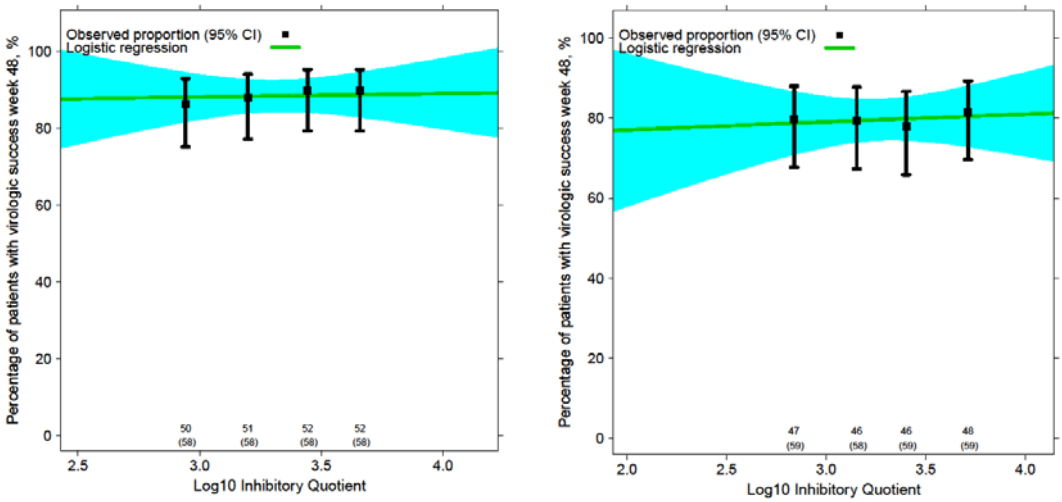
Overall, based on comparing the darunavir exposure from the GS-US-216-115 trial and from the GS-US-216-130, TMC114-C211 and TMC114-C229 trials (Table 4), the once daily 800 mg darunavir exposure is similar when coadministered with either ritonavir 100 mg or cobicistat 150 mg. The mean darunavir C_{0h} was approximately 5% to 10% lower in the GS-US-216-130 trial compared to the TMC114-C211 and TMC114-C229 trials. An evaluation of the C_{24h} differences was not conducted as part of the data analyses for the trial (see below for a discussion of the differences in the C_{24h} values). Overall, the exposure-response relationship for cobicistat 150 mg coadministered with darunavir 800 mg once daily is expected to be similar to ritonavir 100 mg coadministered with darunavir 800 mg once daily.

Table 4-Comparison of darunavir $AUC_{(0-24h)}$, and C_{0h} pharmacokinetic data

	DRV PK Parameter	GS-US-216-0130 DRV 800 mg + COBI 150 mg QD (n = 298)	TMC114-C211[a] DRV 800 mg + RTV 100 mg QD (n = 335)	TMC114-C229[a] DRV 800 mg + RTV 100 mg QD (n = 280)
AUC_{24h}(ng·h/mL)	Mean [SD]	100152 [32042]	93026 [27050]	93334 [28626]
	Median [Range]	96900 [34500-224000]	87854 [45000-219240[	87788 [45456-236920]
C_{0h} (ng/mL)	Mean [SD]	2043 [1257]	2282 [1168]	2160 [1201]
	Median [Range]	1875 [70-6890]	2041 [368-7242]	1896 [184-7881]

Based on the available once daily darunavir exposure-response data when coadministered with ritonavir from the TMC114-C211 and TMC114-C229 trials that were conducted by (b) (4), a clinically relevant exposure-response relationship was not identified (e.g. increasing or decreasing virologic response was not observed either with increasing or decreasing darunavir $AUC_{(0-24h)}$ or C_{0h} values). A similar conclusion was observed based on the inhibitory quotient (IQ) analysis [the IQ is the ratio of C_{0h} (exposure) at steady state and IC_{50} (a measurement of the ability of darunavir to inhibit HIV-1 virus)]-see Figure 1. Please see the Pharmacometrics review (section 4) for further details. The available darunavir exposure-response information with once daily dosing does not provide information to assist with interpreting the potential implications of a 31% decrease in the C_{24h} value. In reviewing the available drug-drug interaction data for darunavir, in the darunavir U.S. prescribing information, a dosage adjustment recommendation for darunavir is not specified for the decreases in the darunavir $AUC_{(0-24h)}$, C_{max}, and C_{min} values of 13%, 15%, and 31% that are observed with concomitant use of efavirenz. Based on the available information, the 31% decrease in the C_{24h} value that was observed with cobicistat coadministered with darunavir once daily is not anticipated to be clinically relevant.

Figure 1-Percentage of subjects achieving virologic success (<50 copies/mL) versus DRV IQ from the TMC114-C211 (left) and TMC114-C229 trials (right). The figures exclude subjects with one or more darunavir concentrations that were below the limit of quantification.



1.3.3 **Exposure-safety analysis**

For cobicistat, an exposure-safety analysis was conducted using exposure and adverse event data from the Phase 2 and Phase 3 trials evaluating cobicistat coadministered with atazanavir (with a fixed dose combination tablet consisting of tenofovir and emtricitabine as a background regimen) and gastrointestinal or hepatic related adverse events. There was no relationship observed between cobicistat exposure and gastrointestinal or hepatic related adverse events. However because of the limited availability of both cobicistat exposure data from the Phase 2 and 3 trials (n=68) and adverse events of interest occurring in the available subjects with cobicistat exposure data, definitive conclusions regarding the exposure-safety relationship for cobicistat can not be made.

For the same reasons that are discussed in section 1.3.2 for the exposure-response analyses, the exposure-safety relationships for darunavir or atazanavir when coadministered with cobicistat once daily is expected to be similar to ritonavir coadministered with darunavir or atazanavir once daily.

Cobicistat has been demonstrated to decrease the calculated creatinine clearance when using the Cockcroft-Gault equation but does not alter the glomerular filtration rate when evaluating iohexol plasma clearance (see the review for GS-US-216-121 in the Clinical Pharmacology review for NDA 203100). Additionally, based on the analyses conducted by the clinical reviewer using data from the GS-US-216-105 and GS-US-216-114 trials, for the 15 renal related adverse events, 5 out of the 6 events in the cobicistat coadministered with atazanavir arm compared to 2 out of the 9 events in the ritonavir coadministered with atazanavir arm were consistent with proximal tubulopathy. Additional analyses were conducted by the Pharmacometrics reviewer evaluating the creatinine clearance data from the GS-US-216-114 trial where atazanavir was coadministered with either ritonavir or cobicistat in combination with a fixed dose combination tablet consisting of tenofovir and emtricitabine. In the GS-US-216-114 trial, for subjects with a baseline creatinine clearance of 70 mL/min or greater, more subjects

in the ritonavir coadministered with atazanavir arm maintained a creatinine clearance within a specified baseline range (70 to 80 mL/min, 80 to 90 mL/min, or greater than 90 ml/min) while on treatment compared to cobicistat coadministered with atazanavir. Similarly, a larger percentage of subjects with baseline creatinine clearance less than 90 mL/min had on treatment creatinine clearances below 50 mL/min for cobicistat coadministered with atazanavir (5 out 45 or 11.1%) compared to ritonavir coadministered with atazanavir (3 out of 58 or 5.2%). Please see the Pharmacometrics review for further details regarding the analyses.

To address this issue, the proposed U.S prescribing information for cobicistat includes a statement recommending that HIV-1 infected patients with a confirmed increase in serum creatinine greater than 0.4 mg/dL should be monitored for renal related adverse events. The same language is included in the U.S prescribing information for the elvitegravir/cobicistat/tenofofovir/emtricitabine fixed dose combination tablets. The serum creatinine threshold of 0.4 mg/dL was chosen based on attempting to balance identifying subjects with potential renal related adverse events against prematurely prompting clinicians to consider making changes in treatment.

1.3.4 Drug-drug interaction information

The applicant did not conduct drug-drug interaction trials evaluating the use of cobicistat with atazanavir or darunavir. Drug-drug interaction trials were conducted that evaluated the use of cobicistat coadministered with elvitegravir that included concomitant use of rosuvastatin or rifabutin. As a single entity, drug-drug interaction trials were conducted with cobicistat and each of the following medications: desipramine, digoxin or efavirenz.

In section 7 of the proposed U.S prescribing information for cobicistat, the clinical recommendations for specific drug-drug interactions were derived based on extrapolating from the available drug interaction information. The metabolism and drug interaction information for atazanavir, darunavir, ritonavir, cobicistat and the concomitant medications, including information regarding potential interactions attributed to cytochrome P450 enzymes or transporters, were reviewed using the U.S. prescribing information or the February 2012 Guidance for Industry: Drug Interaction Studies as reference sources. Only concomitant medications with specific information either in the respective U.S. prescribing information or the February 2012 Guidance for Industry: Drug Interaction Studies, including details regarding routes of cytochrome P450 metabolism, cytochrome P450 inhibition or induction effects or the potential for transporter interactions, are listed in the table in section 7.3 of the proposed U.S prescribing information for cobicistat.

Subsequently, the appropriateness of extrapolating the predicted or observed interaction from the atazanavir, darunavir, or ritonavir U.S. prescribing information to cobicistat coadministered with atazanavir or darunavir was determined and the clinical comments were revised accordingly, if necessary. Major focuses of the extrapolated drug-drug information that was included in section 7.3 included: a) inhibitory effects of cobicistat coadministered with atazanavir or darunavir on the exposure of CYP3A or CYP2D6 substrates, and b) the effects of CYP3A inhibitors or inducers on atazanavir or darunavir exposure when coadministered with cobicistat. The revisions proposed by the review team are displayed in section 3 (Labeling Recommendations).

1.3.5 Clinical pharmacology information for cobicistat

Information regarding the absorption, distribution, metabolism and excretion of cobicistat was previously reviewed as part of the elvitegravir/cobcistat/emtricitabine/tenofovir fixed dose combination tablet NDA-please refer to the clinical pharmacology review for NDA 203100. The impact of renal impairment (GS-US-216-124) or hepatic impairment (GS-US-183-133) on cobicistat exposure was also reviewed as part of NDA 203100.

2 Question based review (QBR)

2.1 General Attributes of the Drug

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug?

In August 2012, cobicistat was approved for marketing in the United States as part of a fixed dose combination (FDC) tablet for the treatment of HIV-1 infection in treatment naïve patients consisting of cobicistat combined with elvitegravir, an integrase strand transfer inhibitor, and two nuclesoside or nucleotide reverse transcriptase inhibitors, tenofovir and emtricitabine. Please refer to the clinical pharmacology review for the elvitegravir/cobcistat/emtricitabine/tenofovir fixed dose combination tablet NDA (NDA 203100) for the following information: a) cobicistat clinical pharmacology information, and b) exposure-safety analyses for cobicistat.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology review?

The drug substance for cobicistat is cobicistat on silicon dioxide which provide a stable solid. According to the applicant, the empirical formula for cobicistat is $C_{40}H_{53}N_7O_5S_2$ with a formula weight of 776. Information on the proposed U.S. commercial formulation (Formulation 3) of cobicistat as a 150 mg tablet strength is provided in Table 1 in section 1.3.1.

2.1.3 What is the proposed mechanism of action and therapeutic indication(s)?

When administered by itself, cobicistat does not have a therapeutic indication. Cobicistat is designed specifically to increase the systemic concentrations of medications that are substrates of the cytochrome P450 3A enzyme system. For the current NDA, the proposed therapeutic indications are the treatment of HIV-1 infection when cobicistat is coadministered with atazanavir, darunavir, (b) (4).

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

The proposed dosage regimen is concomitant use of cobicistat 150 mg with atazanavir 300 mg darunavir 800 mg (b) (4) as a once daily regimen administered orally with a meal.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical studies used to support dosing or claims?

A Phase 3 trial (GS-US-216-114) in HIV-1 infected subjects evaluating concomitant use of atazanavir with cobicistat compared to atazanavir with ritonavir, both in combination with a background regimen of tenofovir and emtricitabine administered as fixed dose combination tablets, was conducted to support the proposed indication for the use of atazanavir coadministered with cobicistat. A multiple dosing trial (GS-US-216-110) in healthy subjects comparing the relative bioavailability of atazanavir coadministered with cobicistat to atazanavir coadministered with ritonavir was also conducted.

The proposed indication for the use of darunavir coadministered with cobicistat is based on a multiple dosing trial (GS- US-216-115) in healthy subjects that evaluated the relative bioavailability of darunavir coadministered with cobicistat to darunavir coadministered with ritonavir. The proposed U.S. commercial formulation of cobicistat was not evaluated in any of the trials evaluating the use of darunavir coadministered with cobicistat that were included in the original submission for the NDA. Subsequently, as supportive information, a Phase 3 trial (GS-US-216-130) evaluating the use of darunavir coadministered with the proposed U.S. commercial formulation of cobicistat was submitted. Only the pharmacokinetic data for darunavir and cobicistat from this trial were reviewed. The efficacy and safety data were not evaluated as part of the NDA review.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?

For the GS-US-216-114 trial, the primary endpoint was plasma HIV-1 RNA viral load < 50 copies/mL. The HIV-1 viral load has been demonstrated to be a valid surrogate to establish the efficacy of antiretroviral medications for the treatment of HIV-1 infection.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The relevant analytes were measured in plasma using validated LC/MS/MS analytical methods. For the cobicistat NDA, the analytes that were measured included darunavir, atazanavir, ritonavir and cobicistat.

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose response, concentration-response) for efficacy?

Atazanavir exposure-response analysis

The exposure-response relationship for cobicistat 150 mg coadministered with atazanavir 300 mg once daily is expected to be similar to ritonavir 100 mg coadministered with atazanavir 300 mg once daily. In the GS-US-216-110 trial, 90% confidence intervals for the atazanavir $AUC_{(0\text{-}24h)}$, C_{max}, and C_{24h} geometric least squares means ratios were within 80% to 125% when comparing the proposed dosage regimen of cobicistat 150 mg coadministered with atazanavir 300 mg once daily to ritonavir 100 mg coadministered with atazanavir 300 mg once daily (see Table 2 in section 1.3.2). A graphical analysis of the atazanavir exposure-response relationship when coadministered with cobicistat based on exposure and efficacy data from the GS-US-216-114 trial was not conducted. However, in the GS-US-216-114 trial, using snapshot analysis, the percentage of HIV-1 infected subjects that achieved the primary endpoint of HIV-1 RNA less than 50 copies/mL at week 48 was 85.2% in HIV-1 infected subjects that received cobicistat 150 mg coadministered with atazanavir 300 mg once daily compared to 87.4% in HIV-1 infected subjects that received ritonavir 100 mg coadministered with atazanavir 300 mg once daily. The percentage difference and the 95.2% confidence interval were -2.2% (-7.4% to 3%), with the lower limit of the confidence interval not exceeding the non inferiority margin of -12%.

Darunavir exposure-response analysis

Overall, based on comparing the darunavir exposure from the GS-US-216-115 trial and from the GS-US-216-130, TMC114-C211 and TMC114-C229 trials (Table 4 in section 1.3.2), the once daily darunavir 800 mg exposure is similar when coadministered with either ritonavir 100 mg or cobicistat 150 mg. Therefore, the exposure-response relationship for cobicistat 150 mg coadministered with darunavir 800 mg once daily is expected to be similar to ritonavir 100 mg coadministered with darunavir 800 mg once daily. When comparing the proposed dosage regimen of cobicistat 150 mg coadministered with darunavir 800 mg once daily to ritonavir 100 mg coadministered with darunavir 800 mg once daily, the 90% confidence intervals for the darunavir $AUC_{(0\text{-}24h)}$, C_{max}, and C_{0h} geometric least squares means ratios were within 80% to 125% but the darunavir C_{24h} was not within 80% to 125%. The darunavir C_{24h} geometric least squares mean was decreased by 31% and the 90% confidence interval was not within 80%-125% (see Table 3 in section 1.3.2). The cause of the difference in the C_{24h} value was attributed to an increase in darunavir concentrations between 20 hours and 24 hours that occurred most frequently when ritonavir was coadministered with darunavir on Day 24. The available darunavir exposure-response information with once daily dosing does not provide information to assist with interpreting the potential implications of a 31% decrease in the C_{24h} value. In reviewing the available drug-drug interaction data for darunavir, in the darunavir U.S. prescribing information, a dosage adjustment recommendation for darunavir is not specified for the decreases in the darunavir $AUC_{(0\text{-}24h)}$, C_{max}, and C_{min} values of 13%, 15%, and 31% that are observed with concomitant use of efavirenz. Based on the available information, a 31% decrease in the C_{24h} value that

was observed with cobicistat coadministered with darunavir once daily is not anticipated to be clinically relevant.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose response, concentration-response) for safety?

For cobicistat, an exposure-safety analysis was conducted using exposure and adverse event data from the Phase 2 and Phase 3 trials evaluating cobicistat coadministered with atazanavir (with a fixed dose combination tablet consisting of tenofovir and emtricitabine as a background regimen) and gastrointestinal or hepatic related adverse events. There was no relationship observed between cobicistat exposure and gastrointestinal or hepatic related adverse events. However, because of the limited availability of both cobicistat exposure data from the Phase 2 and 3 trials (n=68) and adverse events of interest occurring in the available subjects with cobicistat exposure data, definitive conclusions regarding the exposure-safety relationship for cobicistat can not be made.

Using the same rationale outlined for the exposure-response information for darunavir or atazanavir, the exposure-safety relationships for darunavir or atazanavir when coadministered with cobicistat once daily is expected to be similar to ritonavir coadministered with darunavir or atazanavir once daily.

Cobicistat has been demonstrated to decrease the calculated creatinine clearance when using the Cockcroft-Gault equation but does not alter the glomerular filtration rate when evaluating iohexol plasma clearance (see the review for GS-US-216-121 in the Clinical Pharmacology review for NDA 203100). Additionally, based on the analyses conducted by the clinical reviewer using data from the GS-US-216-105 and GS-US-216-114 trials, for the 15 renal related adverse events, 5 out of the 6 events in the cobicistat coadministered with atazanavir arm compared to 2 out of the 9 events in the ritonavir coadministered with atazanavir arm were consistent with proximal tubulopathy. Additional analyses were conducted by the Pharmacometrics reviewer. In the GS-US-216-114 trial, for subjects with a baseline creatinine clearance of 70 mL/min or greater, more subjects in the ritonavir coadministered with atazanavir arm maintained a creatinine clearance within a specified baseline range (70 to 80 mL/min, 80 to 90 mL/min, or greater than 90 ml/min) while on treatment compared to cobicistat coadministered with atazanavir. Similarly, a larger percentage of subjects with baseline creatinine clearance less than 90 mL/min had on treatment creatinine clearances below 50 mL/min for cobicistat coadministered with atazanavir (5 out 45 or 11.1%) compared to ritonavir coadministered with atazanavir (3 out of 58 or 5.2%).

2.2.4.3 Does this drug prolong the QT or QTc interval?

Information regarding the potential for cobicistat to prolong the QT interval is provided in the Clinical Pharmacology review for NDA 203100.

2.2.4.4 Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Currently, the recommended once daily doses with concomitant use of ritonavir 100 mg in the atazanavir and darunavir U.S. prescribing information are 300 mg and 800 mg, respectively.

For the cobicistat NDA, the proposed dosage regimens of cobicistat 150 mg coadministered with either atazanavir 300 mg or darunavir 800 mg once daily are supported by the similarity in once daily atazanavir or darunavir exposures when coadministered with either ritonavir 100 mg or cobicistat 150 mg based on the exposure data from the GS-US-216-110, GS-US-216-115, and GS-216-130 trials and the efficacy data for atazanavir 300 mg coadministered with cobicistat 150 mg or ritonavir 100 mg once daily from the GS-US-216-114 trial. With once daily dosage regimens, based on the similarity in atazanavir or darunavir exposures, the exposure-response relationships for atazanavir or darunavir are also expected to be similar with concomitant use of either cobicistat 150 mg or ritonavir 100 mg.

2.2.5 What are the PK characteristics of the drug and its major metabolite?

Information regarding the pharmacokinetic characteristics of cobicistat is provided in the Clinical Pharmacology review for NDA 203100. In brief, in the GS-US-216-130 trial where HIV-1 subjects were instructed to take cobicistat coadministered with darunavir with food, median cobicistat peak plasma concentrations were observed approximately 3.5 hours post-dose. Steady-state cobicistat C_{max}, AUC_{tau}, and C_{tau} (mean ± SD), values were 0.991 ± 0.3 μg/mL (n=60), 7.6 ± 3.7 μg*hr/mL (n=59), and 0.03 ± 0.1 μg/mL (n=59), respectively. The terminal plasma half-life of cobicistat following administration of cobicistat is approximately 3 to 4 hours based on information from the GS-US-216-101 trial.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, & organ dysfunction) influence exposure &/or response and what is the impact of any differences in exposure on the PDs? What dosage regimen adjustments, if any, are recommended for each of these subgroups?

With the exception of body weight, the covariates that were evaluated had a minimal or no influence on cobicistat exposure based on the results from the cobicistat population PK analysis. For body weight, there was a 25% difference in cobicistat $AUC_{(0\text{-}24h)}$ between the 1st and 4th weight quartile (median body weight of 61 and 90 kg, respectively). However, dosage adjustments are not necessary for any of the covariates that were evaluated. A population PK analysis was conducted to investigate the potential effects of selected covariates, including body weight, race, age, creatinine clearance (measured using the Cockcroft-Gault (C-G) equation), sex, and hepatitis B/C co-infection.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen

adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

Based on the results from the cobicistat population PK analysis that was conducted using data from various Phase 1, Phase 2 and Phase 3 trials, including trials where cobicistat was coadministered with atazanavir, darunavir or elvitegravir, no dosage adjustment are necessary for the covariates discussed below for the specific groups where data is available.

2.3.2.1 Elderly

Higher cobicistat exposure was observed in subjects greater than 65 years old compared to subjects less than 65 years old based on the results from the cobicistat population PK analysis. The information is displayed in Table 1. However, only 16 subjects >65 years were included as part of the cobicistat population pharmacokinetic analysis. 14 of the subjects were from the renal impairment trial (eight subjects with creatinine clearance < 30mL/min, five subjects with creatinine clearance ranging from 75 to 90 mL/min and one subject with a creatinine clearance of 102 mL/min). No definitive conclusions could be made regarding whether cobicistat pharmacokinetics are different between elderly and younger patients. (b) (4)

.

Table 1-Cobcistat population pharmacokinetic analysis comparing subjects less than and greater than 65 years old receiving cobicistat 150 mg once daily

Parameter	Age <65 years old (n=275)	Age ≥65 years (n=16)
AUC_{τ} (ng·h/mL)	11,380 (39)	17,730 (37)
C_{max} (ng/mL)	1,447 (26)	1,888 (35)
C_{0h} (ng/mL)	53 (115)	138 (151)

2.3.2.2 Pediatrics

The safety and effectiveness of cobicistat in HIV-1 pediatric subjects has not been established.

2.3.2.3 Gender

There was no effect of gender on cobicistat exposure based on the results from the cobicistat population PK analysis. However, as indicated in section 2.3.1., body weight did influence cobicistat exposure.

2.3.2.4 Race

The population PK analysis indicated that there was no clinically significant effect of race (whites, blacks and others) on cobicistat exposure.

2.3.2.5 Renal impairment

The effect of renal impairment on the exposure of cobicistat was evaluated as part of the GS-US-216-124 trial that also evaluated the effect of renal impairment on the exposure of elvitegravir. In the GS-US-216-124 trial, elvitegravir and cobicistat were administered as single entities. As stated in the U.S prescribing information for the elvitegravir/ cobicistat/emtricitabine/tenofovir fixed dose combination tablets, clinically significant differences in cobicistat pharmacokinetics were not observed between subjects with severe renal impairment and healthy subjects. Further details regarding the trial evaluating the effect of renal impairment on the exposure of cobicistat is provided in the Clinical Pharmacology review for NDA 203100.

2.3.2.6 Hepatic impairment

The effect of hepatic impairment on the exposure of cobicistat was evaluated as part of the GS-US-183-133 trial that also evaluated the effect of hepatic impairment on the exposure of elvitegravir. In the GS-US-183-133 trial, elvitegravir and cobicistat were administered as single entities. As stated in the U.S prescribing information for the elvitegravir/cobicistat/emtricitabine/tenofovir fixed dose combination tablets, clinically significant differences in cobicistat pharmacokinetics were not observed between subjects with moderate hepatic impairment and healthy subjects. Further details regarding the effect of hepatic impairment on the exposure of cobicistat is provided in the Clinical Pharmacology review for NDA 203100.

2.3.2.7 What pregnancy and lactation use information is there in the application?

There were no trials evaluating the use of cobicistat in pregnant or lactating women that were included in the NDA submission.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors influence dose-exposure and/or response, and what is the impact of any differences in exposure on response?

There were no trials that were submitted in the current NDA submission that evaluated the effect of food on cobicistat exposure. Additionally, the applicant did not conduct drug-drug interaction trials evaluating the use of cobicistat with atazanavir or darunavir. Drug-drug interaction trials were conducted that evaluated the use of cobicistat coadministered with elvitegravir that included concomitant use of rosuvastatin or rifabutin. As a single entity, drug-drug interaction trials were conducted with cobicistat and each of the following medications: desipramine, digoxin or efavirenz. Information regarding these drug-drug interaction trials are included in the Clinical Pharmacology review for NDA 203100.

2.4.2 Drug-drug interactions

The details of the available metabolism, in vitro and in vivo drug-drug interaction data for cobicistat are provided in the Clinical Pharmacology review for NDA 203100. In summary, cobicistat undergoes CYP3A metabolism with additional metabolism by

CYP2D6. Cobicistat inhibits CYP3A and CYP2D6 but is not expected to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9 or CYP2C19. Cobicistat is also not expected to induce CYP1A2 or CYP2B6. The transporters that cobicistat inhibits includes p-glycoprotein (P-gp), organic anion transporting polypeptide (OATP) 1B1 and OATP1B3, and the breast cancer resistance protein (BCRP).

2.4.2.1 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

Cobicistat is designed specifically to increase the systemic concentrations of medications that are substrates of the cytochrome P450 3A enzyme system. Concomitant use of cobicistat 150 mg once daily with either darunavir or atazanavir are proposed: a) atazanavir 300 mg once daily (treatment naïve or treatment experienced patients), b) darunavir 800 mg once daily (treatment naïve patients or treatment experienced patients with no darunavir resistance associated substitutions) (b) (4) .

The trials evaluating the concomitant use of cobicistat with either atazanavir or darunavir in the current NDA have adequately characterized the effect of cobicistat on atazanavir or darunavir.

2.4.2.2 What other co-medications are likely to be administered to the target patient population?

HIV-1 infected patients may receive a variety of concurrent medications for treatment or prevention of comorbidities. These include medications for treatment of tuberculosis, psychiatric disorders (e.g. depression), cardiovascular disorders (e.g. dyslipidemias) and substance abuse. As previously stated, the applicant did not conduct drug-drug interaction trials evaluating the use of cobicistat with atazanavir or darunavir and concomitant medications. However, the review team is discussing additional drug-drug interaction trials as postmarketing requirements or commitments for concomitant medications where actual exposure data is important for developing appropriate dosing recommendations with concomitant use. The drug-drug interaction trials that are being discussed are outlined in section 1.2.

2.4.2.3 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

The concomitant medications that are listed in the table in section 7.3 (see section 3-Labeling Recommendations) reflect the medications that may result in clinically relevant drug-drug interactions when combined with cobicistat coadministered with atazanavir, darunavir, (b) (4) . Major focuses of the extrapolated drug-drug information that was included in section 7.3 included: a) inhibitory effects of cobicistat coadministered with atazanavir or darunavir on the exposure of CYP3A or CYP2D6 substrates, and b) the effects of CYP3A inhibitors or inducers on atazanavir or darunavir exposure when coadministered with cobicistat.

2.4.2.4 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

There are no known pharmacodynamic drug-drug interactions for cobicistat.

2.4.2.5 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

Please see the response in section 2.4.2.2.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

There are no issues related to dose, dosing regimens, or administration that are unresolved and represent significant omissions.

2.5 General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

The applicant states that cobicistat is a biopharmaceutics classification system class 2 compound, which is defined as a low solubility, high permeability compound. However, no specific supportive information was provided in the applicant's Summary of Biopharmaceutic Studies and Associated Analytical Methods.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The Phase 3 trial (GS-US-216-114) in HIV-1 infected subjects evaluating concomitant use of atazanavir with cobicistat compared to atazanavir with ritonavir was conducted with the proposed U.S. commercial formulation of cobicistat.

The GS-US-216-115 trial in healthy subjects that evaluated the relative bioavailability of darunavir coadministered with cobicistat to darunavir coadministered with ritonavir was conducted with cobicistat formulation 1. The relative bioavailability of cobicistat formulation 1 and formulation 2 were evaluated in the GS-US-216-116 trial that was reviewed in a previous NDA submission (see the Clinical Pharmacology review for NDA 203100). The 90% confidence intervals for cobicistat $AUC_{(0\text{-}24h)}$, C_{max}, and C_{24h} geometric least squares mean ratios were within 80% to 125% when comparing cobicistat formulation 2 to cobicistat formulation 1 in the GS-US-216-116 trial (see Table 2). However, a relative bioavailability trial was not conducted evaluating cobicistat formulation 2 and formulation 3. Formulation 3 is the proposed U.S. commercial formulation of cobicistat. The rationale for not requiring an additional relative bioavailability trial comparing cobicistat formulation 3 to formulation 2 is discussed in section 1.3.1.

Table 2-Statistical analyses for cobicistat 150 mg once daily (formulation 1 and formulation 2) from the GS-US-216-116 trial (reviewed as part of NDA 203100)

PK Parameter (N = 35)	GLSMs		GLSM Ratio (%) (90% CI)
	Test Treatment: GS-9350 Formulation 2	Reference Treatment: GS-9350 Formulation 1	
AUC_{tau} (ng•h/mL)	11,788.86	12,004.30	98.21 (94.61, 101.94)
C_{tau} (ng/mL)	58.29	60.52	96.31 (87.12, 106.47)
C_{max} (ng/mL)	1557.73	1538.26	101.27 (97.47, 105.21)

CI: confidence interval, GLSM: geometric least-squares mean, PK: pharmacokinetic
GLSMs were obtained using a mixed-effects model. The model included treatment, sequence, and period as fixed effects, and subject-within-sequence as a random effect.

2.5.2.1 What data support or do not support a waiver of in vivo BE data?

For the cobicistat NDA, a biowaiver of in vivo BE data was not requested for cobicistat formulation 3.

2.5.3 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?

There were no trials that were submitted in the current NDA submission that evaluated the effect of food on cobicistat exposure. The recommendation in the proposed cobicistat U.S. prescribing information to administer cobicistat when coadministered with atazanavir or darunavir with food is consistent with the dosing recommendations for atazanavir or darunavir when coadministered with ritonavir. In the GS-US-216-114 trial, the HIV-1 infected subjects were instructed to administer cobicistat combined with atazanavir with food.

2.5.4 When would a fed BE study be appropriate and was one conducted?

The GS-US-216-115 trial in healthy subjects that evaluated the relative bioavailability of darunavir coadministered with cobicistat to darunavir coadministered with ritonavir was conducted both under fed conditions and with multiple dosing. The trial design was considered acceptable because it reflects the clinical conditions under which darunavir coadministered with ritonavir is administered.

2.5.5 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

Please refer to the cobicistat biopharmaceutics review for information regarding dissolution conditions and specifications.

2.5.6 What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

There are no in vivo BA and BE issues that need to be addressed for the cobicistat NDA submission. Please refer to the cobicistat biopharmaceutics review for information regarding the assessment of the in vitro dissolution data for cobicistat.

2.6 Analytical section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Cobicistat, darunavir, atazanavir and ritonavir plasma samples were analyzed using a LC/MS/MS analytical method for one or more of the following trials: GS-US-216-110, GS-US-216-114, GS-US-216-115, and GS-US-216-130. The Clinical Pharmacology reviewer examined the relevant cobicistat, darunavir, atazanavir and ritonavir method validation reports in addition to the bioanalytical reports for the clinical pharmacology trials that are summarized in section 4 and for the Phase 3 trials. There were no issues identified by the Clinical Pharmacology reviewer that would impact the reliability of the reported cobicistat, darunavir, atazanavir and ritonavir plasma concentration data. Information regarding the FDA Office of Scientific Investigations (OSI) inspections that were requested for the clinical trial sites and the relevant bioanalytical laboratories for the GS-US-216-115 and GS-US-216-116 trials are discussed in section 1.3.1.

The submitted cobicistat long term stability data of 121 days at -10°C to -30°C and 365 days at -60°C to -80°C in K_2EDTA anticoagulated plasma that was generated (b) (4) and referenced by (b) (4) supports the duration of long term cobicistat stability data necessary for the GS-US-216-110, GS-US-216-114, GS-US-216-115, and GS-US-216-130 trials for the cobicistat samples that were analyzed. The same cobicistat analytical method was used by both bioanalytical laboratories.

The darunavir method validation report (a method that is combined with ritonavir) from (b) (4) references 1064 days of long term darunavir stability data at -20°C in heparin anticoagulated plasma that was generated (b) (4) but the applicant did not submit the darunavir long term stability data to support the storage of the darunavir samples from the GS-US-216-115 trial. The darunavir method was transferred (b) (4) . However, the referenced darunavir long term stability data has been previously reviewed for other NDAs and was considered acceptable. Therefore, the long term stability data appeared reasonable to support the storage of the darunavir and ritonavir samples from the GS-US-216-115 trial. Subsequently, however, OSI issued a 483 observation to (b) (4) for not evaluating the long term stability of darunavir in combination with cobicistat (see section 1.3.1). At the time the Clinical Pharmacology review was finalized, the resolution of the 483 observation was still pending. The submitted darunavir long term stability data of 155 days at -20°C and -70°C in K_2EDTA anticoagulated plasma that was generated (b) (4) is not sufficient to cover the duration of long term cobicistat stability data necessary for the GS-US-216-130 trial. However, the darunavir exposure data from the trial is supportive and is not included in the U.S. proposed prescribing information for cobicistat.

The submitted atazanavir long term stability data of 721 days at -70°C in K_2EDTA anticoagulated plasma that was generated by (b) (4) supports the duration of long term atazanavir data necessary for the GS-US-216-110 and GS-US-216-114 trials for the atazanavir samples that were analyzed.

The ritonavir method validation report (a method that is combined with darunavir) from (b) (4) references 1064 days of long term ritonavir stability data at -20°C in heparin anticoagulated plasma that was generated (b) (4) but the applicant did not submit the ritonavir long term stability data to support the storage of the ritonavir samples from the GS-US-216-115 trial. The ritonavir method was transferred (b) (4) . However, the referenced ritonavir long term stability data has been previously reviewed for other NDAs and was considered acceptable. Therefore, the long term stability data can be used to support the storage of the ritonavir samples from the GS-US-216-115 trial. The submitted ritonavir long term stability data of 721 days at -70°C in K_2EDTA anticoagulated plasma that was generated by (b) (4) supports the duration of long term ritonavir data necessary for the GS-US-216-110 and GS-US-216-114 trials for the ritonavir samples that were analyzed.

2.6.2 Which metabolites have been selected for analysis and why?

With the exception of the metabolites that were identified in the mass balance trial (GS-216-111-see the Clinical Pharmacology review for NDA 203100), there were no metabolites that were routinely analyzed to further characterize the exposure or exposure-safety of cobicistat or the exposure, exposure-response, or exposure-safety of darunavir, atazanavir or ritonavir.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

For cobicistat, darunavir, atazanavir and ritonavir, total plasma concentrations were determined. Analysis of free or pharmacologically active concentrations is not expected to provide additional information to further characterize the exposure or exposure-safety of cobicistat or the exposure, exposure-response, or exposure-safety of darunavir, atazanavir or ritonavir.

2.6.4 What bioanalytical methods are used to assess concentrations?

Please see the individual trial reviews in section 4 for information regarding the bioanalysis of cobicistat, darunavir, atazanavir and ritonavir plasma samples in the clinical trials.

3 Labeling Recommendations

The labeling changes below as of March 2013 include the proposed language based on comments from the review team for relevant clinical pharmacology sections of the proposed cobicistat U.S. prescribing information that were sent to the applicant.

Section 4-Contraindications

(b) (4)

16 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

4 Appendices

4.1 Individual Trial Reviews

4.1.1 GS-US-216-110 trial

1. Title

A Phase 1 Multiple Dose Study to Evaluate the Relative Bioavailability and Pharmacokinetics of Atazanavir Coadministered with the Pharmacoenhancer GS-9350 versus Ritonavir

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at Charles River Clinical Services Northwest from December 12, 2008 (first subject screened) to March 10, 2009 (last subject observation).

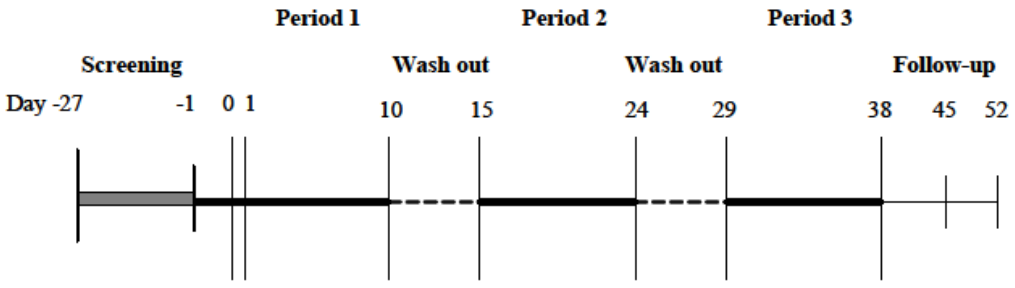
3. Objectives

The primary objective of the trial was to evaluate the pharmacokinetics and relative bioavailability of cobicistat coadministered with atazanavir to ritonavir coadministered with atazanavir.

4. Trial Design

GS-US-216-110 was an open label clinical trial that enrolled healthy subjects 18 to 45 years old. Information on the trial design is displayed in Figure 1.

Figure 1-GS-US-216-110 trial design



Subject Randomization	X			
Intensive PK		X	X	X
Digital ECG Telemetry	X	X	X	X

5. Excluded Medications, Restrictions or Exceptions

With the exception of certain medications (e.g. vitamins, acetaminophen, ibuprofen, hormonal contraceptives), prescription and nonprescription medications, including herbal products, were not permitted with 28 days of initiation of dosing for the trial or during the trial. Antacids were also prohibited during the trial.

6. Dosage and Administration

Subjects received the following three treatments once daily for 10 days with a 4 day washout between the periods in a crossover fashion: a) Treatment A: cobicistat 100 mg coadministered with atazanavir 300 mg, b) Treatment B: cobicistat 150 mg coadministered with atazanavir 300 mg, and c) Treatment C: ritonavir 100 mg coadministered with atazanavir 300 mg. Table 1 below displays the different treatment sequences. Medications were administered within 5 minutes of completing breakfast. The trial report does not specify if subjects were dosed at the same time (e.g. 30 minutes after initiation of the meal).

Table 1-GS-US-216-110 treatment sequences

Period	1	Washout	2	Washout	3
Study Days	1–10	11–14	15–24	25–28	29–38
Sequence 1	A		B		C
Sequence 2	A		C		B
Sequence 3	B		A		C
Sequence 4	B		C		A
Sequence 5	C		A		B
Sequence 6	C		B		A

7. Rationale for Doses Used in the Trial

The dosage regimen of ritonavir 100 mg coadministered with atazanavir 300 mg is consistent with the recommended darunavir/ritonavir dosage regimen in the atazanavir U.S. prescribing information. The different doses of cobicistat will provide information on an appropriate regimen to coadminister with atazanavir 300 mg once daily.

8. Drugs Used in the Trial

Information regarding the medications that were administered in the trial is displayed in Table 2. The atazanavir and ritonavir formulations are the U.S. commercially marketed formulations. The 100 mg cobicistat formulation is the Phase 1 formulation and the 150 mg cobicistat formulation is formulation 1.

Table 2-Information on the medications administered in the GS-US-216-110 trial

	Atazanavir[a]	Ritonavir[b]	Cobicistat	Cobicistat
Strength (mg)	300	100	100	150
Lot No.	8K3066A	641762E23	BB0703A1-A	BB0801A1
Expiration Date	10/2010	06/2010	01/2010	12/2010
Manufacturer/ Supplier	(b) (4)		Gilead Sciences, Inc. Foster City, CA USA	Gilead Sciences, Inc. Foster City, CA USA

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

Cobicistat, atazanavir, and ritonavir blood samples were obtained on days 10, 24 and 38 at predose and up to 24 hours postdose.

Bioanalysis

The method and bioanalysis of cobicistat, atazanavir, and ritonavir are acceptable. Atazanavir and ritonavir plasma samples were analyzed using a validated LC/MS/MS method in K_2EDTA anticoagulated plasma (b) (4). Cobicistat plasma samples were analyzed using a validated LC/MS/MS method in K_2EDTA anticoagulated plasma (b) (4). The blood samples for analysis of atazanavir and ritonavir appears to have been collected in tubes containing K_2EDTA as an anticoagulant. Cobicistat blood samples were collected in tubes containing K_2EDTA as an anticoagulant

For the GS-US-216-110 plasma samples that were analyzed for atazanavir, the lower limit of quantification for atazanavir was 10 ng/mL and the upper limit of quantification was 5000 ng/mL. There were no precision or accuracy issues identified for atazanavir based on the bioanalytical report. For the GS-US-216-110 trial, precision and accuracy were evaluated using plasma atazanavir QC samples at three concentration levels: 30 ng/mL, 800 ng/mL, and 4000 ng/mL. The corresponding atazanavir inter-run accuracy values were 4% for 30 ng/mL, 5.7% for 800 ng/mL, and 1.6% for 4000 ng/mL. The atazanavir inter-run precision values were 8% for 30 ng/mL, 6.9% for 800 ng/mL, and 4.9% for 4000 ng/mL. The lower limit of quantification for ritonavir was 5 ng/mL and the upper limit of quantification was 2500 ng/mL. There were no precision or accuracy issues identified for ritonavir based on the bioanalytical report. For the GS-US-216-110 trial, precision and accuracy were evaluated using plasma ritonavir QC samples at 15 ng/mL, 400 ng/mL, and 2000 ng/mL. The corresponding ritonavir inter-run accuracy values were 1.3% for 15 ng/mL, 2.1% for 400 ng/mL, and 1.8% for 2000 ng/mL. The ritonavir inter-run precision values were 7.2% for 15 ng/mL, 4.9% for 400 ng/mL, and 4.8% for 2000 ng/mL. The lower limit of quantification for cobicistat was 5 ng/mL and the upper limit of quantification was 1000 ng/mL. There were no precision or accuracy

issues identified for cobicistat based on the bioanalytical report. For the GS-US-216-110 trial, precision and accuracy were evaluated using plasma cobicistat QC samples at 15 ng/mL, 75 ng/mL, and 750 ng/mL with some runs also containing 750 ng/mL dilution QC samples. The corresponding cobicistat inter-run accuracy values were 7% for 15 ng/mL, 1.2% for 75 ng/mL, -1.3% for 750 ng/mL, and -6.1% for the 750 ng/mL dilution QC samples . The cobicistat inter-run precision values were 6.2% for 15 ng/mL, 5.4% for 75 ng/mL, 6.1% for 750 ng/mL, and 5.7% for the 750 ng/mL dilution QC samples.

Of the 113 samples selected for incurred sample reanalysis for cobicistat, all samples were within 20% using the percentage values of the repeat and original concentrations. However, it is not clear whether the total number of samples that were reanalyzed represents 5% to 10% of the total number of samples that were initially analyzed.

For the GS-US-216-110 trial, the applicant did not provide specific information on the duration and temperatures that cobicistat, atazanavir, and ritonavir plasma samples were stored at the trial sites, secondary storage faculties (if applicable) and the bioanalytical laboratories. However, the submitted cobicistat long term stability data of 121 days at -10°C to -30°C and 365 days at -60°C to -80°C in K_2EDTA anticoagulated plasma that was generated (b) (4) and the submitted atazanavir and ritonavir long term stability data of 721 days at -70°C in K_2EDTA anticoagulated plasma that was generated (b) (4) appears to covers the duration of long term stability data necessary for the GS-US-216-110 trial.

Pharmacokinetic Assessments

Noncompartmental analysis was performed for atazanavir, cobicistat, and ritonavir. For the noncompartmental analysis, atazanavir, cobicistat, and ritonavir plasma pharmacokinetic parameters were calculated, including t_{max}, C_{max}, C_{24h}, and $AUC_{(0\text{-}24h)}$.

Statistical Analysis

Statistical analyses were conducted evaluating the relative bioavailability for the following comparisons: a) cobicistat 100 mg coadministered with atazanavir 300 mg (Treatment A-test arm) compared to ritonavir 100 mg coadministered with atazanavir 300 mg (Treatment C-reference arm), and b) cobicistat 150 mg coadministered with atazanavir 300 mg (Treatment B-test arm) compared to ritonavir 100 mg coadministered with atazanavir 300 mg (Treatment C-reference arm),

Bioequivalence was demonstrated if the 90% confidence intervals were within 80% to 125% for atazanavir C_{max}, C_{24h}, and $AUC_{(0\text{-}24h)}$.

10. Results

10.1 Subject Demographics and Disposition

Table 3-GS-US-216-110 subject demographics

Characteristic	Safety (N = 42)	Atazanavir PK (N = 36)
Sex (n, %)		
Male	28 (66.7)	25 (69.4)
Female	14 (33.3)	11 (30.6)
Age (years)		
Mean (SD)	28 (8.2)	28 (8.2)
Median	25	26
Min, Max	18, 45	18, 45
Race (n, %)		
White	28 (66.7)	22 (61.1)
Black or African Heritage	10 (23.8)	10 (27.8)
Asian	3 (7.1)	3 (8.3)
Native American or Alaska Native	1 (2.4)	1 (2.8)
Ethnicity (n, %)		
Hispanic/Latino	2 (4.8)	2 (5.6)
Non-Hispanic/Latino	40 (95.2)	34 (94.4)
Height (cm)		
Mean (SD)	172 (9.9)	172 (9.9)
Median	173	174
Min, Max	150, 192	150, 192
Weight (kg)		
Mean (SD)	75.0 (12.74)	75.2 (11.83)
Median	73.9	75.1
Min, Max	45.6, 110.4	45.6, 100.5
Body Mass Index (kg/m^2)[a]		
Mean (SD)	25.3 (3.17)	25.4 (3.17)
Median	25.4	25.8
Min, Max	20.3, 30.6	20.3, 30.4
Estimated Creatinine Clearance (mL/min)[b]		
Mean (SD)	127.0 (27.61)	124.6 (21.42)
Median	128.0	127.2
Min, Max	69.6, 231.9	78.8, 162.8

a Body Mass Index = (weight [kg]/height $[cm]^2$) × 10,000
b Estimated creatinine clearance = (140 – age [y]) × weight [kg]/72 × serum creatinine [mg/dL] for male subjects equation × 0.85 for female subjects

10.2 Concomitant Medications

The concomitant medications that were administered in the trial are not expected to significantly alter the conclusions of the trial.

10.3 Pharmacokinetic and Statistical Analysis

Atazanavir

Table 4-Atazanavir pharmacokinetic parameters derived using noncompartmental analysis with atazanavir 300 mg combined with cobicistat 100 mg or 150 mg or ritonavir 100 mg once daily

Atazanavir PK Parameter	Atazanavir/GS-9350 300/100 mg (N = 35)	Atazanavir/GS-9350 300/150 mg (N = 34)	Atazanavir/r 300/100 mg (N = 36)
AUC_{tau} (ng•h/mL), Mean (% CV)	45,098.7 (30.9)	55,912.7 (28.2)	55,219.0 (27.6)
C_{max} (ng/mL), Mean (% CV)	4417.3 (21.4)	4884.2 (24.9)	5269.1 (23.6)
C_{tau} (ng/mL), Mean (% CV)	837.3 (58.8)	1325.0 (42.7)	1339.6 (40.8)
$T_{½}$ (h), Median (Q1, Q3)	9.73 (7.08, 12.94)	16.68 (11.65, 20.44)	15.74 (13.64, 21.11)
T_{max} (h), Median (Q1, Q3)	3.50 (3.00, 4.00)	3.00 (2.50, 3.50)	3.00 (2.50, 3.50)

CV = coefficient of variation, PK = pharmacokinetic, Q1 = first quartile, Q3 = third quartile

Note: Subject 2489-1010 had an evaluable atazanavir PK profile only for the reference treatment. Subjects 2489-1022, 2489-1023, and 2489-1034 had evaluable profiles only for the test treatments. Subjects 2489-1027 and 2489-1038 had no evaluable PK profiles. These six subjects were excluded from the atazanavir PK analysis set.

Table 5-Statistical analyses for atazanavir

Atazanavir PK Parameter	Geometric Least Squares Means		Geometric Least Squares Mean Ratio (%)	90% Confidence Interval
	Test Treatment	Reference Treatment		
Atazanavir/GS-9350 300/100 mg (test) versus Atazanavir/r 300/100 mg (reference)				
n	35	36		
AUC_{tau} (ng•h/mL)	42,835.83	52,772.91	81.17	76.02, 86.67
C_{max} (ng/mL)	4287.88	5094.52	84.17	77.70, 91.17
C_{tau} (ng/mL)	700.61	1220.18	57.42	51.93, 63.49
Atazanavir/GS-9350 300/150 mg (test) versus Atazanavir/r 300/100 mg (reference)				
n	34	36		
AUC_{tau} (ng•h/mL)	53,272.76	52,772.91	100.95	94.47, 107.87
C_{max} (ng/mL)	4701.26	5094.52	92.28	85.13, 100.03
C_{tau} (ng/mL)	1190.42	1220.18	97.56	88.14, 107.99

Cobicistat

Table 6-Cobicistat pharmacokinetic parameters derived using noncompartmental analysis with atazanavir 300 mg combined with cobicistat 100 mg or 150 mg or ritonavir 100 mg once daily

GS-9350 PK Parameter	Atazanavir/GS-9350 300/100 mg (N = 38)	Atazanavir/GS-9350 300/150 mg (N = 35)
AUC_{tau} (ng•h/mL), Mean (% CV)	5962.3 (23.3)	11,250.9 (24.4)
C_{max} (ng/mL), Mean (% CV)	849.1 (18.1)	1383.2 (19.3)
C_{tau} (ng/mL), Mean (% CV)	21.7 (95.9)	61.6 (93.5)
$T_{½}$ (h), Median (Q1, Q3)	4.07 (3.54, 4.63)	4.43 (3.52, 4.93)
T_{max} (h), Median (Q1, Q3)	3.00 (2.50, 3.50)	3.00 (2.50, 3.50)

CV = coefficient of variation, PK = pharmacokinetic, Q1 = first quartile, Q3 = third quartile

Note: Subjects 2489-1010, 2489-1027, and 2489-1038 did not have evaluable GS-9350 PK profiles and were excluded from the GS-9350 PK analysis set.

Ritonavir

Table 7-Ritonavir pharmacokinetic parameters derived using noncompartmental analysis with atazanavir 300 mg combined with cobicistat 100 mg or 150 mg or ritonavir 100 mg once daily

Ritonavir PK Parameter	Atazanavir/r 300/100 mg (N = 37)
AUC_{tau} (ng•h/mL), Mean (% CV)	11,919.0 (32.6)
C_{max} (ng/mL), Mean (% CV)	2052.9 (28.5)
C_{tau} (ng/mL), Mean (% CV)	74.4 (58.8)
$T_{½}$ (h), Median (Q1, Q3)	5.30 (4.44, 6.09)
T_{max} (h), Median (Q1, Q3)	5.00 (4.50, 5.00)

CV = coefficient of variation, PK = pharmacokinetic

Note: Subjects 2489-1022, 2489-1023, 2489-1027, 2489-1034, and 2489-1038 did not have evaluable ritonavir PK profiles and were excluded from the ritonavir PK analysis set.

10.5 Safety Analysis

All adverse events were mild to moderate in severity and the most common adverse events were ocular icterus, headache, contact dermatitis, and jaundice.

11. Discussion and Conclusions

Based on the results from the GS-US-216-110 trial, the following conclusions can be made.

- Bioequivalence was not achieved for atazanavir C_{max}, C_{24h}, and $AUC_{(0-24h)}$ when comparing cobicistat 100 mg coadministered with atazanavir 300 mg (Treatment A-test arm) to ritonavir 100 mg coadministered with atazanavir 300 mg (Treatment C-reference arm) once daily.
- Bioequivalence was achieved for atazanavir C_{max}, C_{24h}, and $AUC_{(0-24h)}$ when comparing cobicistat 150 mg coadministered with atazanavir 300 mg (Treatment B-test arm) to ritonavir 100 mg coadministered with atazanavir 300 mg (Treatment C-reference arm) once daily.

Based on the results, cobicistat 150 mg coadministered with atazanavir 300 mg once daily is the most appropriate dosage regimen for achieving atazanavir exposures that are comparable to those achieved when coadministered with ritonavir 100 mg once daily.

4.1.2 GS-US-216-115 trial

1. Title

A Phase 1 Multiple Dose Study to Evaluate the Relative Bioavailability and Pharmacokinetics of Darunavir when Coadministered with the Pharmacoenhancer GS-9350 versus Ritonavir

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at Charles River Clinical Services Northwest from June 5, 2009 (first subject screened) to July 30, 2009 (last subject observation).

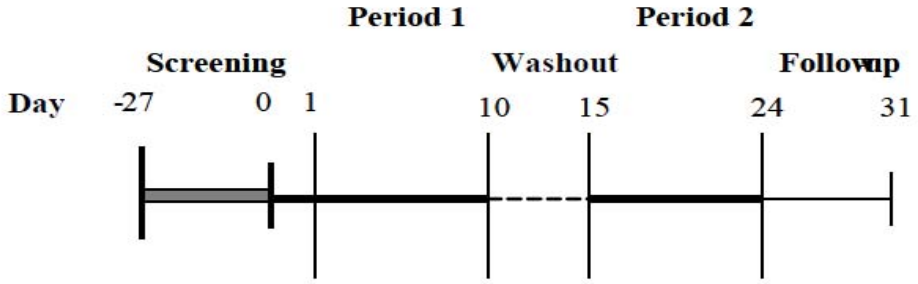
3. Objectives

The primary objective of the trial was to evaluate the pharmacokinetics and relative bioavailability of cobicistat coadministered with darunavir to ritonavir coadministered with darunavir.

4. Trial Design

GS-US-216-110 was an open label clinical trial that enrolled healthy subjects 18 to 45 years old. Information on the trial design is displayed in Figure 1.

Figure 1-GS-US-216-115 trial design



5. Excluded Medications, Restrictions or Exceptions

With the exception of certain medications (e.g. vitamins, acetaminophen, ibuprofen, hormonal contraceptives), prescription and nonprescription medications, including herbal products, were not permitted with 28 days of initiation of dosing for the trial or during the trial. Antacids were also prohibited during the trial.

6. Dosage and Administration

Subjects received the following two treatments once daily with a 4 day washout between the periods in a crossover fashion: a) Treatment A: cobicistat 150 mg coadministered with darunavir 800 mg, and b) Treatment B: ritonavir 100 mg coadministered with darunavir 800 mg. Table 1 below displays the different treatment sequences. Medications were administered within 5 minutes of completing breakfast. The trial report does not specify if subjects were dosed at the same time (e.g. 30 minutes after initiation of the meal).

Table 1-GS-US-216-115 treatment sequences

Period	1	Washout	2
Study Days	1–10	11–14	15–24
Sequence 1	A		B
Sequence 2	B		A

7. Rationale for Doses Used in the Trial

The dosage regimen of ritonavir 100 mg coadministered with darunavir 800 mg is consistent with the recommended darunavir/ritonavir dosage regimen in the atazanavir U.S. prescribing information. The cobicistat dose of 150 mg coadministered with darunavir 800 mg once daily is consistent with the cobicistat dose that was selected to boost atazanavir (b) (4).

8. Drugs Used in the Trial

Information regarding the medications that were administered in the trial is displayed in Table 2. The darunavir and ritonavir formulations are the U.S. commercially marketed formulations. The 150 mg cobicistat formulation is formulation 1.

Table 2-Information on the medications administered in the GS-US-216-115 trial

	GS-9350	RTV [a]	DRV [a]
Strength (mg)	150 mg	100 mg	400 mg
Pharmaceutical form	Tablet	Capsule	Tablet
Lot No.	BB-0902A1	735482E21	9DG597
Batch size	(b) (4)		
Expiration Date	30 April 2011	24 March 2011	31 March 2011
Manufacturer/Supplier	(b) (4)		
Country of purchase			
Site of Release in Europe			

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

Cobicistat, darunavir, and ritonavir blood samples were obtained on days 10 and 24 at predose and up to 24 hours postdose.

Bioanalysis

The method and bioanalysis of cobicistat, darunavir, and ritonavir are acceptable. Darunavir and ritonavir plasma samples were analyzed using a validated LC/MS/MS method in heparin anticoagulated plasma (b) (4). Cobicistat plasma samples were analyzed using a validated LC/MS/MS method in K_2EDTA anticoagulated plasma (b) (4). The blood samples for analysis of darunavir and ritonavir appears to have been collected in tubes containing heparin as an anticoagulant. The blood samples for analysis of cobicistat were collected in tubes containing K_2EDTA as an anticoagulant.

For the GS-US-216-115 plasma samples that were analyzed for darunavir, the lower limit of quantification for darunavir was 5 ng/mL and the upper limit of quantification was 10000 ng/mL. There were no precision or accuracy issues identified for darunavir based on the bioanalytical report. For the GS-US-216-115 trial, precision and accuracy were evaluated using plasma darunavir QC samples at three or more concentration levels: 13.6 ng/mL, 240 ng/mL, 1920 ng/mL (in some runs) and 7680 ng/mL. The corresponding darunavir inter-run accuracy values were -0.7% for 13.6 ng/mL, 0.4% for 240 ng/mL, 0.5% for 1920 ng/mL, and -2.9% for 7680 ng/mL. The darunavir inter-run precision values were 7.3% for 13.6 ng/mL, 5.5% for 240 ng/mL, 4.6% for 1920 ng/mL, and 5.9% for 7680 ng/mL. The lower limit of quantification for ritonavir was 5 ng/mL and the upper limit of quantification was 10000 ng/mL. There were no precision or accuracy issues identified for ritonavir based on the bioanalytical report. For the GS-US-216-115 trial, precision and accuracy were evaluated using plasma ritonavir QC samples at 13.7 ng/mL, 241 ng/mL, 1930 ng/mL (in some runs) and 7710 ng/mL. The corresponding ritonavir inter-run accuracy values were 0.7% for 13.7ng/mL, 0% for 241 ng/mL, -1% for 1930 ng/mL and -1.6% for 7710 ng/mL. The ritonavir inter-run precision values were 6.4% for 13.7 ng/mL, 5% for 241 ng/mL, 2.5% for 1930 ng/mL and 5.7% for 7710 ng/mL. The lower limit of quantification for cobicistat was 5 ng/mL and the upper limit of quantification was 1000 ng/mL. There were no precision or accuracy issues identified for cobicistat based on the bioanalytical report. For the GS-US-216-115 trial, precision and accuracy were evaluated using plasma cobicistat QC samples at 15 ng/mL, 75 ng/mL, 750 ng/mL , and 5000 ng/mL dilution QC samples. The corresponding cobicistat inter-run accuracy values were -6% for 15 ng/mL, 0% for 75 ng/mL, -6% for 750 ng/mL, and -3% for the 5000 ng/mL dilution QC samples . The cobicistat inter-run precision values were 4.1% for 15 ng/mL, 3% for 75 ng/mL, 2.8% for 750 ng/mL, and 4.4% for the 5000 ng/mL dilution QC samples.

For the GS-US-216-115 trial, the applicant did not provide specific information on the duration and temperatures that cobicistat, darunavir, and ritonavir plasma samples were stored at the trial sites, secondary storage faculties (if applicable) and the bioanalytical laboratories. However, the submitted cobicistat long term stability data of 121 days at -10°C to -30°C and 365 days at -60°C to -80°C in K_2EDTA anticoagulated plasma that was generated (b) (4) appears to covers the duration of long term stability data necessary for the GS-US-216-115 trial. The darunavir and ritonavir method validation report (b) (4) references 1064 days of long term darunavir stability data at -20°C in heparin anticoagulated plasma that was generated by (b) (4) but the applicant did not submit the darunavir and ritonavir long term stability data to support the storage of the darunavir and ritonavir samples from the GS-US-216-115 trial. The darunavir and ritonavir method was transferred (b) (4) . However, the referenced darunavir long term stability data has been previously reviewed for other NDAs and was considered acceptable. Therefore, the long term stability data appeared reasonable to support the storage of the darunavir and ritonavir samples from the GS-US-216-115 trial. Subsequently, however, OSI issued a 483 observation (b) (4)

At the time the Clinical Pharmacology review was finalized, the resolution of the 483 observation was still pending.

(Reviewer note: Based on the information in the applicant's Summary of Biopharmaceutic Studies and Associated Analytical Methods, darunavir subject samples were stored at -20°C. However, the 483 observations (b) (4)

The FDA Office of Scientific Investigations (OSI) was requested to inspect the clinical trial sites and the relevant bioanalytical laboratories for the GS-US-216-115 and GS-US-216-116 trials. The inspection findings for the clinical trial site for the GS-US-216-115 trial are pending at the time the Clinical Pharmacology review was finalized and for the bioanalytical laboratory (b) (4) that analyzed darunavir plasma samples the following 483 observations were issued:

a) The long term stability of darunavir in combination with cobicistat was not evaluated.

(b) (4)

OSI's recommendations for addressing the 483 observations are pending at the time the Clinical Pharmacology review was finalized.

Pharmacokinetic Assessments

Noncompartmental analysis was performed for darunavir, cobicistat, and ritonavir. For the noncompartmental analysis, darunavir, cobicistat, and ritonavir plasma pharmacokinetic parameters were calculated, including t_{max}, C_{max}, C_{24h}, and $AUC_{(0-24h)}$.

Statistical Analysis

Statistical analyses were conducted evaluating the relative bioavailability for the following comparison: cobicistat 150 mg coadministered with darunavir 800 mg (Treatment A-test arm) compared to ritonavir 100 mg coadministered darunavir 800 mg (Treatment B-reference arm),

Bioequivalence was demonstrated if the 90% confidence intervals were within 80% to 125% for darunavir C_{max}, C_{24h}, and $AUC_{(0-24h)}$.

10. Results

10.1 Subject Demographics and Disposition

Table 3-GS-US-216-115 subject demographics

Characteristic	Safety (N=33)
Sex	
Male	31 (93.9%)
Female	2 (6.1%)
Age (Years)	
Mean (SD)	27 (7.0)
Median	24
Min, Max	20, 45
Race	
White	18 (54.5%)
Black or African Heritage	11 (33.3%)
Asian	2 (6.1%)
American Indian or Alaska Native	1 (3.0%)
Other	1 (3.0%)
Ethnicity	
Non-Hispanic/Latino	32 (97.0%)
Hispanic/Latino	1 (3.0%)
Weight (kg)	
Mean (SD)	74.9 (10.80)
Min, Max	52.2, 90.7
Body Mass Index (kg/m^2)	
Mean (SD)	24.6 (2.88)
Min, Max	19.2, 29.3
Creatinine Clearance- Cockcroft-Gault (mL/min)	
Mean (SD)	124.4 (20.25)
Median	126.2
Min, Max	79.5, 170.4

Note: Body mass index (BMI) = Weight (kg)/Height (m^2)

Note: Creatinine clearance (mL/min) by Cockcroft-Gault:
For male subjects: [(140 – Age [years]) × body weight (kg)] / (72 × serum creatinine concentration [mg/dL])
For female subjects: [(140 – Age [years]) × body weight (kg) x 0.85] / (72 × serum creatinine concentration [mg/dL])

Note: Due to early discontinuation, Subject 1026 had no DRV PK concentration data and Subject 1001 had DRV PK concentration data only for Treatment A (DRV 800 mg + GS-9350 150 mg), thus the 2 subjects were excluded from the DRV PK analysis set.

10.2 Concomitant Medications

The concomitant medications that were administered in the trial are not expected to significantly alter the conclusions of the trial.

10.3 Pharmacokinetic and Statistical Analysis

Darunavir

Figure 2-Pharmacokiectic profiles for darunavir 800 mg combined with cobicistat 150 mg or ritonavir 100 mg once daily

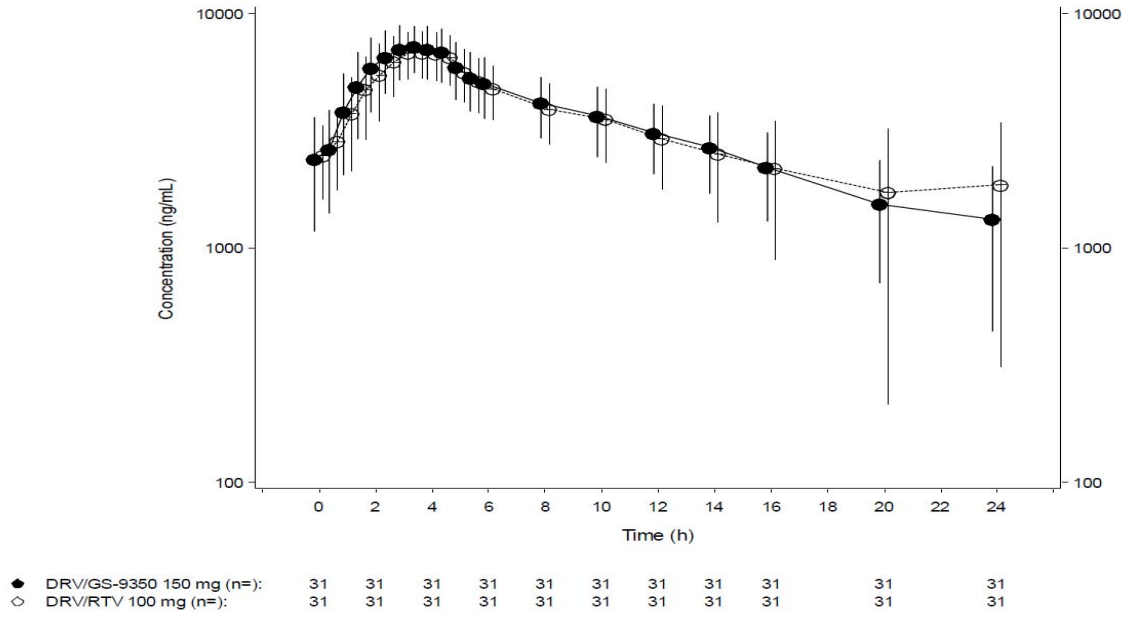


Table 4-Darunavir pharmacokinetic parameters derived using noncompartmental analysis with darunavir 800 mg combined with cobicistat 150 mg or ritonavir 100 mg once daily

DRV Plasma PK Parameters	Treatment A DRV+GS-9350 (N = 31)	Treatment B DRV+RTV (N = 31)
C_{max} (ng/mL) Mean (%CV)	7737.1 (21.8)	7464.2 (20.3)
AUC_{tau} (ng·h/mL) Mean (%CV)	81,084.2 (31.0)	79,987.0 (34.0)
C_{tau} (ng/mL) Mean (%CV)	1332.7 (66.8)	1866.7 (83.3)
C_{last} (ng/mL) Mean (%CV)	1332.7 (66.8)	1866.7 (83.3)
C_{0h} (ng/mL) Mean (%CV)	2395.5 (50.7)	2483.8 (34.3)
T_{max} (h) Median (Q1, Q3)	3.00 (2.72, 3.50)	3.00 (3.00, 4.00)
$T_{½}$ (h) Median (Q1, Q3)	8.29 (5.74, 10.91)	13.79 (7.97, 16.34)[a]
T_{last} (h) Median (Q1, Q3)	24.00 (24.00, 24.00)	24.00 (24.00, 24.00)

Treatment A: DRV (2 × 400 mg tablets) + GS-9350 (1 x 150 mg tablet); Treatment B: DRV (2 × 400 mg tablets) + RTV (1 × 100 mg capsule)
a n=30

Table 5-Statistical analyses for darunavir

DRV Plasma PK Parameters	Geometric Least-Squares Means		Geometric Least-Squares Means Ratio (%) of Test/Reference (Treatment A/Treatment B) (90% CI)
	Test Treatment Treatment A DRV 800 mg + GS-9350 150 mg (N=31)	Reference Treatment Treatment B DRV 800 mg + RTV 100 mg (N=31)	
AUC_{tau} (ng·h/mL)	77,390.28	76,036.36	101.78 (97.40, 106.36)
C_{max} (ng/mL)	7538.12	7292.95	103.36 (100.34, 106.48)
C_{tau} (ng/mL)	1056.59	1521.83	69.43 (59.02, 81.68)
C_{0h} (ng/mL)	2089.67	2337.65	89.39 (80.36, 99.44)

DRV, darunavir; CI, confidence interval; PK, pharmacokinetic

Treatment A: DRV (2 × 400 mg tablets) + GS-9350 (1 × 150 mg tablet); Treatment B: DRV (2 × 400 mg tablets) + RTV (1 × 100 mg capsule)
Note: Ratios were estimated as the geometric LSmeans ratio of Test vs. Reference.

Cobicistat

Table 6-Cobicistat pharmacokinetic parameters derived using noncompartmental analysis with darunavir 800 mg combined with cobicistat 150 mg or ritonavir 100 mg once daily

GS-9350 Plasma PK Parameters	Treatment A DRV+GS-9350 (N = 32)
C_{max} (ng/mL) Mean (%CV)	1375.7 (19.5)
AUC_{tau} (ng·h/mL) Mean (%CV)	10,370.0 (20.7)
C_{tau} (ng/mL) Mean (%CV)	27.0 (69.5)
C_{last} (ng/mL) Mean (%CV)	27.0 (69.5)
T_{max} (h) Median (Q1, Q3)	3.50 (3.00, 4.00)
$T_{½}$ (h) Median (Q1, Q3)	3.28 (3.09, 3.69)
T_{last} (h) Median (Q1, Q3)	24.00 (24.00, 24.00)

Treatment A: DRV (2 × 400 mg tablets) + GS-9350 (1 × 150 mg tablet)

Ritonavir

Table 7-Ritonavir pharmacokinetic parameters derived using noncompartmental analysis with darunavir 800 mg combined with cobicistat 150 mg or ritonavir 100 mg once daily

RTV Plasma PK Parameters	Treatment B DRV+RTV (N = 31)
C_{max} (ng/mL) Mean (%CV)	1159.2 (38.6)
AUC_{tau} (ng·h/mL) Mean (%CV)	6693.7 (33.1)
C_{tau} (ng/mL) Mean (%CV)	60.1 (67.4)
C_{last} (ng/mL) Mean (%CV)	60.1 (67.4)
T_{max} (h) Median (Q1, Q3)	4.08 (4.00, 4.50)
$T_{½}$ (h) Median (Q1, Q3)	6.63 (5.65, 8.19)
T_{last} (h) Median (Q1, Q3)	24.00 (24.00, 24.00)

Treatment B: DRV (2 × 400 mg tablets) + RTV (1 × 100 mg capsule)

10.5 Safety Analysis

There were no grade 3 or 4 adverse events that were reported for the trial. Table 8 lists treatment emergent adverse events that were reported in a minimum of 2 subjects for a treatment.

Table 8-Treatment emergent adverse events that were reported in a minimum of 2 subjects for a treatment

Number (%) of Subjects Experiencing Adverse Events by System Organ Class and Preferred Term	Treatment A DRV 800 mg + GS-9350 150 mg (N=33)	Treatment B DRV 800 mg + RTV 100 mg (N=31)
Subjects Experiencing Any Treatment-Emergent Adverse Event	11 (33.3%)	13 (41.9%)
Nervous System Disorders		
Headache	2 (6.1%)	4 (12.9%)
Skin and Subcutaneous Tissue Disorders		
Rash Maculo-Papular	2 (6.1%)	2 (6.5%)

Note: Adverse events were mapped according to MedDRA 12.0.
Note: Multiple AEs were counted once only per subject per treatment for each system organ class and AE preferred term, respectively.
Note: System Organ Class (SOC) was presented alphabetically and preferred terms were presented by decreasing order based on the total frequencies across treatments.
Note: Treatment-emergent AEs with a treatment were defined as: a) began on or after the first dose date of the treatment up to the first dose date of the following treatment if applicable or up to the last dose date of the same treatment plus 30 days, or b) had no recorded start date, but excluding events with an end date being earlier than the first dose date of the treatment.

11. Discussion and Conclusions

Based on the results from the GS-US-216-110 trial, the following conclusions can be made.

- Bioequivalence was not achieved for darunavir C_{24h}, when comparing cobicistat 150 mg coadministered with darunavir 800 mg (Treatment A-test arm) to ritonavir 100 mg coadministered with darunavir 800 mg (Treatment B-reference arm) once daily.
- Bioequivalence was achieved for darunavir C_{max} and $AUC_{(0-24h)}$ when comparing cobicistat 150 mg coadministered with darunavir 800 mg (Treatment A-test arm) to ritonavir 100 mg coadministered with darunavir 800 mg (Treatment B-reference arm) once daily.

Based on the results, the 90% confidence intervals for darunavir $AUC_{(0-24h)}$, C_{max}, and C_{0h} were within 80% to 125% but the darunavir C_{24h} was not within 80% to 125%. The darunavir C_{24h} geometric least squares mean was decreased by 31% and the 90% confidence interval was not within 80%-125% (see Table 5). The cause of the difference in the C_{24h} value was attributed to an increase in darunavir concentrations between 20 hours and 24 hours that occurred most frequently when ritonavir was coadministered with darunavir on Day 24.

Based on the available once daily darunavir exposure-response data when coadministered with ritonavir from the TMC114-C211 and TMC114-C229 trials that were conducted by (b) (4) (see section 1.3.2), a clinically relevant exposure-response relationship was not identified (e.g. increasing or decreasing virologic response was not observed either with increasing or decreasing darunavir $AUC_{(0\text{-}24h)}$ or C_{0h} values. A similar conclusion was observed based on the inhibitory quotient (IQ) analysis [the IQ is the ratio of C_{0h} (exposure) at steady state and IC_{50} (a measurement of the ability of darunavir to inhibit HIV-1 virus)]-see Figure 1. The available darunavir exposure-response information with once daily dosing does not provide information to help interpret the potential implications of a 31% decrease in the C_{24h} value. In reviewing the available drug-drug interaction data for darunavir, in the darunavir U.S. prescribing information, decreases in the darunavir $AUC_{(0\text{-}24h)}$, C_{max}, and C_{min} values of 13%, 15%, and 31% with concomitant use of efavirenz did not require a dosage adjustment for darunavir. Based on the available information, the 31% decrease in the C_{24h} value that was observed with cobicistat coadministered with darunavir once daily is not anticipated to be clinically relevant.

4.1.3 GS-US-216-130 trial

Reviewer note: A brief summary of GS-US-216-130 is provided below. Only the pharmacokinetic data for darunavir and cobicistat from this trial were reviewed. The efficacy and safety data were not evaluated as part of the cobicistat NDA review.

1. Title

A Phase 3b, Open-Label, Single Arm Study to Evaluate the Safety and Efficacy of Cobicistat-boosted Darunavir Plus Two Fully Active Nucleoside Reverse Transcriptase Inhibitors in HIV-1 Infected, Antiretroviral Treatment-Naïve and -Experienced Adults with No Darunavir Resistance associated Mutations

2. Trial Information

GS-US-216-130 was an open label, single arm, multi-site, 48 week trial with an optional rollover component. The trial evaluated safety and tolerability of darunavir coadminstered with cobicistat (800 mg/150 mg once daily with food) in combination with 2 fully active NRTIs and enrolled treatment naïve and treatment experienced subjects with no darunavir resistance associated substitutions. The HIV-1 RNA levels were ≥ 1000 copies/mL at screening for the enrolled subjects. Subjects with the M184V/I mutation could also receive a third NRTI that was not fully active.

For the week 24 trial report, darunavir as well as the NRTIs were the U.S. commercially marketed formulations. The proposed U.S. commercial formulation of cobicistat (Formulation 3) was administered in the trial.

For pharmacokinetic sampling, single blood draws were conducted during weeks 2 to 48 visits with intensive PK sampling between the week 2 and week 8 visits in a subset of subjects.

3. Bioanalysis

The method and bioanalysis of cobicistat, and darunavir, are acceptable. Darunavir \plasma samples were analyzed using a validated LC/MS/MS method in K_2EDTA anticoagulated plasma that was generated by (b) (4). Cobicistat plasma samples were analyzed using a validated LC/MS/MS method in K_2EDTA anticoagulated plasma by (b) (4). The blood samples for analysis of darunavir cobicistat were collected in tubes containing K_2EDTA as an anticoagulant.

For the GS-US-216-130 plasma samples that were analyzed for darunavir, the lower limit of quantification for darunavir was 5 ng/mL and the upper limit of quantification was 10000 ng/mL. There were no precision or accuracy issues identified for darunavir based on the bioanalytical report. For the GS-US-216-130 trial, precision and accuracy were evaluated using plasma darunavir QC samples at three concentration levels: 15 ng/mL, 500 ng/mL, and 8000 ng/mL. The corresponding darunavir inter-run accuracy values

were 3.3% for 15 ng/mL, 1.4% for 500 ng/mL, 0, and 0.8% for 8000 ng/mL. The darunavir inter-run precision values were 5.8% for 15 ng/mL, 4.3% for 500 ng/mL, and 3.8% for 8000 ng/mL. The lower limit of quantification for cobicistat was 5 ng/mL and the upper limit of quantification was 2500 ng/mL. There were no precision or accuracy issues identified for cobicistat based on the bioanalytical report. For the GS-US-216-130 trial, precision and accuracy were evaluated using plasma cobicistat QC samples at 15 ng/mL, 200 ng/mL, a 2000 ng/mL dilution QC (in some runs) and a 2000 ng/mL QC is some runs. The corresponding cobicistat inter-run accuracy values were -0.2% for 15 ng/mL, 3% for 200 ng/mL, 0.6% for the 2000 ng/mL dilution QC and 3% for 2000 ng/mL. The cobicistat inter-run precision values were 6.2% for 15 ng/mL, 5.3% for 200 ng/mL, 1.1% for the 2000 ng/mL dilution QC and 5% for 2000 ng/mL.

Of the 171 samples selected for incurred sample reanalysis for darunavir, two samples were not within 20% using the percentage values of the repeat and original concentrations. However, it is not clear whether the total number of samples that were reanalyzed represents 5% to 10% of the total number of samples that were initially analyzed.

Of the 80 samples selected for incurred sample reanalysis for cobicistat, no samples were not within 20% using the percentage values of the repeat and original concentrations. However, it is not clear whether the total number of samples that were reanalyzed represents 5% to 10% of the total number of samples that were initially analyzed.

The submitted cobicistat long term stability data of 121 days at -10°C to -30°C and 365 days at -60°C to -80°C in K_2EDTA anticoagulated plasma that was generated (b) (4) and referenced by (b) (4) supports the duration of long term cobicistat stability data necessary for the GS-US-216-130 trial for the cobicistat samples that were analyzed. The submitted darunavir long term stability data of 155 days at -20°C and -70°C in K_2EDTA anticoagulated plasma that was generated by (b) (4) is not sufficient to cover the duration of long term cobicistat stability data necessary for the GS-US-216-130 trial. However, the darunavir exposure data from the trial is supportive and is not included in the proposed prescribing information for cobicistat.

4. Results

Darunavir

Table 1-Darunavir pharmacokinetic parameters derived using noncompartmental analysis with darunavir 800 mg combined with cobicistat 150 mg once daily

DRV PK Parameter[a]	DRV+COBI (N = 59)
AUC_{tau} (ng·h/mL), mean (%CV)	81,645.9 (32.2)
C_{max} (ng/mL), mean (%CV)	7663.2 (25.1)
C_{tau} (ng/mL), mean (%CV)	1310.7 (74.0)
C_{0h} (ng/mL), mean (%CV)	1559.8 (85.1)
T_{max} (h), median (Q1, Q3)	3.50 (2.49, 4.29)
$t_{1/2}$ (h), median (Q1, Q3)	7.24 (5.35, 11.54)

a For C_{max}, n = 60; for T_{max}, n = 60; for C_{tau}, n = 59; for C_{0h}, n = 60; for AUC_{tau}, n = 59, and for $t_{1/2}$, n = 55

Reviewer note: the population PK data for darunavir from the GS-US-216-130 trial is displayed in section 1.3.2-Table 4.

Cobicistat

Table 2-Cobicistat pharmacokinetic parameters derived using noncompartmental analysis with darunavir 800 mg combined with cobicistat 150 mg once daily

COBI PK Parameter[a]	DRV+COBI (N = 59)
AUC_{tau} (ng·h/mL), mean (%CV)	7596.3 (48.1)
C_{max} (ng/mL), mean (%CV)	991.4 (33.4)
C_{tau} (ng/mL), mean (%CV)	32.8 (289.4)
T_{max} (h), median (Q1, Q3)	3.50 (2.01, 4.50)
$t_{1/2}$ (h), median (Q1, Q3)	3.25 (2.91, 3.81)

a For C_{max}, n = 60; for T_{max}, n = 60; for C_{tau}, n = 59; for AUC_{tau}, n = 59, and for $t_{1/2}$, n = 59

5. Discussion and Conclusions

The darunavir C_{max}, C_{24h}, and $AUC_{(0-24h)}$ appeared to be similar to the values observed with the GS-US-216-115 trial. Cobicistat exposures also appear to be lower with the proposed U.S commercial formulation compared to the cobicistat exposure data from the GS-US-216-116 trial that is displayed in section 2.5.2-Table 1 but the effect on darunavir exposures appear to be similar.

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Are the population PK parameters reported in the label (race, gender, geriatric, hepatitis B/C virus co-infections) supported by the population PK analysis submitted by the applicant?

The pharmacokinetic parameters for cobicistat (Cobi) 150 mg q.d. in adults support the applicant's claim of no clinically significant difference in exposure with regards to race and gender. Cobi AUC, C_{max}, and C_{0h} means (% confidence value) were in good agreement with the applicant's results. Shown below are the applicant's results for race (Table 1) and gender (Table 2).

Table 1: Population Pharmacokinetic Estimates of cobi 150 mg q.d. (Comparison Between Races)

Parameter	Other (n=9)	Black (n=69)	White (n=213)
AUC_τ (ng·h/mL)	11,300 (42)	11,600 (36)	12,400 (41)
C_{max} (ng/mL)	1,310 (36)	1,370 (24)	1,470 (29)
C_{0h} (ng/mL)	55 (101)	59 (137)	69 (143)

Table 2: Population Pharmacokinetic Estimates of cobi 150 mg q.d. (Comparison Between Gender)

Parameter	Female (n=98)	Male (n=193)
AUC_τ (ng·h/mL)	14,100 (37)	11,200 (40)
C_{max} (ng/mL)	1,670 (24)	1,320 (26)
C_{0h} (ng/mL)	76 (123)	62 (152)

There was a 26% difference in AUC_τ between females and males based on the population PK analysis, primarily driven by a body weight effect on clearance (median body weight for females and males was 65 kg and 78 kg, respectively).

The applicant's population PK analysis had data from 16 elderly subjects (16 subjects 65 years of age or older; 4 subjects 72 years of age or older). Fourteen of these elderly subjects were from the Phase I open-label renal impairment study evaluating the pharmacokinetics of elvitegravir boosted with Cobi in subjects with severe renal impairment. An age effect was not identified during model development; however a binned analysis demonstrated the subjects with age ≥65 age had higher Cobi exposures

than subjects with age <65 years (Table 3) (56%, 30%, and 160% higher AUC, C_{max}, and C_{min}, respectively). This analysis is similar to the applicant's binned analysis based on an age cut point of 55 years of age (Table 4).

Table 3: Population Pharmacokinetic Estimates of Cobi 150 mg q.d. (Comparison Between Age<65 years and Age≥65 years)

Parameter	Age <65 years (n=275)	Age ≥65 years (n=16)
AUC_{τ} (ng·h/mL)	11,380 (39)	17,730 (37)
C_{max} (ng/mL)	1,447 (26)	1,888 (35)
C_{0h} (ng/mL)	53 (115)	138 (151)

Table 4: Population Pharmacokinetic Estimates of Cobi 150 mg q.d. (Comparison Between Age<55 years and Age≥55 years)

Parameter	Age <55 years (n=254)	Age ≥55 years (n=37)
AUC_{τ} (ng·h/mL)	11,400 (33)	18,000 (43)
C_{max} (ng/mL)	1,390 (24)	1,800 (34)
C_{0h} (ng/mL)	51 (118)	171 (105)

Source: Pooled data following once daily administration of the COBI 150 mg single agent tablet from a total of 9 studies, including 7 studies in healthy subjects (GS-US-216-0115, GS-US-216-0116, GS-US-216-0120, GS-US-216-0121, GS-US-216-0122, GS-US-216-0123, and GS-US-216-0124) and 2 studies in HIV-1 infected subjects (GS-US-216-0105 and GS-US-216-0114).

Similarly, while weight was not identified as a significant covariate on clearance during the applicant's model development, the reviewer identified a significant body weight effect on cobi clearance. The estimated relationship predicts a difference in of 25% in cobi AUC between the 1st and 4th weight quartile (median body weight of the 1st and 4th quartile was 61 and 90 kg, respectively). This observation does not necessitate any Cobi dose alterations for the current submission but should be considered by the applicant during pediatric dose selection.

1.1.2 Are the atazanavir exposures when boosted with cobi similar to the respective exposures when boosted with ritonavir?

Atazanavir boosted with cobi was similar to atazanavir boosted with ritonavir based on the results of GS-US-216-0110 (Phase I bioavailability study, see Clinical Pharmacology Individual Study Review) and the observed atazanavir concentrations from the intensive PK substudies with the Phase 2 and 3 trials (GS-US-216-0105 and GS-US-216-0114). Briefly, there were 30 subjects administered atazanavir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (ATV/Cobi/F/T) and 36 subjects administered atazanavir/ritonavir/emtricitabine/tenofovir disoproxil fumarate (ATV/RTV/F/T) from these two studies who participated in the PK substudy. The overall ATV exposures from

this subset were similar but slightly lower for ATV boosted with Cobi compared to ATV boosted with ritonavir (5%, 14%, and 11% lower AUC, C_{max}, and C_{0h}, respectively).

Table 5: Population Pharmacokinetic Estimates of Cobi 150 mg q.d. in Antiretroviral Treatment Naïve HIV-1-Infected Subjects

Parameter Mean (CV%) (Median) [IQR]	ATV/Cobi/F/T (n=30)	ATV/RTV/F/T (n=36)
AUC_{τ} (ng·h/mL)	39,960 (48) (39514) [28538; 49563]	42206 (56) 46,335 [32561; 58407]
C_{max} (ng/mL)	3,537 (45) (3,683) [2,463; 4,706]	4,124 (57) (4,968) [3,532; 5,695]
C_{0h} (ng/mL)	576 (76) (591) [361; 960]	646 (77) (667) [462; 1,122]

However, in addition to data from the two above sources, the sponsor also conducted a comparative trial between ATV/cobi/F/T and ATV/ritonavir/F/T (GS-US-216-0114).

Based on the applicant's snapshot analysis, the percentage of HIV-1 infected treatment naïve subjects that achieved the primary endpoint of HIV-1 RNA less than 50 copies/mL at week 48 was 85.2% in the ATV boosted with Cobi arm compared to 87.4% in the ATV boosted with ritonavir arm. The percentage difference and the 95.2% confidence interval were -2.2% (-7.4% to 3%), with the lower limit of the non-inferiority margin of -12%.

While HIV-1 infected, treatment experienced subjects were not specifically evaluated in the GS-US-216-114 trial, an ATV/cobi indication for treatment experienced subjects is supported using the following rationale: a) the recommended dosage regimen for HIV-1 infected, treatment experienced adult patients is atazanavir 300 mg coadministered with ritonavir 100 mg once daily, b) the similarity in atazanavir exposures with a 300 mg dose when combined with either ritonavir 100 mg or cobicistat 150 mg once daily in the GS-US-216-110 trial in healthy subjects and in the GS-US 216-114 trial where noninferiority was demonstrated for ATV/cobi in treatment naïve subjects, and c) an expectation that atazanavir exposures when coadministered with ritonavir or cobicistat would be similar regardless of the HIV-1 infected treatment population (naïve or experienced).

1.1.3 Are the darunavir exposures when boosted with Cobi similar to the respective exposures when boosted with ritonavir?

Darunavir (DRV) boosted with cobi was evaluated in GS-US-216-0115 (Phase I bioavailability study, see Clinical Pharmacology Individual Study Review). The top-line results from this study indicated that DRV boosted with Cobi had similar C_{max} and AUC to DRV boosted with ritonavir. However, there was a lower C_{0h} (GLSM Ratio [90% CI]

of 89.4 [80.4; 99.4]) and C_{24h} (GLSM Ratio [90% CI] of 69.4 [59.0; 81.7]) between the two treatment arms. Subsequent evaluation of the results of GS-US-216-0115 demonstrated that the difference in C_{24h} was driven by an increase in the DRV concentration between hour 20 and 24 following the last dose. This phenomenon was predominately observed during a single treatment period (Day 24 DRV/RTV dosing) and was the primary factor contributing to the observed difference between C_{24h} for the two treatment arms. An explanation for this increase could not be determined based on the available information from the GS-US-216-0115 trial. The reviewer also evaluated DRV when coadministered with RTV PK profiles from studies submitted with the original DRV application and could not identify any studies with a flat or increasing DRV concentration over 12 to 24 hours, though none of the studies included sampling between 12 hours and 24 hours. The reviewer also considered published manuscripts through a PubMed search depicting DRV PK profiles and could not identify any cases where the reported DRV PK when coadministered with RTV increase between the 20 to 24 hours, though few publications included sampling between 12 and 24 hours. Altogether, the available evidence from the original DRV application, published manuscripts, and within trial results where the increase was only observed for a single treatment period supports that this observed increase at C_{24h} may not be representative of DRV PK when boosted with RTV.

Figure 1: Summary DRV PK Profiles from GS-US-216-0115 For Period 1 (left) and Period 2 (right) Grouped According to Treatment Arm (blue: DRV/RTV; red: DRV/Cobi). Note the increase in DRV concentration observed between hour 20 and 24 in the DRV/RTV group on Day 24 (Period 2)

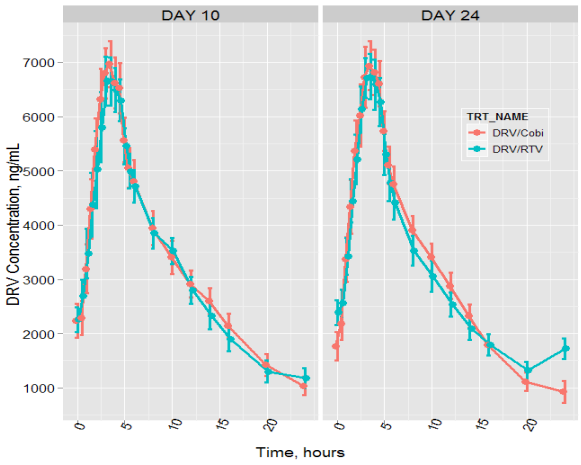


Table 6: Percentage of Subjects in GS-US-216-0115 with An Increase in Concentration Between Hour 20 and 24 Post-Dose (Grouped by Period and Treatment Arm)

	DRV/Cobi	DRV/RTV
Day 10	13% (2/16)	27% (4/15)
Day 24	27% (4/15)	***93% (14/15)***

Subsequently, the review team requested additional DRV/cobi pre-dose data from the ongoing study GS-US-216-0130 to obtain additional information regarding DRV C_{0h} values when boosted with cobi. DRV C_{0h} concentrations from this study were compared with observations from previously completed DRV/ritonavir studies TMC114-C211 and TMC114-C229. The sponsor responded to the information request with data from 298 subjects. A cumulative distribution plot of the DRV C_{0h} values is shown below in Figure 2. A summary of DRV pharmacokinetics from these three studies is shown below in Table 7. The results of these analyses demonstrated that DRV C_{0h} when boosted with Cobi may be 5-10% lower than that DRV C_{0h} when boosted with ritonavir. This is in agreement with the C_{0h} data from GS-US-216-0115 and supports that while DRV C_{0h} exposures when boosted with Cobi may be slightly lower than DRV C_{0h} when boosted with ritonavir, the magnitude of this difference may not exceed 10%.

Figure 2: Cumulative Distribution of C_{0h} from GS-US-216-0130 (DRV/Cobi), TMC114-C211 (DRV/RTV) and TMC114-C229 (DRV/RTV). The plots demonstrate overlap between DRV concentration when boosted with either Cobi or RTV.

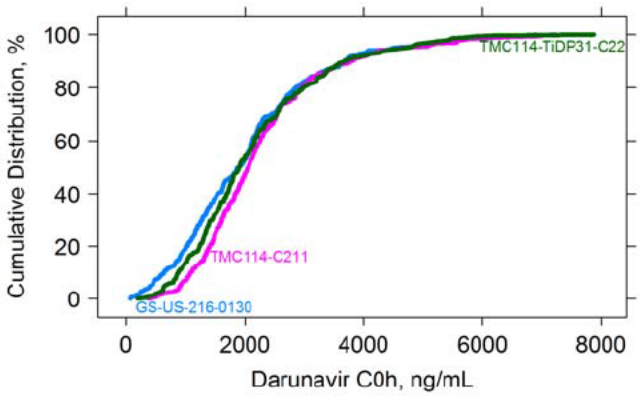


Table 7: Summary DRV PK Parameters Based on Pre-Dose (C_{0h}) and Posthoc Population PK Predictions (AUC) from GS-US-216-0130 (DRV/Cobi), TMC114-C211 (DRV/RTV) and TMC114-C229 (DRV/RTV)

Parameter	Measure	Study		
		GS-US-216-0130 (n=298)	C211 (n=335)	C229 (n=280)
C0h, ng/mL	Mean (SD)	2043 (1257)	2282 (1169)	2160 (1201)
	Median [range]	1875 [70; 6890]	2048 [368; 7241]	1896 [184; 7881]
AUC,	Mean (SD)	100.2 (32)	93.1 (27.1)	93.3 (28.6)

1.1.4 Do the exposure-response efficacy relationships for darunavir predict differences in response when boosted with cobi compared to ritonavir?

No, the darunavir (DRV) exposure-response relationship for DRV C_{0h}, AUC, and inhibitory quotient versus the percentage of subjects achieving virologic success (plasma viral load <50 HIV-1 RNA copies/mL) at Week 48 was flat with respect to data from two previously conducted DRV/RTV trials (TMC114-C211 and TMC114-229). The lack of a significant DRV exposure-response relationship for virologic response supports the previous conclusion that a 10% reduction in DRV C_{0h} that was observed for DRV boosted with cobi compared to DRV boosted with RTV is not expected to appreciably reduce efficacy.

Briefly, TMC114-211 was a Phase III randomized, open-label controlled study of DRV/RTV 800/100 mg q.d. in HIV-1 infected treatment naïve subjects (n=304). TMC114-229 was a Phase III, randomized, open-label study of DRV/RTV 800/100 mg q.d. in HIV-1 infected treatment experienced subjects with no DRV resistance-associated mutations (n=302). In both trials, the sponsor identified flat or inverse exposure-response relationships between DRV C_{0h} or AUC and virologic response across exposure deciles. Baseline viral load was the only significant covariate identified as predictive of virologic success based on a generalized additive model (GAM) analysis for either DRV study.

To identify if there was any loss in efficacy towards lower exposures, the exposure response relationship was further explored by separating the groups into deciles. It was seen that the observed percentage of subjects achieving virologic success was flat or inverted across all deciles (i.e., higher exposures were associated with a lower response) (Table 8). The median C_{0h} in the lowest decile was 909 ng/mL for TMC114-C211 and 644 ng/mL for TMC114-229 and corresponded to a virologic response of 88% and 82%, respectively. Virologic success in deciles with higher C_{0h} values for both trial ranged between 74-100% and 57-89%, respectively. There was no clear trend of decreasing response with the lower exposure deciles or a decline in response in the lowest decile. A similar trend across deciles was observed for AUC_{tau} (not shown).

The sponsor also used the developed DRV exposure-response relationships to predict the impact on efficacy of various reductions DRV C_{0h} reductions. For TMC114-C211, C_{0h}

reductions of 10% and 30% are predicted to result in a 0.1 and 0.3% reduction in response (from 92.8% to 92.7% and 92.5%, respectively). Likewise, from TMC114-C229 C_{0h} reductions of 10% and 30% are not predicted to result in a lower response due to the inverse exposure response relationship identified from that study.

Table 8: Virologic Success by C_{0h} Decile (Q1-Q10) for TMC114-C211 and TMC114-C229

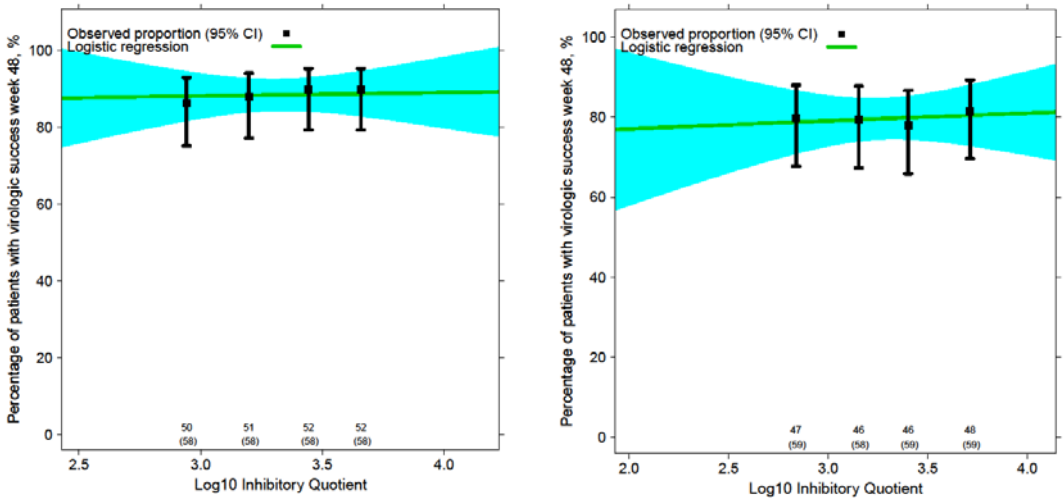
	TMC114-C211			TMC114-C229		
	n	Median C_{0h}	% subjects with virologic success	n	Median C_{0h}	% subjects with virologic success
Q1	34	909	88	28	644	82
Q2	33	1303	82	28	1030	68
Q3	34	1495	88	28	1327	89
Q4	33	1729	91	28	1572	86
Q5	33	1943	84	28	1789	71
Q6	34	2141	74	28	2045	82
Q7	33	2387	82	28	2314	64
Q8	34	2762	100	28	2690	68
Q9	33	3228	85	28	3343	57
Q10	34	4659	79	28	4748	57

Due to the unique nature of the inverted exposure-response relationship identified in TMC114-C229, the reviewer extended the applicant's general additive modeling (GAM) analysis to include a flag for subjects with one or more DRV concentration assessments below the limit of quantification (BLQ) during the sparse sampling from the Phase III studies. In all, 24 subjects (n=335) had a BLQ measurement in TMC114-C211 and 42 subjects (n=280) had a BLQ measurement in TMC114-C229. The virologic response in subjects without a BLQ measurement (88.8% [276/311] for TMC114-C211 and 79.8% [190/238]) was higher compared to the virologic response in subjects with a BLQ measurement on treatment (41.7% [10/24] for TMC114-C211 and 31.0% [13/42]). This factor was identified as the most significant factor for predicting virologic success in the reviewer's GAM analysis, but otherwise identified factors contributing to treatment response were similar to those identified by the sponsor (i.e., baseline viral load). Paradoxically, 20 of the 24 subjects with a BLQ measurement from TMC114-C211 had population PK predicted C_{0h} values in the 3rd or 4th exposure quartile. Similarly, 31 of 42 subjects with a BLQ measurement from TMC114-C229 had population PK predicted C_{0h} values in the 3rd or 4th exposure quartile. Typically, such subjects are commonly represented within the lower exposure quartiles, and the inverse allotment of such subjects in the current exposure-response analysis may have contributed to the inverse relationship observed between exposure and response from TMC114-229. The original DRV population PK model was not evaluated as part of this review, but a possible reason for higher predictions in these subjects with an on treatment BLQ measurement may be

due to censoring of the BLQ measurements during the original population PK analysis. In turn, this may have led to a lower predicted clearance (and by association a higher C_{tau} value) than the subject's actual clearance. Alternatively, these subjects may have compensated for missed doses by taking multiple doses in advance of a measurement, which would also lead to a lower predicted clearance than the subject's actual clearance.

To further explore the possibility of any DRV exposure-response relationships, the reviewer extended the applicant's analysis to include inhibitory quotient as an independent value in the subset of Phase III subjects who did not have a BLQ DRV concentration measurement on treatment. An independent review based on inhibitory quotient (IQ) values [the IQ is the ratio of C_{0h} (exposure) at steady state and IC_{50} (a measurement of the ability of darunavir to inhibit HIV-1 virus)] resulted in similar conclusions of a relatively flat exposure-response relationship between darunavir IQ and virologic response for TMC114-C211 and TMC114-C229. An inverse exposure-response relationship was not identified for TMC114-229; however, the exposure-response relationship was still flat and supports that a 10% reduction in DRV C_{0h} will not impact response.

Figure 3: Percentage of Subjects Achieving Virologic Success (<50 Copies/mL) Versus DRV IQ from TMC114-C211 (left) and TMC114-C229 (right) [subjects with one or more BLQ DRV concentrations were removed from this analysis].



1.1.5 Is there any exposure-response safety relationships for Cobi or tenofovir that explain the imbalance in renal adverse events observed between the treatment arms boosted with Cobi?

An exposure-response relationship could not be established for jaundice, nausea, hyperbilirubinemia, ocular icterus, or diarrhea and cobi exposures. Logistic regression models were evaluated for Cobi C_{max}, $C_{0h,}$ and AUC_{τ} with no significant relationships identified. Modeling results for adverse event rates versus cobi AUC_{τ} are shown below in the reviewer's analysis. These analyses were limited due to the number of subjects from the Phase II/III trials with cobi exposure data available (n=68) and adverse events of interest..

1.1.6 Was there a greater shift in baseline eGFR for ATV/Cobi/F/T compared to ATV/rtv/F/T?

Yes, there were a greater proportion of subjects on ATV/Cobi/F/T compared to ATV/RTV/F/T who had a transitioned from a baseline creatinine clearance within a specified range (70 to 80 mL/min, 80 to 90 mL/min, and greater than 90 ml/min) to a lower creatinine clearance increment while on treatment. In the ATV/RTV/F/T treatment arm, 39% of subjects transitioned to a lower creatinine clearance increment while on treatment compared to 51% in the ATV/Cobi/F/T arm. This was not entirely unexpected given the increased effect on mean serum creatinine that was observed in the ATV/Cobi/F/T treatment group compared to ATV/RTV/F/T. However, a closer look at the percentage of subjects with baseline creatinine clearance <90 mL/min who transitioned to <50 mL/min while on treatment also indicates a larger percentage of subjects on ATV/Cobi/F/T met this criteria (11.1% [n/N=5/45]) compared to ATV/RTV/F/T (5.2% [n/N=3/58]).

Table 9: Baseline Versus Minimum On-Treatment eGFR (Cockcroft Gault) for Subjects in GS-US-216-0114 Grouped According to Treatment Arm

ATV/r+TVD (# subjects: 348)		Minimum On-Treatment eGFR (CG)					
		>=90	80<=x<90	70<=x<80	60<=x<70	50<=x<60	<50
Baseline eGFR (CG)	>=90 (n=290)	69% (n=201)	18% (n=51)	8% (n=24)	3% (n=10)	1% (n=3)	0% (n=1)
	80<=x<90 (n=28)	0% (n=0)	14% (n=4)	43% (n=12)	36% (n=10)	4% (n=1)	4% (n=1)
	70<=x<80 (n=26)	0% (n=0)	0% (n=0)	23% (n=6)	42% (n=11)	31% (n=8)	4% (n=1)
	60<=x<70 (n=3)	0% (n=0)	0% (n=0)	0% (n=0)	0% (n=0)	100% (n=3)	0% (n=0)
	50<=x<60 (n=1)	0% (n=0)	0% (n=0)	0% (n=0)	0% (n=0)	0% (n=0)	100% (n=1)
	<50 (n=0)	0% (n=0)	0% (n=0)	0% (n=0)	0% (n=0)	0% (n=0)	0% (n=0)

ATV/Cobi+TVD (# subjects: 344)		Minimum On-Treatment eGFR (CG)					
		>=90	80<=x<90	70<=x<80	60<=x<70	50<=x<60	<50
Baseline eGFR (CG)	>=90 (n=299)	55% (n=165)	24% (n=72)	14% (n=43)	5% (n=16)	1% (n=2)	0% (n=1)
	80<=x<90 (n=27)	0% (n=0)	7% (n=2)	33% (n=9)	41% (n=11)	11% (n=3)	7% (n=2)

	70<=x<80	(n=14)	0% (n=0)	0% (n=0)	7% (n=1)	50% (n=7)	36% (n=5)	7% (n=1)
	60<=x<70	(n=4)	0% (n=0)	0% (n=0)	0% (n=0)	25% (n=1)	25% (n=1)	50% (n=2)
	50<=x<60	(n=0)	0% (n=0)	0% (n=0)	0% (n=0)	0% (n=0)	0% (n=0)	0% (n=0)
	<50	(n=0)	0% (n=0)	0% (n=0)	0% (n=0)	0% (n=0)	0% (n=0)	0% (n=0)

1.1.7 Is on-treatment serum creatinine increase sensitive for identifying subjects treated with ATV/Cobi/F/T who experience renal adverse events?

Confirming serum creatinine increase of ≥0.4 mg/dL from baseline (e.g., two consecutive measurements) identifies the 5 subjects administered ATV/Cobi/F/T and the 2 subjects administered ATV/rtv/F/T that developed proximal renal tubular dysfunction while limiting the number of subjects who may be prematurely discontinued from treatment. All subjects that developed proximal tubular dysfunction with either ATV/Cobi/F/T or ATV/RTV/F/T discontinued treatment.

Multiple serum creatinine increase thresholds and scenarios were evaluated to determine criteria that would identify subjects who experienced on treatment renal adverse events while limiting the number of subjects who may be prematurely discontinued from treatment (Table 10) due to this hypothesized effect of cobi on tubular secretion of creatinine. The metrics included changes occurring at a single treatment visit or multiple consecutive visits. A metric based on a single serum creatinine measure ≥0.4 mg/dL identified 40 subjects or 11.6% of Phase III subjects administered ATV/Cobi/F/T and 27 subjects or 7.8% of Phase III subjects administered ATV/RTV/F/T) and was deemed too insensitive for identifying subjects with renal adverse events. Increasing the metric to larger serum creatinine changes (≥0.5 or ≥0.6 mg/dL) increases sensitivity, but there were concerns that the magnitude of increase was so large that some subjects experiencing a renal adverse event may be excluded. Alternatively, using a lower metric (serum creatinine ≥0.4 mg/dL) but confirmed at consecutive clinical visits provided an appropriate balance between identifying subjects with renal adverse events and limiting the number of subjects who may be prematurely discontinued from treatment due to increases in serum creatinine from cobi.

Table 10: Number and Percentage of Subjects Treated with ATV/Cobi/F/T or ATV/RTV/F/T from GS-US-216-0114 and GS-US-216-0105 With Single, Multiple, or Consecutive Serum Creatinine Increases Exceeding Thresholds

	Serum Creatinine Increase (single measurement) (mg/dL)

Arm	≥0.3	≥0.4	≥0.5	≥0.6
ATV/Cobi + TVD (n= 344)	29.7% (n=102)	11.6% (n=40)	4.4% (n=15)	2.0% (n=9)
ATV/r + TVD (n= 348)	18.4% (n=64)	7.8% (n=27)	4.6% (n=16)	2.0% (n=7)

	Serum Creatinine Increase (two consecutive) (mg/dL)		
Arm	≥0.3	≥0.4	≥0.5
ATV/Cobi + TVD (n= 344)	9.6% (n=33)	3.2% (n=11)	1.5% (n=5)
ATV/r + TVD (n= 348)	4.6% (n=16)	2.0% (n=7)	0.9% (n=3)

1.2 Recommendations

The application is approvable. Based on the information assessed in this review there are no requested postmarketing trials from a Pharmacometrics perspective, however discussions regarding postmarketing trials are still ongoing.

1.3 Label Statements

N/A

2 PERTINENT REGULATORY BACKGROUND

Cobicistat (Cobi) is a new chemical entity and structural analogue of ritonavir. Similar to ritonavir, Cobi is a cytochrome P450 3A (CYP3A) inhibitor that increases the exposure of CYP3A substrates, including atazanavir (ATV) and darunavir (DRV). The initial proposed indication for the COBI tablet for use once daily use as a pharmacokinetic (PK) enhancer of the HIV-1 protease inhibitors atazanavir and darunavir in adults. Pending regulatory approval, COBI would be the first pharmaceutical with an indication for use as a PK enhancer.

Additionally, COBI is a component in the 4-drug fixed-dose combination tablet (Stribild®, NDA 203100), which is comprised of the integrase inhibitor elvitegravir, COBI, emtricitabine (FTC), and tenofovir disoproxil fumarate (TDF). NDA 203100 was submitted to the Food and Drug Administration (FDA) on October 27th, 2011, with a proposed indication for the treatment of HIV-1 infection in adults who are antiretroviral treatment-naïve or who have no known resistance mutations to the individual components. NDA 203100 was approved by the FDA on August 27th, 2012 for the treatment of HIV-1 infection in adults who are antiretroviral treatment-naïve.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Introduction

The applicant developed a population pharmacokinetic model to explore the impact of intrinsic and extrinsic factors on Cobi exposure. In addition, pharmacokinetic parameters were used by the applicant to explore exposure-response safety relationships between Cobi and key adverse events (e.g. headache, nausea, diarrhea). Finally, the results of bioequivalence studies involving DRV/cobi versus DRV/rtv were evaluated in the context of previously identified exposure-response efficacy relationships from the original DRV submission in HIV-1 infected treatment-naïve adults and treatment-experienced adults with no associated DRV mutations.

3.2 Population Pharmacokinetic Model

Report 5.3.3.5 Population Pharmacokinetics of Cobicistat (Cobi)

The purpose of this project was to develop a population pharmacokinetics model to describe cOBI PK based on data from healthy volunteers and patients and to assess the effects of covariates such as age, gender, race, HIV status (positive or negative), formulation, background treatment, body weight, body mass index, body surface area and creatinine clearance (estimated GFR), HBV and/or HCV coinfection.

3.2.1 Data

COBI exhibits a complex pharmacokinetic profile with both time-dependent (autoinhibition) and dose-dependent (saturable clearance) nonlinearities. Therefore, multiple approaches were tested in modeling the available data. In one approach, all data from day one (single dose) and steady state samples were pooled and various models were tested to describe both autoinhibition and nonlinear clearance of the compound. Since efforts in this approach resulted in failed or unstable models that were highly dependent on initial estimates, a second approach was tested, where different models were tested separately on day 1 data and steady state data. It was further decided to focus the modeling efforts on steady state data, as most of the available data of interest were collected at steady-state.

Reviewer's Comment: Only the datasets, demographic summary and modeling results for the steady state analysis are presented below as these results are more clinically relevant for informing Cobi dose adjustments in special populations following repeated Cobi administration. Similar complex pharmacokinetics kinetics have previously been observed for ritonavir, which is known to inhibit CYP3A4 following the first few days of administration followed by auto-induction of it's own metabolism and that of coadministered protease inhibitors (e.g., highest exposures on lopinavir/ritonavir and saquiniavir/ritonavir are on day 3 of treatment as opposed to steady state based on published TQT studies).

The model was developed based on eleven Phase 1 studies in healthy volunteers (216-0115, 216-0116, 216-0119, 216-0120, 216-0121, 216-0122, 216-0123, 216-0124, 236, 0105, 236-0106, 236-0110) and five studies in HIV-infected patients (Phase 2: 216-0105 and 236-0104; Phase 3: 216-0114, 236-0102, and 236-0103). Missing concentrations

events were retained in the dataset but flagged in order for exclusion from analysis. Missing individual covariates were replaced with median value for the whole data from four subjects were excluded from the final analysis. Inclusion of data from one subject (Study ID 236-0103, Subject ID: 7159) resulted in numerical difficulties during the model building process and removal of the subject's data resolved the issue. Data from three other subjects (Study ID 236-0104, Subject IDs: 4411, 4415, and 4530) were deemed to have incorrect coding and were excluded from the final analysis data set. All BLQ concentrations were treated as missing in the data set. The final data set consisted of 9584 Cobi concentration-time records (8880 intensive and 704 sparse data) from a total of 643 subjects across 16 clinical studies.

The final model was developed based on pooled data included 9584 cobi concentration observations from a total of 643 subjects across 16 clinical studies, including 11 studies in healthy volunteers and 5 studies in HIV-infected patients. A summary description of the studies is provided below (Table 11 and Table 12). The dataset used log-transformed values for Cobi concentrations in all analyses (data set name: ss150mg.csv).

Table 11: Summary of Healthy Volunteer Studies Included in the Cobi Population PK Analysis

Study	Title	Formulation	PK Sampling Times
Study 216-0116	A Phase 1 Multiple Dose Study to Evaluate Two Formulations of GS-9350 Tablets and the Pharmacokinetics of Elvitegravir Tablets administered with GS-9350 Tablets	EVG 150 mg tablet plus COBI 150 mg tablet	0 (predose), 1, 2, 3, 3 5, 4, 4 5, 5, 5 5, 6, 8, 10, 12, 14, 16, 20, and 24 hours
Study 216-0123	A Phase 1 Study Evaluating the Drug Interaction Potential Between Cobicistat- Boosted Elvitegravir Administered Once-Daily and Atazanavir, Rosuvastatin, or Rifabutin	EVG 150 mg tablet plus COBI 150 mg tablet	0 (pre-dose), 0 5, 1, 1 5, 2, 3, 4, 4 5, 5, 6, 8, 10, 12,18, 24, 36, and 48 hours
Study 216-0115	A Phase 1 Multiple Dose Study to Evaluate the Relative Bioavailability and Pharmacokinetics of Darunavir when Coadministered with the Pharmacoenhancer GS- 350 versus Ritonavir	COBI 150 mg tablet plus Darunavir (2 X 400 tablet)	0 (pre-dose), 0 5, 1, 1 5, 2, 2 5, 3, 3 5, 4, 4 5, 5, 5 5, 6, 8, 10, 12, 14, 16, 20, and 24 hours post-dose
Study 216-0120	A Phase 1 Study to Evaluate the Relative Bioavailability and Pharmacokinetics of GS-9350-boosted Elvitegravir upon Co-administration with a Representative H2-Receptor Antagonist or Proton Pump Inhibitor	COBI 150 mg tablet plus EVG 150 mg tablet plus Famotidine 40 mg tablet (12 hr H2RA stagger); or COBI 150 mg tablet plus EVG 150 mg tablet plus Omeprazole 20 mg capsule (2 hr H2RA stagger); or COBI 150 mg tablet plus EVG 150 mg tablet plus Omeprazole 20 mg capsule (12 hr H2RA stagger);	0 (pre-dose), 0 5, 1, 1 5, 2, 2 5, 3, 3 5, 4, 4 5, 5, 6, 8, 10, 12, 14, 16, 20, and 24 hours post-dose
Study 216-0121	A Randomized, Blinded, Placebo-Controlled Phase 1 Study Evaluating the Effect of GS-9350 and Ritonavir on Renal Function as Assessed by Markers of Glomerular Filtration Rate	COBI 150 mg tablet	0 (pre-dose), 0 25, 0 5, 1, 1 5, 2, 2 5, 3, 3 5, 4, 4 5, 5, 6, 8, 10, 12, 16, and 24 hours post-dose
Study 216-0122	A Phase 1 Study to Evaluate the Relative Bioavailability and Pharmacokinetics of Cobicistat–boosted Elvitegravir upon Simultaneous Co-administration with a Representative H2-Receptor Antagonist	COBI 150 mg tablet plus EVG 150 mg tablet plus Famotidine 40 mg tablet	0 (pre-dose), 0 5, 1, 1 5, 2, 2 5, 3, 3 5, 4, 4 5, 5, 6, 8, 10, 12, 14, 16, 20, and 24 hours post-dose
Study 216-0119	A Phase 1 Study to Evaluate the Safety, Tolerability and Pharmacokinetics of Twice-Daily Administration of the Pharmacoenhancer Cobicistat Alone and of Darunavir and Tipranavir, Each Administered Twice-Daily in Combination with Cobicistat or Ritonavir	COBI 150 mg tablet; or COBI 150 mg tablet plus Darunavir 600 mg tablet; or COBI 150 mg tablet plus EVG 150 mg tablet plus Darunavir 600 mg tablet; or COBI 150 mg tablet plus Darunavir 600 mg tablet plus Etravirine (2 x 100 mg tablet); or COBI 150 mg tablet plus Tipranavir (2 X 250 mg capsule)	0 (pre-dose), 1, 2, 3, 3 5, 4, 4 5, 5, 6, 8, 10, and 12 hours post-dose
Study 216-0124	A Phase 1, Open-Label, Parallel-Design, Multiple Dose Study to Evaluate the Pharmacokinetics of Cobicistat-Boosted Elvitegravir in Subjects with Severe Renal Impairment	COBI 150 mg tablet plus EVG 150 mg tablet	0 (pre-dose), 0 25, 0 5, 1, 1 5, 2, 2 5, 3, 3 5, 4, 4 5, 5, 6, 8, 10, 12, 16, and 24 hours post-dose
Study 236-0105	A Phase 1 Study to Determine the Effect of Food on the Pharmacokinetics of Elvitegravir, Emtricitabine, Tenofovir DF plus Pharmacoenhancer GS-9350 Fixed-Dose Combination Tablet	EVG/COBI/FTC/TDF (150 mg/150 mg/200 mg/300 mg) FDC	0 (predose), 0 5, 1, 1 5, 2, 2 5, 3, 3 5, 4, 4 5, 5, 5 5, 6, 8, 10, 12, 14, 16, 20, 24, 36, and 48 hours postdose

Study 236-0106:	A Phase 1, Open Label, Drug Interaction Study Evaluating the Effect of Elvitegravir/Emtricitabine/Tenofovir DF/GS-9350 Fixed-Dose Combination Tablet on the Pharmacokinetics of a representative Hormonal Contraceptive Medication, Norgestimate/Ethinyl Estradiol	EVG/COBI/FTC/TDF (150 mg/150 mg/200 mg/300 mg) FDC	0 (predose), 0 5, 1, 1 5, 2, 2 5, 3, 3 5, 4, 4 5, 5, 5 5, 6, 8, 10, 12, 14, 16, 20, and 24 hours postdose
Study 236-0110	A Phase 1 Multiple Dose Study to Evaluate the Relative Bioavailability of Two Elvitegravir/Emtricitabine/Tenofovir DF/GS-9350 Fixed-Dose Combination Tablet Formulations	EVG/COBI/FTC/TDF (150 mg/150 mg/200 mg/300 mg) FDC	0 (predose), 0 5, 1, 1 5, 2, 2 5, 3, 3 5, 4, 4 5, 5, 5 5, 6, 8, 10, 12, 14, 16, 20, and 24 hours postdose

Table 12: Summary of HIV-1 Infected Patient Studies Included in the Cobi Population PK Analysis

Study	Title	Formulation	PK Sampling Times
Study 216-0114	A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of GS-9350-boosted Atazanavir Versus Ritonavir-boosted Atazanavir Each Administered with Emtricitabine/Tenofovir Disoproxil Fumarate in HIV-1 Infected, Antiretroviral Treatment-Naïve Adults	COBI 150 mg tablet plus ATV 300 mg capsule plus FTC/TDF 200/300 mg tablet	Substudy sampling times: 0 (pre-dose), 1, 2, 3, 3 5, 4, 4 5, 5, 6, 8, 10, 12, and 24 hours post-dose Sparse sampling (single PK blood sample anytime postdose) was also conducted for all subjects at Weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48
Study 236-0102	A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Elvitegravir/Emtricitabine/Tenofovir Disoproxil Fumarate/GS-9350 Versus Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate in HIV-1 Infected, Antiretroviral Treatment-Naïve Adults	EVG/COBI/FTC/TDF (150 mg/150 mg/200 mg/300 mg) FDC	0 (predose), 1, 2, 3, 4, 4 5, 5, 6, 8, 10, 12, and 24 hours postdose
Study 236-0103	A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Elvitegravir/Emtricitabine/Tenofovir Disoproxil Fumarate/GS-9350 Versus Ritonavir-Boosted Atazanavir Plus Emtricitabine/Tenofovir Disoproxil Fumarate in HIV-1 Infected, Antiretroviral Treatment-Naïve Adults	EVG/COBI/FTC/TDF (150 mg/150 mg/200 mg/300 mg) FDC	Substudy sampling times: 0 (predose), 1, 2, 3, 3 5, 4, 4 5, 5, 6, 8, 10, 12, and 24 hours postdose Sparse sampling (single PK blood sample) was also conducted for all subject visits (Weeks 2 through 48)
Study 216-0105	A Phase 2, Randomized, Double-Blinded Study of the Safety and Efficacy of GS-9350–boosted Atazanavir (ATV/GS-9350) Compared to Ritonavir-boosted Atazanavir (ATV/r) in Combination with Emtricitabine/Tenofovir Disoproxil Fumarate (FTC/TDF) in HIV-1 Infected, Antiretroviral Treatment-Naive Adults	COBI 150 mg tablet plus ATV 300 mg capsule plus FTC/TDF 200/300 mg tablet	Substudy sampling times: 0 (pre-dose), 1, 2, 3, 3 5, 4, 4 5, 5, 6, 8, 10, 12, and 24 hours post-dose Sparse sampling (single PK blood sample) was also conducted for all subjects 20−24 hours following an observed (in-clinic) dose at Weeks 8, 24, and 48 In addition, a single PK blood sample was collected at Weeks 2, 4, 12, 16, 32, and 40
Study 236-0104	A Phase 2, Randomized, Double-Blinded Study of the Safety and Efficacy of Elvitegravir/Emtricitabine/Tenofovir Disoproxil Fumarate/GS-9350 Versus Atripla® (Efavirenz 600 mg/Emtricitabine 200 mg/Tenofovir Disoproxil Fumarate 300 mg) in HIV-1 Infected, Antiretroviral Treatment-Naive Adults	EVG/COBI/FTC/TDF (150 mg/150 mg/200 mg/300 mg) FDC	Substudy sampling times: 0 (predose), 1, 2, 3, 4, 4 5, 5, 6, 8, 10, 12, and 24 hours postdose Sparse sampling (single PK blood sample) was also conducted for all subjects 20−24 hours following an observed (in-clinic) dose at Weeks 8, 24, and 48 In addition, a single PK blood sample was collected at Weeks 2, 4, 12, 16, 32, and 40

Summary demographics of the subjects included in the population PK analysis are presented below:

Table 13 General Summary Statistics of the Subjects Included in the Cobi Population PK Analysis

Covariate	Average	Min - Max	n
Age (years)	37 (Median: 36)	18 – 76 (Q1: 29; Q3: 43)	504
Sex			328 (Male), 176 (Female)
Race			358 (White), 128 (Black), 18 (Other)
HIV Disease Status			302 (Healthy subjects), 202 (HIV patients)
Body weight (kg)	75.1 (Median: 76.7)	41.5 – 152.4 (Q1: 66.0; Q3: 85.0)	504
BMI (kg/m^2)	25.6 (Median: 25.3)	17.8 – 48.4 (Q1: 22.8; Q3: 27.1)	504
BSA (m^2)	1.9 (Median: 1.9)	1.3 – 2.8 (Q1: 1.76; Q3: 205)	504
Formulation			337 (COBI single agent), 167 (QUAD)
CG[a] (mL/min)	120.6	14.0 – 266.8	486
MDRD[b] (mL/min)	104.7	10.2 – 189.1	486
HBV status (Hepatitis B Virus)			365 (Negative), 3 (Positive), 136 (Unknown)
HCV status (Hepatitis C Virus)			366 (Negative), 2 (Positive), 136 (Unknown)
Background Treatment[c]			1 (35), 2 (99) , 3 (18) , 6 (69) , 8 (56), 14 (8), 15 (11), Missing (208)

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3.2.2 Methods

Structural Model Development

Log-transformed plasma concentration-time data were analyzed, using the first-order conditional estimation with interaction implemented in NONMEM. Discriminations between hierarchical models were based on the objective function value provided by NONMEM at a significance level of 0.001, equal to a decrease of 10.83 in the OFV, evaluation of the model parameter estimates, and graphical analysis of residuals and predictions.

Different structural PK models, including but not limited to 1-, or 2-compartment models with a zero and/or 1st order absorption rate constant and with or without absorption lag time were tested using intensive data after repeated dosing with 150 mg Cobi. Interindividual variability terms were included on the PK model parameters, where

supported by data. Additive, proportional, and a combination of both were tested in the error model. Furthermore, inclusion of an interindividual variability term on the error model parameters was tested. The final model was based on a dataset including intensive sampling data as well as sparse sample data from studies 236-0104 and 216-0105 (150mg.cvs). Inclusion of sparse data from Study 236-0103 resulted in terminated models and hence intensive data from this study were included in the final model analysis.

Covariate Model Development

The following demographics data were available from subjects: age, gender, race, body weight, body mass index (BMI), body surface area (BSA), formulation, background treatment, and creatinine clearance (estimated by CG or MRD methods), disease status (healthy volunteer or HIV infected), and co-infection with HBV (Hepatitis B Virus) and/or HCV (Hepatitis C Virus) status.

Once the base model was established, various subject characteristics were evaluated for their effect of different model parameters. In a first step, PK model parameters (structural or statistical) were plotted against demographic data, and trends of any effect of the covariates on the PK model parameters were examined. Furthermore, a GAM analysis, as implemented in Xpose, was performed and the results investigated. Once such trends were identified, the demographic parameter was included as a covariate in the PK model, if the observed trend was deemed scientifically plausible.

Final Model Evaluation

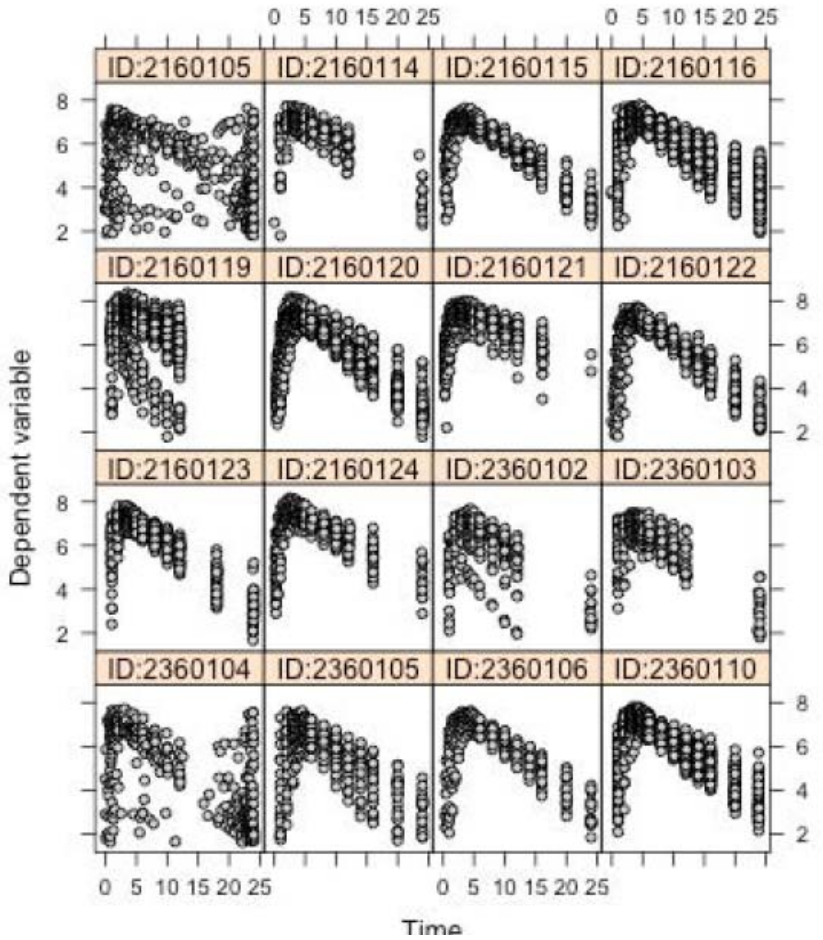
The final model was evaluated using general goodness of fit graphs, model parameter estimates, visual predictive check (using the software Perl Speaks NONMEM) and error estimates using bootstrapping.

3.2.3 Results

3.2.3.1 Observed Concentration-Time Profiles

Cobi concentrations vs. time data in the final dataset (ss150mg.csv) are shown in Figure 4. The plots show Cobi plasma concentrations vs. time since the last dose (TSLD) across the 16 studies.

Figure 4: Cobi Plasma Concentrations versus Time Since the Last Dose (TSLD) Across the 16 Studies Used in the Population PK Analysis



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3.2.3.2 Population PK Model Results

The first stage, base model was developed with concentration-time data after repeated 150 mg cobi doses, which is the clinically relevant dose of Cobi. A one-compartment model with both zero- and first-order absorption and a lag-time (ADVAN2, TRANS2) described the Cobi concentration profiles well. Adding an additional compartment (two-compartment model) did not further improve the model fit. Inter-individual variability could be added for all structural model parameters (clearance, central volume of compartment, first-order absorption rate constant, duration of the zero-order absorption process, and lag-time).

Different residual error models including proportional error model, additive error model and proportional plus additive error model on both normal and log-transformed data were tested. Proportional error model using log-transformed data was selected as the final base model based on the goodness-of-fit check. Furthermore, inclusion of an ETA on residual error was tested.

Of the available covariates, BSA, BMI, and WT were found to be positively correlated with the volume of distribution of cobi. When formally tested in the model, weight was the only covariate to show a statistically significant correlation with the central compartment volume (Vc) of cobi. The background therapy with tipranavir was not tested in the covariate building step due to the limited number of healthy volunteers only who were treated with this combination, relative to the entirety of the dataset (n=11).

The final model was tested on cobi concentration-time data at the 150 mg once daily dose level (ss150mg.csv). The data consisted of intensive sampling from all studies and the sparse samples from studies 216-0105 and 236-0104. Bootstrapping was performed on the final model to define the error of the model parameters. A total of 215 dataset re-samples with replacement of the full data set were performed and then the final model was fitted to each dataset. The results were used to construct the relative standard errors for the model parameters. General goodness of fit plots for the final model is shown in Figure 5, while the final model parameters are listed in Table 14.

Figure 5: General Goodness of Fit Plots for the Final Model

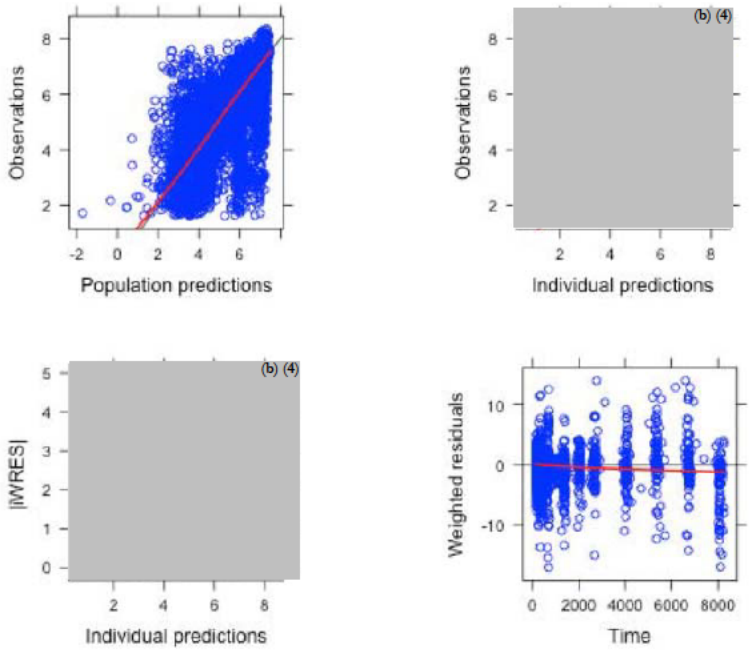

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Table 14: Final Model Parameter Estimates

Parameter	Population Mean		IIV	
	Estimate	RSE (%)	Estimate	RSE (%)
CL/F (L/h)	15.0	2.5	53%	9.5
Vc/F (L)	77.0	1.6	25%	8.5
DUR (h)	1.16	3.6	69%	10.5
K_a (1/h)	0.88	4.0	50%	9.5
t_{lag} (h)	0.18	24.9	130%	17.4
σ1 (proportional)	0.194	3.9	97%	4.3
WT on Vc/F	0.94	2.9	-	-

CL/F: apparent clearance, Vc/F: apparent volume of distribution, DUR: duration of the zero-order absorption, K_a: first-order absorption rate constant, tlag: absorption lag-time, WT: body weight, σ1: proportional error term. RSE values were obtained through bootstrapping (n=215).

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Inclusion of body weight as a power function (median weight of 74.4 kg) on cobi Vc/F resulted in a marginal decrease in the interindividual variability associated with this PK parameter (8.91% to 6.30%). The effect, however, was modest and the resulting decrease in the interindividual variability term associated with cobi volume was 30%. Relative to the median weight value of 74.4 kg in the entirety of the dataset, the range of observed weight of 57 – 101 kg (5th to 95th percentile) resulted in differences of only - 22% and +24% in Cobi volume, respectively. No other demographic or formulation characteristics were found to have any clinically relevant effects on cobi PK.

Reviewer's comment: The structural population PK model development by the sponsor is acceptable. However, the review disagrees with the conclusions regarding no additional clinically relevant effects of demographics on Cobi PK. Using the sponsor's base or final model, a relationship between the interindividual variability for clearance and body weight is observed. This relationship was further explored in the reviewer's analysis and inclusion of body weight on clearance was found to result in a significant improvement in the objective function and modestly reduce interindividual variability. The estimated relationship predicts a difference in of 25% in Cobi AUC between the 1st and 4th weight quartile (median body weight of the 1st and 4th quartile was 61 and 90 kg, respectively). This body weight relationship, while not necessitating any adjustment in adults, should be accounted for during cobicistat dose selection in pediatrics subjects.

3.3 Efficacy of Darunavir in HIV-1 Treatment Naïve Subjects

Report 5.3.4.2 report-body.pdf: Pharmacokinetic and pharmacokinetic/pharmacodynamic analyses of darunavir/ritonavir 800/100 mg once-daily dosing in the Phase III studies TMC114-C211 and TMC114-TiDP31-C229

Based on the information in this report, the potential impact of decreased darunavir (DRV) plasma trough concentrations (C_{0h}) on the antiretroviral (ARV) activity of DRV

coadministered with low-dose ritonavir (rtv) at the dose of 800/100 mg once daily (q.d.) was investigated. To assess this impact, the pharmacokinetic/pharmacodynamic data collected from the DRV/rtv 800/100 mg q.d. treatment arms of the randomized, controlled, open-label, clinical Phase III studies TMC114-C211 and TMC114-TiDP31-C229 were reanalyzed. Study TMC114-C211 included ARV treatment-naïve human immunodeficiency virus - type 1 (HIV-1) infected subjects, and study TMC114-C229 included ARV treatment-experienced HIV-1 infected subjects with no DRV resistance-associated mutations (RAMs). These 2 Phase III studies represent the basis for approval of the DRV/rtv 800/100 mg q.d. dosing indication in treatment naïve subjects and treatment experienced subjects with no darunavir resistance associated substitutions.

3.3.1 Methods

Pharmacokinetic/pharmacodynamic relationships were evaluated between the DRV pharmacokinetic parameters, AUC_{24h} and C_{0h}, and the efficacy parameter: virologic response defined as viral load < 50 copies/mL at Week 48. To investigate the relationship between the pharmacokinetic parameters (log_{10} AUC_{12h} and log_{10} C_{0h}) and the virologic response parameters at Week 48, logistic regression models using the same covariates and time points as mentioned above for the ANCOVA were applied.

3.3.2 Results: TMC114-C211

Of the 343 subjects randomized to be treated with DRV/rtv 800/100 mg q.d., 335 subjects with sparse sampling data were included in the population pharmacokinetic analysis for DRV. The Bayesian estimates of the DRV pharmacokinetic parameters following DRV/rtv 800/100 mg q.d. from the sparse sampling data are summarized in Table 15.

Table 15: Population Pharmacokinetic Estimates of Darunavir: Study TMC114-211

Parameter	Median (Range)
N	335
AUC_{24h}, ng.h/mL	87854 (45000; 219240)
C_{0h}, ng/mL	2041.2 (368.1; 7241.6)

Sponsor's Report: pg 14.

Analyses for the relationships between DRV pharmacokinetics and virologic response (viral load < 50 copies/mL) at Week 48 were performed. These analyses showed that there was no relevant relationship between DRV pharmacokinetics and virologic response at Week 48. A tabulation of virologic response by quartiles of DRV AUC_{24h} and C_{0h} in Table 16 and a graph presenting the pharmacokinetic/pharmacodynamic relationship between DRV pharmacokinetic parameters AUC_{24h} and C_{0h}, and virologic response defined as plasma viral load < 50 copies/mL at Week 48 is shown in Figure 6.

Figure 6: Virologic Response Defined as Viral Load <50 Copies/mL at Week 48 by Quartiles of DRV AUC and C_{0h}: Study TMC114-C211

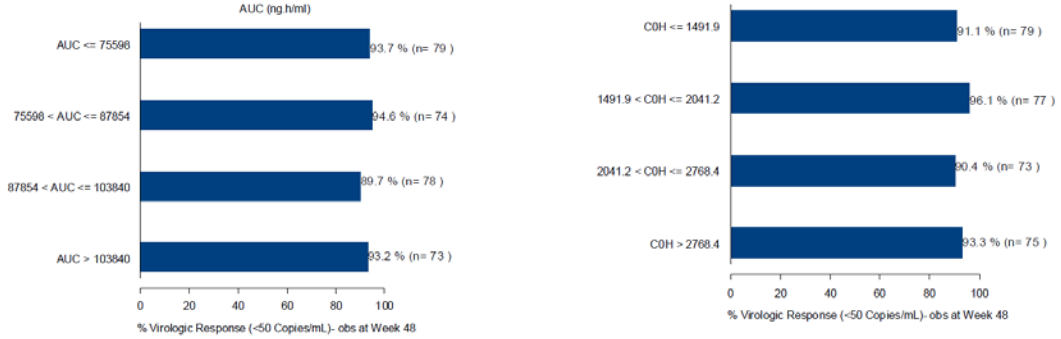

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Table 16: Viral Load <50 Copies/mL at Week 48 by Quartile: Study TMC114-211

PK PARAMETER / VIRAL LOAD: <50 copies/ml AT WEEK 48 (OBSERVED)	QUARTILE RANGE OF PK PARAMETER							
	<= Q1		]Q1; Q2]		]Q2; Q3]		> Q3	
	N	%	N	%	N	%	N	%
AUC (ng.h/ml)								
NO	5	6.3	4	5.4	8	10.3	5	6.8
YES	74	93.7	70	94.6	70	89.7	68	93.2
C0H (ng/ml)								
NO	7	8.9	3	3.9	7	9.6	5	6.7
YES	72	91.1	74	96.1	66	90.4	70	93.3

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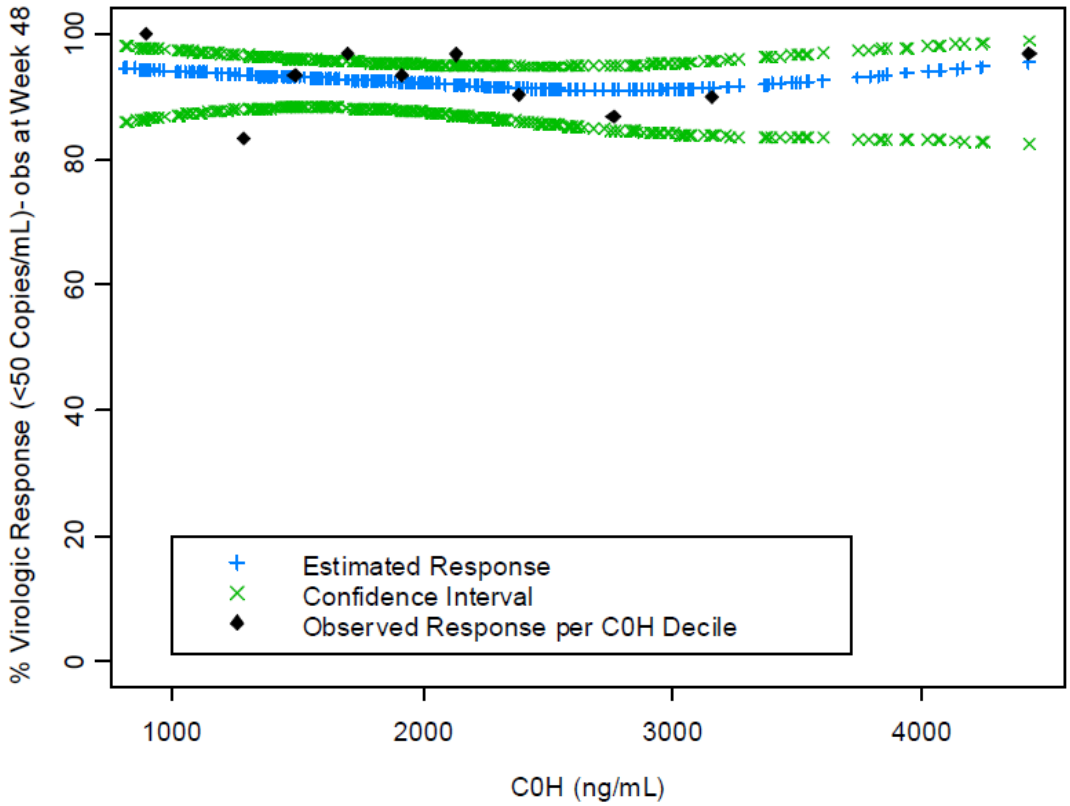
3.3.2.1 Results: TMC114-C211, Generalized Additive Model

The initial pharmacokinetic/pharmacodynamic analysis for study TMC114-C211 was extended using a generalized additive model (GAM). A univariate GAM analysis was undertaken, exploring the relationship between DRV C_{0h} and virologic response. This analysis showed a shallow relationship between DRV C_{0h} and virologic response. A fitted curve and 95% CI as well as observed virologic response per decile (i.e., 304 ordered observations split up in 10 approximately equal-sized sets), is shown in

Figure 7. This plot shows that in the HIV-1 infected, ARV treatment-naïve population from study TMC114-C211, that a flat exposure-response relationship was observed between virologic response and DRV C_{0h}.

Figure 7: Observed and Predicted Virologic Response Using a GAM to Predict Virologic Response Using DRV C0h – Study TMC114-C211



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The same model was used to predict virologic response for a similar population based on a 10%, 20%, 30%, 40%, and 50% reduction in DRV C_{0h} (Table 20).

Table 17: Predicted Mean Virologic Response Using a GAM and Assuming Various Levels in Reduction of DRV C_{0h} – Study TMC114-C211

Reduction in DRV C_{0h}	Mean Virologic Response (< 50 Copies/mL)
0%	92.8%
10%	92.9%
20%	93.0%
30%	93.2%
40%	93.5%
50%	93.9%

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Reviewer's comment: The DRV relative bioavailability trial demonstrated that DRV boosted with Cobi may result in 10% lower C_{0h} or 30% lower C_{24h}. Subsequently, the sponsor evaluated the impact of this lower DRV exposure on response based on data from the initial DRV trials. The sponsor explored DRV exposure values, such as C_{0h} and AUC, and demonstrated that no significant exposure-response relationship could be identified with DRV exposure. This relationship was further evaluated by the reviewer based on inhibitory quotient as the independent variable, which takes into account baseline susceptibility of the virus. These analyses, presented in the Key Questions, demonstrate a similar flat exposure-response relationship and predict a similar efficacy response for the scenario where DRV C_{0h} is 10% lower when boosted with Cobi compared to DRV boosted with ritonavir.

3.3.3 Results: TMC114-C229

Of the 294 subjects randomized to be treated with DRV/rtv 800/100 mg q.d., 280 subjects with sparse sampling data were included in the population pharmacokinetic analysis for DRV. The Bayesian estimates of the DRV pharmacokinetic parameters following treatment with DRV/rtv 800/100 mg q.d. from the sparse sampling data are summarized in Table 18.

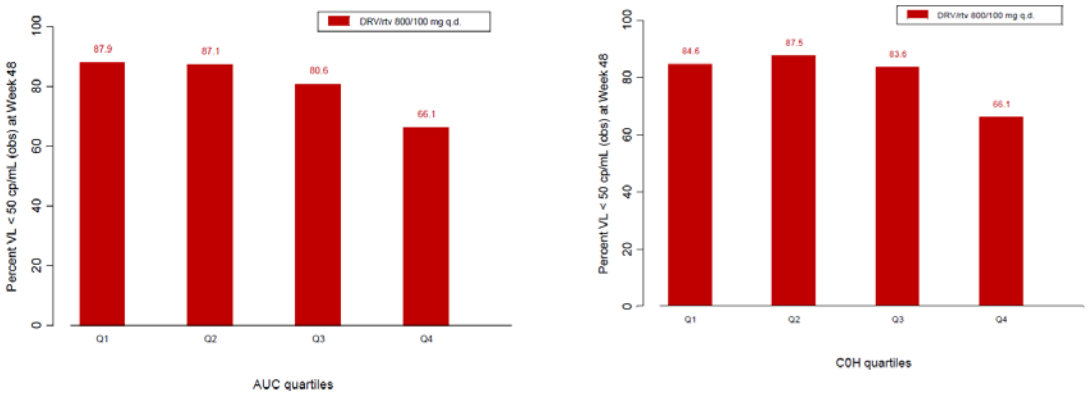
Table 18: Population Pharmacokinetic Estimates of Darunavir: Study TMC114-229

Parameter	DRV/rtv 800/100 mg q.d. Median (Range)
N	280
AUC_{24h}, ng.h/mL	87788 (45456; 236920)
C_{0h}, ng/mL	1896 (184; 7881)

Report: pg 29.

Virologic response defined as plasma viral load < 50 copies/mL at Week 48 following DRV/rtv 800/100 mg q.d. tended to be smaller in subjects with higher AUC_{24h} values (Table 19, Figure 8). No consistent relationship between DRV C_{0h} and virologic response at Week 48 was observed, although virologic response was lower in the highest quartile with the highest C_{0h} values compared to the other C_{0h} quartiles.

Figure 8: Virologic Response Defined as Viral Load <50 Copies/mL at Week 48 by Quartiles of DRV AUC and C_{0h}: Study TMC114-C229



Sponsor's report: pg 43

Table 19: Viral Load <50 Copies/mL at Week 48 by Quartile: Study TMC114-229

PK PARAMETER / VIRAL LOAD: <50 copies/ml AT WEEK 48 (OBSERVED)	QUARTILE RANGE OF PK PARAMETER							
	<= Q1		]Q1; Q2]		]Q2; Q3]		> Q3	
	N	%	N	%	N	%	N	%
AUC 24H (ng.h/ml)								
NO	8	12.1	8	12.9	12	19.4	21	33.9
YES	58	87.9	54	87.1	50	80.6	41	66.1
C0H (ng/ml)								
NO	10	15.4	8	12.5	10	16.4	21	33.9
YES	55	84.6	56	87.5	51	83.6	41	66.1

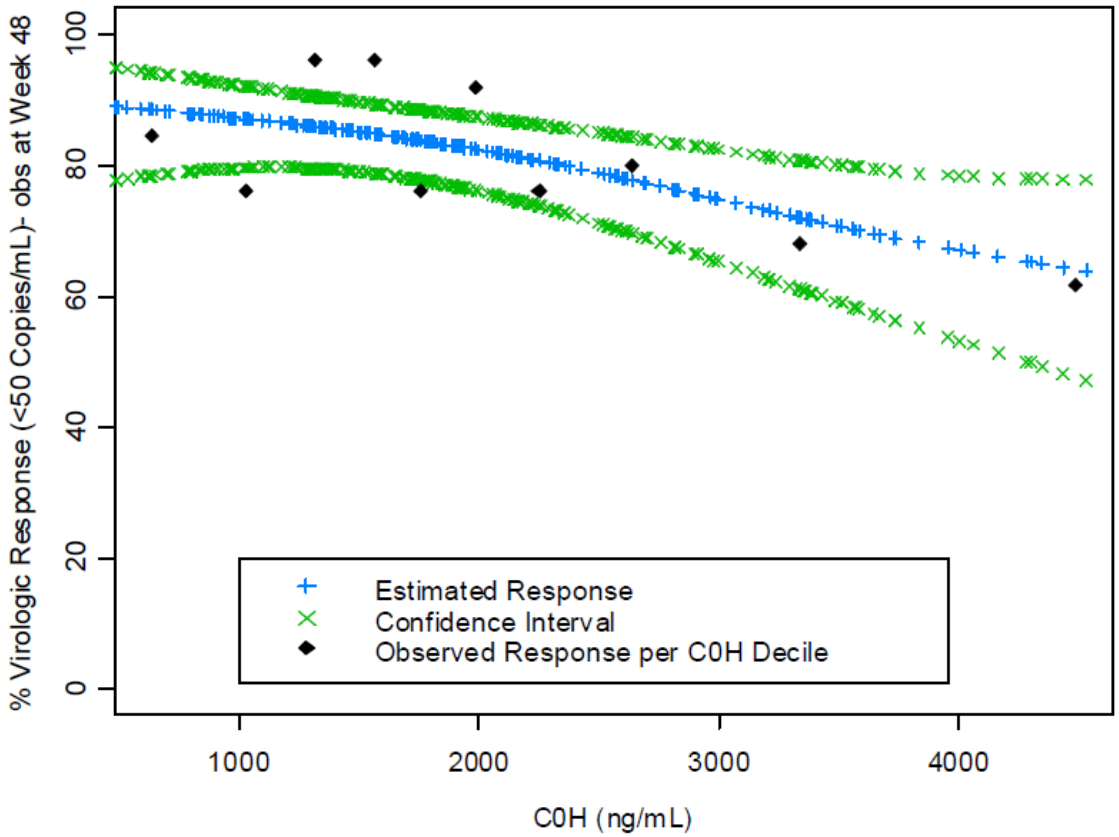
Report: pg 191

3.3.3.1 Results: TMC114-C229, Generalized Additive Model

The initial pharmacokinetic/pharmacodynamic analysis for study TMC114-C229 was extended using a GAM. A univariate GAM analysis was undertaken, exploring the relationship between DRV C_{0h} and virologic response. A fitted curve and 95% confidence interval (CI) as well as observed virologic response per decile (i.e., 252 ordered observations split up in 10 approximately equal-sized sets), is shown in

Figure 9. This plot suggests an inverse relationship between DRV C_{0h} and virologic response in the treatment-experienced HIV-1 infected population of study TMC114-C229; virologic response is somewhat lower in the highest 2 deciles of the observed DRV C0h range. In the first 8 deciles. ng/mL), there is no clear relationship between DRV C_{0h} and virologic response at the observed rate.

Figure 9: Observed and Predicted Virologic Response Using a GAM to Predict Virologic Response Using DRV C0h – Study TMC114-C229



Sponsor's report: pg 49

The same model was used to predict virologic response for a similar population with 10%, 20%, 30%, 40%, and 50% reduction in DRV C_{0h} (Table 20).

Table 20: Predicted Mean Virologic Response Using a GAM and Assuming Various Levels in Reduction of DRV C_{0h} – Study TMC114-C229

Reduction in DRV C_{0h}	Mean Virologic Response (< 50 Copies/mL)
0%	80.6%
10%	81.9%
20%	83.2%
30%	84.4%
40%	85.5%
50%	86.6%

Sponsor's report: pg 50

Reviewer's comment: Similar to the evaluation conducted for the C211 trial,, the rationale for this evaluation was the observed lower DRV C_{0h} and C_{24h} for DRV boosted with Cobi from the bioequivalence trial.. The sponsor explored DRV exposure values, such as C_{0h} and AUC, and demonstrated that an inverse exposure -response relationship was identified with DRV exposure from the available study data. This relationship was further evaluated by the reviewer based on inhibitory quotient as the independent variable, which takes into account baseline susceptibility of the virus. These analyses, presented in the Key Questions, demonstrate a similar flat exposure-response

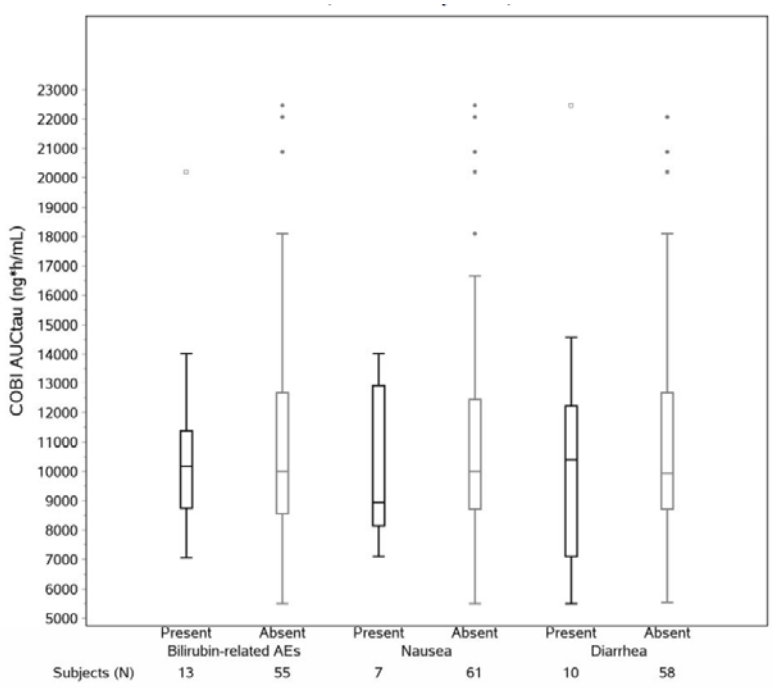
relationship and predict a similar efficacy response for the scenario where DRV C_{0h} is 10% lower when boosted with Cobi compared to DRV boosted with ritonavir. The relevance of a decrease in darunavir exposure (e.g C_{24h}) up to 30% is discussed in the Clinical Pharmacology review.

3.4 Safety of cobi in HIV-1 Treatment Naïve Subjects

Report 2.7 summary-clin-pharm.pdf: Clinical Pharmacology Summary

Pharmacokinetic-pharmacodynamic analyses of the cobi exposure-safety relationship were performed in treatment-naive HIV-1 infected subjects in the ATV/Cobi/F/T Phase 2 (GS-US-216-0105) and Phase 3 (GS-US-216-0114) trials using cobi exposures derived from intensive PK substudies versus safety parameters that included commonly observed adverse events, namely jaundice, ocular icterus, nausea, or diarrhea (Figure 10), in the same subjects. Similar cobi exposures were observed between those subjects experiencing a key adverse event during the studies and those who did not.

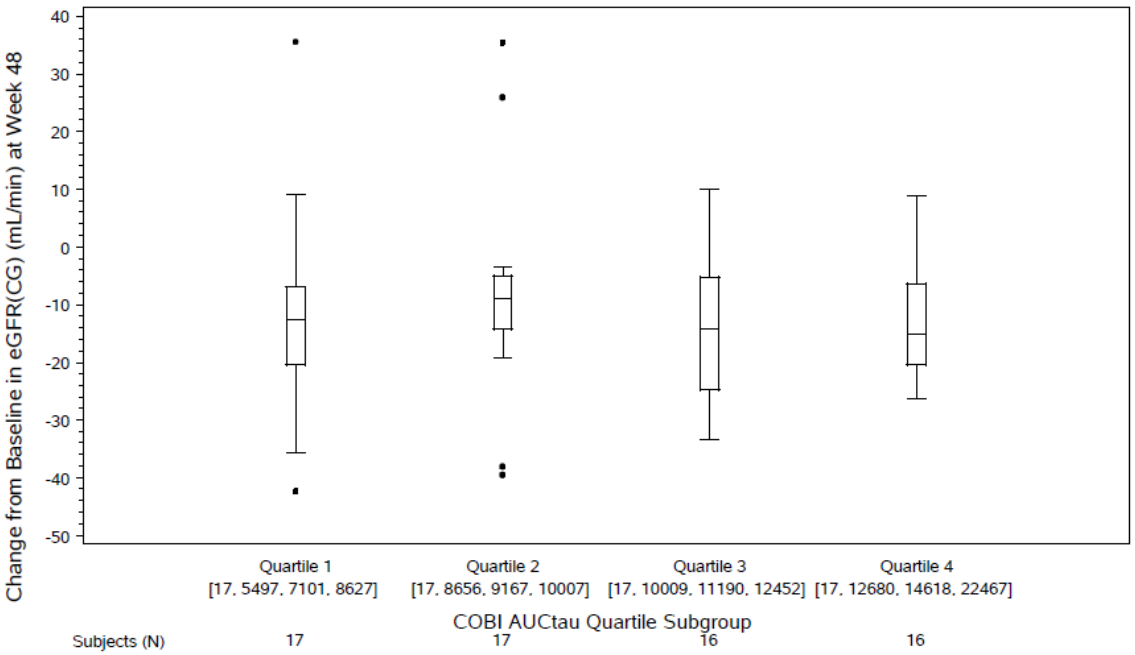
Figure 10: Boxplot of Cobi AUC_{tau} (ng•h/mL) Versus Incidence of Selected Adverse Events (Cobi PK/PD Analysis Set)



Sponsor's clin-pharm-summary.pdf, pg 224

A similar analysis was performed with respect to cobi AUC_{tau} quartiles and maximum decrease in $eGFR_{CG}$ (Figure 11). A non-significant trend of decreasing $eGFR_{CG}$ with increasing cobi AUC_{tau} was observed, though this analysis is limited by the number of subjects with cobi exposure data available.

Figure 11: Boxplot of Maximum Decrease from Baseline in $eGFR_{CG}$ (mL/min) by Cobi AUC_{tau} (ng•h/mL) (Cobi PK/PD Analysis Set)



Sponsor's clin-pharm-summary.pdf, pg 227
Reviewer's comments: No relationship between the most common adverse events and Cobi exposure were observed for jaundice, ocular icterus, diarrhea, or nausea based on the applicant's analysis.

The sponsor evaluated changes in $eGFR_{CG}$ based on cobi exposures. There was substantial overlap between subjects in all exposure quartiles, but there was a trend towards greater changed in $eGFR_{CG}$ in subjects with higher cobi exposure. This analysis is limited due to the number of subjects with cobi exposure data available (n=68).

An additional observation of increased renal adverse events in subjects receiving ATV/Cobi/F/T treatment versus ATV/RTV/F/T comparator arms was observed from the Phase III study. No exposure-response relationship regarding renal adverse events between exposures for Cobi, ATV, ritonavir, TDF, or FTC could be identified from the available data. However, this analysis is limited by the small number of events in the limited number of subjects with cobi (n=68) exposure data available.

4 REVIEWER'S ANALYSIS

4.1 Introduction

The aim of this review to examine whether the label claims and proposed dose are justified by the existing PK, efficacy, and safety data using both population PK and exposure-response analyses.

4.2 Objectives

Analysis objectives are:

1. Evaluate the Cobi population PK model for evidence of a body weight effect on clearance
2. Determine the impact of cobicistat (Cobi) exposure on common adverse events

4.3 Methods

4.3.1 Data Sets

Data sets used are summarized in Table 21.

Table 21. Analysis Data Sets

Study Number	Name	Link to EDR
TMC114-C211; TMC114-C229	Pkpar.xpt, snapshad.xpt, vlad.xpt, sasds.xpt, virology.xpt	
GS-US-216-0130	Adpp2.xpt	
Cobi PopPK	Ss150mg.xpt; run200-ctl.txt; run200-out.txt	
Cobi PK-PD	Adpkpd.xpt	
GS-US-216-0105; GS-US-216-0114	lbad.xpt	

4.3.2 Software

Estimation and simulation were performed NONMEM 7.2 on the Pharmacometrics Group Linux cluster using the front end manager Perl Speaks NONMEM (PsN). Diagnostic graphs, model comparison, and statistical analysis were performed in R (version 10.1).

4.3.3 Models

4.3.3.1 Population Pharmacokinetics

The applicant's final population PK model was used as the starting point for the reviewer's analysis. The structure was a one-compartment model with both zero- and first-order absorption and a lag-time. Interindividual variability was estimated with an exponential structure on apparent oral clearance (CL/F), apparent central volume of distribution (V_c/F), absorption rate constant (ka), the duration of zero-order absorption (D1), lag-time (ALAG1), and as an additional term on intrasubject variability, similar to the sponsor. Proportional residual variability was included. The identified covariate effect of body weight and apparent central volume of distribution was also including on the initial model. The reviewer's analysis focused on evaluating the impact of body weight on the applicant's model.

4.3.3.2 Logistic Regression: Safety Exposure-Response Relationships

Logistic regression models for common adverse events were performed using the applicant's Phase II/III trial data. Three independent variables were used for developing logistic regression plots: steady-state AUC (AUC_τ), maximum concentration (C_{max}), and trough concentration (C_{0h}). AUC_τ and C_{0h} were calculated for each subject using empirical Bayes' estimates from the population PK model. C_{max} was obtained from subjects with intensive PK sampling during Phase III.

4.4 Results

4.4.1 Population Pharmacokinetics

Based on goodness of fit plots, OFV decrease, and impact on IIV plots, the model structure identified by the applicant was improved by the addition of body weight as a power law covariate on apparent clearance. The addition of body weight on clearance resulted in a significant reduction in the objective function value (OFV; -12289 to -12373), modest decreases in the interindividual variability estimates, and further reduced the dependency between body weight and the interindividual variability estimate for apparent clearance from the posthoc estimates (Figure 12). The base model parameters were relatively unchanged compared to the reviewer's run of the applicant's final model (slight differences from the applicant's numbers) (Table 22) despite the addition of body weight as a covariate on apparent clearance.

Figure 12: Interindividual Variability Plots for CL for the Applicant's (Left) and Reviewer's (Right) Final Model.

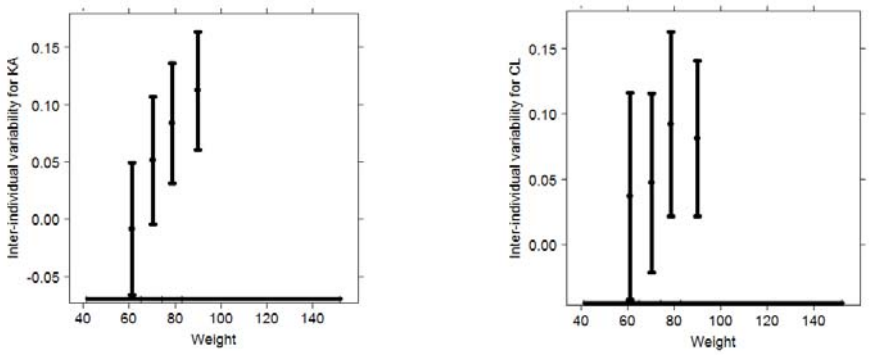


Table 22 Parameter estimates for the reviewer's analysis evaluating inclusion of body weight in the sponsor's final model

Fixed-Effects Parameters	Applicant's Model	Reviewer's Model
KA (Oral Absorption, 1/h)	0.90	0.89
D_1 (Zero-order Absorption, h)	1.26	1.27
ALAG1 (Lag-time, h)	0.21	0.26
Typical CL/F (Clearance, L/hr)	16.3	13.8
Normalized body weight (74.4 kg) on clearance	N/A	0.57
Typical V_c/F (Central volume, L)	76.1	77.2

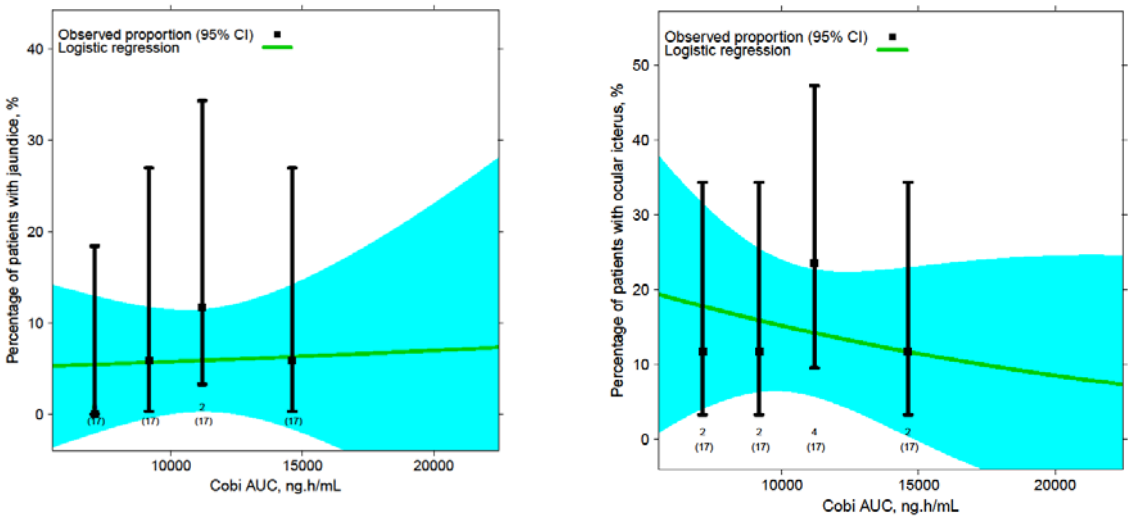
Normalized body weight (74.4 kg) on V_c	0.84	0.92
Inter-Individual Variability Parameters (CV%)	**Estimate**	**Estimate**
KA	51	46
D1	67	79
CL	53	51
V_c	25	25
ALAG1	122	95
Intra-Individual Variability Parameters (sigma)	**Estimate**	**Estimate**
Proportional Error	0.19	0.19

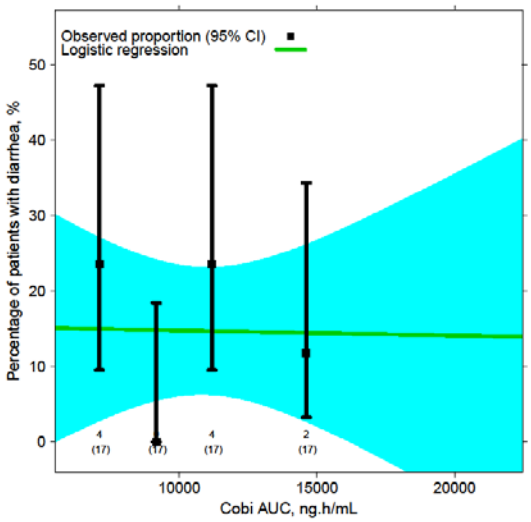
The body weight effect on clearance does not necessitate any dose adjustments in adults based on the current submission; however, the body weight relationship with clearance should be considered when recommending cobicistat dosing for future pediatric studies.

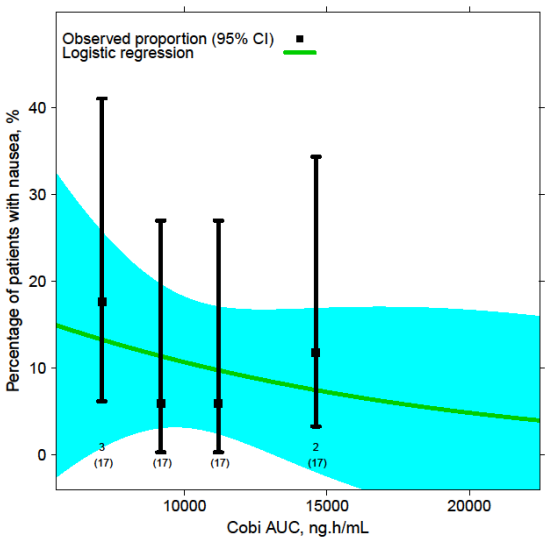
4.4.2 Exposure-Response for Safety: Other Adverse Events

Logistic regression models were evaluated for Cobi $C_{0h,}$ C_{max}, and AUC_τ with no significant relationships identified. Modeling results for adverse event rates versus cobi AUC_τ (Figure 13) indicate no significant relationship.

Figure 13: Percentage of Subjects with Jaundice (top left), Ocular Icterus (top right), Diarrhea (bottom left), and Nausea (bottom right) Adverse Events Versus Cobi AUC_τ for All Treatment Naïve Subjects with PK Sampling (n = 68)







5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
ATV_PK_Distribution.R	File for plotting the distribution of Atazanavir PK parameters from the Phase II/III data	Reviews\Ongoing PM Reviews\Cobicistat_NDA203094_JAF\PPK Analyses
Run200 mod, run200.lst	Sponsor's final PK models	Reviews\Ongoing PM Reviews\Cobicistat_NDA203094_JAF\PPK Analyses
Run1 mod, run1.lst, sdtab1, patab1, cotab1, catab1	Reviewer's final PK model and outputs	Reviews\Ongoing PM Reviews\Cobicistat_NDA203094_JAF\PPK Analyses
Cobi_Safety_ER.R	Cobicistat safety analysis based on Phase II/III exposures data	Reviews\Ongoing PM Reviews\Cobicistat_NDA203094_JAF\ER Analyses
Darunavir_ER_Analysis_Prior.R	Previous Darunavir ER analysis from original submission and PK summary of 0130 and the prior DRV efficacy studies	Reviews\Ongoing PM Reviews\Cobicistat_NDA203094_JAF\ER Analyses
SerumCreatinine_ShiftTables.R	Shift table summaries of serum creatinine from the Phase III study	Reviews\Ongoing PM Reviews\Cobicistat_NDA203094_JAF\ER Analyses

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/s/

STANLEY AU
03/22/2013

JEFFRY FLORIAN
03/22/2013

YANING WANG
03/22/2013
Signing for the pharmacometric review

SHIRLEY K SEO
03/22/2013

BIOPHARMACEUTICS NDA REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 203-094	**Reviewer:** Deepika Arora Lakhani, PhD	
Submission Date:	June 28, 2012 Aug 21, 2012 Nov 27, 2012		
Division:	Division of Antiviral Products	**Team Leader (Acting):** Sandra Suarez Sharp, PhD	
Sponsor:	Gilead Sciences, Inc.	**Biopharmaceutics Supervisor (Acting):** Richard Lostritto, PhD	
Trade Name:	-Tybost- (under review)	**Date Assigned:**	July 5, 2012
Generic Name:	Cobicistat, Tablets	**Date of Review:**	Dec 18, 2012
Indication:	Pharmacokinetic enhancer of the HIV-1 protease inhibitors atazanavir (ATV) and darunavir (DRV) in adults	**Type of Submission:** New Drug Application 505b(1)	
Formulation/ strengths	IR Tablet; 150 mg COBI		
Route of Administration	Oral		

SUMMARY OF BIOPHARMACEUTICS FINDINGS:

The submission is a 505(b)(1) application for film coated cobicistat (COBI) tablet, an immediate-release tablet containing 150 mg of cobicistat. Cobicistat is a new chemical entity and structural analogue of ritonavir (RTV, r) without antiretroviral (ARV) activity. COBI was approved on Aug 27, 2012 under NDA 203-100 as a component in the 4-drug fixed-dose combination tablet (the QUAD STR).

Some aspects of the product and process development of COBI tablet were conducted under a Quality by Design (QbD) paradigm to ensure desired product performance in terms of quality, safety, and efficacy.

This review focuses on: a) the acceptability of the dissolution method and acceptance criterion; b) the role of dissolution to support the bridging between formulation 2 (used in study supporting the Darunavir indication) and the to be marketed cobicistat formulation; c) the role of dissolution as a response parameter (b) (4)

a) Dissolution Method and Acceptance Criterion:

The following method and acceptance criterion were proposed and deemed acceptable:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Acceptance Criterion
COBI	Tablet	Paddle	75	50 mM sodium acetate buffer (pH 4.5)	900 mL	Q= (b) (4) at 15 min

The robustness of the dissolution method was evaluated by assessing the effect of small, deliberate changes

in the tablet formulation composition (b) (4) and processing parameters (b) (4) The dissolution method (b) (4) was deemed acceptable.

b) Dissolution to support the bridging between formulation 2 (used in study supporting the Darunavir indication) and the to be marketed cobicistat formulation

During product development, there were excipient changes made between the commercial formulation and the formulation (formulation 2) that was used in the clinical trial supporting the Darunavir indication. (b) (4) (b) (4) (b) (4) Dissolution profile comparisons (from 3 different pH media) showed no difference between these two formulations (*f2* >50). Though as per SUPAC the formulation change is a Level 3 change, a risk-based approach was utilized and dissolution data was deemed adequate to support that a BE study is not needed to bridge the two formulations.

c) Dissolution as a response parameter (b) (4) (b) (4)

The effect of (b) (4) process parameters was assessed on (b) (4) physical properties (b) (4) (b) (4) and dissolution was tested as a response parameter. During the review cycle, the Applicant was requested to support the design space by providing the *f2* statistical testing for COBI dissolution profile comparisons of tablets manufactured (b) (4) . Data supported that the dissolution profiles of all batches (b) (4) met the *f2* criteria when compared to the reference formulation (clinical batch). Therefore, the proposed ranges (b) (4) are acceptable from Biopharmaceutics perspective. (b) (4)

d) Dissolution to aid selection of design space for film-coating

The effects of the amount of film-coat level (b) (4) and tablet dissolution were evaluated. (b) (4) Dissolution data and *f2* analysis is provided and supports the following ranges: (b) (4) (b) (4)

RECOMMENDATION:

The ONDQA/Biopharmaceutics team has reviewed NDA 203-094 and its amendments submitted on Aug 21, 2012; and Nov 27, 2012. From Biopharmaceutics perspective NDA 203-094 for Tybostat is recommended for approval.

The following dissolution method for the COBI tablets is deemed acceptable:

Apparatus II , 50 mM sodium acetate buffer (pH 4.5), 900 mL, 75 rpm

The following dissolution acceptance criterion was proposed by the Applicant and deemed adequate for

COBI 150 mg IR tablets:

COBI: Q= (b) (4) at 15 mins

Comments to the CMC Reviewer

The following design space or target ranges proposed by the Applicant and recommended by the reviewer are provided below for each parameter:

- COBI (b) (4) design space (b) (4): ACCEPTABLE
- Design space for film coat (b) (4): ACCEPTABLE
- (b) (4) ACCEPTABLE
- (b) (4) ACCEPTABLE

Deepika Arora Lakhani, PhD
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Sandra Suarez Sharp, PhD
Biopharmaceutics Secondary Signature
Office of New Drugs Quality Assessment

cc. *on file; RLostritto; ADorantes*

INTRODUCTION

Cobicistat (COBI) is a new chemical entity and structural analogue of ritonavir (RTV, r) without antiretroviral (ARV) activity. It is a more specific, mechanism-based cytochrome P450 3A (CYP3A) inhibitor than RTV that enhances or "boosts" the exposure of CYP3A substrates, including atazanavir (ATV) and darunavir (DRV). COBI was recently approved under NDA 203-100 as a component in the 4-drug fixed-dose combination tablet (the QUAD STR) which is comprised of the integrase strand-transfer inhibitor (INSTI) elvitegravir (EVG), COBI, and the current standard-of-care dual nucleoside/nucleotide reverse transcriptase inhibitor (NRTI/NtRTI) backbone FTC/TDF (Truvada® [TVD]). The NDA for the QUAD STR (NDA 203100) was submitted to the FDA on 27 October 2011, with an indication as a complete regimen for the treatment of HIV-1 infection in adults who are antiretroviral treatment-naïve or who have no known resistance mutations to the individual components. This NDA was approved on 27 August 2012.

Drug Substance

Cobicistat: COBI (Figure 1) is considered a BCS Class 2 drug due to the lower solubility at higher physiological pHs. COBI has three dissociation constants at 1.8, 2.5, and 6.4 and solubility is affected by pH.

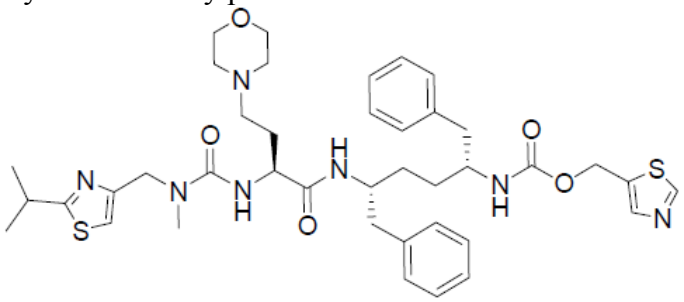

Figure 1. Chemical Structure of Cobicistat

The aqueous solubility of COBI (Figure 2) is low at basic pH (less than 1 mg/mL at pH >5) and is significantly enhanced under acidic conditions (over 70 mg/mL at pH 2.2).

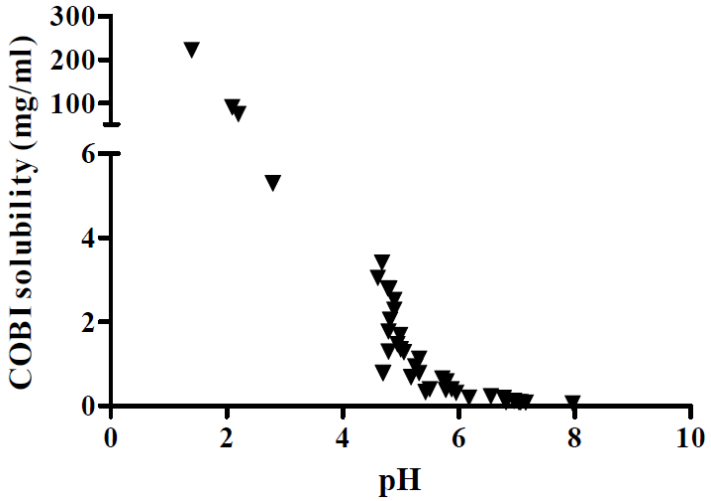

Figure 2. Aqueous Solubility-pH Profile of COBI (free base) at Room Temperature

Drug Product

The COBI tablet is an immediate-release tablet containing 150 mg of cobicistat. The tablets are orange, round, biconvex, film-coated tablets, and debossed with "GSI" on one side and plain-faced on the other side. The composition of the tablets is provided in Table 1.

Table 1. Composition of COBI Tablets

Components	% w/w	Unit Formula (mg/unit)	Quality Standard	Function
Cobicistat on Silicon Dioxide		(b) (4)	In-House	Active
Microcrystalline Cellulose			NF, Ph. Eur., JP	(b) (4)
Croscarmellose Sodium			NF, Ph. Eur., JP	
Magnesium Stearate			NF, Ph. Eur., JP	
Total	100.0	(b) (4)		
Tablet Core				
Film Coat				
		(b) (4)	In-House	Film Coat
			USP, Ph. Eur.	(b) (4)
				(b) (4)

Formulation Development

The formulations manufactured through the clinical development of the proposed product are summarized in Table 2.

Table 2. Quantitative Composition of Cobicistat Tablets, 150 mg, used in Clinical Studies

Ingredient for Tablet Core	**Amount (%w/w)**		
Clinical Phase	**Phase 1/2**	**BE Study**	**Phase 3**
(b) (4)			
(b) (4) Cobicistat on Silicon Dioxide	(b) (4)		
(b) (4) Microcrystalline Cellulose			
Croscarmellose Sodium			
(b) (4) Magnesium Stearate			
(b) (4)			
Total core weight (mg)			
Film-coating			
(b) (4)			

The tablets for the Phase 3 study and the intended commercial product are of identical formulation, manufactured by the same process, (b) (4) with identical tablet dimensions. Three lots of tablets of this formulation were manufactured and used as primary stability lots.

(b) (4)

(b) (4) A pivotal bioequivalence (BE) study GS-US-216-0116 was performed to evaluate the formulation (b) (4) The BE study compared a slightly modified formulation of the final formulation with preliminary formulation (b) (4) The composition

details of the formulations are provided in Table 3, later in the review. According to the Applicant, both the cobicistat tablet formulations (b) (4) were confirmed to be bioequivalent for all 3 pharmacokinetic (PK) parameters tested (AUC_{tau}, C_{max}, and C_{tau}).

A brief overview of the manufacture of the drug product is summarized in the diagram below.

(b) (4)

(b) (4)

DISSOLUTION METHOD

The dissolution method that is being proposed as a quality control tool for Tybost tablets, is summarized below:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)
COBI	Tablet	II (paddle)	75	50 mM sodium acetate buffer (pH 4.5)	900 mL, 37 °C

DISSOLUTION METHOD DEVELOPMENT

Dissolution Apparatus Selection

The paddle apparatus was chosen for the dissolution of cobicistat tablets in order to establish appropriate hydrodynamics.

Dissolution Medium Selection

(b) (4)

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(b) (4)

CONCLUSIONS

The NDA is recommended for Approval from a Biopharmaceutics perspective. The following dissolution method for the COBI Tablet is deemed acceptable:
Apparatus II, 50 mM sodium acetate buffer (pH 4.5), 900 mL, 75 rpm

The following dissolution acceptance criterion was proposed and deemed adequate:
COBI: Q= (b) (4) **at 15 mins**

Comments to the CMC Reviewer
The following design space or target ranges proposed by the Applicant and recommended by the reviewer are provided below for each parameter:

- (b) (4) ACCEPTABLE
- (b) (4) ACCEPTABLE
- (b) (4) ACCEPTABLE

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/s/

DEEPIKA LAKHANI
03/19/2013
Recommend Approval from Biopharmaceutics perspective.

SANDRA SUAREZ
03/19/2013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**203094**	**Brand Name**	**To be determined**
OCP Division (I, II, III, IV, V)	**DCP4**	**Generic Name**	**Cobicistat**
Medical Division	**DAVP**	**Drug Class**	**None**
OCP Reviewer	**Stanley Au**	**Indication(s)**	**Treatment of HIV-1 infection**
OCP Team Leader	**Shirley Seo (acting)**	**Dosage Form**	**Tablets**
Pharmacometrics Reviewer	**Jeff Florian**	**Dosing Regimen**	**150 mg once daily**
Date of Submission	**June 27, 2012**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**March 22, 2013**	**Applicant**	**Gilead Sciences**
Medical Division Due Date (estimated)	**March 29, 2013**	**Priority Classification**	**Standard**
PDUFA Due Date	**April 28, 2013**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed)for the filing review)	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**1) Cobicistat validation reports: 6** **2) Validation reports for other analytes: 24** **3)Bioanalytical Reports (for the cobicistat trials listed below except for GS-US-216-111 and GS-US-216-107): 29**	Not applicable	Not applicable	
I. Clinical Pharmacology				
Mass balance:	**X (GS-US-216-111)**	**1**	**1**	
Isozyme characterization:	**X (AD-216-2025)**	**1**		
Blood/plasma ratio:	**X**	**1 (evaluated as part of mass balance trial)**		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Plasma protein binding:	**X (AD-216-2026)**	**1**		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X (GS-US-216-101, GS-US-216-113)**	**2**	**2**	
multiple dose:	**X((GS-US-216-101, GS-US-216-113)**	**2**	**2**	
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:	**X (GS-US-216-112)**	**1**	**1**	
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK or PK/PD -				
Phase 1 and/or 2, proof of concept:	**X (GS-US-216-105)**	**1**	**1**	
Phase 3 clinical trial:	**X (GS-US-216-114)**	**1**	**1**	
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X (GS-US-216-116)**	**1**	**1**	
ritonavir as reference	**X (GS-US-216-110, GS-US-216-119, GS-US-216-115)**	**3**	**3**	
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
QT trial	**X (GS-US-216-107)**	**1**	**1**	

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Markers of renal function	**X (GS-US-216-121)**	**1**	**1**	
Pediatric development plan				
Trials submitted with elvitegravir PK data or miscellaneous trials	**X (GS-US-201-101, GS-US-183-133, GS-US-216-124, GS-US-201-104, GS-US-216-120, GS-US-216-122, GS-US-216-123, GS-US-236-105, GS-236-106)**	**9**	**9**	
Literature References				
Total Number of Studies		12 (excluding (b) (4) miscellaneous trials)		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?		X		The required bioavailability/ bioequivalence data necessary to support an indication for once daily dosing for darunavir /cobicistat will be a review issue.
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			Based on the GS-US-216-101 trial.
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-	X			

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	submission discussions, submitted in the appropriate format (e.g., CDISC)?				
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		X		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
___Yes_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

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Reviewing Clinical Pharmacologist	Date
Team Leader/Supervisor	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STANLEY AU
08/17/2012

SHIRLEY K SEO
08/20/2012