

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203094Orig1s000**

**203094Orig2s000**

**MICROBIOLOGY / VIROLOGY REVIEW(S)**

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)**

**VIROLOGY REVIEW**

**NDA:** 203-094    **SDN:** 041    **DATE REVIEWED:** 4/25/14  
**Clinical Virology Reviewer:** Takashi E. Komatsu, Ph.D., RAC

**NDA #:** 203-094

Supporting Document Numbers: **041**

**Applicant Name and Address:** Gilead Sciences, Inc.  
 333 Lakeside Drive  
 Foster City, CA 94404

**Reviewer's Name:** Takashi E. Komatsu, Ph.D., RAC

**Initial Submission Dates:**

**Correspondence Date:** March 28, 2014  
**CDER Receipt Date:** March 28, 2014  
**Reviewer Receipt Date:** March 31, 2014  
**Review Complete Date:** July 15, 2014  
**PDUFA Date:** September 28, 2014

**Amendments:**

**Response to Information Request (SDN 042):** March 28, 2014  
**Response to Information Request (SDN 045):** April 3, 2014

**Related/Supporting Documents:**

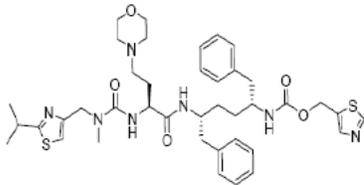
NDA 203,100 for EVG/COBI/FTC/TDF tablet  
 IND 101,283 for cobicistat (COBI)  
 IND 72,177 for elvitegravir  
 IND (b) (4), IND 53,971 and NDA 21-500 for emtricitabine  
 IND 52,849 and ND 21-356 for tenofovir DF  
 IND 67,671 and NDA 21-752 for emtricitabine and tenofovir

**Product Name(s):** TYBOST

**Proprietary:** TYBOST

**Non-Proprietary/USAN:** cobicistat

**Code Name/Number:** COBI 150 mg

Individual Component	<b>cobicistat (COBI)</b>
Structure	
Chemical Name	1,3-thiazol-5-ylmethyl[(2R,5R)-5-[[[(2S)-2-[(methyl[[2-(propan-2-yl)-1,3-thiazol-4-yl]methyl]carbamoyl)amino]-4-(morpholin-4-yl)butanoyl]amino]-1,6-

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)**

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	diphenylhexan-2-yl]carbamate
Molecular Formula	C <sub>40</sub> H <sub>53</sub> N <sub>7</sub> O <sub>5</sub> S <sub>2</sub>
Molecular Mass	776.02
Drug Class	Pharmacoenhancer (No anti-HIV-1 activity)
Supporting Document	IND 102,283

**Indication(s):** Use as a pharmacokinetic enhancer of the HIV 1 protease inhibitors (PIs) atazanavir and darunavir in adults

**Dosage Form(s):** Tablet; Cobicistat 150 mg

**Route(s) of Administration:** Oral

**Recommended Dosage:** One tablet taken once daily with food

**Dispensed:** Rx   X   OTC    (Discipline relevant)

**Abbreviations:** AAG, alpha-1-acid glycoprotein; ABC, abacavir; ADV, adefovir; APV, amprenavir; ARV, antiretroviral; ATR, Atripla; ATV, atazanavir; ATV/r, ritonavir-boosted atazanavir; AZT, zidovudine; bp, base pair; CC<sub>50</sub>, 50% cytotoxic concentration; COBI, cobicistat; ddi, didanosine; DHHS, Department of Health and Human Services; DRV, darunavir; d4T, stavudine; EC<sub>50</sub>, effective concentration inhibiting viral replication by 50%; EC<sub>90</sub>, effective concentration inhibiting viral replication by 90%; EC<sub>95</sub>, effective concentration inhibiting viral replication by 95%; EFV, efavirenz; ETR, etravirine; ETV, entecavir; FBS, fetal bovine serum; FTC, emtricitabine; HAART, highly active antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus (including HIV-1 and -2); HIV-1, human immunodeficiency virus type 1; HIV-2, human immunodeficiency virus type 2; HS, human serum; HSA, human serum albumin; IC<sub>50</sub>, 50% inhibitory concentration; IDV, indinavir; IL-2, interleukin 2; IN, HIV-1 integrase; INSTI, HIV-1 integrase strand transfer inhibitor; LAM, lamivudine; LPV, lopinavir; L-dT, telbivudine; L-FMAU, clevudine; MDR, multidrug-resistant; MOI, multiplicity of infection; MVC, maraviroc; NDA, new drug application; NFV, nelfinavir; NNRTI, HIV-1 non-nucleoside reverse transcriptase inhibitor; NR, virologic non-response; N(t)RTI, HIV-1 nucleos(t)ide reverse transcriptase inhibitor; NVP, nevirapine; PBMC, peripheral blood mononuclear cell; PCR, polymerase chain reaction; PI, HIV-1 protease inhibitor; PI/r, ritonavir-boosted HIV-1 protease inhibitor; PK, pharmacokinetics; PR, HIV-1 protease; QD, once daily; RAL, raltegravir; RBV, ribavirin; RPV, rilpivirine; RT, HIV-1 reverse transcriptase; RTE, resistance testing eligible; RTI, HIV-1 reverse transcriptase inhibitor; RTV, ritonavir; SD, standard deviation; SI, selective index; SQV, saquinavir; SR, suboptimal virologic response; TAM, thymidine analogue mutation; TDF, tenofovir disoproxil fumarate; TFV, tenofovir (active moiety of the diester prodrug TDF); TPV, tipranavir; TVD, Truvada; T-20, enfuvirtide; VF, virologic failure; VR, virologic rebound;

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)**

**VIROLOGY REVIEW**

**NDA:** 203-094    **SDN:** 041    **DATE REVIEWED:** 4/25/14  
**Clinical Virology Reviewer:** Takashi E. Komatsu, Ph.D., RAC

**EXECUTIVE SUMMARY**

This application is a resubmission of an original NDA for TYBOST tablets (cobicistat, COBI, 150 mg) submitted in response to the complete response issued on April 26, 2013 due to several CMC, manufacturing, and Clinical Pharmacology deficiencies. TYBOST is a pharmacoenhancer indicated for use with the HIV-1 protease inhibitors (PIs) atazanavir and darunavir. No Clinical Virology deficiencies were identified in the review of the original submission. The resubmission does not contain any new Clinical Virology data and the Clinical Virology sections of the label have not been changed. Please see the Clinical Virology review of NDA 203094 SDN 000 and NDA 203100 SDN 000 for a detailed analysis of the mechanism of action, antiviral activity in cell culture, cytotoxicity, combination antiviral activity relationships with approved antiretroviral drugs as well as the methods that were used for the analyses for COBI.

**1. Recommendation and Conclusion on Approvability:**

Approval is recommended with respect to Clinical Virology of this original NDA for TYBOST tablet (COBI 150 mg), once daily, as a pharmacokinetic enhancer of the HIV 1 protease inhibitors (PIs) atazanavir and darunavir in adults aged 18 years and over.

**2. Conclusions**

This submission contains the sponsor's responses to the complete response letter issued on 4/26/13. The complete response letter was issued due to several CMC, manufacturing, and Clinical Pharmacology deficiencies. Please see the CMC review by Dr. Fuqiang Liu, Ph.D. and Clinical Pharmacology review by Dr. Stanley Au, Ph.D. for a detailed analysis of the resubmission.

**3. Microbiology Package Insert**

There were no changes made to the Clinical Virology sections of the label in this resubmission.

12.1 Mechanism of Action

Cobicistat is a mechanism-based inhibitor of cytochrome P450 3A (CYP3A). Inhibition of CYP3A-mediated metabolism by cobicistat increases the systemic exposure of CYP3A substrates.

12.4. Microbiology

Antiviral Activity

Cobicistat does not inhibit recombinant HIV-1 protease in a biochemical assay and has no detectable antiviral activity in cell culture against HIV-1, HBV or HCV. The antiviral activity in cell culture of approved HIV-1 antiretroviral drugs was not antagonized by cobicistat.

Resistance

In an analysis of treatment-failure subjects who received cobicistat coadministered with atazanavir in Study 114 through Week 48, evaluable genotypic data from paired baseline and treatment-failure isolates were available for 11 of the 12 virologic failures in the TYBOST group [3%, 11/344]. Among the 11 subjects, 2 developed the

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)**

**VIROLOGY REVIEW**

**NDA:** 203-094    **SDN:** 041    **DATE REVIEWED:** 4/25/14  
**Clinical Virology Reviewer:** Takashi E. Komatsu, Ph.D., RAC

emtricitabine-associated resistance substitution M184V. No subject developed the tenofovir associated resistance substitution K65R or any primary resistance substitution associated with protease inhibitors. In the ritonavir group, evaluable genotypic data is available for all 12 virologic failures [3%, 12/348] and no subject had emergent resistance to any component of the regimen.

**4. Administrative**

**4.1. Reviewer's Signatures**

\_\_\_\_\_  
Takashi E. Komatsu, Ph.D., RAC  
Clinical Virology Reviewer

**4.2. Concurrence**

\_\_\_\_\_  
HFD-530/Clin.Virol.TL/J. O'Rear, Ph.D.

CC:  
HFD-530/NDA # 203094  
HFD-530/Division File  
HFD-530/PM/Winestock

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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TAKASHI E KOMATSU  
07/15/2014

JULIAN J O REAR  
07/15/2014

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)  
VIROLOGY REVIEW**

**NDA#:** 203094 **SDN** 040 (**SN** 040) **DATE REVIEWED:** 3/11/14

**Reviewer:** Takashi E. Komatsu, Ph.D.

**Date Submitted:** 3/5/14

**Date Assigned:** 3/11/14

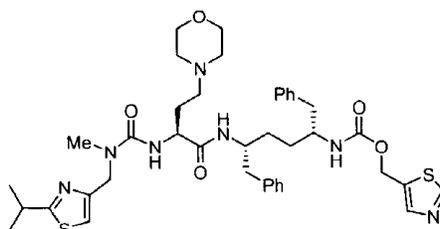
**Date Received:** 3/11/14

**Sponsor:** Gilead Sciences, Inc.  
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**Product Names:** GS-9350, COBI

**Chemical Names:** thiazol-5-ylmethyl (2*R*, 5*R*)-5-((*S*)-2-(3-((2-isopropylthiazol-4-yl)methyl)-3-methylureido)-4-morpholinobutanamido)-1,6-diphenylhexan-2-ylcarbamate

**Structure:**



**Cobicistat**

**Molecular formula:** C<sub>40</sub>H<sub>53</sub>N<sub>7</sub>O<sub>5</sub>S<sub>2</sub>

**Molecular weight:** 776.02

**Drug category:** Pharmacokinetic enhancer

**Indication:**

**Dosage Form/Route of administration:** tablet/Oral

**Supporting documents:**

**Abbreviations:** ATV, atazanavir; COBI, cobicistat; DRV, darunavir; HIV, human immunodeficiency virus; PI, protease inhibitor; RTV, ritonavir;

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)  
VIROLOGY REVIEW**

**NDA#: 203094 SDN 040 (SN 040) DATE REVIEWED: 3/11/14**

**BACKGROUND and SUMMARY**

This submission the sponsor's responses to the Division's comments communicated to the sponsor on 1/16/14 with respect to the Proposed Pediatric Study Request. The Division requested the collection and submission of resistance data from the study to be:

*Resistance: Collect and submit information regarding the resistance profile (genotypic and/or phenotypic) of clinical isolates at baseline and during treatment from pediatric subjects receiving ATV/COBI and DRV/COBI, particularly from those who experience loss of virologic response.*

**Sponsor's Response:** Study 1 is an open-label pediatric pharmacokinetic (PK), safety, and antiviral activity trial of once daily ATV/COBI or once daily DRV/COBI combined with a background regimen in HIV-1 pediatric subjects from 3 months to less than 18 years of age (for ATV/cobicistat) and 3 years to less than 18 years of age (for DRV/cobicistat) who have suppressed viremia (HIV-1 RNA <50 copies/mL at screening) on a stable ATV/RTV or DRV/RTV regimen for at least 3 months prior to screening. Because patients will be virologically-suppressed at the start of the study, Gilead will not be able to collect the resistance profile (genotypic or phenotypic) of clinical isolates at baseline. However, Gilead will collect available historical resistance data.

Therefore, Gilead requests that this paragraph be modified as shown below. Changes to FDA's text are shown in bold print.

*Resistance: Collect and submit information regarding the resistance profile (genotypic and/or phenotypic) of clinical isolates **prior to study enrollment if available** and during treatment from pediatric subjects receiving ATV/COBI and DRV/COBI, particularly from those who experience loss of virologic response.*

**Response (not to be communicated to the sponsor):** The sponsor's proposal is reasonable.

**CONCLUSIONS**

This submission the sponsor's responses to the Division's comments communicated to the sponsor on 1/16/14 with respect to the Proposed Pediatric Study Request. The sponsor's proposal is reasonable. No regulatory action with respect to Clinical Virology is necessary at this time.

**Takashi E. Komatsu, Ph.D.  
Clinical Virology Reviewer**

**CONCURRENCES**

\_\_\_\_\_ **Date:** \_\_\_\_\_  
**HFD-530/Clin Virology TL/J O'Rear**

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)  
VIROLOGY REVIEW  
NDA#: 203094 SDN 040 (SN 040) DATE REVIEWED: 3/11/14**

**cc:  
HFD-530/Original IND  
HFD-530/Division File  
HFD-530/RPM/Min**

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/s/  
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TAKASHI E KOMATSU  
03/11/2014

JULIAN J O REAR  
03/11/2014

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)**

**VIROLOGY REVIEW**

**NDA: 203-094 SDN: 000 DATE REVIEWED: 3/5/13**

**Clinical Virology Reviewer: Takashi E. Komatsu, Ph.D.**

**NDA #: 203-094**

**Supporting Document Numbers: 001**

**Applicant Name and Address:** Gilead Sciences, Inc.  
333 Lakeside Drive  
Foster City, CA 94404

**Reviewer's Name:** Takashi E. Komatsu, Ph.D.

**Initial Submission Dates:**

**Correspondence Date:** June 26, 2012

**CDER Receipt Date:** June 28, 2012

**Reviewer Receipt Date:** June 28, 2012

**Review Complete Date:** 3/5/13

**PDUFA Date:** April 28, 2013

**Amendments:**

**Response to Labeling Revision Request (SDN 010):** October 9, 2012

**Labeling/Package Insert Draft (SDN 022):** February 25, 2013

**Related/Supporting Documents:**

NDA 203,100 for EVG/COBI/FTC/TDF tablet

IND 101,283 for cobicistat (COBI)

IND 72,177 for elvitegravir

(b) (4), IND 53,971 and NDA 21-500 for emtricitabine

IND 52,849 and ND 21-356 for tenofovir DF

IND 67,671 and NDA 21-752 for emtricitabine and tenofovir

**Product Name(s):** TYBOST

**Proprietary:** TYBOST

**Non-Proprietary/USAN:** cobicistat

**Code Name/Number:** COBI 150 mg

Individual Component	cobicistat (COBI)
Structure	
Chemical Name	1,3-thiazol-5-ylmethyl[(2R,5R)-5-[[[(2S)-2-[(methyl[2-(propan-2-yl)-1,3-thiazol-4-yl]methyl]carbamoyl)amino]-4-(morpholin-4-yl)butanoyl]amino]-1,6-diphenylhexan-2-yl]carbamate

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)**

**VIROLOGY REVIEW**

**NDA:** 203-094    **SDN:** 000    **DATE REVIEWED:** 3/5/13

**Clinical Virology Reviewer:** Takashi E. Komatsu, Ph.D.

Molecular Formula	C <sub>40</sub> H <sub>53</sub> N <sub>7</sub> O <sub>5</sub> S <sub>2</sub>
Molecular Mass	776.02
Drug Class	Pharmacoenhancer (No anti-HIV-1 activity)
Supporting Document	IND 102,283

**Indication(s):** Use as a pharmacokinetic enhancer of the HIV 1 protease inhibitors (PIs) atazanavir and darunavir (b) (4) in adults

**Dosage Form(s):**

**Route(s) of Administration:** Oral

**Recommended Dosage:** One tablet taken once daily with food

**Dispensed:** Rx  X  OTC      (Discipline relevant)

**Abbreviations:** AAG, alpha-1-acid glycoprotein; ABC, abacavir; ADV, adefovir; APV, amprenavir; ARV, antiretroviral; ATR, Atripla; ATV, atazanavir; ATV/r, ritonavir-boosted atazanavir; AZT, zidovudine; bp, base pair; CC<sub>50</sub>, 50% cytotoxic concentration; COBI, cobicistat; ddl, didanosine; DHHS, Department of Health and Human Services; DRV, darunavir; d4T, stavudine; EC<sub>50</sub>, effective concentration inhibiting viral replication by 50%; EC<sub>90</sub>, effective concentration inhibiting viral replication by 90%; EC<sub>95</sub>, effective concentration inhibiting viral replication by 95%; EFV, efavirenz; ETR, etravirine; ETV, entecavir; FBS, fetal bovine serum; FTC, emtricitabine; HAART, highly active antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus (including HIV-1 and -2); HIV-1, human immunodeficiency virus type 1; HIV-2, human immunodeficiency virus type 2; HS, human serum; HSA, human serum albumin; IC<sub>50</sub>, 50% inhibitory concentration; IDV, indinavir; IL-2, interleukin 2; IN, HIV-1 integrase; INSTI, HIV-1 integrase strand transfer inhibitor; LAM, lamivudine; LPV, lopinavir; L-dT, telbivudine; L-FMAU, clevudine; MDR, multidrug-resistant; MOI, multiplicity of infection; MVC, maraviroc; NDA, new drug application; NFV, nelfinavir; NNRTI, HIV-1 non-nucleoside reverse transcriptase inhibitor; NR, virologic non-response; N(t)RTI, HIV-1 nucleos(t)ide reverse transcriptase inhibitor; NVP, nevirapine; PBMC, peripheral blood mononuclear cell; PCR, polymerase chain reaction; PI, HIV-1 protease inhibitor; PI/r, ritonavir-boosted HIV-1 protease inhibitor; PK, pharmacokinetics; PR, HIV-1 protease; QD, once daily; RAL, raltegravir; RBV, ribavirin; RPV, rilpivirine; RT, HIV-1 reverse transcriptase; RTE, resistance testing eligible; RTI, HIV-1 reverse transcriptase inhibitor; RTV, ritonavir; SD, standard deviation; SI, selective index; SQV, saquinavir; SR, suboptimal virologic response; TAM, thymidine analogue mutation; TDF, tenofovir disoproxil fumarate; TFV, tenofovir (active moiety of the diester prodrug TDF); TPV, tipranavir; TVD, Truvada; T-20, enfuvirtide; VF, virologic failure; VR, virologic rebound;

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)**

**VIROLOGY REVIEW**

**NDA: 203-094 SDN: 000 DATE REVIEWED: 3/5/13**

**Clinical Virology Reviewer: Takashi E. Komatsu, Ph.D.**

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## DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

### VIROLOGY REVIEW

NDA: 203-094 SDN: 000 DATE REVIEWED: 3/5/13

Clinical Virology Reviewer: Takashi E. Komatsu, Ph.D.

#### EXECUTIVE SUMMARY

This application was submitted in support of a new drug application (NDA) for TYBOST tablets (COBI, 150 mg), a pharmacoenhancer. The proposed indication for the TYBOST tablet is as a pharmacokinetic enhancer of the HIV-1 protease inhibitors (PIs) atazanavir and darunavir, (b) (4) in adults. This application is the first for this indication.

Soon after the introduction of PIs, it was recognized that coadministration of the approved HIV-1 protease inhibitor ritonavir (RTV) with other PIs improves the pharmacokinetics of the approved PI, increasing the serum half life and thereby permitting a more constant exposure to the PI (i.e. reducing  $C_{max}$  and increasing  $C_{min}$ ). RTV was found to be an inhibitor of the CYP3A enzymes involved in the metabolism of PIs. Currently, RTV-boosted HIV-1 PI regimens are a standard of care. However, RTV boosting is limited to PIs in treatment-naïve individuals as absence of a PI could lead to selection of PI resistance-associated substitutions. RTV boosting of PIs has generated a renewed interest in PK principles and their clinical implications.

TYBOST is structurally similar to ritonavir and was designed to be a specific inhibitor of CYP3A without HIV-1 protease inhibitory activity. Enzyme inactivation studies have demonstrated that TYBOST is an efficient inactivator of human hepatic microsomal CYP3A activity, with enzyme kinetic parameters ( $K_i$  and  $k_{inact}$ ) comparable to those of ritonavir. CYP3A-mediated oxidative metabolism is the major biotransformation pathway for TYBOST, as it is for ritonavir; however, unlike ritonavir, TYBOST is a more specific CYP enzyme inhibitor. It is a weak inhibitor of CYP2D6 and does not inhibit CYP1A2, CYP2C9, or CYP2C19. In addition, TYBOST displays low liability for induction through activation of xenobiotic receptors, including the aryl hydrocarbon receptor, pregnane X receptor, and the constitutive androstane receptor, in human hepatocytes. In contrast, ritonavir, a known potent pregnane X receptor activator, produces significant induction of phase I enzymes, including CYP3A, as well as phase II uridine 5'-diphosphoglucuronosyltransferase enzymes and drug transporters, including P-gp, that lead to clinically significant drug-drug interactions. Other favorable characteristics of TYBOST are reduced perturbation of the normal adipocyte functions of lipid accumulation and/or response to insulin.

This NDA package includes clinical data from one pivotal Phase 3 study GS-US-216-0114 (Week-48 data included) and one supportive Phase 2 study GS-US-216-0105 (Week-60 data included). This NDA package also includes one supportive Phase 1 study GS-US-216-0115 (bioequivalence study to support TYBOST as pharmacoenhancer of HIV-1 protease inhibitor darunavir). Studies GS-US-216-0114 and GS-US-216-0105 were conducted to evaluate the antiviral effectiveness (potency and durability) and virological resistance of the 150 mg COBI-boosted 300 mg atazanavir plus TRUVADA<sup>®</sup> (fixed-dose combination tablet containing FTC 200 mg and TDF 300 mg; TVD) in HIV-1-infected, antiretroviral treatment-naïve adult subjects. In these studies, the comparator groups were treated with 100 mg ritonavir-boosted 300 mg atazanavir plus TRUVADA<sup>®</sup> (fixed-dose combination tablet containing FTC 200 mg and TDF 300 mg; TVD).

In study GS-US-216-0114, at Week 48, ATV/co+TVD was noninferior (noninferiority margin of 12%) in the treatment-naïve, HIV-1-infected subject population to ATV/r+TVD in Study 114 with the differences in the virologic success rate of -2.2% (95% CI: -7.4% to 3.0%). In Study 114, 85.2% (293/344) of subjects in the ATV/co+TVD treatment group and 87.4% (304/348) of subjects in the ATV/r+TVD treatment group had virologic success. In antiviral efficacy analyses of ATV/co+TVD in Study 114, the rates of virologic failure (HIV-1 RNA  $\geq 50$  copies/mL) at Week 48 were numerically slightly higher for ATV/co+TVD recipients, compared to those for ATV/r+TVD recipients: 10.2% (35/344) versus 7.8% (27/348). Of note, plasma HIV-1 RNA levels at Baseline were well matched among the treatment groups with a median baseline HIV-1 RNA level of 4.8 log<sub>10</sub> copies/mL for all treatment groups, ranging from 3.6 to 6.9 log<sub>10</sub> copies/mL for the subjects

## DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

### VIROLOGY REVIEW

NDA: 203-094 SDN: 000 DATE REVIEWED: 3/5/13

Clinical Virology Reviewer: Takashi E. Komatsu, Ph.D.

in the ATV/co+TVD treatment arm and from 3.6 to 6.4 log<sub>10</sub> copies/mL for those in the ATV/r+TVD treatment arm. Virologic failure of the ATV/co+TVD recipients was largely due to suboptimal response (including nonresponse) to the treatment (63% [22/35] of the failures in study 114) rather than treatment-emergent virologic rebound (37% [13/35] of the failures). The majority of subjects in this Phase 3 study (Studies 114) were infected with HIV-1 subtype B, reflecting over 98% of US HIV-1 infections. In subjects with subtype B infection, 11.4% (32/281) and 6.3% (18/286) experienced virologic failure in the ATV/co+TVD-treated and ATV/r+TVD-treated arms, respectively. In subjects with non-subtype B infection, 3.2% (2/63) and 12.9% (8/62) experienced virologic failure in the ATV/co+TVD-treated and ATV/r+TVD-treated arms, respectively. The small sample sizes precluded a conclusive determination of whether HIV-1 subtype-specific differences could affect the antiviral effectiveness of ATV/co+TVD.

In Studies GS-US-216-0114 and GS-US-216-0105, all subjects received ATV. At screening, none of the subjects' isolates had primary resistance substitutions for ATV. In Study GS-US-216-0114, five amino acid substitutions developed in the PR in the virologic failure isolates from the 12 subjects in the ATV/co+TVD arm compared to 7 amino acid substitutions in the virologic failure isolates from the 12 subjects in the ATV/r+TVD arm. In Study 105, seven amino acid substitutions developed in the PR in the virologic failure isolates from the 2 subjects in the ATV/co+TVD arm compared to none in the virologic failure isolates from the 2 subjects in the ATV/r+TVD arm. The presence of ATV in these 2 studies confounds any possible interpretation of these results with respect to the question of TYBOST selecting PI resistance substitutions. None of the substitutions that developed are primary PI resistance-associated substitutions.

In Studies GS-US-216-0114 and GS-US-216-0105, all subjects received a TVD background treatment. At screening, all subjects were tested for genotypic sensitivity to FTC and TDF. Based on a reference list of NRTI resistance-associated amino acid substitutions ([IAS-USA, 2011](#)), none had baseline HIV-1 harboring RT substitutions associated with primary resistance to FTC and TDF (K65R, K70E, M184I/V). In the ATV/co+TVD arm of study GS-US-216-0114, there were 2 subjects whose virus developed the emtricitabine resistance-associated amino acid substitutions M184 compared to none in the ATV/r+TVD arm.

## 1. Recommendations

### 1.1. Recommendation and Conclusion on Approvability:

Approval is recommended with respect to Clinical Virology of this original NDA for TYBOST tablet (COBI 150 mg), once daily, as a pharmacokinetic enhancer of the HIV 1 protease inhibitors (PIs) atazanavir and darunavir (b) (4) in adults aged 18 years and over.

### 1.2. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, If Approvable:

## 2. Summary of OND Virology Assessments

### 2.1. Nonclinical Virology

The sponsor did not conduct any new nonclinical virology studies for this submission. All of the nonclinical virology data have been submitted with the Stribild<sup>®</sup> submission (NDA 203100, SDN 000).

### 2.2. Clinical Virology

## DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

### VIROLOGY REVIEW

NDA: 203-094 SDN: 000 DATE REVIEWED: 3/5/13

Clinical Virology Reviewer: Takashi E. Komatsu, Ph.D.

Studies GS-US-216-0114 and GS-US-216-0105 were conducted to evaluate the antiviral effectiveness (potency and durability) and virological resistance of the 150 mg COBI-boosted 300 mg atazanavir plus TRUVADA<sup>®</sup> (fixed-dose combination tablet containing FTC 200 mg and TDF 300 mg; TVD) in HIV-1-infected, antiretroviral treatment-naïve adult subjects. In these studies, the comparator groups were treated with 100 mg ritonavir-boosted 300 mg atazanavir plus TRUVADA<sup>®</sup> (fixed-dose combination tablet containing FTC 200 mg and TDF 300 mg; TVD).

In study GS-US-216-0114, at Week 48, ATV/co+TVD was noninferior (noninferiority margin of 12%) in the treatment-naïve, HIV-1-infected subject population to ATV/r+TVD in Study 114 with the differences in the virologic success rate of -2.2% (95% CI: -7.4% to 3.0%). In Study 114, 85.2% (293/344) of subjects in the ATV/co+TVD treatment group and 87.4% (304/348) of subjects in the ATV/r+TVD treatment group had virologic success. In antiviral efficacy analyses of ATV/co+TVD in Study 114, the rates of virologic failure (HIV-1 RNA  $\geq$ 50 copies/mL) at Week 48 were numerically slightly higher for ATV/co+TVD recipients, compared to those for ATV/r+TVD recipients: 10.2% (35/344) versus 7.8% (27/348). Of note, plasma HIV-1 RNA levels at Baseline were well matched among the treatment groups with a median baseline HIV-1 RNA level of 4.8 log<sub>10</sub> copies/mL for all treatment groups, ranging from 3.6 to 6.9 log<sub>10</sub> copies/mL for the subjects in the ATV/co+TVD treatment arm and from 3.6 to 6.4 log<sub>10</sub> copies/mL for those in the ATV/r+TVD treatment arm. Virologic failure of the ATV/co+TVD recipients was largely due to suboptimal response (including nonresponse) to the treatment (63% [22/35] of the failures in study 114) rather than treatment-emergent virologic rebound (37% [13/35] of the failures). The majority of subjects in this Phase 3 study (Studies 114) were infected with HIV-1 subtype B, reflecting over 98% of US HIV-1 infections. In subjects with subtype B infection, 11.4% (32/281) and 6.3% (18/286) experienced virologic failure in the ATV/co+TVD-treated and ATV/r+TVD-treated arms, respectively. In subjects with non-subtype B infection, 3.2% (2/63) and 12.9% (8/62) experienced virologic failure in the ATV/co+TVD-treated and ATV/r+TVD-treated arms, respectively. The small sample sizes precluded a conclusive determination of whether HIV-1 subtype-specific differences could affect the antiviral effectiveness of ATV/co+TVD.

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### 3. Administrative

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)**

**VIROLOGY REVIEW**

**NDA:** 203-094    **SDN:** 000    **DATE REVIEWED:** 3/5/13

**Clinical Virology Reviewer:** Takashi E. Komatsu, Ph.D.

**3.1. Reviewer's Signatures**

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Takashi E. Komatsu, Ph.D.  
Clinical Virology Reviewer

**3.2. Concurrence**

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HFD-530/Clin.Virol.TL/J. O'Rear, Ph.D.

CC:  
HFD-530/NDA # 203094  
HFD-530/Division File  
HFD-530/PM/Olagundoye

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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TAKASHI E KOMATSU  
03/10/2013

JULIAN J O REAR  
03/10/2013

## VIROLOGY FILING CHECKLIST FOR NDA or Supplement

**NDA Number: 203094**      **Applicant: Gilead Sciences, Inc.**      **Stamp Date: 6/28/12**

**Drug Name: Cobicistat**      **NDA Type: Original**      **Filing Date: 8/27/12**

On **initial** overview of the NDA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comments</b>
1	Is the virology information (preclinical/nonclinical and clinical) described in different sections of the NDA organized in a manner to allow substantive review to begin?	X		Cobicistat is not an antiviral drug: the virology information relates to lack of antiviral activity and impact on the antiviral activity of other antiretroviral drugs
2	Is the virology information (preclinical/nonclinical and clinical) indexed, paginated and/or linked in a manner to allow substantive review to begin?	X		
3	Is the virology information (preclinical/nonclinical and clinical) legible so that substantive review can begin?	X		
4	On its face, has the applicant <u>submitted</u> <i>in vitro</i> data in necessary quantity, using necessary clinical and non-clinical strains/isolates, and using necessary numbers of approved current divisional standard of approvability of the submitted draft labeling?			Not applicable
5	Has the applicant <u>submitted</u> any required animal model studies necessary for approvability of the product based on the submitted draft labeling?			Not applicable
6	Has the applicant <u>submitted</u> all special/critical studies/data requested by the Division during pre-submission discussions?	X		
7	Has the applicant <u>submitted</u> the clinical virology datasets in a format which intends to correlate baseline pathogen with clinical and microbiologic outcome?	X		
8	Has the applicant <u>submitted</u> draft/proposed interpretive criteria/breakpoint along with quality control (QC) parameters and interpretive criteria, if applicable, in a manner consistent with contemporary standards, which attempt to correlate criteria with clinical results of NDA/BLA studies, and in a manner to allow substantive review to begin?			Not applicable
9	Has the applicant <u>submitted</u> a clinical virology dataset in an appropriate/standardized format which intends to determine resistance development by correlating changes in the phenotype (such as <i>in vitro</i> susceptibility) and/or genotype (such as mutations) of the baseline pathogen with clinical	X		Cobicistat acts as a pharmacoenhancer. The resistance datasets are for other drugs in the regimen.

File name: 5\_Microbiology Filing Checklist for a NDA or Supplement 010908

## VIROLOGY FILING CHECKLIST FOR NDA or Supplement

	Content Parameter	Yes	No	Comments
	and microbiologic outcome?			
10	Has the applicant used standardized or nonstandardized methods for measuring microbiologic outcome? If nonstandardized methods were used, has the applicant included complete details of the method, the name of the laboratory where actual testing was done and performance characteristics of the assay in the laboratory where the actual testing was done?	X		
11	Has the applicant <u>submitted</u> draft labeling consistent with current regulation, divisional and Center policy, and the design of the development package?	X		
12	Has the applicant <u>submitted</u> annotated virology draft labeling consistent with current divisional policy, and the design of the development package?	X		
13	Have all the study reports, published articles, and other references been included and cross-referenced in the annotated draft labeling or summary section of the submission?	X		
14	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	

**IS THE VIROLOGY SECTION OF THE APPLICATION FILEABLE?**   YES  

If the NDA is not fileable from the virology 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.

Komatsu, Takashi 7/27/12  
 \_\_\_\_\_  
 Reviewing Virologist Date

\_\_\_\_\_  
 Virology Team Leader Date

File name: 5\_Microbiology Filing Checklist for a NDA or Supplement 010908

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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TAKASHI E KOMATSU  
07/30/2012

JULIAN J O REAR  
07/31/2012