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APPLICATION NUMBER:

203094Orig1s000

203094Orig2s000

MEDICAL REVIEW(S)

Clinical Review

Date	August 1, 2014
From	Sarita Boyd, PharmD
Subject	Clinical Review
NDA/BLA #	NDA 203094 Resubmission
Supplement#	
Applicant	Gilead Sciences
Date of Submission	March 28, 2014
PDUFA Goal Date	September 28, 2014
Proprietary Name / Established (USAN) names	Tybost® (Cobicistat)
Dosage forms / Strength	Tablet (oral) / 150 mg
Proposed Indication(s)	CYP3A inhibitor indicated to increase systemic exposure of atazanavir and darunavir (once daily dosing regimen) in the treatment of HIV-1 infection in adults
Recommended:	Approval

1. Introduction

This review summarizes the safety update for the resubmission of NDA 203094. The review focuses on the updates for Study 114 (Phase 3) and Study 105 (Phase 2), which are randomized, double-blind safety and efficacy trials comparing cobicistat-boosted atazanavir (ATV/co) and ritonavir-boosted atazanavir (ATV/r) each coadministered with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in HIV-1 infected, antiretroviral treatment-naïve adults. Another trial of interest, not submitted to the original NDA for clinical review, is Study 216-0130 (Phase 3b), a single-arm trial evaluating cobicistat-boosted darunavir (DRV/co) plus 2 fully active nucleoside reverse transcriptase inhibitors (NRTIs) in HIV-1 infected adults. Along with these 3 indication-related trials, the review summarizes the safety update for 9 additional trials involving cobicistat.

2. Background

The original NDA submission for cobicistat received a Complete Response on April 16, 2013 due to the results of facility inspection findings. Cobicistat previously received approval as part of the fixed-dose-combination product Stribild® (elvitegravir/cobicistat/emtricitabine/tenofovir). The proposed indication for cobicistat as an individual product is a cytochrome P450 3A (CYP3A) inhibitor indicated to increase systemic exposures of atazanavir (ATV) and darunavir (DRV) once daily dosing regimen in the treatment of HIV-1 infection in adults. The Applicant does not propose an indication for (b) (4)

The NDA resubmission contains a safety update for 12 trials involving cobicistat, with or without ATV or DRV, in the form of summaries as well as patient narratives for deaths, SAEs, and discontinuations due to AEs. Compared to the label in the original NDA submission, the Applicant proposes no safety- or efficacy-related changes to the label in the NDA resubmission.

3. CMC/Device

The original NDA received a Complete Response because of CMC- and facility-related deficiencies. The Applicant has elected to transfer the responsibilities of the Gilead Foster City site to another site. As a result of this transfer, there are no outstanding CMC- or compliance-related issues. Please see Dr. Liu's CMC review for additional information.

4. Nonclinical Pharmacology/Toxicology

The Applicant states there were no significant findings from completed cytotoxicity studies involving cobicistat during the period since the original NDA.

5. Clinical Pharmacology/Biopharmaceutics

The Applicant states there were no significant findings from completed pharmacokinetic drug interaction trials involving cobicistat since the original NDA. Please see Dr. Stanley Au's Clinical Pharmacology review for additional information.

6. Clinical Microbiology

The NDA resubmission contains no new clinical microbiology data.

7. Clinical/Statistical- Efficacy

The NDA resubmission contains no new efficacy data.

8. Safety

Methods

The safety review evaluates AEs not reviewed in the original NDA for 12 trials involving cobicistat. The review focuses on trials comparing ATV/co and ATV/r (216-0114 and 216-0105) and the single-arm DRV/co trial (216-0130), which are directly relevant for the proposed cobicistat indication. The Applicant proposes no safety-related labeling changes and proposes to retain 48-week data for Trials 114 and 105.

The review does not entail independent data analyses because the submission does not contain datasets, and the Applicant is not updating the label with longer term (i.e., greater than 48 weeks) clinical trial data. The submission contains summary information for all 12 trials and includes subject disposition, extent of exposure, deaths, serious adverse events (SAE), AEs leading to treatment discontinuation, and common AEs in the update period. The update period is the time between the 120-day safety update in the original NDA through the data cut dates for the NDA resubmission. The review consists of comparing AEs from the original NDA to the update period and reviewing narratives of new deaths, SAEs, and AEs leading to treatment discontinuation. Ultimately, this review assesses whether safety events occurring in the update period warrant new or additional labeling.

Upon request, the Applicant clarified that the “Original NDA” column numbers in the Resubmission Safety Update tables do not include the 120-day Safety Update information submitted in October 2012. For Trials 114 and 105 only narratives for new events in the ATV/co group not reported in the 120-day Safety Update are discussed, although the tables are reviewed for between-group comparisons.

Summary

Overall, there are no new safety concerns for cobicistat based on adverse event (AE) tables and narratives for new deaths, nonfatal SAEs, and AEs leading to treatment discontinuation. Dr. Miele notes several safety events of interest in the original NDA including renal events (renal impairment, proximal renal tubulopathy, glomerular dysfunction, nephrolithiasis), musculoskeletal events (non-traumatic bone fracture), and hepatobiliary events (cholelithiasis). AEs that occurred in the safety update period are either consistent with proposed labeling, similar to events occurring with ATV/r or ritonavir-boosted DRV (DRV/r), or unlikely related to cobicistat and do not warrant labeling.

Atazanavir/cobicistat Pooled Trials: GS-US-216-0114 and GS-US-216-0105

Study 114 (Phase 3) and Study 105 (Phase 2) are ongoing randomized, double-blind, multicenter trials evaluating the safety and efficacy of ATV/co versus ATV/r each coadministered with FTC/TDF in HIV-1 infected, antiretroviral treatment-naïve adults. Table 1 displays the data cut points for the resubmission safety update compared to the original NDA. The resubmission includes a safety update on all 771 trial participants who received at least one dose of randomized study drug through the data cut date: 394 in the ATV/co group and 377 in the ATV/r group. Safety information for all subjects receiving ATV/co in the double-blind or open-label phases (n=413) are provided separately and are reviewed for new trends or major changes compared to the double-blind phase alone.

Table 1: Clinical Data Included in the Cobicistat NDA Resubmission

Study Number	Data Cut Date			
	Original NDA		Resubmission Safety Update	
GS-US-216-0114	31 Oct 2011	Week 48 analysis	03 Sep 2013	Week 144 analysis
GS-US-216-0105	26 Apr 2011	Week 96 analysis	01 Jul 2013	Interim analysis

Exposure

Table 2 displays the duration of exposure to study drug for the safety analysis set.

Table 2: Duration of Exposure

	Double-Blind Phase		Double-Blind/Open-Label Phases
Exposure (weeks)	ATV/co (n=394)	ATV/r (n=377)	ATV/co (n=413)
Median (Q1-Q3)	145 (61-155)	145 (97-155)	147 (143-156)

Deaths

Since the original NDA, no deaths occurred in the ATV/co group.

Nonfatal Serious Adverse Events

Since the original NDA, 25 (6.3%) additional subjects in the ATV/co group experienced any treatment-emergent SAE compared to 22 (5.8%) in the ATV/r group during the double-blind phase. SAEs were similar between groups in terms of SOC, PT, and incidence. Nine subjects experienced an SAE while receiving open-label ATV/co. Table 3 shows SOCs in which SAEs occurred in the ATV/co group at a greater than 1% increase in the update period.

Table 3: SOCs with Greatest SAE Increase in the Update Period

	Double-Blind Phase ATV/co + TVD (n=394)		Double-Blind Phase ATV/r + TVD (n=377)		All ATV/co + TVD (n=413)
	Original NDA	Safety Update	Original NDA	Safety Update	Safety Update
Any SAE	38 (10%)	63 (16%)	25 (7%)	47 (13%)	72 (17%)
Infections and Infestations	14 (4%)	23 (6%)	14 (4%)	18 (5%)	25 (6%)
Renal and Urinary Disorders	3 (0.8%)	6 (2%)	6 (2%)	10 (3%)	8 (2%)

Overall, 29 subjects experienced an SAE not previously reviewed while receiving ATV/co. Table 4 describes SAEs of interest or occurring in >1 subject. The narratives for all 29 SAEs revealed no new safety concerns. The events were either unlikely related to ATV/co, consistent with AEs occurring with ATV/r, or consistent with the proposed cobicistat label.

Table 4: SAEs of Interest or Occurring in >1 Subject Receiving ATV/co (n=12)

Subject ID	Event	Grade	Related (Investigator/ Reviewer)	Possible Alternate Cause/Confounders	Proposed Labeling
0315-5509	Nephrolithiasis	2	No / Possible		AR
1965-8024	Calculus ureteric	3	No / Possible	History of stones	AR
2058-8425	Nephrolithiasis	2	No / Possible		AR
3976-8057	Calculus ureteric	3	No / Possible	History of stones	AR
	Renal colic	3	No / Possible		AR
1000-8629	Renal hematoma	3	No / No	Renal biopsy	None
2734-8531	Renal failure acute*	2	No / No	Dehydration	W&P
	Diabetes mellitus	2	No / Possible	Chronic steroid use	None
	Hypertriglyceridemia	2	No / Possible		None

Subject ID	Event	Grade	Related (Investigator/ Reviewer)	Possible Alternate Cause/Confounders	Proposed Labeling
2434-8258	Diabetes mellitus (worsening)	2	No / Unlikely	10+ year history of DM; obesity	None
0986-8285	Ovarian cyst	1	No / No	Pre-existing conditions	None
	Cervical dysplasia	2	No / No		None
4143-8442	Cervical dysplasia	3	No / No	HPV	None
2058-8335	Scrotal abscess	2	No / No	Circumcision	None
	Subcutaneous abscess	2	No / No		None
2734-8509	Perineal abscess/cellulitis	2	No / Unlikely		None
	Subcutaneous abscess	2	No / Unlikely		None
3975-8443	Anal abscess	3	No / Unlikely		None

*Subject experienced other SAEs related to pre-existing Crohn's disease
AR = Adverse Reactions, W&P = Warnings and Precautions

AEs Leading to Discontinuation

Since the original NDA, 13 (3.3%) subjects in the ATV/co group experienced an AE leading to premature discontinuation compared to 14 (3.7%) in the ATV/r group during the double-blind phase. Table 5 shows the 10 AEs leading to treatment discontinuation in the ATV/co group not previously reviewed.

Table 5: AEs Leading to ATV/co Discontinuation

Subject ID	Event	Grade	Related to Study Drug (Investigator)	Related to Study Drug (FDA Reviewer)	Proposed Labeling
1603-5527	GFR decreased	2	Yes	Yes	W&P
1001-8670	Nephropathy toxic	2	Yes	Yes	W&P
5122-8338	Nephropathy	3	Yes	Yes	W&P
1000-8629	IgA nephropathy	3	No	No	Not labeled
0731-8087	Ocular icterus	1	Yes	Yes	AR
1291-8579	Ocular icterus	1	Yes	Yes	AR
2475-8467	Ocular icterus	1	Yes	Yes	AR
5130-8134	Jaundice	2	Yes	Yes	AR
0698-8223	Diarrhea	2	Yes	Yes	AR
3672-8145	Subarachnoid hemorrhage	4	No	Unlikely	Not labeled

Consistent with the original NDA, the most common AEs leading to discontinuation were associated with hyperbilirubinemia and renal impairment. At Week 48, a greater number of treatment discontinuations due to ocular icterus occurred in the ATV/co group (2%) compared to the ATV/r group (1%). This trend continued with 3% vs. 1.6% of subjects discontinuing ATV/co vs. ATV/r, respectively, as of the resubmission cut date. A review of the narratives for all 10 new AEs leading to discontinuation revealed no new safety concerns with cobicistat. The events were either consistent with the proposed cobicistat label or unlikely related to ATV/co.

Common Adverse Events

Since the original NDA, 14 (3.6%) additional subjects in the ATV/co group experienced any treatment-emergent AE, all grade and all cause, compared to 10 (2.7%) in the ATV/r group during the double-blind phase. Twenty-five subjects experienced any treatment-emergent AE while receiving open-label ATV/co. Table 6 displays common AEs occurring at a greater than 3% increase in the ATV/co group in the update period; events in ATV/co group occurred at a similar or lower rate than in the ATV/r group. In addition, no new safety concerns arose from a between-group comparison of all common AEs occurring in at least 5% of subjects in either group but at a lower than a 3% increase in the update period. For any given preferred term (PT), the increase in proportion of subjects with an AE in the ATV/co group during the update period was no more than 6%. For these AEs, this type of increase is expected with longer duration of drug exposure and does not change the overall safety or risk/benefit profiles.

Table 6: Common AEs (>3% Increase in the ATV/co Group during the Update Period)

Preferred Term	Double-Blind Phase ATV/co + TVD (n=394)		Double-Blind Phase ATV/r + TVD (n=377)		ALL ATV/co + TVD (n=413)
	Original NDA	Safety Update	Original NDA	Safety Update	Safety Update
Any AE	361 (82%)	375 (95%)	347 (92%)	357 (95%)	397 (96%)
Diarrhea	59 (15%)	83 (21%)	80 (21%)	105 (28%)	89 (22%)
Pyrexia	21 (5%)	37 (9%)	25 (7%)	31 (8%)	38 (9%)
URI	40 (10%)	63 (16%)	30 (8%)	64 (17%)	68 (17%)
Nasopharyngitis	37 (9%)	53 (14%)	56 (15%)	75 (20%)	58 (14%)
Bronchitis	20 (5%)	37 (9%)	20 (5%)	36 (10%)	46 (11%)
UTI	14 (4%)	26 (7%)	20 (5%)	25 (7%)	27 (7%)
Influenza	14 (4%)	27 (7%)	16 (4%)	21 (6%)	32 (8%)
Syphilis	9 (2%)	23 (6%)	11 (3%)	24 (6%)	27 (7%)
Back pain	17 (4%)	31 (8%)	26 (7%)	41 (11%)	33 (8%)
Anogenital warts	12 (3%)	26 (7%)	9 (2%)	19 (5%)	28 (7%)
Headache	41 (10%)	53 (14%)	54 (14%)	70 (19%)	57 (14%)

Darunavir/cobicistat Study: GS-US-216-0130

Study 216-0130 is an ongoing Phase 3b, open-label, single arm, multicenter trial evaluating the safety and efficacy of DRV/co coadministered with 2 fully active NRTIs in HIV-1 infected, antiretroviral treatment-naïve and -experienced adults with no DRV resistance associated mutations. This trial was not part of the original NDA clinical review, nor is it included in the proposed label. The resubmission includes an interim analysis with a data cut date of July 1, 2013. Safety information is available for 313 subjects (295 treatment-naïve and 18 treatment-experienced) who received at least 1 dose of study drug. An important limitation of this trial is the absence of a comparator arm. Safety results were reviewed in relation to AEs labeled for DRV (DRV/r historical data) and the proposed cobicistat label (ATV/co data). Overall, this trial raises no new safety concerns for cobicistat. No labeling edits are recommended based on the submitted results of this study.

Disposition

Overall, 45 (14.4%) subjects discontinued study drug before Week 48. Of the 268 (85.6%) subjects who completed study drug through Week 48, 265 (84.7%) continued to the extension phase. The most common reason for discontinuation was AEs: 15 (5.1%) subjects before Week 48 and 2 subjects in the extension phase.

Exposure

The median duration of exposure to study drug was 76.7 weeks (Q1-Q3: 71.7-84.1) and 72.6 weeks (Q1-Q3: 47.7-84.1) in the treatment-naïve and -experienced groups, respectively.

Deaths

No deaths were reported in this study.

Nonfatal Serious Adverse Events

Overall, 32 (10.2%) subjects experienced any treatment-emergent SAE. SAEs in the following SOCs occurred in >1% of subjects: Infections and Infestations (9 [2.9%]), Psychiatric Disorders (5 [1.6%]), and Gastrointestinal Disorders (4 [1.3%]). The following SAEs occurred in at least 2 subjects: pyrexia (2), pneumonia (2), rash (2), and suicide attempt (2). Table 7 describes the psychiatric-related SAEs, all of which had plausible alternate causes.

Table 7: SAEs of Interest – Psychiatric Disorders

Subject ID	Event	Treat- ment d/c	Related (Investigator/ Reviewer)	Possible Alternate Cause/Confounders	Proposed Labeling
0754-4070	Suicide attempt	N	No / Unlikely	Recently d/c bipolar meds	None
1534-4305	Suicide attempt	N	No / Unlikely	Unspecified traumatic life events; under the influence of marijuana and ethanol at time of event	None
1236-4291	Suicidal ideation Depression	N	No / Unlikely	Recently d/c multiple psych meds	None
0754-4216	Anxiety	Y	No / Unlikely	Pre-existing anxiety/depression; switched to Stribild	None

d/c = discontinuation

Although assessment of AEs in a single-arm, open-label study is challenging, a review of all 32 SAE narratives revealed no new safety concerns with cobicistat. I agree with investigator assessments that 29 cases were not related or unlikely related to DRV/co. Two serious, related rash events are discussed below with AEs leading to treatment discontinuation. One subject (Subject 1780-4245) experienced ectopic pregnancy, which the investigator reported as having an unknown relationship to cobicistat exposure. The Applicant assessed the patient's ectopic pregnancy as likely a background event, which is a reasonable assessment at this time.

AEs Leading to Discontinuation

Overall, 17 (5.8%) subjects experienced any AE leading to discontinuation of study drug. None of the events raised new safety concerns with cobicistat.

Hypersensitivity or rash was the most common AE resulting in treatment discontinuation, occurring in 9 (2.8%) subjects (Subjects 2154-4111, 2843-4190, 0121-4113, 0407-4100, 0589-4316, 0991-4067, 1950-4269, 1978-4069, 2157-4130); all subjects were also taking FTC/TDF. The investigator assessed these AEs as serious (medically significant) in 2 subjects, severe (Grade 3) in 3 subjects, and mild or moderate (Grade 1-2) in 4 subjects. Rash events assessed as serious or Grade 3 are described below.

Subject 2843-4190

A 33-year-old male developed a maculopapular rash on his thorax, arms, and legs on Day 11 after initiating DRV/co and FTC/TDF. He was not taking any other medications. He stopped study drugs and received diphenhydramine for 10 days until the rash resolved. The investigator assessed the rash as serious (medically significant), most likely related to DRV, and possibly related to FTC.

Subject 0121-4113

A 36-year-old male developed a diffuse rash that spread to the face on Day 7 after initiating DRV/co and FTC/TDF. He was not taking any other medications. He received diphenhydramine, but the rash worsened from Grade 2 to Grade 3. He discontinued study drugs, and the rash resolved on Day 11. The investigator assessed the rash as related to DRV/co.

Subject 0589-4316

A 49-year-old female developed pruritus on hands and feet on Day 24 after initiating DRV/co and FTC/TDF. On Day 25 the reaction progressed to a diffuse erythematous rash, some angioedema, and pruritus at which time study drugs were discontinued. Liver enzymes, white blood cell count, and eosinophil count were normal. The next day, the subject had no oral lesions, blistering, or noticeable angioedema. The subject received antihistamines and prednisone, and the event resolved over a few days. The investigator assessed the event as Grade 3 and related to study medications.

Subject 2157-4130

A 24-year-old male developed a Grade 2 non-pruritic rash without oropharynx involvement on Day 10 after initiating DRV/co and FTC/TDF. Liver enzymes, white blood cell count, and eosinophil count were normal. He received antihistamines and continued study drugs. On Day 80 the subject experienced Grade 3 allergic dermatitis with unchanged laboratory results. He received methylprednisolone and discontinued study drugs, and the rash resolved on Day 86.

There were no cases of Stevens-Johnson syndrome or toxic epidermal necrolysis. All 9 events were related to study drug, most likely DRV and possibly cobicistat, and all resolved with discontinuation of DRV/co and treatment with antihistamines and/or corticosteroids. The events are consistent with the proposed cobicistat label and the current DRV label.

An additional safety event of interest resulting in treatment discontinuation was proximal renal tubulopathy in 1 subject (Subject 1236-4051) also taking FTC/TDF. The event is consistent with the proximal renal tubulopathy events seen with COBI and TDF (in combination with either EVG or ATV) as described in Dr. Miele's review and is adequately labeled.

Common AEs

Overall, 290 (92.7%) subjects experienced any treatment-emergent AE, all grade and all cause. The following AEs occurred most frequently (>10%): diarrhea (30.4%), nausea (23.3%), upper respiratory tract infection (16.0%), headache (12.8%), and nasopharyngitis (10.2%). These AEs were also among the most common AEs reported in Studies 114 and 105 with ATV/co. A review of all AEs reported for at least 5% of subjects receiving DRV/co revealed no new safety concerns. However, interpretation of the incidence of various AEs is limited in an open-label, single-arm trial. Overall, the AE profile appears similar to that of DRV/r.

Renal Impairment Study: GS-US-236-0118

Study 118 is an ongoing Phase 3 open-label safety trial evaluating cobicistat in HIV-1-infected subjects with mild to moderate renal impairment. The resubmission contains Week 48 analysis in which subjects on stable ART switched from ritonavir to cobicistat and received at least 1 dose of either EVG/co/FTC/TDF (n=33), ATV/co (n=52), or DRV/co (n=21). This review assesses AEs reported for 73 subjects in the protease inhibitor (PI)/co group (Cohort 2) not previously reviewed. Please refer to Dr. Viswanathan's review (NDA 203100) for results in the EVG/co/FTC/TDF group (Cohort 1).

Five (6.8%) subjects receiving a PI/co experienced the following SAEs (1 subject per event): acute myocardial infarction (DRV/co); acute coronary syndrome (DRV/co); angioedema (ATV/co); suicidal ideation, convulsion, and skull fracture (ATV/co); and nephrolithiasis (ATV/co). Nephrolithiasis occurred 2 months after starting cobicistat and 5 years after starting ATV (Subject 1154-2062), suggesting an association with cobicistat. Medical history and stone analysis are not reported. The other SAEs contain significant confounders as a plausible alternate explanation for each event. Cardiac-related SAEs occurred in subjects (6259-2060 and 1560-2005) > 60 years of age with a history of cigarette smoking and hypercholesterolemia, respectively; both subjects also had mild-to-moderate renal impairment per study inclusion criteria.

Since the original NDA review, 3 subjects experienced an AE leading to treatment discontinuation consisting of affect lability (ATV/co); hematuria and proteinuria (ATV/co), and abnormal GFR, <50 mL/min (ATV/co). These events were possibly related to cobicistat, although baseline medical conditions and laboratory values confound the events affect lability, hematuria, and proteinuria. Both subjects with renal events also received TDF, and these events have been associated with concomitant use of cobicistat and TDF. The AE abnormal GFR did not resolve after discontinuation of cobicistat; however, additional renal laboratory values were generally normal. These AEs do not warrant additional labeling at this time.

Elvitegravir/cobicistat Studies: GS-US-236-0102, GS-US-236-0103, GS-US-236-0104

Studies 102, 103, and 104 are ongoing randomized, double-blind trials evaluating the safety and efficacy of EVG/co/FTC/TDF versus either efavirenz (EFV)/FTC/TDF or ATV/r plus FTC/TDF in HIV-1 infected, antiretroviral treatment-naïve adults. Although data from these trials are not directly relevant to the proposed cobicistat indication, they provide supportive safety information for cobicistat. Table 8 displays the data cut points for the resubmission safety update compared to the original NDA.

Table 8

Study Number	Data Cut Date			
	Original NDA		Resubmission Safety Update	
GS-US-236-0102	26 Jul 2011	Week 48 analysis	29 May 2013	Week 144 analysis
GS-US-236-0103	01 Sep 2011	Week 48 analysis	05 Jul 2013	Week 144 analysis
GS-US-236-0104	17 Mar 2011	Week 96 analysis	01 Jul 2013	Interim analysis

Please refer to Dr. Viswanathan's review of Studies 102 and 103 Week 144 results under NDA 203100. The resubmission contains pooled safety analyses of these 2 studies involving 701 subjects in the EVG/co/FTC/TDF group, 352 subjects in the EFV/FTC/TDF group, and 355 subjects in the ATV/r + FTC/TDF group. Two new treatment-emergent deaths occurred in the EVG/co/FTC/TDF group. One death was a result of an upper gastrointestinal bleed assessed by the investigator as unrelated to study drug. The other death was due to an unknown cause; the site received notification of the death from the subject's family friend with no additional information and was unable to obtain cause of death or additional medical records upon follow-up request. SAEs, AEs resulting in treatment discontinuation, and common AEs that occurred with EVG/co/FTC/TDF versus the comparator groups in the update period do not raise new safety concerns. Overall, the reported PTs and number of events are similar in each group. No labeling edits are recommended based on the safety update for this study.

Please refer to Dr. Kimberly Martin's review of Study 104 interim analysis under NDA 203093 elvitegravir resubmission. The resubmission contains a safety update for 62 subjects who received EVG/co/FTC/TDF for a median of 171 weeks. No new safety concerns emerged in this study during the update period.

Phase 1 Studies: GS-US-216-0125, GS-US-216-0127, GS-US-216-0134, GS-US-236-0130, GS-US-236-0135

The safety update includes final analysis of 5 Phase 1 studies (3 drug-drug interaction studies, 1 relative bioavailability study, and 1 renal effect study) not previously submitted. Cobicistat exposure ranged from single dose to 30-day dosing in a total of 194 subjects. One SAE of ulnar nerve palsy (significant disability) occurred and was not related to study drug. Two subjects in different studies prematurely discontinued study drug due to an AE of erysipelas and urticaria, respectively. Overall, there are no new safety concerns based on these study results.

9. Advisory Committee Meeting

Not applicable to this NDA resubmission.

10. Pediatrics

The NDA resubmission contains no new pediatric data. The Applicant agreed to the Written Request sent by DAVP on March 27, 2014. The Applicant will conduct a trial to evaluate pediatric pharmacokinetics, safety, and antiviral activity of ATV/co in subjects 3 months to <18 years of age and once daily DRV/co in subjects 3 years to <18 years of age. An initial PK study or substudy will allow dose selection, which will be followed by a longer-term pediatric safety and antiviral activity assessment of ATV/co and of DRV/co each combined with a background regimen. The Written Request will fulfill the Postmarketing Requirement (PMR) for pediatric studies, which remains unchanged from the original NDA.

11. Other Relevant Regulatory Issues

There are no other relevant regulatory issues.

12. Labeling

This section summarizes major label changes for the resubmission compared to the label completed just prior to the Complete Response for the original NDA. The major edits made by the Applicant include: (1) re-insertion of DRV throughout relevant sections of the label, and (2) removal of irinotecan from CONTRAINDICATIONS presumably because of its interaction with ATV specifically and not cobicistat. The comments below refer to major FDA-proposed changes.

U.S. Package Insert (USPI)

INDICATIONS AND USAGE

- Rearrangement of the second “Limitation of Use” to accurately convey cobicistat limitations related to drug-drug interactions.

CONTRAINDICATIONS

- Retention of irinotecan and all relevant contraindications for atazanavir or darunavir as well as cobicistat.
- Addition of nevirapine and indinivir (with ATV/co) to maintain consistency with the ATV label.

WARNINGS AND PRECAUTIONS

- Rearrangement [REDACTED] (b) (4) to accurately convey drug-drug interaction precautions.

DRUG INTERACTIONS

Table 6

- Clarification of clinical comments for anticonvulsants:
 - [REDACTED] (b) (4)
[REDACTED] (b) (4) changed to “Consider alternative anticonvulsant or antiretroviral therapy to avoid potential changes in exposures. If coadministration is necessary, monitor for lack or loss of virologic response.”
 - Prediction of potential effect of anticonvulsants that induce CYP3A on DRV changed [REDACTED] (b) (4) to “effect unknown.” Although initially expected, carbamazepine does not alter DRV exposure when coadministered with ritonavir (source: DRV label), but it is unknown if this finding can be extrapolated to coadministration with cobicistat.
- Addition of simeprevir

U.S. Patient Package Insert (USPPI)

- Retention of irinotecan in the list of medications not to take with cobicistat as well as all medications not to take with atazanavir or darunavir.
- Most common side effects of cobicistat with darunavir not included because this information is not present in the USPI. The most common side effects listed pertain to cobicistat with atazanavir.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend approval of cobicistat 150 mg tablet for use as a CYP3A inhibitor to increase systemic exposures of ATV and DRV once daily dosing regimen in the treatment of HIV-1 infection in adults. The recommendation is based on the safety update provided in the NDA resubmission and Dr. Miele’s recommendation for approval of the original NDA.

- Risk Benefit Assessment

The safety update in the resubmission does not alter the risk-benefit assessment made in the original NDA. Overall, no new safety concerns arise from AEs occurring in 12 trials involving cobicistat during the update period. AEs are either consistent with proposed labeling, similar to events occurring with ATV/r or DRV/r, or unlikely related to cobicistat and do not warrant labeling at this time.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

The resubmission contains no new safety information necessitating a REMS.

During the original NDA review cycle, the Applicant agreed to a multi-tiered broad education plan targeting pharmacists and HIV healthcare providers to help reduce the risk of inappropriate use of cobicistat, particularly the inability to interchange cobicistat with ritonavir with respect to drug-drug interactions. However, the clinical recommendations for management of drug interactions with ATV/co and DRV/co compared to ATV/r and DRV/r are more similar than different due to extrapolations from ritonavir to cobicistat drug interaction information. Because the clinical recommendations in the proposed cobicistat label do not reflect a truly unique drug interaction profile compared to ritonavir, multiple messages emphasizing such a point may be confusing. Yet, it is important to stress that cobicistat and ritonavir are not interchangeable within all ARV regimens and note that some recommendations for management of drug interactions with ATV/r and DRV/r have not been extrapolated to ATV/co and DRV/co due to complex and unknown mechanisms including potential transporter-mediated interactions. The Dear Healthcare Professional letter will be edited to reflect the slightly altered message. Other components of the education plan such as a press release and Medscape interview are no longer critical.

- Recommendation for other Postmarketing Requirements and Commitments

PMRs were sent to the Applicant in April 2013. There are no changes to the PMRs. DAVP requested the Applicant provide an updated response for the PMRs including scheduled milestones. PMRs include pediatric studies with ATV/co and DRV/co under the Pediatric Research Equity Act (PREA) and drug-drug interaction studies to evaluate the effects of ATV/co and DRV/co on oral contraceptives, rosuvastatin, and atorvastatin.

- Recommended Comments to Applicant

The labeling comments and request for a PMR update will be sent to the Applicant.

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/s/

SARITA D BOYD
08/01/2014

KIMBERLY A STRUBLE
08/05/2014

**Medical Officer's Review of Proposed Safety Update
NDA 203094, DARRTS SN 32, 33**

Date submitted: August 14, 2013

Date received: August 14, 2013

Date completed: August 26, 2013

Applicant: Gilead Sciences, Inc.

Drug: TYBOST[®] (cobicistat)

Formulation: 150 mg tablet

Indication: CYP3A inhibitor to increase systemic exposures of atazanavir or darunavir

Brief Review

New Drug Application (NDA) 203094 for Tybost[®] (cobicistat, COBI) 150 mg tablets was submitted on June 27, 2012 and received a Complete Response Letter on April 26, 2013 due to significant deficiencies noted during the inspection of the Gilead Sciences (Foster City, CA) facility. This submission details the scope of the Applicant's proposed safety update to be included in the NDA resubmission and includes a request for Agency feedback. No details regarding the Applicant's plan for response to the CMC deficiencies are included in this submission.

1.0 Proposed Safety Update

The safety update will include clinical safety data from:

- Phase 2 and 3 trials with cobicistat: GS-US-216-0105 and -0114; these data will be pooled for the safety analysis.
- Phase 3 Study GS-US-216-0130, an open-label trial of COBI-boosted darunavir in HIV-infected treatment-naive and –experienced adults with no darunavir resistance-associated mutations (data not previously submitted to NDA)
- Phase 1 Studies GS-US-216-0125 (methadone and buprenorphine/naloxone drug interaction study), GS-US-216-0127 (pediatric formulations of COBI) and GS-US-216-0134 (TDF drug interaction study)
- Phase 2 and 3 trials with Stribild[®]: GS-US-236-0102, GS-US-236-0103 and GS-US-236-0104; data from -0102 and -0103 will be pooled for the safety analysis.
- Phase 3 Study GS-US-236-0118, an open-label safety study of COBI-containing regimens in HIV-infected subjects with mild to moderate renal impairment
- Phase 1 Study GS-US-236-0135, a drug interaction study with Stribild and telaprevir (data not previously submitted to NDA)

- Phase 1 Study GS-US-236-0130 evaluating the effect of COBI on select renal function parameters (data not previously submitted to NDA)

The data cut-off dates used for the key trials included in this Safety Update are listed in Table 1. The difference in percentage for a given adverse event between this Safety Update and the original NDA will be calculated.

Table 1: Data Cut Used in Original NDA vs. this Safety Update (SU)

Study	Data Cut Date ¹	
	Original NDA	This SU
GS-US-216-0114	31 October 2011 (Week 48 Analysis)	03 September 2013 ³ (Week 144 LPLV)
GS-US-216-0105	26 April 2011 (Week 96 Analysis)	01 July 2013
GS-US-216-0130	None ²	01 July 2013
GS-US-236-0102	26 July 2011 (STB Week 48/ISS Analysis)	29 May 2013 (Week 144 LPLV/ISS Analysis)
GS-US-236-0103	1 September 2011 (STB Week 48/ISS Analysis)	5 July 2013 (Week 144 LPLV/ISS Analysis)
GS-US-236-0104	17 March 2011 (Week 96 Analysis)	01 July 2013

LPLV = Last Patient Last Visit

¹ The date used to cut the AE eCRF data are presented.

² Data were not included in the original NDA.

³ Planned cut date based on the projected last patient Week 144 visit

The Applicant proposes to include the safety update in Module 5.3.5 (Reports of Efficacy and Safety Studies) in NDA 203094, and not update Modules 2.6.2 (Pharmacology Written Summary), 2.6.4 (Pharmacokinetics Written Summary), 2.6.6 (Toxicology Written Summary) and 2.7.4 (Summary of Clinical Safety).

2.0 Medical Reviewer's Assessment

This Medical Officer has reviewed the Statistical Analysis Plan (SAP) for the proposed Safety Update and concurs with the scope and layout of the Safety Update for the cobicistat NDA resubmission. The format for the proposed update is consistent with the 120-day Safety Update submitted to the original NDA.

Peter Miele, M.D.
Medical Officer
FDA/CDER/OAP/DAVP

Concurrence:
HFD-530/TL/Lewis

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/s/

PETER S MIELE
09/09/2013

LINDA L LEWIS
09/10/2013

CLINICAL REVIEW

Application Type	New Drug Application
Application Number(s)	203094
Priority or Standard	Standard
Submit Date(s)	June 26, 2012
Received Date(s)	June 28, 2012
PDUFA Goal Date	April 28, 2013
Division / Office	Division of Antiviral Products/ Office of Antimicrobial Products
Reviewer Name(s)	Peter S. Miele, MD
Review Completion Date	March 22, 2013
Established Name	cobicistat
(Proposed) Trade Name	Tybost
Therapeutic Class	Cytochrome P450 3A Inhibitor
Applicant	Gilead Sciences, Inc.
Formulation(s)	150 mg tablet
Dosing Regimen	1 tablet by mouth once daily

Indication(s)	CYP3A inhibitor to increase systemic exposures of atazanavir and darunavir
Intended Population(s)	Adults with HIV-1 infection

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends approval of the cobicistat (COBI) 150 mg tablet for use as a once daily cytochrome P450 3A (CYP3A) inhibitor to increase the systemic exposures of the HIV-1 protease inhibitors (PI) atazanavir (ATV) 300 mg once daily and darunavir (DRV) 800 mg once daily in HIV-1 infected adults. This recommendation is based on the clinical pharmacological, safety and effectiveness data submitted in new drug application (NDA) 203094. Two bioavailability trials in healthy volunteers demonstrated bioequivalent steady-state concentrations of ATV or DRV when coadministered with COBI or ritonavir (RTV). Further, clinical use data from one pivotal and one supportive randomized, double-blind and active-controlled clinical trial in HIV-1 infected treatment-naive adults showed that the antiviral efficacy of ATV coadministered with COBI (ATV/co) was similar to that of ATV coadministered with ritonavir (ATV/r) in suppressing HIV-1 RNA at 48 weeks. According to my review of the clinical data, the safety of COBI tablets is acceptable and no deficiencies were identified in this NDA that would preclude approval.

1.2 Risk Benefit Assessment

Once daily COBI has demonstrated robust pharmacokinetic enhancement of the PIs ATV and DRV through CYP3A inhibition in two Phase 1 trials and potent and durable antiretroviral (ARV) activity when coadministered with ATV and emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in one Phase 2 trial and one Phase 3 trial.

Cobicistat, when compared with RTV, more selectively inhibits CYP3A, displaying weak to minimal inhibition of other cytochrome P450 enzymes; it is a less potent inducer of other metabolizing enzymes in vitro, and it has been shown to have less potential for clinically significant drug interactions via these non-CYP3A pathways.

Review of the clinical data indicates that the safety profile of COBI tablets is not wholly dissimilar from that of low-dose RTV, which is commonly used in clinical practice to increase the concentrations of other PIs. In the Phase 2 and 3 clinical trials with COBI, the rates of treatment-emergent adverse events (AE), discontinuations due to AEs, and drug-related AEs were comparable between the ATV/co and ATV/r treatment groups. The most common AEs in both groups, of any severity or causality, were jaundice, ocular icterus, nausea and diarrhea. Review of the laboratory, ECG, and subgroup analysis data revealed no significant differences between the groups, including changes in lipid parameters from baseline at Week 48.

Nearly all of the important safety findings noted in these trials have previously been reported with RTV or with the coadministered drugs used in the study regimens (ATV, FTC and TDF). Indeed, other than an artificial increase in serum creatinine and a corresponding reduction in estimated glomerular filtration rate (eGFR), no new safety issues emerged that were related specifically to COBI. Nonetheless, this issue of an artificially decreased eGFR with COBI is not an insignificant one and prescribers will need to keep this effect in mind, particularly when COBI is being coadministered with drugs dependent on eGFR for dosing or when use of COBI is being considered for use in patients with renal impairment.

More concerning, however, is the slightly greater incidence of proximal renal tubulopathy (PRT) observed with the coadministration of COBI and TDF compared with RTV and TDF (1.3% versus 0.5%, respectively) in the pooled safety analysis of the COBI Phase 2 and 3 trials. This imbalance was also previously described in the registrational trials of STRIBILD®, the fixed-dose combination tablet of COBI 150 mg, the investigational integrase inhibitor elvitegravir (EVG), FTC, and TDF, when COBI-treated subjects were compared to non-COBI treated subjects, all receiving TDF as part of their background regimen. In both development programs, renal laboratory abnormalities improved but did not normalize in the COBI-treated subjects after removal of study drugs, but none required renal replacement therapy. Although an explanation for this apparent increased incidence of PRT with COBI and TDF coadministration has not yet been elucidated, the phenomenon does not appear to be related to plasma tenofovir concentrations. Cobicistat is known to inhibit certain renal efflux transporters (OCTN1 and MATE1), but not the ones associated with tenofovir renal elimination (OAT1, OAT3, MRP4). As with STRIBILD, careful renal assessments at baseline and during treatment are strongly recommended when COBI is used in combination with TDF.

The use of COBI to increase ATV exposures also resulted in a higher proportion of subjects with Grade 2-4 bilirubin-related AEs considered drug-related by the investigators and a higher proportion of subjects with Grade 3-4 total bilirubin increases when compared with ATV/r in the pooled safety analysis. However, the rates of drug discontinuation due to bilirubin-related AEs were comparable between the two groups.

In addition, the incidence of nephrolithiasis through Week 48 in the pooled safety analysis was greater in COBI-treated subjects than in RTV-treated subjects (2.0% vs. 0.0%, respectively). Subsequent information provided by the Applicant revealed that the incidence of nephrolithiasis between the two groups became more comparable through 96 weeks of treatment. At worst, however, it may be said that COBI increases the risk of early-onset nephrolithiasis (median time to onset 24 weeks) compared with RTV, where published reports have suggested a median time to onset of renal stones of 24 months in patients treated with ATV/r. However, no subjects in the COBI trials discontinued study drug because of nephrolithiasis, and most of the events were not serious. Moreover, insufficient information was collected in these trials to characterize the

composition of the renal stones and assess causality - although there was evidence of calcium oxalate crystalluria in most cases, which might have played a role.

Another concern with COBI is the lack of available drug interaction information for concomitant use with several commonly used drugs in an HIV-infected population, such as lipid lowering agents (i.e., statins) or hormonal contraceptives. Also, in contrast to RTV, there is insufficient data to support the use of COBI other than once daily or with PIs other than ATV or DRV. If practitioners falsely assume that COBI and RTV can always be used interchangeably, there is the potential risk that poorly characterized drug interactions will occur.

In conclusion, the effectiveness of COBI as a CYP3A inhibitor to increase the concentrations of ATV and DRV has been adequately demonstrated. The overall safety profile of COBI tablets is acceptable. That said, COBI does not offer any particular advantage over RTV as a CYP3A inhibitor. The overall safety and tolerability of COBI is not significantly better than RTV, and in some instances, may be slightly worse (e.g. bilirubin-related events, increased risk of PRT with concomitant use of TDF, and possible earlier onset of renal stones). In addition, the use of COBI compromises a practitioner's ability to reliably calculate eGFR in a patient, which may be important to the dosing of concomitant medications. Also worth considering in this risk-benefit assessment is the fact that low-dose RTV has been used to increase the exposures of other PIs for nearly a decade. The drug interaction profile of RTV, while complex, is generally well characterized at this point.¹ Moreover, information about RTV coadministration appears in labeling for all commonly used PIs. In contrast, the scope of well characterized drug interactions with COBI is limited. For this reason, the indication for COBI is exceedingly narrow. Simply put, the contribution of COBI to the HIV armamentarium at this stage is minimal, and because of the relative lack of clinical pharmacology data with other ARV and non-ARV drugs, COBI is not as useful or versatile as RTV. Further, as noted earlier, there is the risk that practitioners might mistakenly use COBI interchangeably with RTV, which may lead to negative outcomes. The aforementioned issues, while not insignificant, however, do not constitute a rationale for withholding approval of COBI tablets in my opinion. The limitations of use and safety issues associated with COBI are clearly specified in the proposed labeling. Further, the important safety concerns related to COBI use, such as the renal issues, can be properly monitored and managed in a clinical setting. Finally, an education campaign targeting HIV prescribers and pharmacists is planned pending approval of the COBI tablet to highlight the unique aspects of the drug and help differentiate it from RTV.

¹ Josephson F. Drug-drug interactions in the treatment of HIV infection: focus on pharmacokinetic enhancement through CYP3A inhibition. *J Intern Med* 2010; 268:530-9.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarketing Risk Evaluation and Mitigation Strategies (REMS) are recommended based on the safety profile of COBI tablets.

As previously noted, a primary safety concern related to COBI tablets is the potential for adverse drug-drug interactions with concomitant medications. The most serious of these interactions are appropriately described in the proposed labeling, which includes a number of contraindicated drugs. However, there are other medications for which possible drug interactions are complex or unknown, and while the experience with RTV has allowed predictions to be made for certain drugs, the pharmacokinetic profiles of COBI and RTV are sufficiently distinct that the RTV experience cannot be extrapolated to all situations. Importantly, COBI and RTV are not interchangeable and COBI should not be viewed as a substitution for RTV.

To that end, the Applicant has committed to an education plan to coincide with the anticipated approval to help reduce the risk of inappropriate use of COBI tablets. The education plan enforces the following messages:

- The administration of COBI tablets should be limited for use only as a CYP3A inhibitor with the protease inhibitors ATV and DRV administered once daily. Cobicistat tablets should not be indiscriminately substituted for low-dose RTV as a CYP3A inhibitor for other protease inhibitors, or to be used as a CYP3A inhibitor of DRV administered twice daily;
- COBI 150 mg tablets administered once daily with ATV or DRV should not be used in combination with other antiretroviral agents that require CYP3A inhibition (i.e. another protease inhibitor (b) (4)) or with products/regimens containing COBI or RTV;
- Any use of concomitant medications should be informed by and consistent with the drug interaction-related safety information in the CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS sections of the proposed COBI labeling.

These instructive points will be the components of a multi-tiered, broad education plan targeting pharmacists and HIV health care providers. Using labeling for the COBI tablets as the primary reference for the correct administration, use and safety information, the Applicant will provide proactive communications to help educate providers on the correct use of COBI tablets.

The proactive communications will include:

- a Dear Health Care Provider (DHCP) letter reinforcing the appropriate use of COBI tablets as specified in labeling and summarized above;

- an informational COBI tablets website with a section directed to healthcare providers that instructs upon the appropriate use of the product, emphasizing that COBI tablets should only be used as a CYP3A inhibitor for ATV and DRV administered once daily;
- COBI tablets prescribing considerations which will be emailed to registered pharmacists (“e-Pharm Alert”) through a third party-maintained distribution list, as a means of reinforcing the communication of the appropriate use of COBI tablets to pharmacists;
- an informational print brochure distilling key information on the appropriate use of COBI tablets from the U.S. prescribing information, which will be made available at antiretroviral professional conferences.

FDA will also initiate a communication plan to complement the Applicant’s efforts, reiterating the key message that COBI is not universally interchangeable with RTV. At a meeting with the FDA Office of Communications, the following components of the FDA communication plan were agreed upon:

- press release
- Medscape interview
- E-mail blast
- FDA listserve (HIV/AIDS)
- stakeholder call

This reviewer considers the sum of these approaches adequate to serve as a platform to educate health care providers on the correct use of the COBI tablet and help mitigate the possibility of incorrect use.

1.4 Recommendations for Postmarket Requirements and Commitments

Considerations for postmarketing studies at this time include the following:

- Deferred pediatric trials required under the Pediatric Research Equity Act (PREA) 21 CFR 314.55 (b) and 601.27 (b). Please refer to Section 7.6.3 for discussion of the Applicant’s pediatric development plan. A Written Request (WR) for pediatric trials is currently being drafted.
- Drug interaction studies of ATV/co and DRV/co with:
 - TDF and H₂-receptor antagonists (for ATV/co only)
 - TDF and proton pump inhibitors (for ATV/co only)
 - hormonal contraceptive agents

- HMG-CoA reductase inhibitors atorvastatin and rosuvastatin
- A bioavailability trial comparing EVG exposures for EVG/co as single agents versus STRIBILD

2 Introduction and Regulatory Background

2.1 Product Information

Generic Name: Cobicistat (COBI)

Proposed Name: TYBOST

Chemical Class: New dosage form

Cobicistat was approved on August 27, 2012 as part of the fixed-dose combination tablet STRIBILD™ (EVG 150 mg, COBI 150 mg, FTC 200 mg, and TDF 300 mg). The present NDA is for a new dosage form for COBI as a stand-alone 150 mg tablet.

Pharmaceutical Class: Cytochrome P450 3A inhibitor

Pending regulatory approval, the COBI 150 mg tablet would be the first pharmaceutical agent with an indication for use as a CYP3A inhibitor.

Proposed Indication: Once daily use as a CYP3A inhibitor to increase systemic exposures of ATV (300 mg once daily) and DRV (800 mg once daily) in HIV-1 infected adults 18 years of age and older.

As the body of clinical data currently supports COBI as a CYP3A inhibitor of ATV and DRV, the Applicant plans to restrict the indication in adult populations (and eventually pediatrics) to COBI coadministration with these two PIs. The Applicant does not plan to evaluate any additional PI/COBI combinations.

Moreover, although COBI was initially developed to serve as CYP3A inhibitor of the investigational integrase inhibitor EVG, adequate safety and effectiveness data are lacking for EVG boosted by COBI (EVG/co) as stand-alone products. Large scale clinical trials of EVG/co have only evaluated the combination as found in the fixed-dose tablet STRIBILD. A bioavailability trial to support linking of the safety and efficacy of the STRIBILD tablet to the stand-alone EVG and COBI products is lacking at this time.

Brief Description of Drug: Cobicistat is a mechanism-based CYP3A inhibitor that enhances or “boosts” the exposure of CYP3A substrates, including PIs (b) (4). A mechanism-based inhibitor is a substrate for an enzyme, which through the process of its metabolism, generates a metabolite that irreversibly inhibits the enzyme. Cobicistat is a structural analogue of RTV, but is devoid of ARV activity.

2.2 Tables of Currently Available Treatments for Proposed Indications

No product is currently approved for use as a CYP3A inhibitor.

The HIV-1 protease inhibitor RTV (NORVIR), commonly used at sub-therapeutic doses to boost other PIs owing to its ability to inhibit CYP3A, is not approved for this indication.

2.3 Availability of Proposed Active Ingredient in the United States

Cobicistat as a single agent is not currently available in the United States or elsewhere.

Cobicistat 150 mg, however, has been co-formulated with EVG 150 mg, FTC 200 mg, and TDF 300 mg in the fixed-dose combination tablet STRIBILD, which was approved in the United States on August 27, 2012 for the treatment of HIV-1 infection in treatment-naive adults.

2.4 Important Safety Issues with Consideration to Related Drugs

Currently, no products pharmacologically related to COBI (i.e., CYP3A inhibitors devoid of ARV activity) have received FDA approval. However, COBI is a structural analogue of RTV and the primary pharmacodynamic effect of COBI (i.e., inhibition of CYP3A) is common to both drugs. As such, the most important safety issues related to these drugs are their potential for drug-drug interactions, both their effect on other drug concentrations (as perpetrators) and the effect of other drugs on their concentrations (as victims). As with RTV, coadministration of COBI with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated. Conversely, coadministration of COBI with drugs that induce CYP3A may result in decreased plasma concentrations of COBI and consequently that of the COBI-boosted PI, leading to loss of therapeutic effect and possible development of resistance, and must be avoided.

As a structural analogue of RTV, the major side effects associated with RTV may also apply to COBI and these include gastrointestinal intolerance (nausea, diarrhea), metabolic abnormalities (glucose intolerance, hypercholesterolemia and hypertriglyceremia) and PR interval prolongation.

Lastly, although COBI does not have ARV activity and resistance is not expected to be a major safety concern, clinical trials with STRIBILD have shown the development of a

disproportionate number of substitutions in the protease sequence in subjects treated with STRIBILD compared with subjects treated with another non-PI based regimen, ATRIPLA® (efavirenz/FTC/TDF). None of these protease substitutions were considered primary resistance mutations, and their clinical relevance is unclear, but the potential for development of PI resistance with COBI bears further monitoring. Please refer to Section 4.1 for further details.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

This section summarizes the notable regulatory events related to this submission. It should be noted that the development program for COBI tablets was closely related to and integrated with the development programs for EVG and STRIBILD tablets.

- IND 72177 for EVG tablets was opened on April 18, 2005. From the onset, the development of EVG (boosted with RTV) was intended for a treatment-experienced indication. However, agreement on a noninferiority margin for the pivotal Phase 3 trials proved challenging and enrollment in the trials lagged due to decreasing numbers of eligible participants.
- IND 101283 for COBI (GS-9350) tablets was opened on April 10, 2008, following pre-IND consultation obtained on February 6, 2008. In both submissions, the Applicant indicated its intention to initially pursue registration of GS-9350 as part of a fixed-dose combination (FDC) tablet including EVG/FTC/TDF as a complete regimen for HIV-1 infected treatment-naive adults. The Applicant also indicated its plans to pursue registration of COBI to enhance the PK exposure of ATV, possibly as part of a fixed-dose combination tablet with ATV/FTC/TDF.
- IND 103093 for the EVG/COBI/FTC/TDF FDC tablet was opened on August 29, 2008.
- On January 14, 2009 a Type C meeting for INDs 72177, 101283, and 103093 was held to discuss the integrated development and registration plans for EVG, COBI and the EVG/COBI/FTC/TDF FDC tablet. The following issues were discussed with the Applicant:
 - There was agreement with the Applicant's proposal to combine the two ongoing Phase 3 trials for EVG/r in treatment-experienced subjects to enroll a total of 700 subjects, and further that the registration of EVG tablets would be supported by clinical data from the FDC tablet trials in treatment-naive subjects, provided the EVG exposures were confirmed to be similar between the FDC tablet (EVG/co) and EVG/r.
 - There was agreement with the Applicant's plans to develop and register COBI tablets initially as a CYP3A inhibitor for ATV, supported by one Phase 2 and one Phase 3 trial of ATV/co vs. ATV/r in treatment-naive

- subjects, and further supported by 48-week safety data from the Phase 3 trials of the EVG/COBI/FTC/TDF FDC tablets. FDA noted that while the ATV/co trials would allow for direct comparison of COBI to RTV to assess safety, the trials of the FDC tablet would not allow for isolation of the safety profile of COBI.
- FDA strongly encouraged the Applicant to perform PK trials of COBI with as many other PIs as possible given the potential for off-label use of COBI and other PIs, which may constitute a significant safety issue if other drug-drug interactions were not explored.
 - FDA recommended the Applicant also perform COBI PK trials in treatment-experienced subjects suppressed on a PI/r regimen.
- An End of Phase 2 (EOP2) meeting was held for IND 101283 (COBI) on March 12, 2010. The following issues were addressed:
- There was agreement that the Phase 3 clinical trial of COBI may proceed.
 - There was agreement that the proposed development plan would support the registration of COBI as a CYP3A inhibitor of ATV, DRV, and EVG.
 - In the case of DRV, the Applicant acknowledged that DRV C_{tau} was not bioequivalent between RTV and COBI boosting, but that C_0 was bioequivalent and a valid assessment of DRV trough concentration as used by Tibotec (the drug manufacturer of DRV) and reflected in DRV labeling. FDA noted that the DRV indication would be a review issue.
 - FDA endorsed provision of additional data, including collaboration with sponsors of PIs, to justify and thereby provide a basis for the use of COBI to boost other agents as appropriate.
 - There was discussion to evaluate the drug interaction potential of COBI with key concomitant medications and to study COBI in special populations.
 - There was agreement that studies would be performed to evaluate COBI as a potential substrate, inducer, or inhibitor for transporters OATP1B1, OATP1B3 and BCRP
 - The Applicant indicated that a clinical trial would be conducted to evaluate the PK and safety of COBI administered twice daily, and if supportive, additional data would be generated, including with twice-daily DRV and also tipranavir (TPV).
 - Given the observed increase in serum creatinine with COBI in the Phase 2 trial, and the known renal toxicities with TDF, the Applicant indicated its plans to assess estimated creatinine clearance on a regular basis in the Phase 3 trial.
 - Regarding renal transporters, the Applicant noted that a research program was ongoing to study the effect of COBI on active tubular secretion of creatinine, including interactions with the transporters OCT2, MATE1, and MATE2-K.

- FDA requested that the Applicant conduct a dedicated renal impairment study with COBI. The Applicant proposed such a study in non-HIV infected subjects. The Agency clarified that it wanted to see longer term data in HIV-infected subjects and that this could be accomplished by allowing enrollment in the Phase 3 trial of subjects with lower eGFR than was originally planned.
 - FDA queried the Applicant on COBI's effect on PR prolongation and bilirubin levels. The Applicant responded that an effect on PR prolongation was not observed in the Phase 2 trial of COBI, nor were increases in bilirubin, liver enzymes, or PR prolongation observed in the Phase 2 trial with the EVG/COBI/FTC/TDF FDC tablet.
 - FDA acknowledged its plans to issue a Written Request (WR) for Pediatric Studies for COBI, but that internal discussion were needed to determine how much pediatric PK and safety data would be needed across age groups for a new CYP3A inhibitor.
- A Type C meeting for June 21, 2010 was scheduled to discuss the FDA snapshot analysis methodology, which was new at the time, for assessing efficacy.
 - A pre-NDA meeting was scheduled on March 30, 2012, but cancelled by the Applicant upon receiving FDA preliminary comments. Key issues addressed in the correspondence included the following:
 - The Applicant indicated that it would be seeking an indication for COBI as a CYP3A inhibitor of ATV and DRV based on the pivotal Phase 3 trial (Study GS-US-216-0114) in treatment-naive adults showing non-inferiority of ATV/co to ATV/r, and on a Phase 1 comparative bioavailability (BA) trial (Study GS-US-216-0115) in healthy volunteers showing the ability of COBI to increase the exposure of DRV similar to RTV.
 - FDA agreed with the proposed indication, but noted that final wording would be contingent upon review of the data.
 - FDA did not consider data from the Phase 2 and 3 trials with the EVG/COBI/FTC/TDF FDC tablet vital to the approval of COBI.
 - FDA emphasized that labeling should be clear that COBI is not interchangeable with RTV to boost any PIs other than ATV or DRV. In addition, labeling should be explicit about not using COBI with saquinavir, fosamprenavir, tipranavir, lopinavir/ritonavir, or twice-daily darunavir.
 - FDA indicated that formal REMS were not anticipated for the COBI tablet, but requested a description of the Applicant's proposed education plan.
 - FDA agreed with the Applicant's proposal to pool data from the COBI Phase 2 and 3 trials in the integrated summaries.
 - FDA agreed with the content of the proposed COBI NDA Safety Update.
 - The Applicant indicated that additional exposure-response analyses were performed to bridge the DRV exposures obtained from once-daily dosing

of DRV/r in the TMC114-C229 and TMC114-C211 clinical trials to the DRV exposures observed with COBI in Study GS-US-216-0115, and that a pharmacokinetics/pharmacodynamics (PK/PD) report would be provided with the COBI NDA.

- NDA 203100 for the EVG/COBI/FTC/TDF (STRIBILD) FDC tablet was approved by FDA on August 27, 2012.

2.6 Other Relevant Background Information

As noted in Section 2.5, COBI was originally developed to serve as a CYP3A inhibitor to increase EVG exposures with the STRIBILD FDC tablet. In the COBI NDA, however, the Applicant is seeking an indication for once daily use as CYP3A inhibitor of ATV and DRV only. (b) (4)

(b) (4)

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

At the filing of this NDA, the Office of Scientific Investigations was consulted to inspect clinical trial sites from the pivotal Phase 3 Study GS-US-236-0114. Please refer to the Clinical Inspection Summary by Dr. Antoine El-Hage for full details. Three sites, two domestic and one foreign (Dominican Republic), were selected because of their

enrollment of large numbers of subjects. In brief, the inspections revealed no regulatory violations and the data submitted from these sites were deemed acceptable in support of the application. Results of the bioanalytical laboratory inspections for the BA trials are currently pending and will be reported in the Cross-Discipline Team Leader (CDTL) memorandum to this NDA.

3.2 Compliance with Good Clinical Practices

The clinical trials submitted in this application were conducted under a U.S. Investigational New Drug Application (IND) and in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice guidelines. The trial protocols and amendments were reviewed and approved by a duly constituted Independent Ethics Committees (IEC) or Institutional Review Boards (IRB). Protocol amendments after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements. Written informed consent was obtained from all subjects prior to any study-related procedures.

3.3 Financial Disclosures

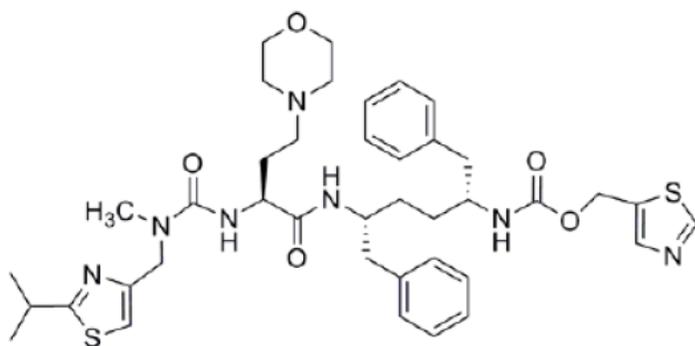
The Applicant certifies that it has not entered into any financial arrangement with the trial investigators whereby the value of compensation to the investigator could be affected by the outcome of the trial as defined in 21 CFR 54.2(a). The Applicant has obtained financial disclosure from all investigators and sub-investigators participating in the COBI Phase 2 and 3 clinical trials (Studies GS-US-216-0105 and -0114) and has identified 18 investigators or sub-investigators who had accepted payments greater than \$25,000, and four investigators or sub-investigators with an equity interest greater than \$50,000 with Gilead Sciences, Inc. These investigators or sub-investigators were responsible for enrolling approximately 10% of the pooled subject population used for the analyses of safety and efficacy (N=771); however, the maximum enrollment at any particular site was 17 (2%) subjects and the majority (13/18) of these sites enrolled less than five (0.6%) subjects each. Given the relatively small percentage of subjects enrolled by any individual site, and the use in these trials of blinding, randomization, and an objective primary endpoint (HIV RNA < 50 copies/mL), the potential for bias due to financial interest is reasonably mitigated.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please refer to the Chemistry Manufacturing and Controls Review by Dr. Fuquiang Liu for full details.

The chemical name for COBI is 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. The molecular formula is $C_{40}H_{53}N_7O_5S_2$ and its molecular weight is 776.0 Daltons. Cobicistat has the following chemical structure:



(b) (4)

The drug substance for cobicistat is defined as “cobicistat on silicon dioxide”. The drug substance is isolated by adsorption of cobicistat onto silicon dioxide (b) (4).

The drug substance is a white to pale yellow powder and is hygroscopic, (b) (4).

(b) (4)

The COBI tablet is an immediate-release, solid dosage form for oral administration. The proposed commercial formulation is an orange, round, biconvex, film-coated tablet, debossed with “GSI” (Gilead Sciences Inc., Gilead) on one side and plain faced on the other side and contains 150 mg of cobicistat. The tablets include the following inactive ingredients: silicon dioxide, microcrystalline cellulose, croscarmellose sodium, magnesium stearate. The tablets are film-coated with a coating material containing the following inactive ingredients: polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, sunset yellow FCF (FD&C Yellow #6), aluminum lake, and yellow iron oxide.

The dissolution profile for the proposed commercial tablet formulation showed that greater than (b) (4) of cobicistat was dissolved within 20 minutes.

4.2 Clinical Microbiology

Please refer to the Virology Review by Dr. Takashi Komatsu for full details.

Cobicistat is similar in structure to RTV. Cobicistat increases systemic levels of the PIs ATV and DRV and the integrase inhibitor EVG, whose bioavailability and elimination are affected by CYP3A-enzyme mediated metabolism. Cobicistat, however, 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.

In vitro PD drug-drug interaction studies with approved HIV-1 ARV drugs demonstrated that the antiviral activity of these drugs in cell culture is not antagonized by COBI.

In the COBI Phase 2 Study GS-US-216-0105, two COBI-treated subjects qualified for resistance analysis while on therapy due to a suboptimal response and/or virologic rebound. Neither subject had evidence of genotypic or phenotypic resistance to ATV, FTC, or TDF at baseline or at Week 48.

In the COBI Phase 3 Study GS-US-216-0114, evaluable genotypic data from paired baseline and treatment-failure isolates were available for 11 of 12 virologic failures in the ATV/co + FTC/TDF group (11/344 [3%]). Among these 11 subjects, two subjects developed the FTC-associated resistance substitution M184V. No subject developed the TDF resistance substitution K65R or any primary resistance substitution associated with protease inhibitors. In the ATV/r + FTC/TDF group, 12 subjects were analyzed for resistance development (12/348 [3%]), none of whom developed resistance to any component of the regimen.

As noted in Section 2.4, because COBI is structurally similar to RTV, possible protease inhibitory activity in vivo was assessed in the STRIBILD registrational trials by comparing the protease sequences in failure isolates from the STRIBILD and ATRIPLA treatment arms. A disproportionate number of substitutions in the protease sequence developed on-treatment in the STRIBILD group (9 substitutions/14 subjects) compared with the ATRIPLA group (4 substitutions/15 subjects). Three of the 9 protease substitutions in isolates from the STRIBILD group have been associated with resistance to protease inhibitors (M36I, D60E, and V77I). However, none of these substitutions are considered primary resistance mutations.

In the COBI Phase 2 Study GS-US-216-0105, seven amino acid substitutions developed in the protease sequence in the virologic failure isolates from the two subjects in the ATV/co group compared to none in the virologic failure isolates from two subjects in the ATV/r group. In the Phase 3 Study GS-US-216-0114, five amino acid

substitutions developed in the protease sequence in the virologic failure isolates from the 12 subjects in the ATV/co group compared to seven amino acid substitutions in the virologic failure isolates from the 12 subjects in the ATV/r group. The presence of ATV in these two trials, however, confounds any possible interpretation of these results with respect to the question of COBI selecting PI resistance substitutions. The clinical relevance of these substitutions is unclear at this time as the numbers of subjects with these substitutions in the STRIBILD and COBI development programs have been small; however, this issue will require further monitoring.

4.3 Preclinical Pharmacology/Toxicology

Please refer to the Pharmacology/Toxicology Review by Dr. Laine Myers for full details. All nonclinical studies required to support chronic use have been performed and submitted as a part of the nonclinical assessment of COBI. Moreover, no anticipated relevant PK or significant toxicological interactions are expected with COBI in combination with ATV or DRV, beyond the anticipated increases in PI exposures with COBI.

General Toxicology Studies

Repeat-dose nonclinical studies with COBI identified target organ toxicity in the liver (mouse, rat, and dog) and thyroid (rat). Slight hematological changes were noted in rats and slight chemistry changes were observed in mice, rats, and dogs, with urinalysis changes primarily noted at high doses in rats and dogs. The thyroid changes in rats, secondary to microsomal enzyme induction and thyroid hormone imbalance, were considered by the Applicant to be rodent-specific. Liver changes in mice, rats, and dogs included microsomal enzyme induction, increased weights, and hepatocellular hypertrophy or vacuolation. These effects appeared to be reversible after a 1-month or 3-month recovery period. Urinalysis changes included higher urine volume, lower urine specific gravity, and increases in electrolyte excretion. These changes were reversible, and there was no evidence of progression after long-term dosing, or association with remarkable serum chemistry or histopathological correlates. Other potential toxicities related to COBI included PR interval prolongation in the 4-week dog toxicity study and decreases in left ventricular function in isolated rabbit hearts.

Carcinogenesis and Mutagenesis

Cobicistat was negative for mutagenic potential in a bacterial reverse mutation test, negative in a forward mutation test in mouse lymphoma cells, and negative in an in vivo rat micronucleus assay.

In the 2-year carcinogenicity study in mice, no drug-related increase in tumor incidence was observed at COBI exposures 7 to 16 times (males and females, respectively) the human systemic exposure at the therapeutic daily dose.

In the 2-year carcinogenicity study in rats, increases in follicular cell adenomas and/or carcinomas in the thyroid gland were observed at doses of 25 and 50 mg/kg/day in males, and at 30 mg/kg/day in females. At the highest doses tested, systemic exposures were approximately 2 times the human systemic exposure at the therapeutic daily dose. The follicular cell findings are considered rat-specific, secondary to hepatic microsomal enzyme induction and thyroid hormone imbalance, and are not considered relevant to humans. In rats, COBI induces hepatic CYP3A activity due to a species-specific activation of pregnane X receptor (PXR), which does not occur in humans. The observed toxicity profile on the thyroid, therefore, is rodent-specific and it is unlikely that COBI presents a risk to the human thyroid. These effects, associated with liver enzyme induction, bear no relevance for man as a similar association between liver enzyme induction and carcinogenesis does not exist in humans.

Reproductive Toxicology Studies and Studies in Juvenile Rats

A full reproductive toxicology panel was performed. Cobicistat demonstrated no adverse effects on fertility or embryo-fetal viability in a fertility study in male and female rats, with No Observed Adverse Effect Levels (NOAEL) corresponding to 3.9-fold (males) and 5.1-fold (females) exposures over the human therapeutic exposures. There were no effects on early embryonic development, embryo-fetal development (rats and rabbits), postnatal development or lactation. In rats, at 125 mg/kg/day, increases in post-implantation loss and decreased fetal weights were associated with significant maternal toxicity. The NOAEL for maternal toxicity in these animals was 75 mg/kg/day (including reproduction, viability, growth and development), corresponded to exposure margins of 1.7 (rats) and 4.3 (rabbits) over the human therapeutic exposures. Cobicistat was excreted in the milk of lactating rats with milk to plasma ratios ranging from 1.3 to 1.9. Cobicistat was well tolerated in juvenile rats at dose levels and exposures similar to those used in the repeat-dose studies with older rats.

Special Toxicology Studies

Cobicistat was a mild irritant to rabbit skin, was not a strong eye irritant, and was negative for delayed-type hypersensitivity. Results from a 4-week immunotoxicity study in rats showed a decrease in the T-cell dependent immunoglobulin G (IgG) antibody response in females only. In standard 13-week mouse, 26-week rat, and 39-week dog toxicity studies, microscopic changes suggestive of immunotoxicity were not observed in lymphoid organs, and immunophenotyping of peripheral blood cells in the chronic rat and dog studies did not reveal any adverse effects.

4.4 Clinical Pharmacology

Please refer to the Clinical Pharmacology Review by Dr. Stanley Au for full details.

4.4.1 Mechanism of Action

Cobicistat is a mechanism-based CYP3A inhibitor that enhances the exposure of CYP3A substrates. It is a structural analogue of RTV but devoid of antiviral activity.

4.4.2 Pharmacodynamics

Cobicistat is a potent inhibitor of CYP3A and a weak inhibitor of CYP2D6.

At high concentrations, COBI is a weak activator of human PXR and increases hepatocyte CYP3A4 mRNA and protein. At very high concentrations, COBI is a weak inhibitor of p-glycoprotein (P-gp or MDR1) and breast cancer resistance protein (BCRP).

Cobicistat is a moderate inhibitor of the OATP1B1 and OATP1B3 transporters and may result in higher peak concentrations and lower first-pass metabolism of agents that are substrates for these transporters.

In sum, the plasma concentration of drugs that are primarily metabolized by CYP3A or CYP2D6, or are substrates of P-gp, BCRP, OATP1B1 or OATP1B3 may be increased if the drug is coadministered with COBI.

Cobicistat also inhibits the organic cation transporter 2 (OCT2), the renal efflux transporters OCTN1, and the multidrug and toxin extrusion protein 1 (MATE1), which may affect the tubular secretion of endogenous substrates of these transporters (e.g. creatinine). Inhibition of OCT2 and MATE1 transporters by COBI may explain the clinical finding of a reduction in renal creatinine clearance without a change in actual glomerular filtration rate; i.e., COBI affects the active secretion of creatinine, but not passive filtration (see below).

- **Study GS-US-216-0121** was a Phase 1 trial evaluating the effect of COBI on serum creatinine in subjects with normal renal function (eGFR \geq 80 mL/min, N=12) and mild-to-moderate renal impairment (eGFR 50-79 mL/min, N=18). A statistically significant decrease in eGFR, calculated by Cockcroft-Gault method, from baseline was observed after 7 days of treatment with COBI 150 mg among subjects with normal renal function (-9.9 ± 13.1 mL/min) and among subjects with mild-to-moderate renal impairment (-11.9 ± 7.0 mL/min). These decreases were reversible as assessed on Day 14, seven days after COBI was discontinued. In contrast, no statistically significant changes in eGFR relative to baseline were observed at Day 7 in subjects who received RTV or placebo. The actual glomerular filtration rate, as determined by the clearance of the probe drug iohexol, however, was not altered from baseline following treatment of COBI among subjects with normal renal function or mild-to-moderate renal impairment, indicating that COBI inhibits tubular secretion of creatinine, reflected as a

reduction in eGFR, without affecting the actual glomerular filtration rate. Please see Section 7.4.5 for discussion of the safety findings from this trial.

Cobicistat shows weak or undetectable inhibition of MRP1, MRP2, MRP4, and MATE2-K, and the renal uptake transporters, OAT1 and OAT3. As such, COBI (via OCT2, MATE1) displays unique and non-overlapping interactions with transporters relative to those involved in tenofovir renal elimination (OAT1, OAT3, MRP4).

Unlike RTV, COBI does not exhibit any activity against host protease cathepsin D and is less inhibitory against host proteasome activity. In vitro data from studies with differentiated adipocytes suggest that COBI may have reduced effects on lipid metabolism and adipocyte functions compared with RTV.

Please refer to Section 6.1.8 for discussion of other PK/PD relationships investigated in the Phase 1 Studies GS-US-216-0101, -0116, -0110, and -0115.

4.4.3 Pharmacokinetics

Absorption

Absorption is not influenced by local gastrointestinal pH. Cobicistat displays high solubility and permeability, and its absorption potential is high. Peak concentrations are observed ~4 to 5 hours following oral administration. Absorption of COBI is influenced by food (refer to the Food Effect section below for details).

Distribution

Cobicistat is highly protein bound (97-98%) and excluded from the cellular components of the blood. The mean blood to plasma ratio is approximately 0.5. The distribution of COBI into peripheral compartments (e.g., cerebrospinal fluid or genital tract secretions) has not been evaluated in humans.

Metabolism

Cobicistat is primarily metabolized and eliminated by the liver. It is extensively metabolized in vitro via CYP3A (major) and CYP2D6 (minor) mediated oxidation. Therefore, COBI exposures are decreased when COBI is coadministered with moderate-strong CYP3A inducers. Primary metabolites include isopropyl oxidation (M31, E3, GS-9612), cleavage at the N-methylurea (M26, E5, GS-341842), cleavage of the carbamate (M21, E1, GS-9454), and cleavage and deethylation of the morpholine (M39). CYP3A can catalyze all reactions, while CYP2D6 contributes to the generation of M31 (E3). Mean plasma exposure of M31 was < 3% of COBI exposure (AUC) at the 150 mg dose in clinical studies following single- or multiple-dose administration.

Elimination

Following administration of [¹⁴C] COBI, 86.2% of the dose was recovered in feces, consistent with hepatobiliary excretion, and primarily as parent drug or metabolites M21 or M31. Renal elimination was a minor pathway with 8.2% of the administered dose recovered in urine primarily as unchanged parent drug. In plasma, COBI was the predominant species, representing 98.6% of the circulating radioactivity; observed metabolites were at undetectable or very low concentrations relative to systemic exposure of COBI.

Food Effect

A food effect trial was not conducted for COBI stand-alone tablets. In clinical trials, COBI was coadministered with ATV or DRV, which were to be taken under fed conditions in accordance with the prescribing information for these agents. In order to align with prescribing information for the coadministered PIs, it is recommended that COBI-containing regimens be taken with food.

The effect of food on the PK of COBI and coadministered agents, however, was evaluated in two trials:

- **Study GS-US-201-0101** evaluated the effect of food on the PK of COBI in healthy volunteers following administration of COBI as the stand-alone tablet in combination with the investigational PI GS-8374, which is no longer in development. Upon administration of the COBI with GS-8374, COBI AUC_{inf} and C_{max} were 66% and 24% higher, respectively, following a light meal compared with administration under fasted conditions.
- **Study GS-US-236-0105** evaluated the effect of food (under fasted conditions and two different fed conditions: light meal or high-calorie/high-fat meal) on the PK of EVG, COBI, FTC, and tenofovir following administration of the STRIBILD tablet in healthy volunteers. Cobicistat exposure parameters AUC_{inf}, AUC_{last}, and C_{max} were bioequivalent under light meal and fasted conditions. Minor decreases in exposure parameters were observed with a high-calorie/high-fat meal relative to a light meal (ranging from 19% to 27%) or fasted state (ranging from 17% to 24%), but did not affect the ability of COBI to appropriately increase EVG exposures.

Cobicistat Exposures in Healthy Volunteers and HIV-1 Infected Subjects

A cross-study comparison of COBI PK parameters between healthy subjects (Study GS-US-216-0110) and HIV-1 infected subjects from the Phase 2 Study GS-US-216-0105 (intensive and sparse) and the Phase 3 Study GS-US-216-0114 (intensive) following multiple-dose administration of ATV/co (300/150 mg) indicated that COBI

AUC_{τ} , C_{\max} , and C_{τ} were comparable between these populations. Cobicistat exposures following multiple-dose administration of DRV/co (800/150 mg) in healthy subjects (Study GS-US-216-0115) were generally comparable to COBI exposures observed with ATV/co.

5 Sources of Clinical Data

The proposed indication for COBI as a CYP3A inhibitor is directly supported by clinical pharmacology data from Studies GS-US-216-0110, GS-US-216-0115, GS-US-216-0105, and GS-US-216-0114, which showed that COBI effectively increases the exposures of ATV and DRV.

Phase 1 Studies GS-US-216-0110 and GS-US-216-0115 were BA trials in healthy subjects that demonstrated comparable steady-state concentrations of ATV and DRV, respectively, when these PIs were boosted with either COBI or RTV.

The pivotal Phase 3 Study GS-US-216-0114 and the supportive Phase 2 Study GS-US-216-0105 provided the primary data for the characterization of the tolerability, safety, and effectiveness of a COBI-containing regimen (ATV/co) in HIV-infected, treatment-naive subjects. Both trials are ongoing double-blind and active-controlled trials of adequate design and duration, with well-established endpoints. Pooling of study data from these two trials was considered appropriate due to similarities in study design and subject populations.

5.1 Tables of Studies/Clinical Trials

The pivotal COBI Phase 3 trial and supportive Phase 2 trial, both conducted in HIV-1 infected treatment-naive subjects, are summarized in Table 1. In addition, the key Phase 1 BA trials pertinent to the indication are included, as well as other Phase 1 trials referred to in this review. A large number of other Phase 1 clinical pharmacology trials were also submitted but are not listed here. Please refer to the Clinical Pharmacology Review by Dr. Stanley Au for further details of these trials. Lastly, the Phase 2 and 3 trials with STRIBILD are included for supportive safety information.

Table 1: Summary of Key Clinical Trials of Cobicistat

Trial	Study Design	Objectives	Number of Subjects	Duration
Phase 2 and 3 Trials of Cobicistat				
Safety and Effectiveness				
GS-US-216-0114	Phase 3 randomized, double-blind, active-controlled, multicenter study	Evaluate the efficacy of ATV/co + TRUVADA® (TVD) vs. ATV/r +TVD in HIV-1 infected, treatment-naïve adults; primary endpoint HIV-1 RNA < 50 copies/mL at Week 48	Randomized: 698 Treated:692 (COBI 344, RTV 348)	48 weeks of 96 weeks planned. (Blinded study ongoing)
GS-US-216-0105	Phase 2 randomized, double-blind, active-controlled, multicenter study	Evaluate the efficacy of ATV/co +TVD vs. ATV/r +TVD in HIV-1 infected, treatment-naïve adults; primary endpoint HIV-1 RNA < 50 copies/mL at Week 24	Randomized:85 Treated:79 (COBI 50, RTV 29)	60 weeks double-blind phase. Open-label extension phase (ATV/co + TVD) ongoing.
Phase 1 Trials of Cobicistat				
Bioavailability PK/PD & Dose Selection				
GS-US-216-0101	Randomized, double-blind, single-center, placebo- and active-controlled, single and multiple dose-ranging study	Evaluate the safety and tolerability of escalating single and multiple oral doses of COBI; characterize the single-dose PK and steady-state PK and PD (anti-CYP3A activity) of COBI	Randomized: 60 Completed: 48	14 days
GS-US-216-0110	Randomized, open-label, multiple dose, 6-sequence, 3-period crossover study	Evaluate the relative bioavailability and PK of ATV when coadministered with COBI vs. RTV	Randomized: 42 Completed: 33	30 days
GS-US-216-0115	Randomized, open-label, multiple dose, 2-sequence, 2-period crossover study	Evaluate the relative bioavailability and PK of DRV when coadministered with COBI vs. RTV	Randomized: 33 Completed: 31	20 days
Bioequivalency				
GS-US-216-0116	Randomized, 2-cohort, open-label, multiple-dose, crossover study	Evaluate multiple-dose PK of a new formulation of COBI, administered alone; evaluate multiple-dose PK of EVG as a stand-alone tablet administered with a new formulation of COBI tablet	Randomized: 62 Completed: 57	20 days
Food Effect				

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GS-US-201-0101	Randomized, double-blind, placebo-controlled, single-center, single- and multiple-dose escalation study	Evaluate the safety, tolerability, and PK of GS-8374 (investigational PI) following single and multiple-dose administration in combination with COBI. Explore the effect of food on the PK of GS-8374 + COBI	Randomized: 41 Completed: 37	11 days
GS-US-236-0105	Randomized, open-label, single-center, single-dose, 6-sequence, 3-treatment, 3-period crossover study	Evaluate the effect of food (a high-calorie/high-fat meal or a light meal) on the PK of EVG, FTC, TFV, and COBI when administered as an STRIBILD	Randomized: 24 Completed: 24	1 day
Safety PK/PD				
GS-US-216-0107	Randomized, partially blinded, single-center, single-dose, placebo- and positive (moxifloxacin)-controlled, 8-sequence, 4-period crossover, thorough QT/QTc study	Evaluate the effects of COBI on time-matched, baseline-adjusted, placebo-corrected QTcF	Enrolled: 48 Completed: 48	22 days
GS-US-216-0121	Two-cohort study. Cohort 1: randomized, double-blind, placebo (negative)-controlled, single-center, multiple-dose, parallel-group cohort Cohort 2: single-treatment, open-label, multicenter, multiple-dose cohort	Cohort 1: Evaluate renal function and renal creatinine handling before, during, and following 7 days of COBI or RTV in healthy subjects. Cohort 2: Evaluate renal function and renal creatinine handling in stable mild/moderate renal impairment before, during, and following completion of 7 days of COBI, and assess the PK and safety of COBI in stable mild/moderate renal impairment	Enrolled: 54 Completed: 54	7 days
PK and Drug-Drug Interaction				
GS-US-216-0113	Open-label, single-center, single- and multiple-dose, staggered dose-escalation cohort study	Evaluate the PK of COBI following oral administration at single (400 mg) and multiple doses (300 mg x 7 days)	Enrolled: 24 Completed: 24	1-7 days
GS-US-216-0119	Partially randomized, open-label, single-center, multiple-dose, multiple-	Evaluate the safety, tolerability, and PK of COBI administered twice daily and the potential of COBI to boost plasma	Enrolled: 48 Completed: 46	10-30 days

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	cohort, crossover study	concentrations of coadministered DRV or TPV (all administered twice daily) relative to RTV		
GS-US-236-0106	Fixed-sequence, open-label, single-center, multiple-dose study	Determine effect of the STRIBILD on PK of a representative hormonal contraceptive medication, Ortho Tri-Cyclen® Lo (NGM/EE)	Enrolled: 21 Completed: 15	56-84 days
Special Populations				
GS-US-216-0124	Open-label, parallel-group, multiple-dose study	Evaluate PK, safety, and renal function prior to, during, and after dosing with EVG/co in subjects with severe renal impairment	Enrolled: 24 Completed: 23	7 days
GS-US-183-0133	Open-label, parallel-group, multiple-dose study	Evaluate differences in PK and safety of EVG + COBI in subjects with moderate hepatic impairment (CPT Classification B) compared to matched subjects with normal hepatic function	Enrolled: 20 Completed: 20	10 days
Supportive Safety Trials with STRIBILD				
GS-US-236-0102	Phase 3 randomized, double-blind, active-controlled, multicenter study	Evaluate the efficacy of STRIBILD vs. ATRIPLA in HIV-1 infected, treatment-naive adult subjects	Randomized: 707 Treated: 700	48 weeks
GS-US-236-0103		Evaluate the efficacy of STRIBILD vs. ATV/r + TVD in HIV-1 infected, treatment-naive adult subjects	Randomized: 715 Treated: 708	48 weeks
GS-US-236-0104	Phase 2 randomized, double-blind, active-controlled, multicenter study	Evaluate the efficacy of STRIBILD vs. ATRIPLA in HIV-1 infected, treatment-naive adult subjects	Randomized: 71 Treated: 71	24 weeks
GS-US-236-0118	Phase 3 open-label, multicenter, multiple cohort study	Evaluate the safety of COBI-containing regimens in HIV-1 infected adult subjects with mild to moderate renal impairment (eGFR 50-89 mL/min)	Enrolled: 86	Ongoing

5.2 Review Strategy

The clinical review for this NDA was based primarily on the double-blind data from the COBI Phase 2 and 3 trials, GS-US-236-0105 and GS-US-236-0114. The safety review was conducted by this reviewer using pooled data from both trials. The Safety Update Report containing safety data through the cut-off date of April 23, 2102 for the two COBI trials, as well as for the three STRIBILD trials and the Phase 3 Study GS-US-236-0118 in treatment-naïve or treatment-experienced HIV-infected subjects with mild to moderate renal impairment was also reviewed. For the analysis of the primary efficacy endpoint, Week 48 data from Study -0114 only were used, with supportive information obtained from the pooled data of both trials. The review of efficacy was conducted in collaboration with Dr. Yanming Yin, the statistical reviewer from the Division of Biometrics.

5.3 Discussion of Individual Studies/Clinical Trials

Data from Studies GS-US-216-0105 and GS-US-216-0114 formed the principle basis for characterizing the safety and efficacy of COBI as a CYP3A inhibitor in antiretroviral treatment-naïve adults. Both trials were randomized, double-blind, multicenter, active-controlled trials comparing ATV/co to ATV/r, each administered with FTC/TDF. The trials were nearly identical except for sample size, location of study sites, and minor differences in eligibility criteria as noted below.

- Study GS-US-216-0105 was a Phase 2 trial planned for 75 subjects and was conducted at a total of 32 study sites exclusively in the United States.
- Study GS-US-216-0114 was a Phase 3 trial planned for 700 subjects and was conducted in 143 study sites in the United States, Canada, Mexico, Australia, Brazil, Dominican Republic, Thailand, and Europe.
- In both trials, eligible subjects were ARV treatment-naïve HIV-1 infected adults (age \geq 18 years) with plasma HIV-1 RNA levels \geq 5000 copies/mL at screening and no evidence of resistance to study drugs.
- Both trials stratified randomization by HIV-1 RNA level (\leq 100,000 copies/mL or $>$ 100,000 copies/mL) at screening.
- In both trials, women of childbearing age were required to use two forms of highly effective contraception methods (one of which had to be an effective barrier method) from screening throughout the duration of study treatment and for 30 days following last dose of study drug. Female subjects who utilized hormonal contraceptive as one of their birth control methods must have used the same method for at least three months prior to study dosing.
- Both trials used the percentage of subjects with HIV-1 RNA $<$ 50 copies/mL by the FDA snapshot analysis algorithm as the primary endpoint (at Week 24 for Study GS-US-216-0105 and at Week 48 for Study GS-US-216-0114).

Further details of the individual trial designs are discussed below.

Study GS-US-216-0105

Study GS-US-216-0105 is an ongoing Phase 2, randomized double-blind, multicenter, active-controlled trial to evaluate the safety and efficacy of a regimen containing ATV/co versus ATV/r, each administered with FTC/TDF (TRUVAD®, TVD) in HIV-1 infected, antiretroviral treatment-naive adults.

Subjects were randomized in a 2:1 ratio to one of the following two treatment groups:

- Treatment Group 1: COBI 150 mg + ATV 300 mg + single tablet FTC 200 mg/TDF 300 mg + placebo to match ritonavir 100 mg once daily (n = 50)
- Treatment Group 2: ritonavir 100 mg + ATV 300 mg + single tablet FTC 200 mg/TDF 300 mg + placebo to match COBI 150 mg once daily (n = 25)

Randomization was stratified by HIV RNA level ($\leq 100,000$ copies/mL or $> 100,000$ copies/mL) at screening. Subjects received double-blinded treatment through Week 48 and returned for study visits at Weeks 2, 4, 8, 12, 16, and then every 8 weeks through Week 48. After Week 48, subjects continued to take blinded study drug and attend visits every 12 weeks until treatment assignments were unblinded, at which point all subjects returned for an Unblinding Visit (Week 60) and were given the option to participate in an open-label rollover extension phase to receive ATV/co + TVD. Subjects who did not choose to participate in the open-label phase were required to return to the clinic for a 30-day follow-up visit.

An intensive PK substudy was performed at the Week 2, 4, or 8 visit in a subset of subjects at selected study sites (target n = 24 evaluable subjects).

Main eligibility criteria were:

- Plasma HIV-1 RNA levels ≥ 5000 copies/mL at screening
- CD4 cell count > 50 cells/ μ L
- No prior use of any approved or experimental anti-HIV drug
- No NRTI, NNRTI or primary PI resistance mutations (by current IAS-USA guidelines in a screening genotype report)
- Normal electrocardiogram (ECG)
- Estimated glomerular filtration rate (eGFR) ≥ 80 mL/min according to the Cockcroft-Gault (CG) formula
- Not hepatitis B surface antigen (HBsAg) or hepatitis C antibody positive
- No PR interval ≥ 200 msec or ≤ 120 msec on ECG at screening

A sample size of 50 subjects in the COBI group (Treatment Group 1) was chosen to estimate the regimen response rate of HIV RNA < 50 copies/mL at Week 24 to allow for the planning of Phase 3 trials. A total sample size of 75 subjects had very low power

(26% power if a response rate of 84% for both groups and a noninferiority margin of 0.12 was assumed) to evaluate noninferiority with respect to the response rate at Week 24; therefore, non-inferiority of the two treatment groups was not formally evaluated in this trial.

The first subject was screened on May 4, 2009 and the last subject was randomized on June 16, 2009. A total of 85 subjects were enrolled and 79 subjects were dosed. The database finalization for the Week 48 analysis was June 15, 2010. Up to Week 60, subjects continued to take their blinded study drugs and attended scheduled visits until treatment assignments had been unblinded (June 28, 2010). At this point, all subjects were given the option to participate in an open-label rollover extension and receive COBI, ATV, and TVD until COBI tablets become commercially available. Last subject observation for the CSR was June 17, 2011.

Study GS-US-216-0114

Study GS-US-216-0114 is an ongoing Phase 3, randomized double-blind, multicenter, active-controlled trial to evaluate the safety and efficacy of a regimen containing ATV/co versus ATV/r, each administered with TVD in HIV-1 infected, antiretroviral treatment-naive adults.

Subjects were randomized in a 1:1 ratio to one of the following two treatment groups:

- Treatment Group 1: COBI 150 mg + ATV 300 mg + single tablet FTC 200 mg/TDF 300 mg + placebo to match ritonavir 100 mg once daily (n = 350)
- Treatment Group 2: ritonavir 100 mg + ATV 300 mg + single tablet FTC 200 mg/TDF 300 mg + placebo to match COBI 150 mg once daily (n = 350)

Randomization was stratified by HIV RNA level ($\leq 100,000$ copies/mL or $> 100,000$ copies/mL) at screening. Subjects will receive double-blinded treatment through Week 96 and will return for study visits at Weeks 2, 4, 8, 12, 16, and then every 8 weeks through Week 48, then every 12 weeks through Week 96. After Week 96, subjects will continue to take blinded study drug and attend visits every 12 weeks until treatment assignments are unblinded, at which point all subjects will return for an Unblinding Visit and be given the option to participate in an open-label rollover extension phase to receive ATV/co + TVD until COBI tablets become commercially available or until the Applicant elects to terminate development of the COBI tablets. Subjects who do not choose to participate in the open-label extension phase will be required to return to the clinic for a 30-day follow-up visit.

An intensive PK substudy was performed between the Week 2 and 8 visits in a subset of subjects in both treatment groups at selected study sites (target n = 48 evaluable subjects).

Main eligibility criteria were:

- Plasma HIV-1 RNA levels ≥ 5000 copies/mL at screening
- No prior use of any approved or experimental ARV drug for any length of time
- Screening genotype report shows sensitivity to FTC, TDF, and ATV
- Normal ECG
- eGFR ≥ 70 mL/min according to the CG formula
- Not receiving or anticipated to receive drug treatment for hepatitis C
- No PR interval ≥ 220 msec on ECG at screening

A total sample size of 700 subjects randomized in a 1:1 ratio to two treatment groups was estimated to have at least 95% power to establish noninferiority between the two groups with respect to the response rate of HIV RNA < 50 copies/mL at Week 48. For sample size and power computations it was assumed that both treatment groups would have a response rate of 0.795 (based on Gilead Study GS-01-934), that the noninferiority margin was 0.12, and that the significance level of the test was at a 1-sided, 0.025 level.

The first subject was screened on April 26, 2010 and the last subject was randomized on November 30, 2010. A total of 698 subjects were randomized. Last subject observation for the CSR was November 29, 2011. The database finalization for the Week 48 analysis was December 1, 2011, when treatment unblinding took place.

6 Review of Efficacy

Efficacy Summary

The proposed indication for the COBI 150 mg tablet as a once daily CYP3A inhibitor to increase systemic exposures of ATV or DRV is directly supported by clinical pharmacology data from two Phase 1 BA trials in healthy volunteers. In Studies GS-US-216-0110 and GS-US-216-0115, comparable steady-state concentrations of ATV and DRV, respectively, were demonstrated when these PIs were boosted with COBI or RTV.

The effectiveness of the COBI tablet as a CYP3A inhibitor in an ATV-based regimen was further demonstrated in the pivotal Phase 3 Study GS-US-216-0114, with supportive data from the Phase 2 Study GS-US-216-0105, in HIV-infected treatment-naive adults. Subject demographics and disposition in these clinical trials were comparable between the ATV/co and ATV/r treatment groups. In the pivotal Phase 3 trial, 85% of subjects in the ATV/co group achieved the primary endpoint of HIV RNA < 50 copies/mL at Week 48 compared with 87% of subjects in the ATV/r group, for a treatment difference of -2.2% (95% CI: -7% to 3%), adjusted for baseline HIV-1 RNA. The rates of virologic failure were low and comparable between the two treatment groups and both groups demonstrated similar increases from baseline in CD4 cell counts at Week 48. Efficacy results from the pooled Phase 2 and 3 trials were

consistent with the Phase 3 findings. No differences in COBI effectiveness were discernible based on age, sex, race, or baseline HIV RNA viral load or CD4 cell count in these trials.

6.1 Indication

The proposed indication for the COBI tablet is for use as a once-daily CYP3A inhibitor to increase systemic exposures of the protease inhibitors ATV and DRV in adults.

6.1.1 Methods

The proposed indication was directly supported by clinical pharmacology data from Studies GS-US-216-0110 and GS-US-216-0115, which compared the steady-state PK of ATV and DRV, respectively, when boosted with either COBI or RTV. Please see Section 6.1.8 for discussion of these two trials.

The efficacy of a COBI-boosted PI regimen to achieve viral load suppression was based primarily on 48-week data from the pivotal Phase 3 Study GS-US-216-0114. Supportive Week 48 efficacy data was obtained from the Phase 2 Study GS-US-216-0105 and from the pooled data of these two trials, as both trials employed COBI as a CYP3A inhibitor of ATV in HIV-infected treatment-naive adults.

The Week 48 data from Study GS-US-216-0114 alone were used for the primary endpoint analysis (percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48), and will be reported in labeling. For other efficacy analyses conducted as part of this review, pooled 48-week data from Studies -0105 and -0114 were used unless otherwise indicated.

6.1.2 Demographics

Table 2 displays the subject demographics in the pooled analysis of the COBI Phase 2 and 3 trials. Overall, demographic and general baseline characteristics were similar between the two treatment groups and consistent with a treatment-naive population. The overall mean age of subjects was 37 years (range 19-70); 84% were male, 60% were White, 20% were Black and 11% were Asian. The vast majority of subjects were HBV and HCV negative. The mean (standard deviation [SD]) value for body mass index (BMI) at baseline was 25 (4.6) kg/m². In addition, the two groups were comparable with regards to mean eGFR at baseline, calculated by various methods.

Table 2: Demographics and Baseline Subject Characteristics in Phase 2 and 3 Trials (Pooled Analysis GS-US-216-0105 and -0114)

Baseline Subject Characteristic	Number of Subjects (%)	
	ATV/co (N=394)	ATV/r (N=377)

Age (years)		
Mean [SD]	37 [9.7]	37 [9.8]
Sex		
Male	334 (85)	312 (83)
Female	60 (15)	65 (17)
Race		
White	229 (58)	231 (61)
Black or African American	83 (21)	72 (19)
Asian	44 (11)	39 (10)
Other	34 (9)	29 (8)
American Indian or Alaska Native	1 (<1)	2 (1)
Native Hawaiian or Pacific Islander	1 (<1)	1 (<1)
Not Permitted ^a	2 (1)	3 (1)
Ethnicity		
Not Hispanic or Latino	287 (73)	277 (74)
Hispanic or Latino	105 (27)	97 (26)
Not Permitted ^a	2 (<1)	3 (1)
HIV Risk Factors ^b		
Homosexual Sex	265 (67)	251 (67)
Heterosexual Sex	122 (31)	128 (34)
Intravenous Drug Use	8 (2)	8 (2)
Unknown	10 (3)	5 (1)
Other ^c	5 (1)	6 (2)
HBV Surface Antigen Status		
Negative	378 (96)	368 (98)
Positive	16 (4)	9 (2)
HCV Antibody Status		
Negative	373 (95)	360 (96)
Positive	21 (5)	16 (4)
Indeterminate	0	1 (<1)
Body Mass Index (kg/m ²)		
Mean [SD]	25 [4.5]	25 [4.8]
Estimated GFR		
Mean, by Cockcroft-Gault (mL/min) [SD]	116 [28]	119 [32]
Mean, by MDRD (mL/min/1.73 m ²) [SD]	102 [17]	104 [21]
Mean, by Cystatin C Clearance (mL/min/1.73 m ²) [SD] ^d	N=385	N=360
	102 [22]	101 [20]

a) Not Permitted = Regulators do not allow collection of ethnicity information

b) Subjects may have more than one HIV risk factor category; therefore, percentages may exceed 100

c) Other = Occupational exposure, tattoos, piercings

d) Adjusted for age, sex and race

Abbreviations: HBV = hepatitis B virus; HCV = hepatitis C virus; GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; SD = standard deviation

Source: ADSL, ADLB analysis datasets for Integrated Summary of Safety (ISS)

Table 2 displays the baseline HIV-1 disease characteristics in the pooled analysis. Baseline disease characteristics were similar between the two treatment groups. The overall mean (SD) baseline plasma HIV-1 RNA was 4.81 (0.595) log₁₀ copies/mL (range 3.2–6.4) overall. The overall mean (SD) baseline CD4+ cell count was 353 (174.8) cells/μL (range 1–1455) and 17% of subjects had CD4+ cell counts ≤ 200 cells/ μL. The majority of subjects (61%) had baseline HIV-1 RNA ≤ 100,000 copies/mL and 83% had asymptomatic HIV-1 infection.

Table 3: Baseline HIV-1 Disease Characteristics in Phase 2 and 3 Trials (Pooled Analysis GS-US-216-0105 and -0114)

Baseline HIV Disease Characteristic	Number of Subjects (%)	
	ATV/co (N=394)	ATV/r (N=377)
HIV-1 RNA (log ₁₀ copies/mL)		
Mean [SD]	4.78 [0.6]	4.83 [0.6]
HIV-1 RNA Category (copies/mL)		
≤ 100,000	250 (63)	223 (59)
> 100,000	144 (37)	154 (41)
CD4 Cell Count (/μL)		
Mean [SD]	355 [174.5]	351 [175.4]
CD4 Percentage (%)		
Mean [SD]	20.6 [8.8]	20.9 [8.5]
CD4 Cell Count Category (/μL)		
≤ 50	12 (3)	13 (3)
51 to ≤ 200	58 (15)	51 (14)
201 to ≤ 350	130 (33)	133 (35)
351 to ≤ 500	140 (36)	128 (34)
> 500	54 (14)	52 (14)
≤ 350	200 (51)	197 (52)
> 350	194 (49)	180 (48)
HIV Disease State		
Asymptomatic	326 (83)	317 (84)
Symptomatic HIV Infection	32 (8)	33 (9)
AIDS	36 (9)	27 (7)

Abbreviations: SD = standard deviation

Source: ADSL, ADLB analysis datasets for Integrated Summary of Safety (ISS)

6.1.3 Subject Disposition

Pooled subject disposition for all screened subjects in Studies -0105 and -0114 is presented in Table 4. A total of 1008 subjects were screened in the two trials; of these, 783 were randomized to study drug (405 in the pooled ATV/co group and 378 in the

pooled ATV/r group). For both treatment groups, the intent-to-treat (ITT) and safety analysis sets were the same (394 subjects for the pooled ATV/co group and 377 subjects for the pooled ATV/r group).

A total of 12 subjects were randomized but never treated in the pooled analysis. Notably, the ATV/co group had 11 of these subjects. In light of this imbalance, the reasons for non-treatment in these 12 subjects were reviewed. Among the subjects randomized to ATV/co, six subjects withdrew consent and five subjects were removed by the investigators because of protocol violations. The subject randomized to the ATV/r group was removed from the trial because of a protocol violation. These 12 cases occurred equally between the Phase 2 and 3 trials (six cases each). In Study -0114, however, the six cases occurred at six different sites. In Study -0105, two investigators removed two subjects each from the ATV/co group because of protocol violations.

Table 4: Subject Disposition in Phase 2 and 3 Trials Double-Blind Treatment Period (Pooled Analysis GS-US-216-0105 and -0114)

Subject Disposition	Number of Subjects (%)		
	ATV/co	ATV/r	Total
Screened			1008
Screen Failures			225
Randomized	405	378	783
Randomized but Never Treated	11	1	12
Treated (ITT and Safety Population)	394 (100)	377 (100)	771 (100)
Prematurely Discontinued Study Drug	55 (14)	44 (12)	99 (13)
Adverse event	27 (7)	26 (7)	53 (7)
Lack of efficacy	2 (1)	0	2 (<1)
Lost to follow-up	12 (3)	6 (2)	18 (2)
Investigator discretion	4 (1)	2 (1)	6 (1)
Pregnancy	1 (<1)	3 (1)	4 (1)
Protocol violation	0	2 (1)	2 (<1)
Subject non-compliance	4 (1)	3 (1)	7 (1)
Withdrew consent	5 (1)	2 (1)	7 (1)
Still Taking Study Drug at Data Cut-off	339 (86)	333 (88)	672 (87)
Discontinued Trial Early (Randomized Phase)	39 (10)	26 (7)	65 (8)
Adverse event	15 (4)	11 (3)	26 (3)
Lack of efficacy	1 (<1)	0	1 (<1)
Lost to follow-up	14 (4)	7 (2)	21 (3)
Investigator discretion	3 (1)	1 (<1)	4 (1)
Pregnancy	0	2 (1)	2 (<1)
Subject non-compliance	2 (1)	2 (1)	4 (1)

Withdrew consent	4 (1)	3 (1)	7 (1)
Still Being Followed in Trial	355 (90)	351 (93)	706 (92)

Abbreviations: ITT = Intent-to-treat

Source: ADSL dataset for Integrated Summary of Safety (ISS)

In the pooled analysis, the percentage of subjects who discontinued study drug prior to the Week 48 data cut-off date was generally similar between the two treatment groups; 14% in the ATV/co group and 12% in the ATV/r group. The reasons for discontinuation were comparable between the two groups, as outlined in Table 4. In the ATV/co group, the most common reasons for premature discontinuation of study drug were AEs (7%), loss to follow-up (3%), and withdrew consent, investigator discretion, and subject noncompliance (1% each). The most common reasons in the ATV/r group were AEs (7%), loss to follow-up (2%), and pregnancy and subject noncompliance (1% each).

Likewise, the percentage of subjects who discontinued the trial prior to the Week 48 data cut-off was similar between the two groups, as were the reasons for discontinuation. At the time of the NDA submission, 90% of subjects in the pooled ATV/co group and 93% of subjects in the pooled ATV/r group were still being followed in their respective trials.

In the Phase 2 Study GS-US-216-0105, 45/50 (90%) subjects randomized to the ATV/co group and 24/29 (75%) subjects randomized to the ATV/r group completed the double-blind treatment phase. Of these, 44 subjects from the ATV/co group and 19 subjects from the ATV/r group enrolled in the open-label extension phase to receive ATV/co (N=63). Five subjects discontinued ATV/co in the open-label phase for the following reasons:

- ATV/co → ATV/co: 1 death, 1 lack of efficacy, 2 lost to follow-up
- ATV/r → ATV/co: 1 adverse event

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint was the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the FDA snapshot analysis algorithm. For the primary endpoint analysis, data from Study GS-US-216-0114 only were used and reported in labeling. The ITT analysis set (i.e., subjects who were randomized and received at least 1 dose of study drug) was the primary analysis set for efficacy (ATV/co 344, ATV/r 348). Virologic outcomes at Week 48 for Study -0114 are presented in Table 5.

Table 5: Virologic Outcome (HIV RNA < 50 copies/mL, Snapshot Analysis) at Week 48 (Study GS-US-216-0114, ITT Analysis Set)

FDA Snapshot Category	Number of Subjects (%)	
	ATV/co	ATV/r

	(N=344)	(N=348)
HIV RNA < 50 copies/mL	293 (85)	304 (87)
HIV RNA ≥ 50 copies/mL	20 (6)	14 (4)
HIV RNA ≥ 50 copies/mL in Week 48 Window ^a	6 (2)	7 (2)
Discontinued Drug due to Lack of Efficacy	1 (<1)	0
Discontinued Study Drug due to Other Reasons and Last Available HIV RNA ≥ 50 copies/mL	13 (4)	7 (2)
No Virologic Data in Week 48 Window	31 (9)	30 (9)
Discontinued Study Drug due to AE or Death	22 (6)	23 (7)
Discontinued Study Drug due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL	9 (3)	7 (2)
Missing Data During Window but on Study Drug	0	0

a) Week 48 window is between Study Day 309 and 378 (inclusive).

Source: ADEFF dataset for Integrated Summary of Efficacy (ISE)

In Study GS-US-216-0114, 85% of subjects in the ATV/co group and 87% of subjects in the ATV/r group had HIV-1 RNA < 50 copies/mL at Week 48. The difference between the treatment groups was -2.2% (95% CI: -7.4% to 3.0%), adjusted for baseline HIV-1 viral load. The proportion of subjects with HIV RNA ≥ 50 copies/mL at Week 48 were 6% and 4% in the ATV/co and ATV/r groups, respectively; a greater number of subjects in the ATV/co group discontinued study drug due to other reasons with last available HIV RNA ≥ 50 copies/mL.

In the pooled analysis of Studies GS-US-216-0105 and -0114, the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 was 85% in the ATV/co group and 87% in the ATV/r group, for a treatment difference of -2.5% (95% CI: -7.5% to 2.5%), adjusted for baseline HIV-1 viral load and study. The proportion of subjects with HIV RNA ≥ 50 copies/mL at Week 48 was 6% in the ATV/co group and 5% in the ATV/r group. Reasons for virologic failure in the Week 48 analysis window were balanced between the treatment groups.

Please see the Biometrics Review by Dr. Yanming Yin for further details of the statistical analyses performed for the primary endpoint.

6.1.5 Analysis of Secondary Endpoints(s)

In Study GS-US-216-0114, the secondary efficacy endpoint was the achievement and maintenance of confirmed HIV-1 RNA < 50 copies/mL through Week 48 using the FDA-defined Time to Loss of Virologic Response (TLOVR) algorithm. The TLOVR analysis was not performed in Study GS-US-216-0105.

Using the TLOVR algorithm, the Applicant reports that 82.8% of subjects in the ATV/co group and 85.3% of subjects in the ATV/r group in Study -0114 achieved and

maintained confirmed HIV-1 RNA < 50 copies/mL through Week 48 and were considered responders. The HIV-1 RNA stratum-weighted difference between the two groups at Week 48 was -2.6% (95% CI: -8.1% to 2.8%), which was similar to the difference obtained by the snapshot analysis. At Week 48, 3.5% of subjects in the ATV/co group and 4% of subjects in the ATV/r group had confirmed viral rebound or never achieved viral suppression through Week 48 and were thus considered nonresponders by the TLOVR algorithm.

6.1.6 Other Endpoints

In Studies GS-US-216-0105 and -0114, both treatment groups had substantial increases in CD4 cell count from baseline through Week 48. In the pooled analysis, the mean (SD) increase from baseline in CD4 cell count at Week 48 was 217 (156.2) cells/ μ L in the ATV/co group and 218 (151.7) cells/ μ L in the ATV/r group. The mean (SD) increase from baseline in CD4% at Week 48 was 9.6% (4.8) in the ATV/co group and 9.8% (5.2) in the ATV/r group.

6.1.7 Subpopulations

The primary analysis of virologic response (HIV-1 RNA < 50 copies/mL, snapshot analysis) was analyzed for each of the following subgroups using the ITT pooled analysis set:

- Age (years): < 40 and \geq 40
- Sex: male and female
- Race: white and nonwhite
- Baseline HIV-1 RNA level (copies/mL): \leq 100,000 and >100,000
- Baseline CD4 count (cells/ μ L): \leq 350 and >350

Subgroup analyses of virologic outcomes are shown in Table 6. Across the various selected subgroups, the percentages of subjects with HIV-1 RNA < 50 copies/mL at Week 48 (snapshot analysis) were high and generally comparable. Homogeneity tests performed by the Applicant reportedly did not find significant differences in treatment effect between subgroups. It should be noted, however, that women only made up 16% of the subject population in the pooled analysis.

Table 6: Virologic Outcomes (HIV RNA < 50 copies/mL, Snapshot Analysis) at Week 48 by Subgroups in Phase 2 and 3 Trials Double-Blind Treatment Period (Pooled Analysis GS-US-0105 and -0114)

Subpopulations	Number of Subjects (%)	
	ATV/co	ATV/r
Age (years)		
< 40	192/240 (80)	195/226 (86)
\geq 40	142/154 (92)	134/151 (89)
Sex		

Male	283/334 (85)	278/312 (89)
Female	51/60 (85)	51/65 (79)
Race		
White	195/229 (85)	205/231 (89)
Nonwhite	139/165 (84)	124/146 (85)
Black	62/83 (75)	59/72 (82)
Non-Black	272/311 (88)	270/305 (89)
Baseline HIV-1 RNA (copies/mL)		
≤ 100,000	212/250 (85)	196/223 (88)
> 100,000	122/144 (85)	133/154 (86)
Baseline CD4 cell count (/μL)		
≤ 350	176/200 (88)	176/197 (89)
> 350	158/194 (81)	153/180 (85)

Source: ADEFF dataset for Integrated Summary of Efficacy (ISE)

Within the pooled ATV/co group, subjects < 40 years of age were less likely to achieve HIV-1 RNA < 50 copies/mL at Week 48 than those aged ≥ 40 years (80% vs. 92%, respectively). Similarly, subjects with baseline CD4 count > 350 cells/μL had lower rates of viral load suppression at Week 48 than those with baseline CD4 count ≤ 350 cells/μL (81% vs. 88%, respectively) and Black or African-American subjects had relatively lower rates than non-Black subjects (75% vs. 88%, respectively). However, within these subgroups, the percentages of subjects who met the primary endpoint were not substantially different between treatment groups. Nonetheless, based on logistic regression modeling performed by FDA, younger age, CD4 cell count ≤ 350 cells/μL, and African-American race were each associated with a lower probability of achieving the primary endpoint. Please refer to the Biometrics Review by Dr. Yanming Yin for further details.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The 150 mg dose of COBI was selected based on study results from Study GS-US-216-0101, and additionally from Study GS-US-216-0110 with ATV and Study GS-US-216-0115 with DRV, in healthy volunteers. These were the key dose-finding and confirmation trials for COBI, results of which are described here. In addition, please refer to the Clinical Pharmacology Review by Dr. Stanley Au for further details.

- **Study GS-US-216-0101** was a first-in-human Phase 1 single- and multiple-dose BA trial in 60 healthy volunteers that evaluated the safety, tolerability, and PK/PD of COBI at doses ranging from 50 to 200 mg. Results from this trial provided proof-of-concept for COBI as a CYP3A inhibitor by demonstrating the ability of COBI (100 mg and 200 mg once daily) to boost systemic exposures of the CYP3A probe substrate midazolam to similar levels as RTV 100 mg once daily. Based on the results of this trial, COBI 100 mg and 150 mg doses were used for evaluation in combination with ATV in Study GS-US-216-0110.

- A second Phase 1 trial, **Study GS-US-216-0116**, was a bioequivalence trial comparing two formulations of the COBI 150 mg tablet. Results from this trial demonstrated that COBI plasma exposures were bioequivalent between the two formulations, as assessed by AUC_{tau} , C_{max} , and C_{tau} . In addition, the trial showed bioequivalent midazolam exposures, indicating similar inhibition of CYP3A by the two COBI formulations. Lastly, the trial also evaluated EVG plasma exposures as boosted by COBI (Formulation 2) versus RTV and found that they were bioequivalent.
- **Study GS-US-216-0110** was a Phase 1 multiple-dose BA trial of COBI 100 mg and 150 mg coadministered with ATV 300 mg once daily in 36 healthy volunteers. This trial demonstrated that COBI 150 mg provides bioequivalent ATV exposures as RTV 100 mg. The lower 100 mg dose of COBI also increased ATV exposure, but at lower concentrations than those obtained with COBI 150 mg or RTV 100 mg. The geometric least squares means (GLSM) comparisons between ATV/co and ATV/r are displayed in Table 7.

Table 7: Comparisons of Atazanavir Pharmacokinetic Parameters for Cobicistat versus Ritonavir (Study GS-US-216-0110)

ATV PK Parameter	Geometric Least Squares Means		Geometric Least Squares Mean Ratio (%)	90% Confidence Interval
	Test Treatment	Reference Treatment		
ATV/COBI 300/100 mg (test) versus ATV/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
ATV/COBI 300/150 mg (test) versus ATV/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

Source: NDA 203094 Integrated Summary of Efficacy (ISE) report, page 11.

- **Study GS-US-216-0115** was a Phase 1 was a multiple-dose BA trial of COBI 150 mg with DRV 800 mg once daily in 31 healthy volunteers. This trial demonstrated that DRV exposures (AUC and C_{max}) were bioequivalent when coadministered with COBI 150 mg or RTV 100 mg once daily, and DRV C_{trough} was substantially above the in vitro protein-binding adjusted IC_{50} for wild-type virus. Overall, DRV exposures were in a range associated with durable efficacy

and long-term safety as demonstrated in previous clinical trials of DRV. However, there was a lower C_{0h} (GLSM Ratio [90% CI] of 89.4 [80.4-99.4]) and C_{24h} or C_{tau} (GLSM Ratio [90% CI] of 69.4 [59.0-81.7]) between the DRV/co and DRV/r arms (see Table 8).

Table 8: Summary of Darunavir Steady-state Pharmacokinetic Parameters with Cobicistat and Ritonavir Coadministration (Study GS-US-216-0115)

DRV Plasma PK Parameters	Treatment A DRV+COBI (N=31)	Treatment B DRV+RTV (N=31)	Geometric Least-Squares Means Ratio (%) of Test/Reference (Treatment A/Treatment B) (90% CI)
C_{max} (ng/mL) Mean (%CV)	7737.1 (21.8)	7464.2 (20.3)	103.36 (100.34, 106.48)
AUC _{tau} (ng-h/mL) Mean (%CV)	81,084.2 (31.0)	79,987.0 (34.0)	101.78 (97.40, 106.36)
C_{min} (ng/mL) Mean (%CV)	1332.7 (66.8)	1866.7 (83.3)	69.43 (59.02, 81.68)
C_{0h} (ng/mL) Mean (%CV)	2395.5 (50.7)	2483.8 (34.3)	89.39 (80.36, 99.44)

Source: NDA 203094 Integrated Summary of Efficacy (ISE) report, page 14.

Further evaluation of the data 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 in the DRV/r arm. This phenomenon was only observed during a single treatment period and was the primary factor contributing to the observed difference in C_{24h} between the two treatment arms. An explanation for this increase in the DRV/r arm could not be determined based on the available information from the GS-US-216-0115.

Subsequently, the Pharmacometrics review team requested additional DRV/co pre-dose data from the ongoing Study GS-US-216-0130 (see Section 6.1.10) to obtain further information regarding DRV C_{0h} values when coadministered with COBI. The Applicant responded to the information request with data from 298 subjects; DRV C_{0h} concentrations from this trial were compared with observations from the previous trials with DRV/r, Studies TMC114-C211 and TMC114-C229 in treatment-naive and treatment-experienced subjects with no DRV resistance-associated substitutions, respectively. The results showed that DRV C_{0h} when boosted with COBI may be 5-10% lower than DRV C_{0h} when boosted with RTV. This is in agreement with the C_{0h} data from Study GS-US-216-0115 and supports that while DRV C_{0h} exposures when boosted with COBI may be slightly lower compared with RTV, the magnitude of this difference is not likely to exceed 10%. Please see the Pharmacometrics Review by Dr. Jeffry Florian for further details of the analyses performed with PK data from Study -0130.

The 150 mg dose of COBI has subsequently been evaluated as a CYP3A inhibitor of ATV in HIV-1 infected treatment naive subjects in Studies GS-US-216-0105 and -0114.

In these trials, ATV exposures were comparable when coadministered with COBI 150 mg once daily or RTV 100 mg once daily. Further, the 150 mg dose of COBI has been evaluated as a CYP3A inhibitor of EVG, as co-formulated in the STRIBILD tablet, in treatment-naïve subjects in Studies GS-US-236-0102, -0103, and -0104; however, the COBI 150 mg tablet as stand-alone product has not been evaluated with EVG alone.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The FDA guidance for industry *Antiretroviral Drugs Using Plasma HIV RNA Measurements - Clinical Considerations for Accelerated and Traditional Approval* states that 48-week data can be used for traditional approval. The Agency considers 48-week efficacy data sufficient for demonstration of persistence of efficacy in HIV-1 infected treatment-naïve subjects. Please refer to Section 6.1.4 for a discussion of the 48-week data in the COBI Phase 2 and 3 trials.

The pivotal Phase 3 Study GS-US-216-0114 is designed to continue for a minimum of 96 weeks. As such, additional double-blinded efficacy and safety data will be generated by the Applicant and reviewed by FDA.

6.1.10 Additional Efficacy Issues/Analyses

- **Study GS-US-216-0130** is an ongoing, Phase 3b, open-label, single-arm study evaluating the safety and efficacy of DRV/co plus two fully active NRTIs in HIV-1 infected, treatment-naïve and -experienced adults with no DRV resistance-associated substitutions. The trial is expected to provide representative data for DRV/co treatment; however, these data are not needed to support the currently proposed DRV/co indication as BA data from Study GS-US-216-0115 were considered sufficient to ensure comparable DRV exposures between DRV/co and DRV/r. Study GS-US-216-0130 is fully enrolled and Week 24 data are expected by Q4 2012.

7 Review of Safety

Safety Summary

The safety of COBI tablets is supported by two adequate, double-blind, and active-controlled clinical trials, the Phase 2 and 3 Studies GS-US-216-0105 and -0114, in HIV-1 infected treatment-naïve subjects (N=771) randomized to once daily ATV 300 mg/COBI 150 mg or ATV 300 mg/RTV 100 mg, both in combination with TVD. Based on the pooled 48-week double-blind data, with adequate durations of exposures, the safety profile of COBI tablets does not appear to be substantially different from that of low-dose RTV. Both treatment groups had a similar overall incidence of treatment-emergent adverse events (AE). The most frequently reported AEs in the ATV/co treatment group

(occurring in >10% of subjects) were jaundice, ocular icterus, nausea and diarrhea, with comparable rates of each in the ATV/r group.

A relatively low percentage of subjects in either treatment group discontinued study drug to due to a treatment-emergent AE (7%); the most common AEs leading to study drug discontinuation were related to hyperbilirubinemia (e.g. jaundice, ocular icterus), with no notable difference seen between the two groups in the frequency of these events. By Kaplan-Meier estimates, the time to premature discontinuation of study drug was also not significantly different between the groups.

In addition, both groups had a similar percentage of subjects with AEs that were considered study drug-related by the investigators (57% each). The ATV/co group, however, had a higher incidence of Grade 2-4 drug-related AEs (25% vs. 21 % in the ATV/r group). This was mostly due to a greater percentage of subjects in the ATV/co group with Grade 2-4 drug-related cholestatic and jaundice events (10% vs. 6%, respectively, by Standard MedDRA Query [SMQ]). Likewise, the ATV/co group had a higher incidence of Grade 3-4 increased total bilirubin compared with the ATV/r group (67% vs. 56%, respectively). On the other hand, the percentage of subjects who discontinued study drug because of a bilirubin-related AE was low and comparable between the groups (ATV/co 4%, ATV/r 3%).

The incidence of serious AEs (SAE) was also slightly higher in the ATV/co group compared with the ATV/r group (10% vs. 7 %, respectively), but no distinctive pattern was noted between the two groups with respect to SAEs. Serious adverse events considered related to treatment were infrequent and comparable between the treatment groups. No deaths were reported in either treatment group during the double-blind randomized period. One death was reported in the ATV/co group early in the open-label phase of Study -0105; however, based on limited secondary sources, this death was not likely related to study drug.

Because of the disproportionate number of proximal renal tubulopathy cases reported in the STRIBILD group of the STRIBILD registrational trials (Studies GS-US-236-0102 and -1013), renal events were closely scrutinized in the COBI Phase 2 and 3 trials. The overall incidence of renal AEs was similar in both treatment groups, although subjects in the ATV/co group who developed renal events tended to have less predisposing risk factors (e.g., age, race, sex, medical history, concomitant medications) than subjects in the ATV/r group. The rates of clinically significant renal AEs (SAEs or AEs leading to study drug discontinuation), the percentages of subjects with graded proteinuria, glycosuria, or hypophosphatemia, and the mean change from baseline in urine fractional excretion of phosphate at Week 48 were also similar between the two treatment groups. However, consistent with the STRIBILD experience, there was a greater incidence of proximal renal tubulopathy leading to study drug discontinuation in the ATV/co group than in the ATV/r group (1.3% overall vs. 0.5%, respectively). Renal laboratory abnormalities improved but did not normalize in these COBI-treated subjects

after removal of study drug, but no subject in either treatment group required renal replacement therapy. The reasons for this increased risk of proximal renal tubulopathy with concomitant use of COBI and TDF are not understood at this time, but do not appear to be related to plasma tenofovir concentrations.

Consistent with the known inhibitory effect of COBI on renal tubular creatinine secretion, the percentage of subjects with graded increases in serum creatinine was greater in the ATV/co group compared with the ATV/r group (7% vs. 4%, respectively), although most of these laboratory abnormalities were mild. Increases in serum creatinine were noted as early as Week 2 of treatment, with corresponding decreases in eGFR by Cockcroft-Gault method. In contrast, the mean cystatin C-derived GFR did not decrease from baseline at Week 48 in either treatment group. Thus, COBI does not appear to affect actual renal glomerular function. Moreover, no significance difference was noted between the two groups when a threshold of 0.4 mg/dL increase from baseline in serum creatinine was used to identify subjects with potentially meaningful glomerular dysfunction. Importantly, when renal laboratory abnormalities for possible glomerular dysfunction (serum creatinine increase \geq 0.4 mg/dL) and tubular dysfunction (hypophosphatemia, glycosuria, and proteinuria) were assessed together, there were no additional subjects with other renal abnormalities that were not already identified and reported as AEs. The overlap of possible glomerular and tubular dysfunction was uncommon, occurring in two subjects, both in the ATV/co group (0.5% overall).

There were also a disproportionate number of subjects in the ATV/co group with nephrolithiasis in the 48-week double-blind pooled analysis (ATV/co 8, ATV/r 0). As detailed biochemical analyses of the stones were not performed, the composition of these kidney stones could not be specified. Six of the eight subjects, however, had calcium oxalate crystals seen in their urine either at baseline or while on study drug, but the denominator of total subjects with calcium oxalate crystalluria was not provided. After the original NDA submission, the Applicant reported that an additional subject in the ATV/co group in the open label phase of Study -0105 and five subjects in the ATV/r group of Study -0114 had developed nephrolithiasis, for a revised incidence of 2.3% for the ATV/co group and 1.3% for the ATV/r group. While causality in these cases is difficult to ascertain, and calcium oxalate crystalluria may appear to be a risk factor, treatment with ATV/co nonetheless appears to be associated with earlier onset of kidney stones compared with ATV/r (i.e., Week 24 for ATV/co versus after Week 48 for ATV/r). These events were generally not serious and did not lead to discontinuation of treatment, but will be reported in labeling.

No substantial differences were noted between the ATV/co and ATV/r treatment groups when other safety issues were analyzed, including cardiac, gastrointestinal, musculoskeletal (including bone fractures), rash events, and metabolic changes, such as change in serum fasting lipids from baseline. Nonclinical studies had suggested a potential for COBI to prolong PR interval and decrease left ventricular function. While dose-dependent increases in PR interval were observed in Phase 1 trials of COBI at

supratherapeutic doses, clinically significant prolongation of PR interval was not observed in Phase 1 trials at therapeutic dosing (150 mg once daily) or in the pooled ECG data from the Phase 2 and 3 clinical trials. A dedicated echocardiogram substudy in healthy volunteers (N=34) also did not reveal any significant changes in left ventricular function with COBI administration. Thyroid function and immunoglobulin levels were also assessed in the Phase 2 Study GS-US-216-0105 because of nonclinical observations, but no significant effect of COBI was observed on these measures relative to baseline when compared with RTV. Lastly, the overall incidence of malignancy in the pooled analysis was low and balanced between treatment groups.

Based on PK data from 68 subjects in the pooled Phase 2 and 3 trials, a COBI exposure-safety relationship was not identified for the major safety concerns identified with ATV/co administration, e.g. hyperbilirubinemia-related AEs, nausea, or diarrhea and selected liver-related laboratory tests (Grade 3 or 4 total bilirubin, ALT, and AST), serum creatinine, estimated creatinine clearance, and urine fractional excretion of phosphate; however, these analyses were limited by the small sample size. Additionally, no relationship was observed between the safety of COBI and various subgroups defined by demographics (age, sex, or race) or baseline disease characteristics (HIV RNA viral load, CD4 cell count, or co-infection with HBV or HCV).

As a potent CYP3a inhibitor, the potential for drug interactions with COBI is significant. In the pooled Phase 2 and 3 analysis, there was no clear evidence of adverse drug interactions among subjects taking COBI and HMG-CoA reductase inhibitors or hormonal contraceptive therapy, for example, but the number of subjects taking these concomitant medications was limited (N=26 for each drug class).

Cobicistat is a Category B drug; its safety in pregnancy has not been studied. Based on the pooled safety analysis, no significant reproductive concerns were identified. Finally, the safety and effectiveness of COBI in pediatrics have not been evaluated. A pediatric development plan is proposed for use of COBI with ATV or DRV in treatment-experienced children 3 to <18 years of age; this plan, however, is contingent on successful development of age-appropriate COBI formulations.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The principal sources of safety data for this NDA review were the two randomized, double-blind, active-controlled clinical trials in HIV-infected, treatment-naive subjects: the pivotal Phase 3 Study GS-US-216-0114 and the supportive Phase 2 Study GS-US-216-0105. The evaluation of safety was based primarily on the Integrated Summary of Safety (ISS), which pooled data collected during the randomized, double-blind treatment period for each trial. Important safety findings from the STRIBILD development program (NDA 203100) were also considered as supportive safety information.

A Safety Update Report for the Phase 2 and 3 COBI studies and for the Phase 2 and 3 STRIBILD studies (Studies GS-US-236-0102, -0103, -0104), as well as for Study GS-US-236-0118, a renal safety study of STRIBILD and COBI in HIV-infected subjects with renal impairment, was submitted on October 29, 2012 and also reviewed in support of this application.

7.1.2 Categorization of Adverse Events

For the clinical trials of COBI, clinical and laboratory-related adverse events (AE) were classified using the Medical Dictionary for Regulatory Activities (MedDRA), with System Organ Class (SOC), High Level Group Term (HLGT), High Level Term (HLT), Preferred Term (PT), and Lower Level Term (LLT) assigned to each AE in the clinical databases. Throughout the clinical development of COBI, different MedDRA versions were used to classify AEs; however, Studies GS-US-216-0105 and -0114 and the ISS used MedDRA Version 14.0. Severity grading for clinical AEs and laboratory abnormalities was assessed according to the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities, unless otherwise indicated.

For the purposes of the safety evaluation, treatment-emergent AEs were defined as events in a given study period that met one of the following criteria:

- Began on or after the date of the first dose of study drug and on or before the date of the last dose of study drug plus 30 days
- Had no recorded start date and the stop date was not before the first dose of study drug

Exceptions to the above definition were AEs with an onset on the same or next calendar day that a previous event resolved. These AEs were not counted as treatment-emergent if all of the following criteria were met:

- The events had the same MedDRA LLT
- The later event had the same or lower severity grade
- The later event had the same or less seriousness
- The later event was not related to study drug

Given the side effect profiles of the concomitant ARV drugs administered in these trials (i.e., ATV, FTC, TDF), the Applicant identified the following treatment-emergent AEs of interest or importance based on the pooled data from both trials (MedDRA Preferred Terms listed):

- Renal events
 - *Fanconi syndrome, Fanconi syndrome acquired, renal failure, renal failure acute, renal tubular disorder*

The following MedDRA Preferred Terms were added by this reviewer to further identify potential renal events of interest: *renal impairment, nephropathy, nephritis, proteinuria, pyuria, leukocyturia, glycosuria, chromaturia, hematuria, hemorrhagic urinary tract, nephrolithiasis, hydronephrosis, nocturia, polyuria, renal colic, blood creatinine increased, creatinine renal clearance decreased, and glomerular filtration rate decreased, and glomerular filtration rate abnormal*

- Fracture events
 - *acetabular fracture, ankle fracture, avulsion fracture, bone fissure, bone fragmentation, cervical vertebral fracture, clavicle fracture, complicated fracture, compression fracture, epiphyseal fracture, facial bones fracture, femoral neck fracture, fibula fracture, flail chest, foot fracture, forearm fracture, fracture, fracture delayed union, fracture displacement, fracture malunion, fracture nonunion, fractured coccyx, fractured ischium, fractured sacrum, fractured skull depressed, greenstick fracture, hand fracture, hip fracture, humerus fracture, ilium fracture, jaw fracture, lower limb fracture, lumbar vertebral fracture, multiple fractures, open fracture, osteoporotic fracture, patella fracture, pathological fracture, pelvic fracture, pseudarthrosis, pubis fracture, radius fracture, rib fracture, scapula fracture, scapulothoracic dissociation, skull fracture, skull fractured base, spinal fracture, sternal fracture, stress fracture, synostosis, thoracic vertebral fracture, tibia fracture, traumatic fracture, ulna fracture, upper limb fracture, wrist fracture*
- Hepatic events
 - *acute hepatic failure, hepatic failure, liver injury*
- Rash events
 - *dermatitis, drug eruption, eczema, exfoliative rash, pruritus, pruritus generalized, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash morbilliform, rash papular, rash pruritic, rash pustular, rash vesicular, seborrheic dermatitis, seborrheic dermatitis, seborrheic keratosis, skin reaction, urticaria*

The following MedDRA Preferred Terms were added by this reviewer to further identify potentially important rash events: *dermatitis allergic, drug hypersensitivity* (unless the specific non-study drug was specified), *bullous dermatitis, prurigo, and eosinophilic pustular folliculitis rash*. In addition, terms containing the words 'blister', 'erythema', 'edema', 'exfoliation', or 'swelling' were reviewed closely.

Where Preferred Terms were potentially too narrow and could result in an underestimation of the true incidence for a particular AE or syndrome, higher MedDRA terms (e.g., HLT, HGLT, or SOC) or Standardized MedDRA Query (SMQ) terms were used to group similar events.

Exploratory analyses were conducted using the FDA MedDRA Adverse Event Diagnosis (MAED) service to compare AE frequencies across treatment groups by different levels of the MedDRA hierarchy and by broad and narrow SMQs.

To identify potential subclinical cases of renal toxicity that may not have been reported as AEs, categorical analyses of renal laboratory abnormalities were performed using the pooled data to evaluate for possible glomerular dysfunction (serum creatinine confirmed increase ≥ 0.4 mg/dL) and proximal tubular dysfunction (confirmed ≥ 1 grade-level increase in graded hypophosphatemia, confirmed ≥ 1 grade-level increase in graded glycosuria concurrent with confirmed serum glucose ≤ 100 mg/dL, and confirmed ≥ 2 grade-level increase in graded proteinuria).

Treatment-emergent laboratory abnormalities were defined as abnormalities that increased at least 1 toxicity grade from baseline at any time post-baseline up to and including the date of last dose of study drug plus 30 days. If the corresponding baseline laboratory data were missing, then any abnormality of at least Grade 1 was considered as treatment emergent.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

Safety data were pooled from the Phase 2 and 3 clinical trials of COBI in HIV-1 infected treatment-naive subjects (Studies GS-US-216-0105 and -0114). These trials allowed for a direct comparison of COBI and RTV because they were designed to keep all other components of the ARV regimen (i.e., ATV and FTC/TDF) identical. For the pooled analyses, safety data from Study GS-US-216-0105 included only data collected during the randomized, double-blind period (i.e., up to Week 60, before subjects took first dose of open-label drug). Safety data from Study GS-US-216-0114 were derived from the Week 48 analysis period, which was performed when all randomized subjects had completed the Week 48 visit or discontinued from study drug before the Week 48 visit. Both trials used MedDRA Version 14.0 to categorize adverse events. Because of similarities in study design, comparator arm, and subject population, pooling of the safety data from these two trials was considered appropriate.

For the analysis of safety, the pooled dataset included all randomized subjects who received at least 1 dose of study drug. Of the 783 randomized subjects, 771 were included in the safety analysis set, including 394 subjects randomized to ATV/co and 377 subjects randomized to ATV/r.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The dose and formulation of COBI selected for marketing is the 150 mg tablet. This was the dose and formulation used in the Phase 2 and 3 trials of COBI (Studies GS-US-216-0105 and -0114). Therefore, the use of these trials to assess the safety of the proposed dose and formulation intended for marketing is appropriate.

In the pooled safety analysis, the median duration of study drug exposure was 48.4 weeks (Quartile 1-Quartile 3 [Q1-Q3]: 48-60) in the ATV/co group and 48.3 weeks (Q1-Q3: 48-60) in the ATV/r group. The percentage of subjects receiving study drug was similar between the two groups at each assessed time point. The percentage of subjects with greater than 48 weeks of study drug exposure was also similar between the two groups: 282 (72%) subjects in the ATV/co group and 258 (68%) subjects in the ATV/r group.

7.2.2 Explorations for Dose Response

Exposure-safety relationships were evaluated by the Applicant and FDA. Please refer to the Pharmacometrics Review by Dr. Jeffry Florian for further details of the FDA analyses.

The Applicant performed PK/PD analyses of the COBI exposure-safety relationship in the COBI Phase 2 and 3 trials using COBI exposures derived from population PK modeling versus safety parameters that included commonly observed AEs, namely bilirubin-related AEs (i.e., jaundice, ocular icterus, hyperbilirubinemia, or blood bilirubin increased), nausea, or diarrhea. The exposure-safety analysis was based on intensive PK sampling in 68 subjects. The Applicant's analyses showed comparable COBI exposures with overlapping values regardless of the incidence of bilirubin-related AEs, nausea, or diarrhea. No relevant exposure-AE trends were observed. Results from logistic regression modeling performed by FDA also indicated no significant relationship between COBI exposures and the risk of jaundice, ocular icterus, nausea and diarrhea.

Exploratory PK-PD analyses of the COBI exposure-safety relationship were also performed by the Applicant for selected liver-related laboratory tests (Grade 3 or 4 total bilirubin, ALT, and AST), serum creatinine, eGFR, and urine fractional excretion of phosphate. No relationship between COBI exposures and change in eGFR or other selected laboratory parameters was observed based on the available COBI pharmacokinetic data.

Since COBI exposures (AUC_{tau} and C_{max}) following multiple-dose administration of ATV/co in the COBI Phase 2 and 3 trials were in the range observed following multiple-

dose administration of DRV/co 800/150 mg in the Phase 1 Study GS-US-216-0115 (see Section 6.1.8), the COBI exposure-safety relationship is expected to be comparable when COBI is administered with ATV or DRV.

Pharmacokinetic data from Studies GS-US-216-0105 and -0114 also demonstrated that mean tenofovir exposures (C_{max} and AUC_{tau}) with COBI or RTV were in the range of historical exposures observed with boosted-PIs (including ATV) or rilpivirine (which like COBI is an intestinal P-gp inhibitor) in HIV-1 infected patients. Results were also consistent with those observed with TDF in combination with boosted PIs in healthy volunteers. In sum, the data suggest that COBI does increase TDF exposure beyond what has been historically observed with RTV-containing regimens, consistent with the observation that COBI does not inhibit the transporter proteins responsible for tenofovir excretion (i.e., OAT1, OAT3, and MRP4).

7.2.3 Special Animal and/or In Vitro Testing

A comprehensive nonclinical program of COBI has been conducted. All nonclinical studies required to support chronic use have been submitted as a part of the nonclinical assessment for COBI. Please refer to Section 4.3 and the Pharmacology/Toxicology Review by Dr. Laine Myers for additional details. This reviewer considers the nonclinical studies performed in support of this NDA to be adequate.

7.2.4 Routine Clinical Testing

Routine clinical evaluations for safety (through Week 48) in Studies GS-US-216-0105 and -0114 included assessment of AEs and changes in concomitant medications at all scheduled visits (Weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48), a complete physical examination at Weeks 24 and 48 and symptom-directed physical examination as needed at the other scheduled visits, safety laboratory assessments at all scheduled visits, and ECG assessments at screening and Week 48. Weight was measured at every scheduled visit. Subjects with SAEs were followed through the last day of study and/or until the investigator and/or Applicant determined that the subject's condition was stable.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please refer to Section 4.4.2 for a discussion of COBI pharmacodynamics and Section 4.4.3 for a discussion of COBI pharmacokinetics. Please refer to Section 7.5.5 for a discussion of drug-drug interactions. Additionally, please refer to the Clinical Pharmacology Review by Dr. Stanley Au for further details.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Cobicistat is a first-in-class drug. That said, the clinical experience from the STRIBILD development program and the known safety profiles of RTV, as well as ATV, and TVD were taken into consideration, as these drugs were coadministered with COBI in the trials evaluating safety.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported in the Phase 1 trials with COBI or STRIBILD. Likewise, no deaths were reported in either treatment group during the randomized, double-blind phase of Study GS-US-216-0105 or during Study GS-US-216-0114.

One subject died during the open-label phase of Study GS-US-216-0105 due to an accidental death of unknown cause. His narrative is as follows:

Subject 2475-5545 was a 28-year-old white male with HIV and medical history significant for herpes simplex, depression, bipolar disorder, generalized anxiety disorder, peripheral neuropathy, vertigo, hypercholesterolemia, and insomnia. He was randomized to ATV/co +TVD and started study drug on June 1, 2009. Baseline HIV RNA was 4.06 log₁₀ copies/mL and baseline CD4 cell count was 390 cells/μL (28.3%). His viral load was undetectable by Week 8 (Study Day 86) and remained < 50 copies/mL through Week 48 (Study Day 333). He initiated ATV/co +TVD in the open-label phase of the trial on July 30, 2010 (Study Day 425). Significant concurrent medications included bupropion, clonazepam, zolpidem and ibuprofen. On October 21, 2010, the subject failed to appear for his Week 12 visit. Investigative site staff contacted the subject's father who reported that his son had passed away (b) (6). The father was reluctant to disclose the cause of death but stated it was "accidental". He refused to provide any further details and it is not known if an autopsy was performed.

7.3.2 Nonfatal Serious Adverse Events

The protocols for GS-US-216-0105 and -0114 defined an SAE as any adverse drug experience that results in any of the following outcomes:

- Death
- Life-threatening situation (subject is at immediate risk of death)
- In-patient hospitalization or prolongation of existing hospitalization (excluding those for study therapy or placement of an indwelling catheter, unless associated with other SAEs).
- Persistent or significant disability/incapacity.

- Congenital anomaly/birth defect in the offspring of a subject who received investigational medicinal product.
- Other: medically significant events that may not be immediately life-threatening or result in death or hospitalization, but based upon appropriate medical and scientific judgment, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

The above definition is consistent with the FDA and ICH definition of an SAE.

In the pooled safety analysis of COBI Phase 2 and 3 trials, the percentage of subjects with SAEs was 10% in the ATV/co group and 7% in the ATV/r group. The leading SOC for SAEs was 'Infections and Infestations', followed by 'Renal and Urinary Disorders' and 'Gastrointestinal Disorders', with no discernible differences noted between the two treatment groups. The SAEs in the Infections and Infestations SOC were generally considered unrelated to study drug by the investigators. By MedDRA Preferred Term, no single SAE occurred in more than 1% of subjects in either treatment group. Table 9 displays the SAEs that occurred in more than one subject in either treatment group listed by MedDRA SOC and Preferred Term; for SAEs where there was only one subject by MedDRA Preferred Term, only the SOC is reported.

Table 9: Treatment-Emergent Serious Adverse Events Occurring in ≥ 2 Subjects in Either Treatment Group in Phase 2 and 3 Trials Double-Blind Treatment Period (Pooled Analysis GS-US-216-0105 and -0114)

MedDRA Term	Number of Subjects (%)	
	ATV/co (N=394)	ATV/r (N=377)
SYSTEM ORGAN CLASS		
Preferred Term		
<i>Any Serious Adverse Event</i>	38 (10)	25 (7)
INFECTIONS AND INFESTATIONS	14 (4)	14 (4)
Pneumonia	2 (1)	2 (1)
Cellulitis	2 (1)	1 (<1)
Herpes zoster	3 (1)	0
Sepsis	1 (<1)	2 (1)
Appendicitis	0	2 (1)
Influenza	2 (1)	0
Pneumocystis jiroveci pneumonia	1 (<1)	1 (<1)
RENAL AND URINARY DISORDERS ^a	3 (1)	6 (2)
Fanconi syndrome acquired	1 (<1)	1 (<1)
Renal failure acute	0	4 (1)
Renal failure	0	1 (<1)
Nephropathy	1 (<1)	0
Calculus ureteric	1 (<1)	0
Nephritis	0	1 (<1)
GASTROINTESTINAL DISORDERS	6 (2)	2 (1)
GENERAL DISORDERS AND ADMINISTRATION SITE	4 (1)	4 (1)

CONDITIONS		
Chest pain	2 (1)	2 (1)
Pyrexia	1 (<1)	2 (1)
PSYCHIATRIC DISORDERS	6 (2)	2 (1)
Depression	2 (1)	1 (<1)
Drug dependence	2 (1)	0
INVESTIGATIONS	4 (1)	1 (<1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	3 (1)	1 (<1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	3 (1)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2 (1)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (<1)	1 (<1)
METABOLISM AND NUTRITION DISORDERS	1 (<1)	1 (<1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2 (1)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (<1)	1 (<1)
NERVOUS SYSTEM DISORDERS	1 (<1)	1 (<1)

a) All serious adverse events are listed for the Renal and Urinary Disorders SOC.

Source: ADAE dataset for Integrated Summary of Safety (ISS)

The overall incidence of SAEs considered related to study drug by the investigators was low and balanced between the two treatment groups. Eleven subjects experienced 12 study drug-related SAEs (ATV/co 5 [1%], ATV/r 6 [2%]). One subject in the ATV/r group (Subject 4169-8476) developed concomitant SAEs of Grade 2 fever and rash on Study Day 10 that were considered related to study drug; study drug was interrupted and the events resolved within two days of study drug cessation. Two subjects, one in each treatment group, had a Grade 3 SAE of Fanconi syndrome necessitating study drug discontinuation; the ATV/co subject (Subject 0691-8292) developed Fanconi syndrome on Study Day 85, while the ATV/r subject (Subject 1978-8016) developed Fanconi syndrome later in the treatment course, on Study Day 218. In both cases, the event was considered resolved after cessation of study drug. Two additional subjects in the ATV/r group had SAEs of renal failure and one subject in the ATV/co group had an SAE of nephropathy; these and all renal AEs are discussed further in Section 7.3.5.1. By MedDRA Preferred Term, no SAE considered study drug-related occurred in more than one subject (Table 10).

Table 10: Treatment-Emergent Serious Adverse Events Considered Related to Study Drug by Investigator in Phase 2 and 3 Trials Double-Blind Treatment Period (Pooled Analysis GS-US-216-0105 and -0114)

MedDRA Preferred Term	Number of subjects (%)	
	ATV/co (N=394)	ATV/r (N=377)
Any SAE Related to Study Drug	5 (1)	6 (2)
Fanconi syndrome acquired	1 (<1)	1 (<1)
Nephropathy	1 (<1)	0

Rhabdomyolysis	1 (<1)	0
Abortion spontaneous	1 (<1)	0
Depression	1 (<1)	0
Renal failure acute	0	1 (<1)
Renal failure	0	1 (<1)
GGT increased	0	1 (<1)
Priapism	0	1 (<1)
Pyrexia	0	1 (<1)
Rash	0	1 (<1)

Abbreviations: GGT = gamma-glutamyltransferase; SAE = serious adverse event
Source: ADAE dataset for Integrated Summary of Safety (ISS)

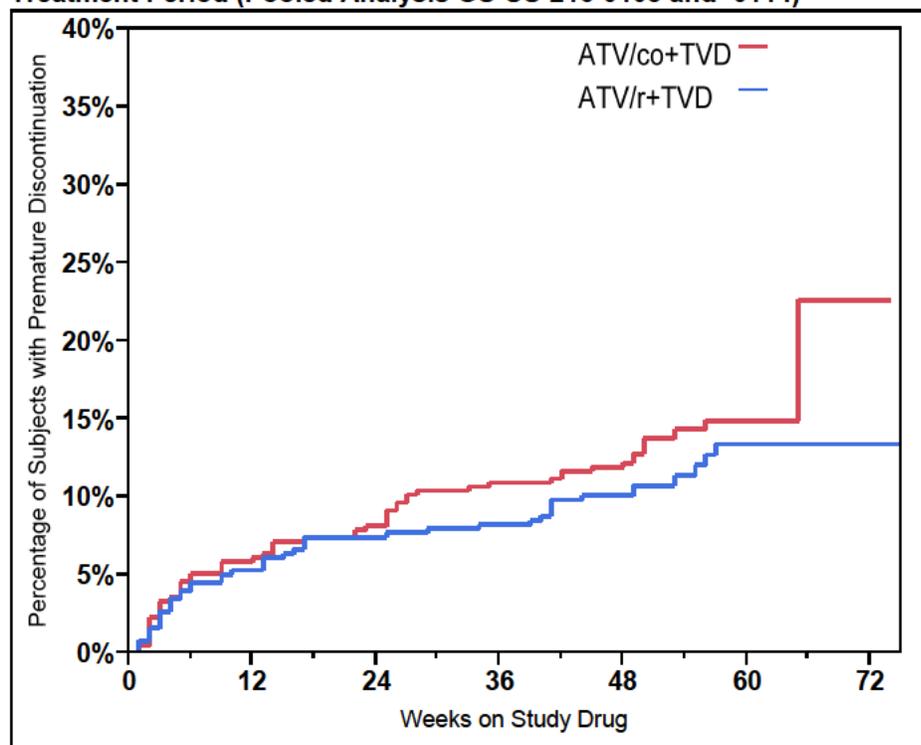
In the Safety Update Report, the Applicant reports that 14 additional subjects experienced treatment-emergent SAEs in the pooled randomized data from Studies -0105 and -0114. The overall percentage of subjects experiencing SAEs remains higher in the ATV/co group (ATV/co 45 [11%]; ATV/r 31 [8%]). By MedDRA Preferred Term, two SAEs now occurred in $\geq 1\%$ of subjects in any treatment group: ‘cellulitis’ (ATV/co 3 [1%], ATV/r 2 [1%]) and ‘renal failure acute’ (ATV/co 0, ATV/r 4 [1%]). The number of subjects with SAEs considered by the investigator to be related to study drug was updated to 13 overall (ATV/co 6 [2%], ATV/r 7 [2%]). The two new drug-related SAEs of ‘groin abscess’ in Subject 5131-8599 (ATV/co group) and ‘arrhythmia’ in Subject 1480-8039 (ATV/r group) occurred in Study GS-US-216-0114 and were reported after the data cut-off for the original NDA. The frequency of SAEs reported in the open-label phase of Study -0105 did not significantly change the overall frequency as reported in the randomized phase alone.

In the Phase 1 COBI trials, one treatment-emergent SAE (spontaneous abortion) was reported in a healthy 32-year-old Hispanic female in Study GS-US-216-0116 and one SAE (diabetic foot ulcer) was reported in a subject with severe renal impairment in Study GS-US-216-0124. The SAE of spontaneous abortion was considered related to study drug; however, the event occurred within 14 days of pregnancy confirmation and the subject had 3 previous pregnancies and 3 fetal losses, all within < 20 weeks of gestation (2 were elective abortions and 1 was a spontaneous abortion). The SAE of diabetic foot ulcer was not considered related to study drug by the investigator.

7.3.3 Dropouts and/or Discontinuations

In the pooled safety analysis, the percentage of subjects who discontinued study drug prematurely at Week 48 was 14% for ATV/co and 12% for ATV/r. There was no significant difference in time to premature study drug discontinuation between the two treatment groups based on Kaplan-Meier estimates (Figure 1).

Figure 1: Time to Premature Discontinuation of Study Drug in Phase 2 and 3 Trials Double-Blind Treatment Period (Pooled Analysis GS-US-216-0105 and -0114)



Source: derived from ADTTE dataset for Integrated Summary of Safety (ISS)

In the pooled safety analysis, the percentage of subjects who discontinued study drug prematurely due to an AE was the same in each treatment group (ATV/co 27 [7%], ATV/r 27 [7%]). Adverse events associated with hyperbilirubinemia such as jaundice (ATV/co 9 [2%], ATV/r 7 [2%]) and ocular icterus (ATV/co 8 [2%], ATV/r 5 [1.3%]) were the only AEs that led to study drug discontinuation in >1% of subjects in either treatment group. When these terms are grouped together, however, the ATV/co group had a slightly higher percentage of these subjects. These bilirubin-related events are consistent with ATV labeling. All other individual AEs were reported in ≤1% of subjects by MedDRA Preferred Term. Table 11 displays all the treatment-emergent AEs leading to study drug discontinuation by MedDRA SOC and Preferred Term.

Table 11: Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation in Phase 2 and 3 Trials Double-Blind Treatment Period (Pooled Analysis GS-US-216-0105 and -0114)

MedDRA Term	Number of subjects (%)	
	ATV/co (N=394)	ATV/r (N=377)
SYSTEM ORGAN CLASS		
Preferred Term		
<i>Any Adverse Event Leading to Study Drug Discontinuation</i>	27 (7)	27 (7)
HEPATOBIILIARY DISORDERS	11 (3)	9 (2)

Jaundice		9 (2)	7 (2)
Hyperbilirubinemia		1 (<1)	2 (1)
Hypertransaminasemia		1 (<1)	0
EYE DISORDERS		9 (2)	5 (1)
Ocular icterus		8 (2)	5 (1)
Eye irritation		1 (<1)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		7 (2)	3 (1)
Rash		1 (<1)	2 (1)
Rash generalised		1 (<1)	0
Rash maculo-papular		2 (1)	0
Dermatitis allergic		2 (1)	0
Erythema		0	1 (<1)
Pruritus generalised		1 (<1)	0
IMMUNE SYSTEM DISORDERS	Drug hypersensitivity	1 (<1)	0
GASTROINTESTINAL DISORDERS		2 (1)	2 (1)
Vomiting		2 (1)	0
Constipation		0	1 (<1)
Nausea		0	1 (<1)
RENAL AND URINARY DISORDERS		3 (1)	5 (1)
Fanconi syndrome acquired		1 (<1)	1 (<1)
Renal failure		0	2 (1)
Renal impairment		1 (<1)	1 (<1)
Nephropathy		1 (<1)	0
Renal failure acute		0	1 (<1)
INVESTIGATIONS		4 (1)	2 (1)
Blood creatinine increased		1 (<1)	1 (<1)
ALT increased		1 (<1)	0
Blood bilirubin increased		0	1 (<1)
Creatinine renal clearance decreased		1 (<1)	0
Glomerular filtration rate abnormal		1 (<1)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		1 (<1)	2 (1)
Malaise		1 (<1)	0
Mucosal inflammation		0	1 (<1)
Pyrexia (FUO)		0	1 (<1)
INFECTIONS AND INFESTATIONS		0	4 (1)
Hepatitis C		0	1 (<1)
Lymph node tuberculosis		0	1 (<1)
Progressive multifocal leukoencephalopathy		0	1 (<1)
Tuberculosis		0	1 (<1)
METABOLISM AND NUTRITION DISORDERS		0	2 (1)
Hypoglycemia		0	1 (<1)
Metabolic acidosis		0	1 (<1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Rhabdomyolysis	1 (<1)	0
NEOPLASMS BENIGN, MALIGNANT AND	Burkitt's	1 (<1)	0

UNSPECIFIED (INCL CYSTS AND POLYPS)	lymphoma		
NERVOUS SYSTEM DISORDERS	Dysgeusia	0	1 (<1)

Abbreviations: ALT = alanine aminotransferase; FUO = fever of unknown origin

Source: ADAE dataset for Integrated Summary of Safety (ISS)

Most of the AEs (84%) leading to study drug discontinuation were considered related to study drug by the investigators, with the AEs related to hyperbilirubinemia, rash, and renal impairment being the most frequently cited. No notable between-group differences were observed in the frequencies of study drug-related AEs leading to discontinuation, whether by MedDRA Preferred Term or higher level terms.

In the Safety Update Report, the Applicant reports that the percentage of subjects discontinuing study drug due to treatment-emergent AEs remained similar in all treatment groups (ATV/co 31 [8%], ATV/r 31 [8%]), and the all ATV/co group from the open-label phase of Study -0105, 35 subjects [9%]). Again, most of these AEs were considered related to study drug by the investigators. New study drug-related AEs leading to discontinuation of study drug since the COBI tablet NDA was submitted occurred in four subjects in the ATV/co group and five subjects in the ATV/r. Further, Subject 0744-5524 (in the ATV/r group of Study -0105) experienced an AE of renal failure that was reported as leading to discontinuation in the original NDA, but the reason for discontinuation was revised to a protocol violation in the Safety Update.

In the updated pooled safety analysis of the STRIBILD Phase 3 trials, similar percentages of subjects discontinued study drug due to a treatment-emergent AE in each treatment group (STRIBILD 5%, ATR 7%, and ATV/r 6%). No individual AE that resulted in study drug discontinuation was reported in >1% of subjects in the STRIBILD group. That said, the notable AEs that led to study drug discontinuation more frequently in the STRIBILD group than in either of the comparator groups included a constellation of renal AEs (e.g., 'renal', 'Fanconi syndrome', and 'increased blood creatinine'). Such has not been the case in the COBI clinical trials overall.

7.3.4 Significant Adverse Events

Causality for all AEs was assessed by the investigators as either related to study drug/procedure or not. In the pooled safety analysis, 440 (57%) subjects had AEs considered by the investigators to be related to study drug, with an equal percentage of subjects in each treatment group (ATV/co 224 [57%], ATV/r 216 [57%]). The most frequently reported drug-related AEs (occurring in > 10% of subjects) in the ATV/co group were ocular icterus, jaundice, and nausea (Table 12).

Table 12: Treatment-Emergent Adverse Events (All Grades) Considered Related to Study Drug by Investigators Occurring in ≥ 2% of Subjects Receiving Cobicistat in Phase 2 and 3 Trials Double-Blind Treatment Period (Pooled Analysis GS-US-216-0105 and -0114)

MedDRA Preferred Term	Number of subjects (%)	
	ATV/co	ATV/r

	(N=394)	(N=377)
<i>Any Adverse Event Related to Study Drug</i>	224 (57)	216 (57)
Ocular icterus	58 (15)	63 (17)
Jaundice	53 (13)	42 (11)
Nausea	47 (12)	43 (11)
Diarrhea	33 (8)	40 (11)
Hyperbilirubinemia	25 (6)	18 (5)
Fatigue	20 (5)	19 (5)
Rash or Rash generalised	19 (5)	17 (5)
Flatulence	20 (5)	12 (3)
Headache	16 (4)	20 (5)
Dizziness	14 (4)	10 (2)
Abdominal pain upper	10 (3)	9 (2)
Abdominal distension	8 (2)	8 (2)
Blood bilirubin increased	9 (2)	5 (1)
Vomiting	8 (2)	6 (2)
Somnolence	6 (2)	3 (1)
Decreased appetite	6 (2)	2 (1)

Source: ADAE dataset for Integrated Summary of Safety (ISS)

As discussed in Section 7.3.2, eleven subjects in the pooled analysis had 12 drug-related AEs that were considered serious (ATV/co 5 [1%], ATV/r 6 [2%]). Of these, five subjects had SAEs in the 'Renal and Urinary Disorders' SOC (ATV/co 2, ATV/r 3). Renal AEs are discussed further in Section 7.3.5.1.

With respect to severity, 75% of drug-related AEs were mild (Grade 1). Drug-related AEs of greater severity (Grade ≥ 2) were reported more frequently in the ATV/co treatment group (Table 13). A total of 275 Grade ≥ 2 drug-related AEs were reported in 177 subjects overall (ATV/co 98 [25%], ATV/r 79 [21%]). The imbalance between the two groups was driven primarily by the incidence of drug-related cholestasis and jaundice AEs. The differences between the groups in these event rates were small by individual MedDRA Preferred Terms, but were greater when the events were grouped together by MedDRA HLT or SOC. When the SMQ for 'Cholestasis and Jaundice of Hepatic Origin' was analyzed, the difference between the two treatment groups was 4.57%. Because this SMQ is itself a branch of the 'Hepatic Disorders' and 'Drug-related Hepatic Disorders' SMQs, these higher level SMQs were also analyzed and the difference between the two treatment groups was observed to be 5.54%. In contrast, the incidence of drug-related Grade ≥ 2 gastrointestinal disorders (nausea, vomiting) or rash events (various terms) was not significantly different between the two groups, regardless of MedDRA hierarchy level or SMQ analysis. Drug-related AEs Grade ≥ 2 in the 'Renal and Urinary Disorders' SOC occurred in 12 (1.6%) subjects total (ATV/co 7 [2%], ATV/r 5 [1%]), but no drug-related renal AE occurred in more than 1% of subjects in either treatment group by MedDRA Preferred Term. Renal adverse events are discussed in greater detail in Section 7.3.5.1.

Table 13 displays the treatment-emergent AEs Grade ≥ 2 considered related to study drug by the investigators and that occurred in $\geq 2\%$ of subjects in either group; AEs are displayed by MedDRA SOC, HLT, and Preferred Term, as well as SMQ term where appropriate.

Table 13: Treatment-Emergent Adverse Events Grades 2-4 Considered Related to Study Drug by Investigator Occurring in $\geq 2\%$ of Subjects in Either Treatment Group in Phase 2 and 3 Trials Double-Blind Treatment Period (Pooled Analysis GS-US-216-0105 and -0114)

Narrow SMQ	MedDRA Term	Number of subjects (%)		RD	P-value
	SYSTEM ORGAN CLASS	ATV/co (N=394)	ATV/r (N=377)		
	High Level Term				
	Preferred Term				
<i>Any Drug-Related Adverse Event Grade 2-4</i>		98 (25)	79 (21)		
Hepatic Disorders/ Drug-related Hepatic Disorders – comprehensive search		49 (12)	26 (7)	5.54	0.011
Cholestasis and Jaundice of Hepatic Origin		41 (10)	22 (6)	4.57	0.025
	HEPATOBIILIARY DISORDERS	34 (9)	19 (5)	3.59	0.063
	Cholestasis and Jaundice	34 (9)	19 (5)	3.59	0.063
	Jaundice	20 (5)	10 (3)	2.42	0.95
	Hyperbilirubinemia	17 (4)	12 (3)	1.13	0.453
	Blood bilirubin increased	7 (2)	5 (1)	0.45	0.773
	EYE DISORDERS	13 (3)	5 (1)	1.97	0.94
	Ocular Disorders NEC	13 (3)	5 (1)	1.97	0.94
	Ocular icterus	13 (3)	5 (1)	1.97	0.94
Gastrointestinal nonspecific inflammation and dysfunctional conditions		20 (5)	20 (5)	-0.23	1
	GASTROINTESTINAL DISORDERS	20 (5)	20 (5)	-0.23	1
	Diarrhea	6 (2)	5 (1)	0.2	1
	Nausea	9 (2)	7 (2)	0.43	0.82
Rash Events	Cumulative rash events	20 (5)	15 (4)		
	Dermatitis allergic	3 (1)	1 (<1)	0.5	0.624
	Drug hypersensitivity	1 (<1)	0	0.25	1
	Eosinophilic pustular folliculitis	1 (<1)	0	0.25	1
	Pruritus generalised	1 (<1)	0	0.25	1
	Rash generalised	6 (2)	2 (1)	0.99	0.287
	Rash	3 (1)	7 (2)	-1.1	0.214
	Rash maculo-papular	3 (1)	5 (1)	-0.56	0.497
	Rash macular	2 (1)	0	0.51	0.5
	Rash papular	0	1 (<1)	-0.27	0.489
	Rash morbilliform	1 (<1)	0	0.25	1
	Urticaria	0	1 (<1)	-0.27	0.489

Abbreviations: NEC = Not Elsewhere Classified; RD = Risk Difference (per hundred); SMQ = Standardized MedDRA Query
P-values unadjusted, output generated by MAED service for exploratory analyses only

Source: ADAE dataset for Integrated Summary of Safety (ISS)

A total of 56 drug-related AEs of Grade 3-4 severity were reported among 44 (6%) subjects, with a slightly higher percentage in the ATV/co group (ATV/co 27 [7%], ATV/r 17 [5%]). Nearly all (55/56) of these AEs were Grade 3. The most frequent Grade \geq 3 drug-related AEs were in the SOCs of 'Hepatobiliary Disorders', 'Investigations', and 'Renal and Urinary Disorders', with comparable rates in each treatment group by MedDRA SOC. No Grade \geq 3 drug-related AE occurred in greater than 1% of subjects by MedDRA Preferred Term in either treatment group.

One subject in the pooled analysis reported a Grade 4 drug-related AE. This subject's narrative is as follows:

Subject 5217-8501 (Study GS-US-216-0114): A 49-year-old insulin-dependent diabetic male randomized to the ATV/r treatment group developed Grade 4 acute renal failure on Study Day 112 in the setting of salmonella enteritis and hypovolemic shock leading to hospitalization and study drug discontinuation. The renal events in this case were thought to be due to pre-renal etiology and acute tubular necrosis (ATN). There were no reports of renal impairment before the enteritis event. Although the investigator assessed the event of acute renal failure as related to study drug, causality in this case is confounded by the events of enteritis, metabolic acidosis, and hypovolemic shock.

7.3.5 Submission Specific Primary Safety Concerns

Given the association between TDF and bone and renal events, and the association between ATV and hepatobiliary events, prespecified AEs of interest for the COBI pooled safety analyses included selected non-traumatic bone fractures and selected renal and hepatic events. In addition, selected rash events were considered important for comparison between the two treatment groups.

7.3.5.1 Renal Safety

Renal Adverse Events

For the initial assessment of renal AEs, all AEs in the 'Renal and Urinary Disorders' SOC and 'Renal Function Analyses' HLT under the 'Investigations' SOC, and all prespecified renal AEs of interest using the Applicant's definition and as expanded by this reviewer [see Section 7.1.2] were included.

In the pooled double-blind analysis, a total of 89 renal adverse events of interest, regardless of causality or severity, were reported among 63 subjects, with a lower incidence observed in the ATV/co group compared with the ATV/r group (7% vs. 9%, respectively).

Table 14 summarizes the selected treatment-emergent renal adverse events of interest by MedDRA HLT and Preferred Term. Multiple AEs that were similar in nature were counted only once per subject for each MedDRA HLT and Preferred Term.

Table 14: Selected Treatment-Emergent Renal Adverse Events of Interest (Any Causality, All Grades) in Phase 2 and 3 Trials Double-Blind Treatment Period (Pooled Analysis GS-US-216-0105 and -0114)

MedDRA Term	Number of subjects (%)		RD	P-value
	ATV/co (N=394)	ATV/r (N=377)		
High Level Term				
Preferred Term				
<i>Any Renal Adverse Event of Interest</i>	27 (7)	36 (9)		
Nephropathies and Tubular Disorders NEC	2 (1)	1 (<1)	0.24	1
Fanconi syndrome acquired	1 (<1)	1 (<1)	-0.01	1
Nephropathy	1 (<1)	0	0.25	1
Renal Failure and Impairment	1 (<1)	7 (2)	-1.6	0.034
Renal failure	0	2 (1)	-0.53	0.239
Renal failure acute ^a	0	4 (1)	-1.06	0.057
Renal impairment	1 (<1)	1 (<1)	-0.01	1
Renal Function Analyses	5 (1)	9 (2)	-1.12	0.288
Blood creatinine increased	1 (<1)	3 (1)	-0.54	0.363
Creatinine renal clearance decreased ^b	2 (1)	5 (1)	-0.82	0.277
Glomerular filtration decreased	1 (<1)	1 (<1)	-0.01	1
Glomerular filtration abnormal	1 (<1)	0	0.25	1
Renal Lithiasis	8 (2)	0	2.03	0.008
Nephrolithiasis ^{c, d}	8 (2)	0	2.03	0.008
Urinary Abnormalities	13 (3)	17 (5)	-1.21	0.458
Chromaturia	3 (1)	2 (1)	0.23	1
Glycosuria	1 (<1)	1 (<1)	-0.01	1
Hematuria	5 (1)	8 (2)	-0.85	0.411
Leukocyturia	0	1 (<1)	-0.27	0.489
Proteinuria	1 (<1)	1 (<1)	-0.01	1
Pyuria	4 (1)	6 (2)	-0.58	0.538
Urinary Tract Signs and Symptoms NEC	3 (1)	5 (1)	-0.56	0.497
Nocturia	2 (1)	2 (1)	-0.02	1
Polyuria	0	1 (<1)	-0.27	0.489
Renal colic	1 (<1)	1 (<1)	-0.01	1
Hemorrhage urinary tract	0	1 (<1)	-0.27	0.489

Abbreviations: NEC = Not Elsewhere Classified; RD = Risk Difference (per hundred)

P-values unadjusted, output generated by MAED service for exploratory analyses only

- a) Subject 3030-8654 (Study GS-US-216-0114) in the ATV/r group had two Grade 4 adverse events, "acute renal failure" and "nephritis", reported on Study Day 17. For purposes of tabulation, this subject was only counted once under the MedDRA Preferred Term 'renal failure acute'.
- b) Subject 0986-8197 (Study GS-US-216-0114) in the ATV/co group had Grade 1 "decreased glomerular filtration rate" reported on Study Day 39 and Grade 1 "low creatinine clearance" reported on Study Day 225. Because these terms essentially describe similar events, this subject was only counted once under the MedDRA Preferred Term 'creatinine renal clearance decreased'.

- c) Subject 0986-8244 (Study GS-US-216-0114) in the ATV/co group had two Grade 2 adverse events, “left hydronephrosis” and “bilateral renal lithiasis”, reported on Study Day 311. For purposes of tabulation, this subject was only counted once under the MedDRA Preferred Term ‘nephrolithiasis’.
- d) Subject 1965-8024 (Study GS-US-216-0114) in the ATV/co group had Grade 1 “kidney stone” on Study Day 29 and Grade 3 “ureteral stones” on Study Day 86. Because these terms describe events with similar pathophysiology, this subject was only counted once under the MedDRA Preferred Term ‘nephrolithiasis’.

Source: ADAE dataset for Integrated Summary of Safety (ISS)

As shown in Table 14, the event rates were not significantly different between the two treatment groups for the majority of renal events, regardless of MedDRA hierarchy level, although there was a trend towards lower incidence in the ATV/co group. A significant exception to this, however, was in the incidence of nephrolithiasis events, which occurred exclusively in the ATV/co group. The nephrolithiasis cases are discussed in further detail below.

The mean age for subjects with renal AEs was 40 years (range 25-68 years), with similar age distribution in both groups. There were, however, two subjects ≥ 60 years of age with renal AEs in the ATV/r group, whereas there were none such subjects in the ATV/co group. There was also a higher proportion of Black or African American subjects with renal AEs in the ATV/r group (N=10 [46%]) compared with the ATV/co group (N=3 [20%]). In addition, while 75% of subjects with renal AEs overall were male, there was a slightly higher proportion of female subjects with renal AEs in the ATV/r group (N=10 [27%]) compared with the ATV/co group (N=6 [22%]).

The mean baseline creatinine clearance rate for the 63 subjects with renal AEs was 106 mL/min (range 56-260 mL/min) by the Cockcroft-Gault formula, with a median rate of 100.6 mL/min (IQR 84-122 mL/min). Mean baseline eGFR was similar in each treatment group; however, 21 (33%) subjects had a baseline eGFR < 90 mL/min and most of these (14 of 21) were in the ATV/r group. There were only two subjects with renal AEs who had baseline eGFR < 70 mL/min: Subject 0744-5524 in Study -0105 in the ATV/r group and Subject 0986-8278 in Study -0114 in the ATV/co group.

Fourteen (14) of the 63 subjects who developed renal AEs had pre-existing medical conditions that may have predisposed them to renal events (ATV/co 6, ATV/r 8), such as diabetes mellitus (ATV/co 3, ATV/r 6), hypertension (ATV/co 3, ATV/r 3), and nephrolithiasis (ATV/co 1, ATV/r 2). Further, 29 subjects reported concomitant use of nephrotoxic agents, including non-steroidal anti-inflammatory drugs (ATV/co 5, ATV/r 7), antivirals (e.g., acyclovir, ganciclovir) (ATV/co 2, ATV/r 10), antibiotics (e.g., sulfa drugs, pentamidine, gentamicin, amphotericin) (ATV/co 6, ATV/r 14), and diuretics (ATV/co 0, ATV/r 3).

In sum, although the overall incidence of renal AEs was comparable between the two treatment groups, subjects in the ATV/r group tended to have more risk factors for renal events (e.g., age, race, sex, medical history, concomitant medications).

It should also be noted that 21 of the 63 subjects (33%) with renal AEs of interest were reported from a single site (Site 0986, Study -0114, in the Dominican Republic). Nine of these subjects were in the ATV/co group and 12 were in ATV/r group. To characterize this group, the mean age was 39 years (range 28-53), 11 were male, 19 were Black or mixed race (white/black), and mean eGFR at baseline was 104.8 mL/min (range 69.9-260) with a median of 100 mL/min (IQR 81-110). Eight of the 21 subjects reported taking one or more concomitant nephrotoxic agents: acyclovir (N=4), diclofenac (N=2), and ibuprofen (N=4). In addition, two subjects had a history of diabetes mellitus (Subjects 0986-8193 and 0986-8510); the latter also had a history of nephrolithiasis.

After eliminating duplicate events that were coded differently, there were 75 unique renal AEs of interest by MedDRA Preferred Term among the 63 subjects - 74 AEs when maximum toxicity grade for each individual event was considered. Of these 74 renal AEs, more than half were Grade 1 (44/74 [59%]) and another quarter were Grade 2 (18/74 [24%]). The proportions of subjects with Grade 1 and 2 renal events were similar between the two treatment groups. Grade 3 renal events occurred in 6 (2%) subjects in the ATV/co group versus 4 (1%) in the ATV/r group; Grade 4 renal events occurred in only two subjects, both in the ATV/r group (1%). No subject in either treatment group required dialysis or any another form of renal replacement therapy. Table 15 summarizes the Grade 3-4 renal AEs of interest reported in the pooled analysis.

Table 15: Selected Treatment-Emergent Renal Adverse Events of Interest Grade 3-4 by Maximum Toxicity in Phase 2 and 3 Trials Double-Blind Treatment Period (Pooled Analysis GS-US-216-0105 and -0114)

MedDRA Preferred Term	Number of subjects (%)	
	ATV/co (N=394)	ATV/r (N=377)
Grade 3		
Creatinine renal clearance decreased	1 (<1)	0
Fanconi syndrome acquired	1 (<1)	1 (<1)
Nephrolithiasis	1 (<1)	0
Hematuria ^a	1 (<1)	0
Renal colic ^a	1 (<1)	0
Nephropathy	1 (<1)	0
Renal failure	0	1 (<1)
Renal failure acute	0	2 (1)
Grade 4		
Renal failure acute	0	2 (1)

a) The events of 'hematuria' and 'renal colic' in the ATV/co group were associated with nephrolithiasis.
Source: ADAE dataset for Integrated Summary of Safety (ISS)

Thirty-four (45%) of the 75 unique renal AEs of interest were considered study drug-related by the investigators, with equal frequencies in both treatment groups. Most AEs under the MedDRA HLT 'Renal Function Analyses' were considered study drug-related.

Likewise, all cases of 'Fanconi syndrome' and 'nephropathy' were considered drug-related. The eight cases of MedDRA HLT 'renal failure and impairment', however, varied in their causality; the one case of renal impairment in the ATV/co group was considered drug-related, but the remaining seven cases in the ATV/r group were split (4 related, 3 not related).

Overall, eight subjects had renal AEs that were serious (ATV/co 2 [1%], ATV/r 6 [2%]). The two renal SAEs in the ATV/co group were Grade 3 Fanconi Syndrome on Study Day 85 in Subject 0691-8292 and Grade 3 nephropathy on Study Day 176 in Subject 4142-8361. The renal SAEs in the ATV/r group consisted of acute renal failure (N=4), renal failure (N=1), and Fanconi syndrome (N=1).

Twelve subjects discontinued study drug during the double-blind treatment period because of a renal AE, with an equal percentage of subjects in each treatment group (ATV/co 6 [2%], ATV/r 6 [2%]). The renal events leading to study drug discontinuation fell into three categories: renal failure/impairment, nephropathies (e.g., Fanconi syndrome), or abnormal renal function (e.g., blood creatinine increased, decreased creatinine clearance).

Table 16 summarizes the 15 subjects with clinically significant renal AEs (i.e., SAEs or AEs leading to study drug discontinuation) in the pooled double-blind analysis.

Table 16: Subjects with Clinically Significant Treatment-Emergent Renal Adverse Events (Serious Adverse Events or Adverse Events Leading to Study Drug Discontinuation) in Phase 2 and 3 Trials Double-Blind Treatment Period (Pooled Analysis GS-US-216-0105 and -0114)

Study	Subject ID	Age	Sex	MedDRA Preferred Term	Study Day		Toxicity Grade	Serious	Related to Study Drug	Action with Study Drug	Status at End of Reporting
					Start	End					
ATV/co											
216-0114	0691-8292	47	F	Fanconi syndrome acquired	85	124	3	Yes	Yes	Discontinued	Resolved
	0986-8278	36	F	Glomerular filtration rate abnormal	57	83	2	No	Yes	Discontinued	Resolved
	0986-8283	51	M	Creatinine renal clearance decreased	337	--	3	No	Yes	Discontinued	Ongoing
	2840-8066	30	M	Blood creatinine increased	425	--	1	No	Yes	Discontinued	Ongoing
	4127-8204	49	F	Renal impairment	341	--	2	No	Yes	Discontinued	Ongoing
	4142-8361	43	M	Nephropathy	176	--	3	Yes	Yes	Discontinued	Ongoing
ATV/r											
216-0105	0744-5524	53	F	Renal failure	8	--	2	No	Yes	Discontinued	Ongoing
216-0114	0352-8358	44	M	Renal failure acute	313	316	3	Yes	No	Interrupted	Resolved
	1978-8016	48	M	Fanconi syndrome acquired	218	246	3	Yes	Yes	Discontinued	Resolved
	2734-8202	41	F	Renal failure acute	184	190	3	Yes	No	No change	Resolved
	3030-	40	M	Renal failure	17	21	4	Yes	No	Interrupted	Resolved

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	8654			acute							
	3976-8058	48	M	Renal failure	337	--	3	Yes	Yes	Discontinued	Ongoing
	4169-8476	32	F	Renal impairment	225	299	2	No	Yes	Discontinued	Resolved
	5131-8639	35	M	Blood creatinine increased	254	--	2	No	No	Discontinued	Ongoing
	5217-8501	49	M	Renal failure acute	112	142	4	Yes	Yes	Discontinued	Resolved

Source: ADAE dataset for Integrated Summary of Safety (ISS)

As shown in Table 16, the renal AEs that led to study drug discontinuation in the six COBI-treated subjects were all considered drug-related by the investigators. The mean age of these six subjects was 43.6 years (range 30-49 years) and the median time to onset of the renal AE was 256.5 days (Q1-Q3: 78-362). By comparison, although there were more such events in the ATV/r group, only five of nine events were considered drug-related. On the other hand, a greater proportion of renal AEs in the ATV/r group were serious and the median time to event onset was shorter (218 days; Q1-Q3: 65-284). The mean age of the nine subjects in the ATV/r group (43.3 years) was comparable to that of the ATV/co group. The ratio of men to women in the ATV/co group was 1:1, but 2:1 in the ATV/r group.

One additional subject (Subject 2843-5562) had a renal AE of decreased GFR during the open-label phase of Study -0105 (Study Day 566) that led to study drug discontinuation. This subject had originally been randomized to ATV/r and rolled over to ATV/co after Week 48. The renal AE occurred 197 days after initiating COBI. The AE resolved after discontinuation of COBI. No additional subjects with other potential renal events were identified in the open-label phase of Study GS-SU-216-0105.

As noted previously, for Subject 0744-5524 in the ATV/r group who had an AE of 'renal failure' leading to discontinuation reported in the original NDA, per the Safety Update Report, the reason for study drug discontinuation was updated to protocol violation.

Also per the Safety Update Report, two additional subjects (Subject 1000-8629 in the ATV/co group and Subject 0589-8565 in the ATV/r group) experienced renal events of interest ('renal failure'), and another subject (Subject 3030-8654 in the ATV/r group) experienced a second event ('acute renal failure'). The two AEs of 'renal failure' were assessed as Grade 1, and the event in COBI-treated subject was assessed as related to study drug. The second event of 'acute renal failure' in Subject 3030-8654 was assessed as serious, Grade 4, and not related to study drug; no action with study drug was taken.

Proximal Renal Tubulopathy

In the original review of NDA 203100 for STRIBILD tablets, several subjects who discontinued STRIBILD because of renal AEs in the pivotal trials were also noted to have evidence of proximal renal tubulopathy, which was in contrast to the comparator groups (ATRIPLA and ATV/r + TVD) where no such cases were identified. In addition, the incidence of SAEs related to renal or urinary disorders was higher in the STRIBILD group (0.4%) than in either control group (both 0.0%). Overall, the incidence of proximal tubulopathy leading to study drug discontinuation was much greater in the pooled Phase 3 trials of STRIBILD than would have been expected solely due to TDF based on the results of previous clinical trials which used TDF as one component of a study treatment regimen. Although the mechanism is not yet understood at this time, the

combination of COBI and TDF appears to exacerbate the proximal tubular effects of TDF.

To evaluate whether a similar phenomenon was occurring in the COBI development program, the clinical and laboratory characteristics of the subjects with clinically significant renal AEs (SAEs or AEs leading to study drug discontinuation) in the pooled Phase 2 and 3 trials (i.e., Table 16) were analyzed by the Applicant and FDA using the following criteria for tubular dysfunction:

- confirmed ≥ 1 grade-level increase in graded hypophosphatemia,
- confirmed ≥ 1 grade-level increase in graded glycosuria concurrent with confirmed serum glucose ≤ 100 mg/dL, and
- confirmed ≥ 2 grade-level increase in graded proteinuria

Consistent with the Applicant's analysis, this reviewer found that five of the six subjects (83%) in the ATV/co treatment group (1.3% overall) had laboratory abnormalities suggestive of proximal renal tubulopathy (at least 2 of the 3 criteria listed above). In contrast, only two of the nine subjects (22%) in the ATV/r group (0.5% overall) had such abnormalities. All seven of these subjects with evidence of tubulopathy were followed in Study GS-US-216-0114. Table 17 summarizes the renal laboratory and urinary abnormalities observed in these seven subjects.

Table 17: Renal Tubular Dysfunction in Subjects with Clinically Significant Treatment-Emergent Renal Adverse Events (Serious Adverse Events or Adverse Events Leading to Study Drug Discontinuation) Double-Blind Treatment Period (Study GS-US-216-0114)

Subject ID	Serum Creatinine (mg/dL) Creatinine Clearance _{CG} (mL/min) (Study Day)			Urine Protein ^{a, b}	Urine Glucose ^{a, b}	Serum Phosphate (mg/dL) ^b	Comments
	Baseline	At D/C	At Last Available Visit				
ATV/co							
0691-8292	0.7 97.2 (1)	0.89 74.1 (119)	0.79 85.8 (344)	trace, 3+, neg	neg, 3+, neg	4.1, 1.9, 4.2	By Week 4 (SD 29), subject's eGFR had decreased to 73.9 mL/min with 1+ proteinuria. Proteinuria 2+ reported at Week 8 (SD 57). AE of 'Fanconi Syndrome acquired' reported on SD 85. Study drugs stopped on SD 119. Renal ultrasound on SD 124 normal; AE of Fanconi syndrome considered resolved with sequelae on same date (SD 124). Serum creatinine, BUN, bicarbonate and potassium within normal limits throughout study.
0986-8283	1.02 100 (1)	3.58 26.7 (342)	1.93 50.9 (378)	neg, 2+, neg	neg, 1+, neg	3.4, 2.0, 3.3	Subject had several renal AEs: two AEs of low CrCl (SD 15-57 and SD 82-281). Drug not stopped for these mild AEs. Developed non-serious, drug-related nephrolithiasis on SD 92 and non-serious hematuria on SD 281. On same date (SD

							281), AE of low CrCl ↑ in severity from mild to moderate (CrCl=55.5 mL/min; sCr = 1.73 mg/dL). On SD 337, AE of increased serum creatinine progressed from moderate to severe (sCr = 3.26 mg/dL) with CrCl decreased to 29.5 mL/min, urine glucose 1+, urine protein 2+. By SD 342, sCr and CrCl worsened and serum phosphate ↓ to 2.0 mg/dL. Study drug stopped on SD 345. AE of low CrCl (severe) was ongoing at data cutoff.
2840-8066	1.03 122.4 (1)	1.79 76 (450)	1.79 76 (450)	neg, 2+ , 2+	neg, 1+ (SD 226), neg	3.1, 2.2, 2.2	During study, subject's sCr showed slow but progressive rise, with corresponding decline in eGFR. On SD 425, non-serious, drug-related AE of 'increased creatinine' reported (sCr = 1.69 mg/dL; CrCl = 81.8 mL/min). Study drug stopped on SD 450, at which time urine protein was 2+. No glycosuria noted at time of study drug discontinuation, but trace or 1+ urine glucose was documented at earlier visits. AE of increased creatinine was ongoing at data cutoff.
4127-8204	0.68 77.4 (1)	1.19 43.8 (358)	0.94 52.6 (426)	trace, 2+ , 1+	neg, 1+ , neg	3.7, 3.3, 3.6	By Week 2, subject's eGFR had decreased to 57.2 mL/min with sCr = 0.92

							mg/dL. On SD 341 (Week 48), non-serious AE of 'renal impairment' reported (sCr = 1.1 mg/dL; CrCl = 47.6 mL/min; urine protein 1+). Study drug stopped SD 364 due to CrCl < 50 mL/min on SD 358. Urine glucose 1+ and urine protein 2+ at study drug discontinuation. AE of renal impairment (moderate, drug-related) ongoing at data cutoff.
4142-8361	1.06 87.7 (1)	5.52 12.1 (176)	2.19 35.1 (211)	neg, 2+, NA	neg, 3+, NA	4.4, 2.8, NA	Subject with history of Type II DM, HCV, and opiate addiction. By SD 58, sCr = 1.43 mg/dL and CrCl = 63.4 mL/min, with urine protein 2+. Renal parameters mildly improved at SD 114 (Week 16), but sCr = 5.07 mg/dL at SD 170 (Week 24), with CrCl = 16.6 mL/min, urine glucose 3+ (fasting glucose = 137), and urine protein 2+. Subject hospitalized for acute renal failure on SD 176; study drugs stopped same date. Blood cultures grew <i>E. cloacae</i> ; urine cultures negative. Renal ultrasound showed bilateral diffuse parenchymal damage, possibly consistent with HIV nephropathy. Hospital doctors suspected tenofovir-associated tubular

							nephropathy, possible Fanconi syndrome. Renal biopsy showed marked interstitial nephritis with necrosis. Subject discharged from hospital on SD 207 (sCr = 2.06 mg/dL). AE of 'interstitial nephropathy' (serious, severe, and drug-related) was ongoing at data cutoff.
ATV/r							
1978-8016	0.91 73.9 (1)	1.6 46.2^c (232)	1.17 56.7 (418)	neg, 2+, trace	neg, 2+, trace	2.6, 2.1, 2.6	By SD 113, gradual decline noted in subject's eGFR (CrCl 65 mL/min; sCr = 1.05 mg/dL; 3+ glycosuria, and 1+ proteinuria). Parameters continued to slowly worsen over next 3 months. By SD 232, sCr = 1.6 mg/dL and CrCl = 46.2 mL/min, with 2+ urine protein, 2+ urine glucose, and serum phosphate = 2.1 mg/dL. AE of 'Fanconi syndrome acquired' reported. Study drugs stopped on SD 237. Nephrology report on SD 264 attributed Fanconi syndrome to TDF. Event considered resolved by SD 246. By SD 320, CrCl = 66.7 mL/min, sCr = 1.04 mg/dL, urine glucose normal, trace proteinuria, and serum phosphate = 3.3 mg/dL.
3976-8058	1.0	1.59	1.48	neg, 2+, trace	neg, 3+, trace	2.6, 1.6, 2.9	Renal dysfunction noted by

	102 (1)	69.2 (397)	75.5 (421)				Week 48 (SD 337), with CrCl ↓ to 69.2 mL/min, sCr = 1.59 mg/dL, urine protein 1+, and serum phosphate = 2.6 mg/dL. By SD 385, renal parameters worsened and study drug stopped on SD 396. Renal function parameters improved with cessation of study drug. Event considered ongoing at data cutoff.
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Results in **bold** indicate values outside the normal range. Normal ranges for creatinine clearance not provided, but protocol for GS-US-216-0114 required stopping study drug for creatinine clearance < 50 mL/min.

Abbreviations: AE= adverse event; CG = Cockcroft-Gault; CrCl = creatinine clearance; D/C = study drug discontinuation; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; HCV = hepatitis C virus; NA = not available; neg = negative; sCr = serum creatinine; SD = study day
 TDF = tenofovir disoproxil fumarate;

- a) Urine glucose and urine protein by urine dipstick
- b) Laboratory values listed represent baseline value, followed by value reported at the study drug discontinuation visit (or visit most closely preceding discontinuation), and value at last available visit.
- c) These values were not reported in laboratory dataset but were confirmed in the case narrative for Subject 1978-8016.

Source: ADLB dataset for Integrated Summary of Safety (ISS); Clinical Study Report for Study GS-US-216-0114

Among the five subjects in the ATV/co group with findings consistent of proximal renal tubulopathy, the mean baseline CD4 count was 295 cells/ μ L (range 145-478) and only Subject 0691-8292 had a baseline CD4 count < 200 (CD4 count = 145 cells/ μ L). One subject (Subject 4142-8361) had a previous history of Type 2 diabetes mellitus. None of the five subjects in the ATV/co group had a history of hypertension and none received a concomitant nephrotoxic agent during the trial.

Since the original NDA, an additional subject in the ATV/r group of Study -0114 (Subject 0986-8193) discontinued study drug on Study Day 443 because of decreased creatinine clearance. Review of this subject's laboratory findings, as reported in the Safety Update Report, suggests likely proximal renal tubulopathy. On the other hand, Subject 2843-5562, who discontinued ATV/co for reported decreased eGFR in the open-label phase of Study -0105, did not have evidence of proximal renal tubular compromise.

This reviewer also performed a categorical analysis of subclinical proximal renal tubulopathy on the entire pooled safety dataset and found no additional subjects that met the criteria for proximal tubulopathy that were not already included in Table 17.

Overall, proteinuria was observed for a similar percentage of subjects in each treatment group in the double-blind period (ATV/co 129 [33%], ATV/r 121 [32%]). Proteinuria tended to be isolated and transient and the majority of cases were Grade 1. One subject in the ATV/co group (Subject 3030-8612 in Study -0114) had Grade 3 proteinuria, but this subject had trace proteinuria and Grade 2 hematuria at baseline that fluctuated through Week 48.

The incidence of glycosuria was also similar in both treatment groups (ATV/co 19 [5%], ATV/r 15 [5%]). Overall, glycosuria tended to occur transiently and in isolation. Grade 3 abnormalities occurred twice as often in the ATV/co group than in the ATV/r group, but the total numbers of subjects were small (10 vs. 5, respectively). Subjects with Grade 3 glycosuria also typically had notable urine glucose at screening or baseline, or concurrent hyperglycemia (serum glucose <100 mg/dL). No Grade 4 glycosuria was reported.

Table 18 summarizes the proteinuria and glycosuria observed in the double-blind pooled analysis. The analysis set was limited to subjects with at least one post-baseline laboratory value for each test. Subjects were counted only once by maximum post-baseline toxicity grade.

Table 18: Treatment-Emergent Proteinuria and Glycosuria in Phase 2 and 3 Trials Double-Blind Treatment Period (Pooled Analysis GS-US-216-0105 and -0114)

Maximum Post-Baseline Toxicity Grade	Number of Subjects (%)	
	ATV/co (N=392)	ATV/r (N=375)
Urine Protein		
<i>All Grades</i>	129 (33)	121 (32)

Grade 1 (1+ proteinuria)	107 (27)	103 (27)
Grade 2 (2-3+ proteinuria)	21 (5)	18 (5)
Grade 3 (4+ proteinuria)	1 (<1)	0
Urine Glucose		
<i>All Grades</i>	19 (5)	17 (5)
Grade 1 (2+ glycosuria)	1 (<1)	5 (1)
Grade 2 (3+ glycosuria)	8 (2)	7 (2)
Grade 3 (4+ glycosuria)	10 (3)	5 (1)

Source: ADLB dataset for Integrated Summary of Safety (ISS)

Urine phosphate was assessed in Study GS-US-216-0114 at baseline and at Weeks 2, 4, 24, and 48. Baseline median values for urine fractional excretion of phosphate were 8.7% in both groups (Q1-Q3: 6-13%), with mean values of 9.8% for the ATV/co group and 9.6% for the ATV/r group. In both treatment groups, there were small mean increases from baseline in urine fractional excretion of phosphate at each post-baseline visit, with slightly greater increases in the ATV/co group (see Table 19).

Table 19: Mean Change in Urine Fractional Excretion of Phosphate (%) by Study Week Double-Blind Treatment Period (Study GS-US-216-0114)

Study Week	ATV/co			ATV/r		
	N	FePO4 (%)	SD	N	FePO4 (%)	SD
Baseline	319	9.8%	5%	320	9.6%	5%
	Mean Δ from Baseline (%)			Mean Δ from Baseline (%)		
Week 2	300	+2.5%	6%	308	+2.0%	6%
Week 4	309	+2.1%	7%	310	+1.8%	6%
Week 24	286	+2.3%	6%	292	+1.5%	6%
Week 48	270	+1.9%	7%	284	+1.7%	6%

Abbreviations: FePO4 = fractional excretion of phosphate; Δ = change

Source: ADLB dataset for Integrated Summary of Safety (ISS)

The Applicant proposes, and this review concurs, to include risk of proximal renal tubulopathy in the WARNINGS AND PRECAUTIONS section of the proposed labeling when COBI is used with TDF. As can be seen in Table 17, in each of the five cases of proximal tubulopathy in COBI-treated subjects, evidence of renal dysfunction developed far in advance of study drug discontinuation, often within the first month of treatment. As such, labeling will recommend that prior to initiating therapy with COBI estimated creatinine clearance should be assessed in all patients, and when COBI is used with TDF, urine glucose and urine protein should also be documented at baseline. Thereafter, routine monitoring of eGFR, urine glucose, and urine protein should be performed, and serum phosphorus should be measured in patients at risk for renal impairment.

Glomerular Dysfunction

A separate categorical analysis for possible glomerular dysfunction was conducted. Because a small increase in serum creatinine (~0.1 mg/dL) is expected due to the inhibitory effect of COBI on renal tubular creatinine secretion, a threshold of 0.4 mg/dL was used to identify subjects with potentially meaningful glomerular dysfunction. This threshold was derived from pooled data (N=701) from the STRIBILD Phase 3 Studies GS-US-236-0102 and -0103 (Week 48 analyses) where the mean + 2 SDs change in serum creatinine in the STRIBILD group was 0.4 mg/dL. The underlying assumption is that a serum creatinine increase > 0.4 mg/dL is less likely to be solely due to the inhibitory effect of COBI on renal tubular creatinine secretion and should warrant further investigation.

A total of 26 subjects had confirmed serum creatinine increase \geq 0.4 mg/dL from baseline (ATV/co 16 [4%], ATV/r 10 [3%]). Of these, six subjects discontinued study drug due to a renal AE (Subjects 0986-8278, 0986-8283, 2840-8066, 3976-8058, 4169-8476, and 5217-8501); their AEs are summarized in Table 16. Four of these six subjects (0986-8278, 0986-8283, 4169-8476, and 5217-8501) also had eGFR that fell below 50 mL/min (by Cockcroft-Gault formula). An additional two subjects in the ATV/co group (Subjects 0524-8239 and 0986-8197) had creatinine clearance < 50 mL/min at Week 40 but did not interrupt or discontinue study drug as a result.

Further analysis was conducted to evaluate whether any of the 26 subjects with confirmed serum creatinine increase \geq 0.4 mg/dL from baseline also had evidence of proximal renal tubular dysfunction. Four of the 26 subjects had Grade 2 proteinuria events (ATV/co 2, ATV/r 2). However, when renal laboratory abnormalities for possible glomerular dysfunction and tubular dysfunction were assessed together, there were no additional subjects with other renal abnormalities that were not already identified and reported as AEs. The overlap of possible glomerular and tubular dysfunction was uncommon, occurring in two COBI-treated subjects (0.5% of COBI subjects overall).

With respect to decreased eGFR, 11 subjects in the pooled analysis experienced reduction in creatinine clearance rates during treatment to below 50 mL/min (ATV/co 6 [2%], ATV/r 5 [1%]); all cases occurred in Study GS-US-216-0114. Seven of these subjects (ATV/co 4, ATV/r 3) discontinued study drug due to renal AEs (Subjects 0986-8278, 0986-8283, 1978-8016, 4127-8204, 4142-8391, 4169-8476, and 5217-8501) and their cases are summarized in Table 16. Compared to the overall study population, these 11 subjects were slightly older, had a lower body mass index (BMI), and lower creatinine clearance rates at baseline; these differences were more pronounced among the subgroup of subjects in the ATV/r group. For instance, among the six subjects in the ATV/co group, the mean age at entry was 44 years (SD 5.4; range 36-51 years), mean baseline BMI was 22.4 kg/m² (SD 3.2), and mean creatinine clearance at baseline was 80.8 mL/min (SD 11.8; range 68-100 mL/min). Among the five subjects in the ATV/r group, mean age at entry was 50 years (SD 16; range 32-70), mean baseline BMI was 21.3 kg/m² (SD 3.45), and mean creatinine clearance at baseline was 77.5 mL/min (SD 16.9; range 54-101 mL/min). Lastly, four of the 11 subjects who developed low

creatinine clearance also had evidence of possibly tubular dysfunction (Subjects 0986-8283, 1978-8016, 4127-8204, and 4142-8361) and have been previously discussed (Table 17).

An additional categorical analysis of subjects with eGFR \leq 90 mL/min (by Cockcroft-Gault) at baseline was carried out by this reviewer to evaluate the renal safety in subjects with mild to moderate renal impairment enrolled in the Phase 2 and 3 trials. Of note, the renal function inclusion criteria were slightly different between the two protocols; i.e., creatinine clearance \geq 80 mL/min for Study GS-US-235-0105 and \geq 70 mL/min for Study GS-US-216-0114.

In the pooled analysis, 110 subjects were identified with mild to moderate renal impairment at baseline (ATV/co 50 [13%], ATV/r 60 [16%]). Of these, 21 subjects experienced renal AEs of interest, with twice as many subjects in the ATV/co group as the ATV/r group (14 and 7 subjects, respectively). Not surprisingly, the incidence of renal AEs was higher in this subgroup of subjects compared to the overall study population. For the ATV/co group, the incidence of renal AEs was 14% in this subgroup compared with 7% for the pooled COBI-treated group overall (Table 14); for the ATV/r group, it was 23% and 9%, respectively. For serious renal AEs or renal AEs leading to study drug discontinuation, the incidence within this subgroup was similar between the two treatment arms (ATV/co 3/50 [6%], ATV/r 4/60 [7%]), but greater compared with the overall study population (2%).

Further, nine subjects were identified with baseline creatinine clearance $<$ 70 mL/min (ATV/co 4 [1%], ATV/r 5 [1%]). Of these, two subjects (one in each treatment group) had renal AEs of interest:

- **Subject 0986-8278** (ATV/co, Study -0114): had eGFR 69.95 mL/min at baseline, developed eGFR $<$ 50 mL/min on Study Day 57 that was considered related to study drug and had study drug withdrawn per the protocol.
- **Subject 0744-5524** (ATV/r, Study -0105): had eGFR 63.49 mL/min at screening and 56.45 mL/min at baseline (a protocol violation). This subject had study drug withdrawn on Study Day 6 and a Grade 2 AE of 'renal failure' reported on Study Day 8 that was considered related to study drug by the investigator, although causality seems unlikely given baseline and subsequent eGFR values. (The Safety Update Report re-categorizes the reason for discontinuation in this subject as protocol violation.)

Laboratory findings related to serum creatinine, phosphorus and magnesium are summarized by toxicity grade in Table 20. The analysis set was limited to subjects with at least one post-baseline laboratory value for each test. Subjects were counted only once by their maximum post-baseline toxicity grade. In the pooled safety analysis, the ATV/co group had a slightly higher overall incidence of graded serum creatinine increases than the ATV/r group (7% vs. 4%, respectively), but the majority of these

events were mild. A similar pattern was noted for the incidence of graded low serum phosphorus. Mean values for serum phosphorus, however, were within normal ranges at all assessed time points for both groups and no Grade 3 or 4 low serum phosphorus abnormalities were reported.

Table 20: Treatment-Emergent Serum Creatinine, Phosphorus, and Magnesium Laboratory Abnormalities in Phase 2 and 3 Trials Double-Blind Treatment Period (Pooled Analysis GS-US-216-0105 and -0114)

Maximum Post-Baseline Toxicity Grade	Number of Subjects (%)	
	ATV/co	ATV/r
Serum Creatinine (mg/dL)	N=393	N=375
<i>Any Grade</i>	28 (7)	15 (4)
Grade 1 (> 1.5 to 2.0 mg/dL)	25 (6)	14 (4)
Grade 2 (> 2.0 to 3.0 mg/dL)	1 (<1)	0
Grade 3 (> 3.0 to 6.0 mg/dL)	2 (1)	0
Grade 4 (> 6.0 mg/dL)	0	1 (<1)
Serum Phosphate (mg/dL)	N=392	N=375
<i>Any Grade</i>	29 (7)	21 (6)
Grade 1 (2.0 mg/dL to < LLN)	18 (5)	11 (3)
Grade 2 (1.5 to < 2.0 mg/dL)	11 (3)	10 (3)
Serum Magnesium (mg/dL)	N=393	N=375
<i>Any Grade</i>	2 (1)	0
Grade 1 (1.45 mg/dL to < LLN)	0	0
Grade 2 (1.09 to < 1.45 mg/dL)	2 (1)	0

Source: ADLB dataset for Integrated Summary of Safety (ISS)

In the pooled safety analysis, mean increases in serum creatinine were noted as early as Week 2 in the ATV/co group. Thereafter, mean serum creatinine values generally stabilized through Week 48. The mean change from baseline, however, was consistently greater in the ATV/co group than the ATV/r group at every study visit. Mean change from baseline at Week 48 was 0.14 mg/dL in the ATV/co group and 0.10 mg/dL in the ATV/r group (see Table 21 and Figure 2).

Table 21: Mean Change from Baseline in Serum Creatinine (mg/dL) by Study Week in Phase 2 and 3 Trials Double-Blind Treatment Period (Pooled Analysis GS-US-216-0105 and -0114)

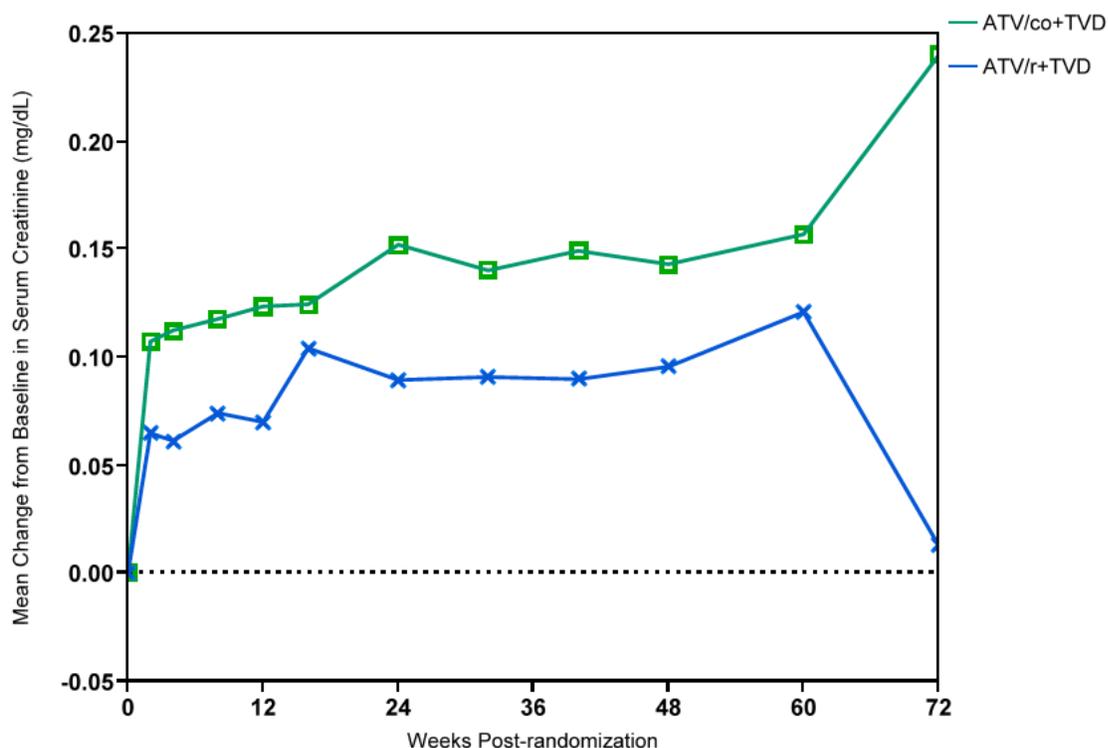
Study Week	ATV/co			ATV/r		
	N	Serum Creatinine (mg/dL)	SD	N	Serum Creatinine (mg/dL)	SD
Baseline	394	0.92	0.16	377	0.90	0.16
	Mean Δ from Baseline (mg/dL)			Mean Δ from Baseline (mg/dL)		
Week 2	382	0.11	0.12	372	0.06	0.11
Week 4	387	0.11	0.12	369	0.06	0.10
Week 8	372	0.12	0.12	362	0.07	0.11
Week 12	369	0.12	0.13	357	0.07	0.11

Week 16	366	0.12	0.12	355	0.10	0.62
Week 24	361	0.15	0.24	348	0.09	0.12
Week 32	351	0.14	0.12	344	0.09	0.12
Week 40	350	0.15	0.13	344	0.09	0.12
Week 48	348	0.14	0.17	338	0.10	0.13
Week 60	150	0.16	0.14	132	0.12	0.15
Week 72	10	0.24	0.13	7	0.01	0.33

Abbreviations: Δ = change

Source: ADLB dataset for Integrated Summary of Safety (ISS)

Figure 2: Mean Change from Baseline in Serum Creatinine (mg/dL) by Study Week in Phase 2 and 3 Trials Double-Blind Treatment Period (Pooled Analysis GS-US-216-0105 and -0114)



Source: Derived from ADLB dataset for Integrated Summary of Safety (ISS)

Correspondingly, while modest decreases in mean eGFR (by Cockcroft-Gault) were observed post-baseline in both treatment groups, the mean reduction from baseline was greater in the ATV/co group at all visits, as shown in Table 22 and Figure 3.

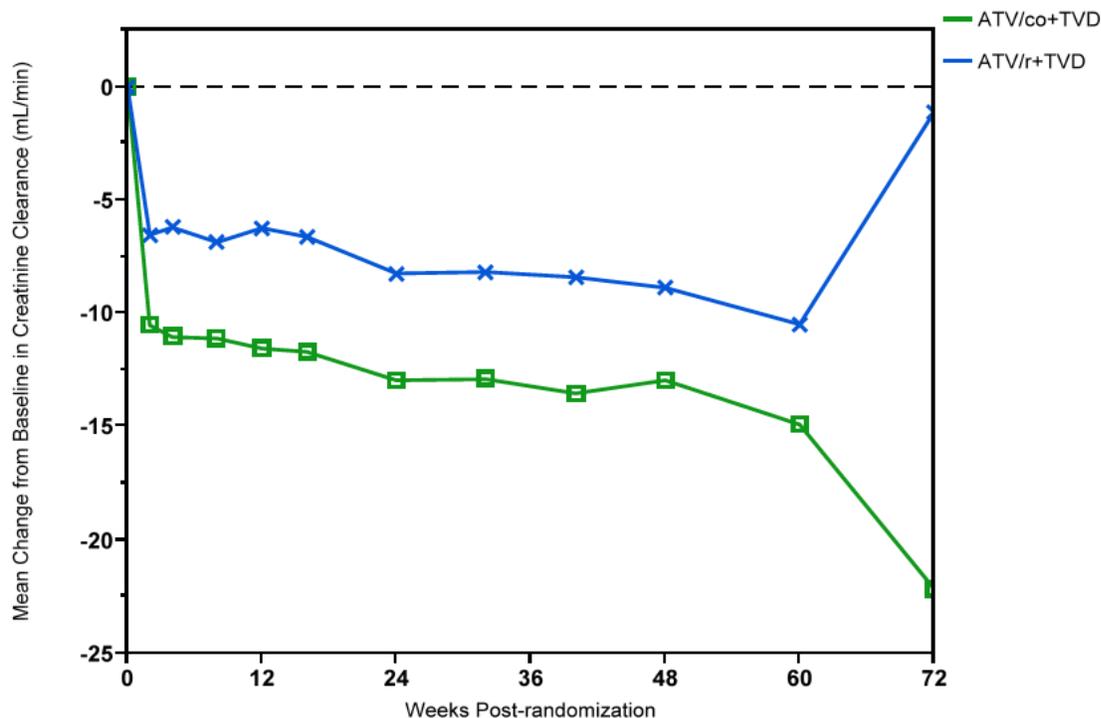
Table 22: Mean Change in Estimated Creatinine Clearance (mL/min) by Study Week, Cockcroft-Gault Method, in Phase 2 and 3 Trials Double-Blind Treatment Period (Pooled Analysis GS-US-216-0105 and -0114)

Study Week	ATV/co			ATV/r		
	N	eGFR (mL/min)	SD	N	eGFR (mL/min)	SD
Week 16	366	0.12	0.12	355	0.10	0.62
Week 24	361	0.15	0.24	348	0.09	0.12
Week 32	351	0.14	0.12	344	0.09	0.12
Week 40	350	0.15	0.13	344	0.09	0.12
Week 48	348	0.14	0.17	338	0.10	0.13
Week 60	150	0.16	0.14	132	0.12	0.15
Week 72	10	0.24	0.13	7	0.01	0.33

Baseline (mL/min)	394	116	28	377	119	32
	Mean Δ from Baseline (mL/min)			Mean Δ from Baseline (mL/min)		
Week 2	382	-10.53	13.91	372	-6.55	13.51
Week 4	387	-11.05	13.88	369	-6.22	13.40
Week 8	383	-11.12	13.49	370	-6.88	13.69
Week 12	375	-11.56	15.00	365	-6.25	13.35
Week 16	377	-11.71	13.69	363	-6.64	14.59
Week 24	369	-12.96	15.33	358	-8.25	13.40
Week 32	361	-12.91	14.15	355	-8.19	14.41
Week 40	361	-13.54	14.05	355	-8.42	14.70
Week 48	361	-12.96	15.05	352	-8.88	14.74
Week 60	154	-14.92	14.94	135	-10.50	15.10
Week 72	10	-22.16	14.27	8	-1.13	23.55

Abbreviations: eGFR = estimated glomerular filtration rate; Δ = change
 Source: ADLB dataset for Integrated Summary of Safety (ISS)

Figure 3: Mean Change from Baseline in Estimated Glomerular Filtration Rate (mL/min) by Study Week, Cockcroft-Gault Method, in Phase 2 and 3 Trials Double-Blind Treatment Period (Pooled Analysis GS-US-216-0105 and -0114)



Source: Derived from ADLB dataset for Integrated Summary of Safety (ISS)

Results for eGFR calculated using the modified diet in renal disease equation (MDRD) were consistent with those observed for eGFR by the Cockcroft-Gault Method.

In contrast, mean cystatin C-derived GFR did not decrease from baseline at Week 48 in either treatment group in the pooled analysis. Cystatin C assessments were collected at baseline and Weeks 2, 4, 24, and 48. Mean baseline values were similar in both treatment groups and changes from baseline were comparable at most time points (see Table 23 and Figure 4). At Week 48, the mean change from baseline in cystatin C-derived GFR was 5.77 mL/min/1.73m² in the ATV/co group and 7.9 mL/min/m² in the ATV/r group. These findings corroborate the results from the Phase 1 Study GS-US-216-0121, which showed that COBI inhibits tubular secretion of creatinine as reflected by a reduction in eGFR without affecting the actual glomerular filtration rate (see Section 4.4.2)

Table 23: Mean Change from Baseline in Estimated Glomerular Filtration Rate (mL/min/1.73 m²) by Study Week, Cystatin C Clearance, in Phase 2 and 3 Trials Double-Blind Treatment Period (Pooled Analysis GS-US-216-0105 and -0114)

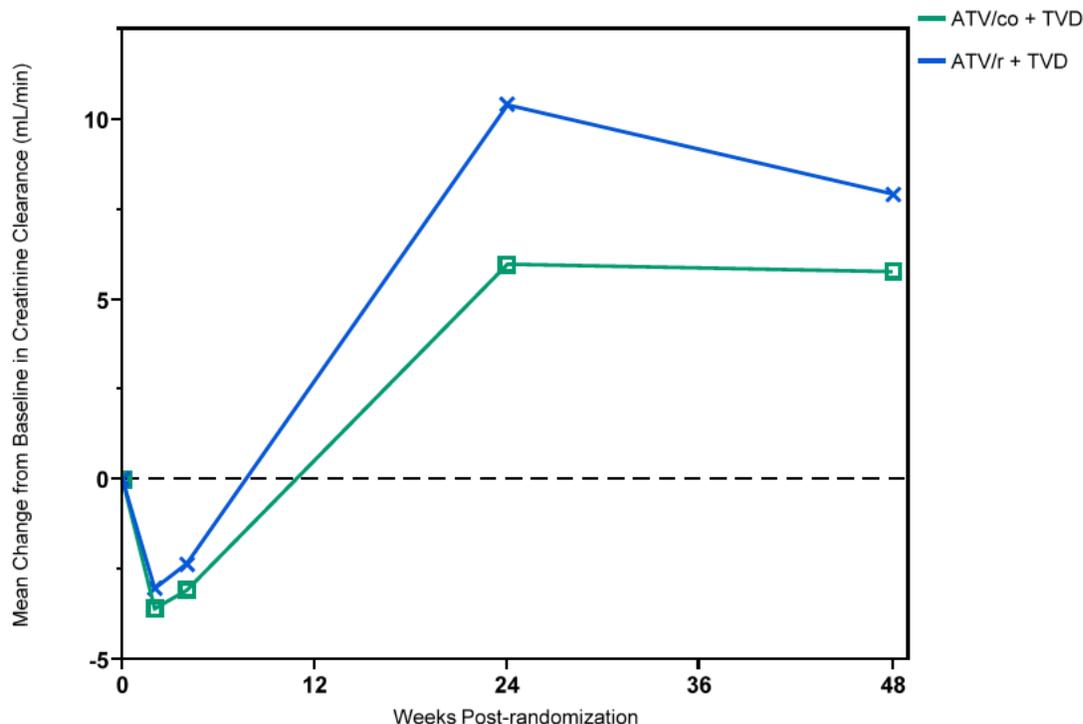
Study Week	ATV/co			ATV/r		
	N	eGFR ^a	SD	N	eGFR ^a	SD
Baseline	385	101.67	21.97	360	100.5	19.75
	Mean Δ from Baseline ^a			Mean Δ from Baseline ^a		
Week 2	367	-3.58	12.63	349	-3.02	12.59
Week 4	333	-3.07	13.30	325	-2.34	11.67
Week 24	354	5.98	17.82	334	10.40	21.19
Week 48	335	5.77	17.96	325	7.93	19.12

Abbreviations: eGFR = estimated glomerular filtration rate; Δ = change

a) Cystatin C-derived eGFR units are mL/min/1.73m²

Source: ADLB dataset for Integrated Summary of Safety (ISS)

Figure 4: Mean Change from Baseline in Estimated Glomerular Filtration Rate (mL/min/1.73 m²) by Study Week, Cystatin C Clearance, in Phase 2 and 3 Trials Double-Blind Treatment Period (Pooled Analysis GS-US-216-0105 and -0114)



Source: Derived from ADLB dataset for Integrated Summary of Safety (ISS)

Safety Update Report: Study GS-US-236-0118 and STRIBILD clinical trials

- **Study GS-US-236-0118** is a dedicated open-label study of COBI and STRIBILD currently being conducted in HIV-infected subjects with mild to moderate renal impairment (eGFR between 50-89 mL/min, inclusive). An interim report for Study -0118 was submitted with the Safety Update Report to this NDA. As of June 25, 2012, 30 subjects had been enrolled in Cohort 1 (STRIBILD) and 56 subjects had been enrolled in Cohort 2 (ATV/co or DRV/co). The median duration of exposure to study drug was 16.0 weeks (Q1-Q3: 12.1-32.1) in Cohort 1 and 16.1 weeks (Q1-Q3: 10.6-31.9) in Cohort 2.

No deaths have been reported in Study -0118. Two SAEs (both in Cohort 1) have been reported:

- a Grade 2 increase in blood creatinine phosphokinase in Subject 0986-1010 on Study Day 1 that was considered to be related to study drug by the investigator (SAE resolved on Study Day 14)

- Grade 3 events of hepatitis C and Hodgkin's disease in Subject 3672-1020 on Study Day 93. Study drug was discontinued on same day. Events were not considered related to study drug by the investigator.

A total of six subjects discontinued study drug because of an AE: two subjects (7%) in Cohort 1 and four subjects (7%) in Cohort 2. The AEs that led to drug discontinuation are as follow:

- Cohort 1: blood creatinine increase in one subject and HCV and Hodgkin's disease in one subject (see above)
- Cohort 2: gastrointestinal disorders in two subjects (constipation, flatulence, nausea), and fatigue, arthralgia, and headache in one subject each

Subject 4143-1013 in Cohort 1 discontinued study drug due to Grade 2 elevation in serum creatinine on Study Day 15 that was considered study drug-related. The event was ongoing at the time of data cutoff. This subject had no other laboratory abnormalities that were suggestive of proximal renal tubulopathy. No other subject met the criteria for subclinical kidney disease and no other subjects have had renal AEs reported thus far. Small and similar changes in median serum creatinine and eGFR values were observed in both treatment cohorts. Grade 1 and 2 abnormalities in serum creatinine occurred with similar frequency in both cohorts and no Grade 3 or 4 events were reported in either cohort.

The Safety Update Report also included updated safety information from the STRIBILD clinical trials. A detailed review of renal AEs and laboratory parameters for Studies GS-US-236-0102 and -0103 indicated that the overall renal safety profile for STRIBILD is consistent with the renal safety profile of ATV/co + FTC/TDF as observed in the COBI Phase 2 and 3 trials.

Nephrolithiasis

According to U.S. approved labeling for ATV (Reyataz®), cases of nephrolithiasis have been reported during post-marketing surveillance in HIV-infected patients treated with ATV, but estimates of frequency cannot be made.² A recent single-center study from Japan describes an incidence rate of 23.7 cases per 1000 person-years in patients taking ATV/r (n=31) compared to 2.2 cases per 1000 person-years in patients taking other PI regimens (n=775), with median time to nephrolithiasis in the ATV/r group of 24.5 months after commencement of ARV therapy.³

² REYATAZ® (atazanavir) tablets US Prescribing Information. Bristol-Myers Squibb Co. Princeton, NJ. Revised February 2012

³ Hamada, Y, Nishijima T, Watanabe K, et al. High incidence of renal stones among HIV-infected patients on ritonavir-boosted atazanavir than in those receiving other protease inhibitor-containing antiretroviral therapy. Clin Infect Dis 2012; 55:1262-9.

In the pooled analysis of COBI Phase 2 and 3 clinical trials, 10 nephrolithiasis events were reported in eight subjects. All eight subjects were in the ATV/co treatment group (2%) and no cases of nephrolithiasis were reported in the ATV/r treatment group. Cases of nephrolithiasis were reported in both Studies -0105 and -0114, but only from U.S. or Dominican sites. All eight subjects were male (mean age 43.8 years) and all were of white or mixed (white/black) race. Three of the eight subjects (1236-5515, 1965-8024, and 0698-8166) had history of nephrolithiasis. Mean (SD) baseline serum creatinine for these eight men was 1.0 (0.16) mg/dL (range 0.81-1.25 mg/dL) with a mean (SD) baseline creatine clearance of 105.6 (16) mL/min by Cockcroft-Gault method (range 84-132 mL/min). The median time to onset of nephrolithiasis was 176 days (Q1-Q3: 90-229 days), or around Week 24. None of the nephrolithiasis events led to study drug discontinuation and most were not considered serious. One case of ureteral stones, however, was serious and required hospitalization (Subject 1965-8024). Table 24 summarizes the eight COBI-treated subjects with nephrolithiasis events; two subjects (Subjects 0986-8244 and 1965-8024) had more than one event during the double-blinded treatment period.

Table 24: Treatment-Emergent Nephrolithiasis Events in Phase 2 and 3 Trials Double-Blind Treatment Period (Pooled Analysis GS-US-216-0105 and -0114)

Subject ID	Age	Study Day Onset	Serious Adverse Event	Related to Study Drug	Serum Creatinine (mg/dL) ^a		History of Kidney Stones
					Creatinine Clearance ^{a, b} (mL/min)		
GS-US-216-0105							
0364-5510	56	147	No	Yes	0.99 -> 1.14		No
					104 -> 94		
0433-5565	43	223	No	Yes	1.11 -> 1.4		No
					88 -> 71		
1236-5515	48	174	No	No	0.85 -> 1.13		Yes
					132 -> 99		
GS-US-216-0114							
0698-8166	45	245	No	No	0.81 -> 0.92		Yes
					122 -> 111		
0986-8244 ^c	33	178	No	Yes	1.25 -> 1.41		No
		311	No	Yes	107 -> 95 -> 90		
0986-8283	51	92	No	Yes	1.02 -> 1.29		No
					100 -> 78		
0986-8458	28	217	No	No	1.16 -> 1.31		No
					109 -> 96		
1965-8024 ^c	46	29	No	No	1.19 -> 1.37 -> 1.23		Yes
		85	Yes	No	84 -> 77 -> 84		

- a) Values shown are baseline and at study visit closest to and preceding nephrolithiasis event. For subjects with more than one event, the latter values represent the study visits closest to each event
 - b) Creatinine clearance rate by Cockcroft-Gault formula
 - c) Subjects 0986-8244 and 1965-8024 had two separate reported events of nephrolithiasis each.
- Source: ADLB dataset for Integrated Summary of Safety (ISS); MH datasets for Studies GS-US-216-0105 and -0114*

Aside from Subject 0986-8283, subjects with nephrolithiasis did not have evidence of significant renal impairment during treatment. Consistent with the COBI effect on eGFR, however, all had a modest decline in eGFR in the period preceding the nephrolithiasis event, with a median decrease in creatinine clearance of 12.5 mL/min (range 6-33 mL/min). None had aciduria as evidenced by low urine pH. As only one case was considered a serious event, case narratives for the majority of these cases were not submitted with the original NDA. Based on the information provided for Subjects 0986-8283 and 1965-8024, however, it did not appear that the kidney stones were submitted for biochemical analyses. Moreover, there was insufficient PK data in these eight subjects to evaluate for a possible correlation between ATV exposures and nephrolithiasis.

On the other hand, six of the eight subjects (1236-5515, 0364-5510, 1965-8024, 0698-8166, 0986-8244, and 0986-8458) had calcium oxalate crystals seen in the urine either at baseline or while on study drug. As calcium oxalate stones are the most common type of kidney stones in the general population, this finding may have contributed to the nephrolithiasis in these six subjects; however, without knowing the composition of the stones, it is difficult to assess causality with certainty. Moreover, the incidence of calcium oxalate crystalluria in the overall study population was not reported.

A request for further information regarding these nephrolithiasis events was sent to the Applicant during the NDA review cycle; case narratives for the eight subjects noted above were submitted in response. The response confirmed that detailed biochemical analyses of the stones were not performed, thus the composition of the kidney stones could not be specified. However, the response also indicated that longer term 96-week data from Study GS-US-216-0114, which had recently become available, showed that the overall rates of nephrolithiasis in that trial were eventually similar in the two treatment groups (ATV/co 1.5% [5/344]; ATV/r 1.4% [5/348]); no new cases of nephrolithiasis occurred in the ATV/co group between Week 48 and 96, while five new cases were reported in the ATV/r group. No additional information about the ATV/r cases in Study -0114 was provided.

In addition, a new subject in the ATV/co group of Study GS-US-216-0105 (Subject 0663-5568) developed a Grade 2 nephrolithiasis event during the open-label phase of the trial (Study Day 449). The event was not considered related to study drug by the investigator nor resulted in study drug discontinuation. This subject, too, had calcium oxalate crystals observed in the urine throughout treatment.

By comparison, in the pooled analysis of 96-week data from the STRIBILD Phase 3 trials, the incidence of nephrolithiasis was 1% (7/701) in the STRIBILD group, 1% (4/355) in the ATV/r+ TVD group, and 2.6% (9/352) in the ATRIPLA group. Nephrolithiasis was not observed in the Phase 1 trials of STRIBILD or COBI.

In summary, coadministration of COBI with ATV plus TVD was associated with a 2.3% (9/394) overall incidence rate of nephrolithiasis in the pooled Phase 2 and 3 safety analysis, including the open-label phase of Study -0105, compared with a 1.3% (5/377) rate for ATV/r, including 96-week data from Study -0114. While causality is difficult to ascertain given the lack of information regarding stone composition in these cases, it appears that calcium oxalate crystalluria may be a risk factor, although the denominator of total subject with calcium oxalate crystalluria was not provided. That said, ATV/co may be associated with earlier onset of kidney stones compared to ATV/r (i.e., around Week 24 for ATV/co versus after Week 48 for ATV/r, the latter timing being consistent with published reports). These events, however, were generally not serious and did not lead to discontinuation of treatment. Nonetheless, this reviewer recommends that labeling for COBI reflect the Week 48 nephrolithiasis findings from the pooled analysis as this may be important information to prescribers and patients considering an ARV regimen that contains COBI.

7.3.5.2 Musculoskeletal Adverse Events

In the safety review of STRIBILD Phase 3 clinical trials, the percentage of subjects with musculoskeletal AEs (by MedDRA SOC) was noted to be greater in the STRIBILD treatment group (21%) compared with the ATRIPLA or ATV/r + TVD comparator groups (16% each). In the pooled analysis of COBI Phase 2 and 3 trials, the incidence of musculoskeletal AEs was 17% in the ATV/co group and 15% in the ATV/r group. The vast majority of these events (95%) were mild or moderate in severity (i.e. Grade 1 or 2), with most being Grade 1.

Nine Grade 3 musculoskeletal AEs were reported among seven subjects (ATV/co 4, ATV/r 3), all in Study GS-US-216-0114. In the ATV/co group, the Grade 3 musculoskeletal AEs included one event each of right ankle arthritis, bursitis, low back pain, and rhabdomyolysis; the latter two events were considered related to study drug by the investigators. No Grade 4 musculoskeletal AEs were reported.

In the case of the Grade 3 rhabdomyolysis (Subject 0986-8250), the AE was reported in a 20-year-old Hispanic male on Study 36 in conjunction with elevated bilirubin (4.4 x ULN) and creatinine kinase (12,584 U/L [reference range 18-198]); there was no history of injury or vigorous exercise or exertion around the time of the creatinine kinase increase. The event was considered serious (medically significant) and led to study drug discontinuation on Study Day 60. This is the only subject who discontinued study drug due to a musculoskeletal AE. No cases of rhabdomyolysis were reported in the ATV/r group.

The only other subject with a serious musculoskeletal AE was another subject in the ATV/co group of Study -0114 (Subject 1994-8339), a 51-year-old black male with medical history significant for AIDS and chronic muscle weakness of both legs who had recurrent AEs of mild to moderate bilateral lower extremity weakness while on treatment with ATV/co. The lower extremity weakness was reported on three separate occasions (Study Days 14, 162, and 180), each associated with hospitalization but none considered related to study drug. This subject was eventually withdrawn from the trial on Study Day 175 due to non-compliance with taking his study medications.

No sizeable differences in AE incidence rates were noted between the ATV/co and ATV/r treatment groups when the MedDRA High Level Group Terms 'Musculoskeletal and Connective Tissue Disorders NEC' or 'Muscle Disorders' were analyzed. Likewise, no substantial differences were noted between groups when individual MedDRA Preferred Terms such as 'back pain', 'musculoskeletal pain', 'myalgia', or 'pain in extremity' were considered or when the broad SMQ 'Rhabdomyolysis/myopathy' was analyzed. There were no muscle injury or muscle rupture events reported in the pooled analysis. Table 25 summarizes the musculoskeletal AEs by MedDRA HLGT and Preferred Terms reported in $\geq 1\%$ of subjects in either treatment group.

Table 25: Treatment-Emergent Musculoskeletal Adverse Events (Any Causality, All Grades) in $\geq 1\%$ of Subjects in Either Treatment Group in Phase 2 and 3 Trials Double-Blind Treatment Period (Pooled Analysis GS-US-216-0105 and -0114)

MedDRA	Number of Subjects (%)		RD	P-value
	ATV/co (N=394)	ATV/r (N=377)		
High Level Group Term				
Preferred Term				
<i>Any Musculoskeletal Adverse Event</i>	49 (12)	48 (13)		
Musculoskeletal and Connective Tissue Disorders NEC	36 (9)	41 (11)	-1.74	0.471
Back pain	17 (4)	26 (7)	-2.58	0.157
Pain in extremity	13 (3)	10 (3)	0.65	0.675
Musculoskeletal chest pain	1 (<1)	3 (1)	-0.54	0.363
Musculoskeletal pain	3 (1)	1 (<1)	0.5	0.624
Neck pain	2 (1)	0	0.51	0.5
Muscle Disorders	13 (3)	13 (3)	-0.15	1
Myalgia	9 (2)	11 (3)	-0.63	0.654
Muscle spasms	2 (1)	2 (1)	-0.02	1
Muscular weakness	2 (1)	2 (1)	-0.02	1

Abbreviations: NEC = Not Elsewhere Classified; RD = Risk Difference (per hundred)
P-values unadjusted, output generated by MAED service for exploratory analyses only
Source: ADAE dataset for Integrated Summary of Safety (ISS)

Table 26 summarizes the creatinine kinase laboratory values by maximum toxicity grade reported in the pooled analysis. The incidence of graded abnormal creatinine

kinase elevations was overall greater in the ATV/co group, but most events were Grade 1 or 2.

Table 26: Treatment-Emergent Creatinine Kinase Laboratory Abnormalities in Phase 2 and 3 Trials Double-Blind Treatment Period (Pooled Analysis GS-US-216-0105 and -0114)

Maximum Post-Baseline Toxicity Grade	Number of Subjects (%)	
	ATV/co (N=393)	ATV/r (N=375)
<i>Any Grade</i>	70 (18)	54 (14)
Grade 1 (3.0 to < 6.0x ULN)	35 (9)	23 (6)
Grade 2 (6.0 to < 10.0x ULN)	14 (4)	9 (2)
Grade 3 (10.0 to < 20.0x ULN)	10 (3)	7 (2)
Grade 4 (\geq 20.0x ULN)	11 (3)	15 (4)

Source: ADLB dataset for Integrated Summary of Safety (ISS)

Among the 26 subjects (13 per treatment group) taking concomitant HMG-CoA reductase inhibitors, either at baseline or initiated post-randomization, five subjects (ATV/co 3, ATV/r 2) experienced 10 musculoskeletal AEs by MedDRA SOC. In the ATV/co group, these AEs were ‘back pain’ (1 subject), ‘bone pain’ (1 subject), and ‘pain in extremities’ (2 subjects); none of these events were considered related to study drug by the investigators and all were mild or moderate in severity. In contrast, there was one such subject in the ATV/r group with Grade 3 AEs of arthralgias and myalgias; however, these events were attributed to concomitant varenicline use. None of the 13 subjects in the ATV/co group had AEs consistent with transaminitis or creatinine kinase increase, but two subjects had treatment-emergent Grade 1-2 elevated creatinine kinase noted in their laboratory results, compared to none in the ATV/r cohort, and four subjects had Grade 1 increases in ALT, AST, or GGT reported during treatment, compared to three subjects in the ATV/r group who had Grade 1-3 increases. The small number of subjects taking concomitant HMG-CoA reductase inhibitors in these trials precludes a meaningful assessment of potential drug-drug interactions with COBI. However, drug-drug interactions are recognized between ritonavir-boosted PIs and HMG-CoA reductase inhibitors. These interactions are complex and may not be predictive of the drug-drug interactions that may occur with PI + COBI. For this reason, the review team will request post-marketing studies to evaluate drug-drug interactions between ATV/co and DRV/co and atorvastatin and rosuvastatin.

There was a greater incidence of AEs under the HGLT ‘Joint Disorders’ in the ATV/co group (4.3%) compared with the ATV/r group (1.9%). This difference was driven chiefly by the difference in the percentage of subjects with the MedDRA Preferred Term ‘arthralgia’ (ATV/co 14 [4%], ATV/r 5 [1%]). No notable differences, however, were observed when other Preferred Terms such as ‘arthritis’, ‘arthropathy’, ‘joint stiffness’, or ‘joint swelling’ were analyzed. Except for ‘arthralgias’ and ‘arthritis’, no AEs by MedDRA Preferred Term occurred in \geq 1% in the ATV/co group. Nearly all AEs reported under the MedDRA HGLT ‘Joint Disorders’ or ‘Tendon, Ligament, and Cartilage Disorders’

were mild or moderate in severity and most were not considered related to study drug; only two events (one event of mild arthritis in the ATV/r group and one event of mild arthralgia in the ATV/co group) were considered drug-related, but neither led to study drug interruption or discontinuation. Tendonitis was reported in only three subjects in the pooled analysis (ATV/co 1 [$<1\%$], ATV/r 2 [1%]).

7.3.5.3 Bone Fractures

Bone fracture adverse events were evaluated as AEs of interest for the COBI Phase 2 and 3 clinical trials because bone toxicity has been associated with tenofovir use. Prespecified fracture events included all Preferred Terms with “fracture” as the primary or secondary term (see Section 7.1.2 – Categorization of Adverse Events).

In the pooled safety analysis, seven bone fracture AEs were reported among six subjects, with an equal percentage of subjects in each treatment group (ATV/co 2 [1%], ATV/r 4 [1%]). All events were reported in Study GS-US-216-0114. Six of the seven reported fractures were related to traumatic injury.

A nontraumatic fracture (spinal compression fracture) was reported in one subject in the ATV/r group:

- **Subject 5217-8501:** a 49-year-old male with past medical history significant for insulin-dependent diabetes mellitus. On Study Day 112, subject had Grade 3 AE of spinal compression fracture (based on spinal X-ray) reported concurrently with Grade 3 AE of osteoporosis. Vitamin D supplementation was initiated. An MRI also was suggestive of an old compression fracture at L1 vertebral levels. The AE of spinal compression and osteoporosis were considered by the investigator to be unrelated to study drug and did not lead to discontinuation of study drug; however, the subject discontinued study drug for the concurrent AE of acute renal failure (see Table 16).

In the Safety Update Report to this NDA, seven new fracture events in six subjects (three in each treatment group) were reported since the original NDA was submitted. All new events were in Study GS-US-216-0114 and none was reported as nontraumatic. No bone fractures were reported in any study phase of Study -0105.

In the pooled safety analysis of STRIBILD Phase 3 trials, bone fractures were reported in similar percentages of subjects in each treatment group (STRIBILD 14 [2%], ATV/r + TVD 14 [4%]; ATRIPLA 8 [2%]). The majority of reported fractures were due to traumatic injury; nontraumatic fractures were reported in three subjects in the ATV/r +TVD group, but none was considered related to study drug by the investigators.

No bone mineral density (BMD) analyses were performed in the COBI Phase 2 or 3 trials. However, dual-energy x-ray absorptiometry (DEXA) scans were performed in a

subset of subjects at selected sites in the STRIBILD Phase 3 Study GS-US-236-0103. There were numerically smaller mean percentage decreases from baseline in BMD at the lumbar spine and hip in the STRIBILD group compared with the ATV/r +TVD group (changes at Week 48: spine -2.63% in the STRIBILD group vs. -3.33% in the ATV/r +TVD group; hip -3.06% in the STRIBILD group vs. -3.88% in the ATV/r +TVD group); however, these differences were not statistically significant.

In summary, there was no significant difference in the rate of fracture events between the two treatment groups in the pooled safety analysis of COBI Phase 2 and 3 trials (ATV/co 1.3% [5/394], ATV/r 1.9% [7/377]). The vast majority of fracture events were trauma-related and not related to study drug.

7.3.5.4 Hepatobiliary Adverse Events

Hepatic and Hepatobiliary Adverse Events

Hepatic events were prospectively evaluated as AEs of interest for the integrated COBI studies based on nonclinical (liver changes in mice, rats, and dogs) and Phase 1 clinical findings with COBI and because liver toxicity has been associated with ATV use. As noted in Section 7.1.2, hepatic events of interest included the followed MedDRA Preferred Terms: acute hepatic failure, hepatic failure, and liver injury. In the pooled safety analysis of the Phase 2 and 3 trials of COBI, no subject in either treatment group had a hepatic AE of interest as defined by the prespecified criteria. This applies to the 120-Day Safety Update for both COBI trials as well.

In the pooled analysis, 461 hepatobiliary-related adverse events (of any causality and any severity) were identified using the MedDRA SOCs ‘Hepatobiliary Disorders’, ‘Investigations’ (i.e., MedDRA HLT ‘Liver Function Analysis’), and ‘Eye Disorders’ (i.e., MedDRA HLT ‘Ocular Disorders NEC’ or ‘Scleral Structural Change, Deposit and Degeneration’ for cases of scleral icterus). These AEs were reported in 298 (39%) subjects, with comparable percentages of subjects in each treatment group (ATV/co 159 [40%], ATV/r 139 [37%]). Table 27 summarizes the hepatobiliary AEs (as defined above) by MedDRA HLT and Preferred Term.

Table 27: Selected Treatment-Emergent Hepatobiliary Adverse Events (Any Causality, All Grades) in Phase 2 and 3 Trials Double-Blind Treatment Period (Pooled Analysis GS-US-216-0105 and -0114)

MedDRA Term	Number of Subjects (%)		RD	P-value
	ATV/co (N=394)	ATV/r (N=377)		
High Level Term				
Preferred Term				
<i>Any Hepatobiliary Adverse Event</i>	159 (40)	139 (37)		
Cholestasis and Jaundice	97 (25)	75 (20)	4.73	0.12

Jaundice		74 (19)	55 (15)	4.19	0.124
Hyperbilirubinemia		43 (11)	34 (9)	1.9	0.4
Ocular Disorders NEC	Ocular Icterus	68 (17)	68 (18)	-0.78	0.778
Scleral Structural Change, Deposit and Degeneration	Scleral Discoloration	1 (<1)	1 (<1)	-0.01	1
Cholecystitis and Cholelithiasis	Cholelithiasis	1 (<1)	1 (<1)	-0.01	1
Hepatobiliary Signs and Symptoms	Hepatomegaly	2 (1)	0	0.51	0.5
Hepatocellular Damage and Hepatitis NEC		1 (<1)	1 (<1)	-0.01	1
Hepatic steatosis		1 (<1)	0	0.25	1
Hepatitis alcoholic		0	1 (<1)	-0.27	0.489
Hepatic Enzymes and Function Abnormalities	Hypertransaminasemia	1 (<1)	0	0.25	1
Liver Function Analyses		20 (5)	13 (3)	1.63	0.29
AST increased		4 (1)	4 (1)	-0.05	1
ALT increased		5 (1)	2 (1)	0.74	0.452
GGT increased		1 (<1)	4 (1)	-0.81	0.208
Liver function test abnormal		1 (<1)	1 (<1)	-0.01	1
Transaminases increased		1 (<1)	1 (<1)	-0.01	1
Hepatic enzyme increased		1 (<1)	0	0.25	1

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; NEC = Not Elsewhere Classified; RD = Risk Difference (per hundred)
P-values unadjusted, output generated by MAED service for exploratory analyses only
Source: ADAE dataset for Integrated Summary of Safety (ISS)

As shown in Table 27, the difference between the two treatment groups in terms of hepatobiliary-related AE incidence was driven chiefly by the difference in the incidence of jaundice. When broad or narrow SMQs for hepatic or biliary disorders were considered, the differences between the two treatment groups were not substantial.

There were only two hepatobiliary-related AEs in the pooled analysis that were serious in nature, one in each treatment group and both in Study GS-US-216-0114:

- **Subject 1967-8085 (ATV/co):** had a Grade 2 event of increased hepatic enzyme on Study Day 71 that was not considered related to study drug and did not result in drug discontinuation. The subject had a history of hepatitis C virus infection with mildly elevated AT levels at baseline and was asymptomatic from the AE. The AE was considered resolved on Study Day 91.
- **Subject 5127-8398 (ATV/r):** had a Grade 3 event of increased gamma glutamyltransferase (GGT) on Study 85 that was considered study drug-related and resulted in study drug interruption on Study Day 89. The subject had elevated aminotransferase (AT) levels at baseline (GGT 3.7x ULN) that were attributed to underlying fatty change in the liver and the subject's alcohol

consumption. Study medication was restarted on Study Day 107 when GGT levels returned to baseline and the AE was considered resolved.

The majority of hepatobiliary-related AEs (62%) were Grade 1. The proportion of Grade ≥ 2 AEs was greater in the ATV/co group (42%) compared with the ATV/r group (32%). Overall, two-thirds of Grade ≥ 2 hepatobiliary-related AEs were considered related to study drug by the investigators, with similar distribution of causality in each group. As noted in Section 7.3.4, for the hepatic disorders SMQs (broad or narrow), the difference between the two treatment groups in drug-related Grade ≥ 2 events was noteworthy at 5.54% (see Table 13); the difference was also notable when the biliary disorders SMQs (broad or narrow) were analyzed. No obvious trends, however, were noted between the two groups for these AEs by MedDRA Preferred Term.

A similar number of subjects discontinued or interrupted study drug due to a hepatobiliary-related AE in each treatment group (ATV/co 15 [4%]; ATV/r 15 [4%]). Among the 28 subjects who permanently discontinued study drug (ATV/co 14 [4%], ATV/r 12 [3%]), the types of AEs that led to study drug discontinuation were comparable between the two groups (e.g., jaundice, ocular icterus, increased AT levels, or hyperbilirubinemia) with no discernible pattern noted between them.

Cholelithiasis

Cholelithiasis, cases of which have been identified with ATV use during postmarketing, was reported infrequently in the COBI Phase 2 and 3 trials. In the pooled safety analysis, one subject in each treatment group (0.3%) reported cholelithiasis. In neither case was the event considered serious or related to study drug by the investigator, nor did either event result in study drug discontinuation or interruption. The subject in the ATV/r group (Subject 0684-8210) had a history of biliary calculi at baseline and elective cholecystectomy was planned prior to enrollment. Neither subject had detailed biochemical analyses of the gallstones performed, so composition of the stones could not be specified. In the Week 96 safety data from Study GS-US-216-0114, reported in the Safety Update Report, two additional new cases of cholelithiasis (one in each treatment group) were reported. A similar low incidence of cholelithiasis was observed in the STRIBILD development program.

Drug-Induced Liver Injury

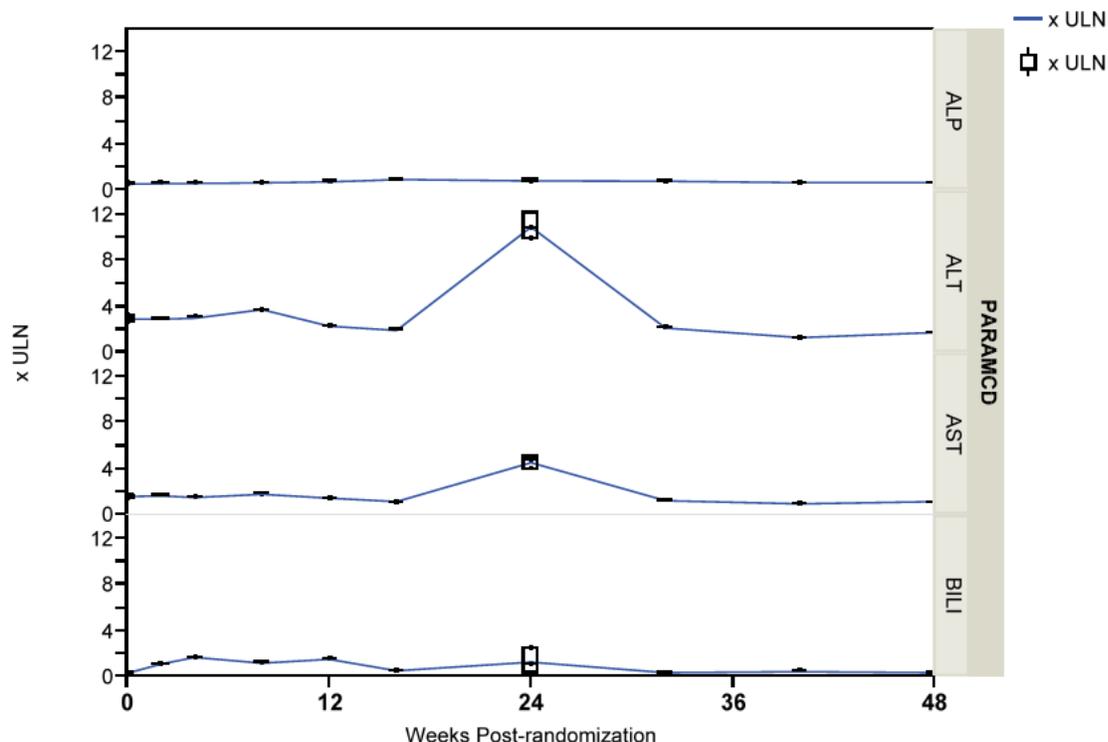
No subject in the pooled safety analysis of COBI Phase 2 and 3 trials was found to have evidence of drug-induced liver injury (DILI) based on review of AEs and laboratory parameters. No subject met Hy's Law as defined in the FDA guidance for industry *Drug-Induced Liver Injury: Premarketing Clinical Evaluation*; i.e., elevated AT $> 3x$ ULN associated with increase in total bilirubin $\geq 2x$ ULN with no substantial elevation in

alkaline phosphate (< 2x ULN).⁴ In Hy's Law cases, bilirubin levels typically rise concomitantly or after the increase in AT levels and there are no other potential causes for liver dysfunction. Among the few subjects in the pooled analysis who had concomitant hyperbilirubinemia and transaminitis, most had elevated transaminase levels at baseline with preexisting comorbidities such as co-infection with hepatitis B or C virus or chronic alcoholism. One subject in the ATV/co group of Study -0114 (Subject 1603-8082) had AST 4.3x ULN and total bilirubin 2.3x ULN reported at Week 48, but ALT was <2x ULN throughout the course of treatment and the subject did not discontinue study drug due to any AE.

Another ATV/co subject in the same trial (Subject 0581-8230) had a history of hepatitis B virus co-infection and elevated transaminases at baseline (ALT 2-3x ULN); this subject, however, developed ALT levels 12x ULN (Grade 4) at Week 24 associated with nausea and vomiting, increase in AST levels 5x ULN, and increase in total bilirubin levels 2.4x ULN. The subject discontinued study drug on Study Day 171; repeat total bilirubin on that same day, however, was only 1.3x ULN. The following day he experienced mild right upper quadrant pain that was considered related to study drug; the pain resolved five days later. His transaminase and bilirubin levels returned to baseline levels shortly after study drug discontinuation. The subject began alternate treatment for HIV infection with etravirine and TVD on Study Day 178. Figure 5 illustrates the time course of transaminase, total bilirubin and alkaline phosphatase levels in this subject during treatment and after study drug discontinuation (y-axis = integer x ULN for each analyte); for Week 24, the total bilirubin is the mean of values reported for Study Days 169 and 171. Although the time course of laboratory test abnormalities in this subject appears to meet the criteria for Hy's Law, his abnormal transaminase levels at baseline, the lack of a confirmed increase in total bilirubin, and underlying chronic hepatitis B infection confound the assessment of DILI.

⁴ <http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf>.

Figure 5: Time Course of Selected Liver-Related Laboratory Tests in Subject 0581-8230 (Study GS-US-216-0114)



Y-axis = laboratory value as integer x ULN for each analyte.

Note: Week 24 total bilirubin value represents the mean values from two consecutive study visits within the visit window.

Abbreviations: ALP = alkaline phosphatase, ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = total bilirubin

Source: ADLB dataset for Integrated Summary of Safety (ISS)

Table 28 summarizes the treatment-emergent liver-related laboratory abnormalities observed in the pooled double-blind analysis of COBI Phase 2 and 3 clinical trials. The analysis set was limited to subjects with at least one post-baseline laboratory value for each test. Subjects were counted only once for their maximum post-baseline toxicity grade. Overall, the incidence of graded AST or ALT abnormalities was greater in the ATV/co group than in the ATV/r group. Most of these abnormalities were Grade 1 or 2, but a small between-group difference was still observed for Grade 3-4 abnormalities (ATV/co 3% vs. ATV/r 2%). Similarly, although the overall rates of graded hyperbilirubinemia were similar between the groups, the incidence of Grade 3-4 abnormalities was higher in the ATV/co group (ATV/co 65% vs. ATV/r 56%).

Table 28: Treatment-Emergent Liver-Related Laboratory Abnormalities in Phase 2 and 3 Trials Double-Blind Treatment Period (Pooled Analysis GS-US-216-0105 and -0114)

Maximum Post-Baseline Toxicity Grade	Number of Subjects (%)	
	ATV/co (N=393)	ATV/r (N=375)
Alanine Aminotransferase (U/L)		
<i>Any Grade</i>	72 (18)	47 (13)
Grade 1 (1.25 to 2.5x ULN)	36 (9)	30 (8)
Grade 2 (>2.5 to 5.0x ULN)	25 (6)	10 (3)
Grade 3 (>5.0 to 10.0x ULN)	6 (2)	5 (1)
Grade 4 (>10.0x ULN)	5 (1)	2 (1)
Aspartate Aminotransferase (U/L)		
<i>Any Grade</i>	83 (21)	53 (14)
Grade 1 (1.25 to 2.5x ULN)	57 (15)	29 (8)
Grade 2 (>2.5 to 5.0x ULN)	16 (4)	16 (4)
Grade 3 (>5.0 to 10.0x ULN)	6 (2)	4 (1)
Grade 4 (>10.0x ULN)	4 (1)	4 (1)
Gamma Glutamyl Transferase (U/L)		
<i>Any Grade</i>	51 (13)	43 (12)
Grade 1 (1.25 to 2.5x ULN)	32 (8)	25 (7)
Grade 2 (>2.5 to 5.0x ULN)	11 (3)	14 (4)
Grade 3 (>5.0 to 10.0x ULN)	5 (1)	3 (1)
Grade 4 (>10.0x ULN)	3 (1)	1 (<1)
Total Bilirubin (mg/dL)		
<i>Any Grade</i>	379 (96)	362 (97)
Grade 1 (>1 to 1.5x ULN)	22 (6)	34 (9)
Grade 2 (>1.5 to 2.5x ULN)	102 (26)	117 (31)
Grade 3 (>2.5 to 5.0x ULN)	193 (49)	169 (45)
Grade 4 (>5.0x ULN)	62 (16)	42 (11)
Alkaline Phosphatase (U/L)		
<i>Any Grade</i>	30 (8)	36 (10)
Grade 1 (1.25 to 2.5x ULN)	29 (7)	34 (9)
Grade 2 (>2.5 to 5.0x ULN)	0	2 (1)
Grade 3 (>5.0 to 10.0x ULN)	1 (<1)	0

Source: ADLB dataset for Integrated Summary of Safety (ISS)

A total of four subjects had confirmed total bilirubin >10x ULN (ATV/co 1 [$<1\%$], ATV/r 3 [1%]); all were reported in Study GS-US-216-0114. The study protocol for Study -0114 specified that such subjects discontinue study drug. Of the four subjects with total bilirubin >10x ULN, only the three subjects in the ATV/r group discontinued study drug (Subjects 1221-8353, 2675-8456, and 3975-8597). Subject 1003-8582 in the ATV/co group had recurrent and confirmed total bilirubin >10x ULN during treatment, but

remained on study drug through Week 48. Another subject in the ATV/r group (Subject 1236-8372) developed total bilirubin of 14.6 mg/dL on Study Day 14 with jaundice and ocular icterus and had study drug discontinued that day for the latter AEs; his total bilirubin, however, was down to 6.3 mg/dL the following day.

Lastly, no cases of hepatic failure (acute or otherwise) were reported in the clinical trials with STRIBILD. There was one case of liver injury in a subject treated with STRIBILD in Phase 3; this subject, however, had a history of hepatitis C and abnormal laboratory values at baseline. The subject discontinued study drug on Study Day 35 due to an AE of moderate 'liver injury' that was serious in nature and judged related to study drug by the investigator. The subject did not meet Hy's Law criteria. No other cases of liver injury AEs were reported in the Safety Update to the STRIBILD trials.

7.3.5.5 Gastrointestinal Adverse Events

Nearly half (47%) of all subjects in the COBI Phase 2 and 3 clinical trials had gastrointestinal AEs, with similar percentages of subjects reported in both treatment groups (ATV/co 184 [47%], ATV/r 180 [48%]). In both groups, about two-thirds of the gastrointestinal events occurred within the first three months of treatment. Median time to onset was 24 days (Q1- Q3: 4-130) in the ATV/co group and 28 days (Q1- Q3: 3-177) in the ATV/r group. Table 29 summarizes the more common gastrointestinal AEs (occurring in $\geq 2\%$ of subjects in either treatment group) in the pooled safety analysis. With the exception of diarrhea, which was reported more frequently in the ATV/r group, there was no notable difference between the two treatment groups in the incidence of gastrointestinal AEs by individual MedDRA Preferred Terms.

Table 29: Treatment-Emergent Gastrointestinal Adverse Events (Any Causality, All Grades) in $\geq 2\%$ of Subjects in Either Treatment Group in Phase 2 and 3 Trials Double-Blind Treatment Period (Pooled Analysis GS-US-216-0105 and -0114)

MedDRA Preferred Term	Number of Subjects (%)		RD	P-value
	ATV/co (N=394)	ATV/r (N=377)		
<i>Any Gastrointestinal Adverse Event</i>	184 (47)	180 (48)	-1.04	0.773
Nausea	66 (17)	59 (16)	1.1	0.697
Diarrhea	59 (15)	80 (21)	-6.25	0.025
Vomiting	27 (7)	17 (5)	2.34	0.166
Flatulence	25 (6)	15 (4)	2.37	0.147
Abdominal pain	18 (5)	18 (5)	-0.21	1
Abdominal pain upper	13 (3)	16 (4)	-0.94	0.572
Hemorrhoids	13 (3)	11 (3)	0.38	0.87
Abdominal distension	11 (3)	11 (3)	-0.13	1
Constipation	11 (3)	9 (2)	0.4	0.822
Dyspepsia	9 (2)	14 (4)	-1.43	0.292
Toothache	9 (2)	8 (2)	0.16	1

Gastritis	6 (2)	4 (1)	0.46	0.753
Rectal hemorrhage	6 (2)	2 (1)	0.99	0.287

Abbreviations: RD = Risk Difference (per hundred)

P-values unadjusted, output generated by MAED service for exploratory analyses only

Source: ADAE dataset for Integrated Summary of Safety (ISS)

Eight subjects had gastrointestinal AEs that were serious, with the ATV/co group having a greater number of these subjects (ATV/co 6 [2%], ATV/r 2 [1%]), but none of these SAEs were deemed related to study drug by the investigators and only three subjects had study drug interrupted (not withdrawn) for these SAEs (ATV/co 2, ATV/r 1).

In general, the ATV/co group also had a greater proportion of subjects who interrupted or discontinued study drug due to a gastrointestinal AE, but the numbers were small in each group and the difference between the two groups was not sizable (ATV/co 6 [2%], ATV/r 3 [1%]). Nonetheless, the gastrointestinal AEs leading to study drug interruption or discontinuation differed between the two treatment groups. For instance, in the ATV/co group, three subjects interrupted or discontinued study drug due to 'abdominal pain', two for 'vomiting', and one for 'diarrhea', whereas no subjects in the ATV/r interrupted or discontinued study drug for these particular AEs. The gastrointestinal AEs leading to study drug interruption or discontinuation in the ATV/r group consisted of 'constipation', 'nausea', and 'peritonitis' (one subject each). Median time for study drug interruption or discontinuation due to a gastrointestinal AE was also shorter for the ATV/co group (9 days) compared with the ATV/r group (29 days). Overall, however, only four subjects (two per treatment group) permanently discontinued study drug because of a gastrointestinal AE; both subjects in the ATV/co group discontinued due to 'vomiting' (Study Day 4 and 168), whereas the two subjects in the ATV/r group did so for 'nausea' (Study Day 25) and 'constipation' (Study Day 70).

The vast majority of gastrointestinal AEs were mild or moderate in severity; Grade 3 AEs were reported in only 13 subjects (ATV/co 9 [2%], ATV/r 4 [1%]), most of which were not considered related to study drug. Severe (Grade 3) gastrointestinal AEs that were considered drug-related consisted of 'nausea' and 'diarrhea' and were reported in only two subjects in each treatment group. No Grade 4 gastrointestinal events were reported.

About 43% of the gastrointestinal AEs were considered related to study drugs by the investigators. Study drug-related gastrointestinal AEs, of all grades, were reported in 27% of subjects in each treatment group. The most common drug-related gastrointestinal AEs (occurring in $\geq 2\%$ of subjects overall) were nausea, diarrhea, flatulence, abdominal pain, abdominal distension and vomiting. With the exception of diarrhea (greater in the ATV/r group) and flatulence (greater in the ATV/co group), the incidence rates for these AEs were similar in both groups.

7.3.5.6 Cardiovascular Adverse Events

In the pooled safety analysis, a total of 34 subjects reported 40 AEs in the 'Cardiac Disorders' and/or 'Vascular Disorders' MedDRA SOCs, all in Study GS-US-216-0114 (ATV/co 16 [4%], ATV/r 18 [5%]). Only four of these 40 events were considered related to study drug by the investigators: one case each of Grade 1 cervical lymphedema and Grade 1 right bundle branch block in two subjects in the ATV/co group and two cases of Grade 1 hypertension in two subjects in the ATV/r group. The vast majority of cardiovascular AEs were mild or moderate in severity (Grade 1 or 2); Grade 3-4 AEs were reported in only three subjects (ATV/co: Subject 3030-8654 with a Grade 3 SAE of heart palpitations; ATV/r: Subject 5217-8501 with a Grade 4 SAE of hypovolemic shock and Subject 8217-8505 with a Grade 3 AE of hypotension). None of the Grade > 2 AEs was considered study drug-related by the investigators.

Five subjects had AEs in the 'Cardiac Disorders' SOC (ATV/co 3 [1%], ATV/r 2 [1%]); given the small number, no cardiac AE was reported in more than one subject in either treatment group by MedDRA Preferred Term (Table 30). A total of 31 subjects had AEs in the 'Vascular Disorders' SOC, with comparable percentages in each treatment group (ATV/co 14 [4%], ATV/r 17 [5%]). Other than 'hypertension', no vascular AE was reported in > 1% of subjects by MedDRA Preferred Term in either treatment group.

Hypertension as a treatment-emergent AE (MedDRA Preferred Terms: 'essential hypertension', 'hypertension', 'hypertensive crisis') was reported in 19 subjects overall, with comparable percentages of subjects in both treatment groups (ATV/co 7 [2%], ATV/r 12 [3%]). The AEs of hypertension in the ATV/co group were predominantly Grade 1; there were no cases of hypertensive crisis in this group. Hypotension as an AE was reported in only one subject (in the ATV/r group), but occurred in the context of influenza and vomiting. None of the hypotensive episodes were considered related to study drug by the investigators.

Table 30 summarizes the cardiovascular AEs by MedDRA SOC and Preferred Term as reported in the pooled double-blind analysis. MedDRA Preferred Terms similar in nature were pooled together for the AEs of 'hypertension' and 'flushing'.

Table 30: Treatment-Emergent Cardiovascular Adverse Events (Any Causality, All Grades) in Phase 2 and 3 Trials Double-Blind Treatment Period (Pooled Analysis GS-US-216-0105 and -0114)

MedDRA Term	Number of Subjects (%)	
	ATV/co (N=394)	ATV/r (N=377)
SYSTEM ORGAN CLASS		
Preferred Term		
<i>Any Cardiovascular Adverse Event</i>	16 (4)	18 (5)
CARDIAC DISORDERS	3 (1)	2 (1)
Angina pectoris	1 (<1)	0
Arrhythmia	0	1 (<1)
Bundle branch block right	1 (<1)	0

Palpitations	0	1 (<1)
Tachycardia	1 (<1)	0
VASCULAR DISORDERS	14 (4)	17 (5)
Hypertension ^a	7 (2)	11 (3)
Hypertensive crisis	0	2 (1)
Flushing ^b	1 (<1)	3 (1)
Hypotension	1 (<1)	0
Hypovolemic shock	0	1 (<1)
Orthostatic hypotension	1 (<1)	0
Lymphoedema	1 (<1)	0
Thrombosis	1 (<1)	0
Venous thrombosis	1 (<1)	0
Venous stenosis	1 (<1)	0

a) MedDRA Preferred Terms for hypertension include 'hypertension' and 'essential hypertension'.

b) MedDRA Preferred Terms for flushing include 'flushing' and 'hot flush'.

7.3.5.6 Rash Adverse Events

Treatment-emergent rash events were selected for comparison between the ATV/co and ATV/r groups in the pooled analysis. Using the Sponsor's definition for important rash events, as augmented by this reviewer (see Section 7.1.2 – Categorization of Adverse Events), a total of 206 rash events, of any causality and severity, were identified among 156 subjects, with a comparable percentage of subjects in each treatment group (ATV/co 77 [20%], ATV/r 79 [21%]). The most frequently reported rash AEs by MedDRA Preferred Term in the ATV/co group were 'rash', 'pruritus', and 'rash generalised'. As shown in Table 31, there were no notable differences between the groups in the frequencies or types of rash events by MedDRA Preferred Term.

Table 31: Selected Treatment-Emergent Rash Adverse Events (Any Causality, All Grades) in Phase 2 and 3 Trials Double-Blind Treatment Period (Pooled Analysis GS-US-216-0105 and -0114)

MedDRA Preferred Term	Number of Subjects (%)	
	ATV/co (N=394)	ATV/r (N=377)
<i>Any Selected Rash Adverse Event</i>	77 (20)	79 (21)
Rash	24 (6)	23 (6)
Pruritus	14 (4)	18 (5)
Rash generalised	9 (2)	5 (1)
Dermatitis	5 (1)	7 (2)
Rash papular	2 (1)	9 (2)
Eczema	3 (1)	6 (2)
Rash maculo-papular	3 (1)	6 (2)
Seborrheic dermatitis	6 (2)	2 (1)
Rash macular	4 (1)	2 (1)
Dermatitis allergic	3 (1)	3 (1)
Pruritus generalised	3 (1)	3 (1)

Erythema	2 (1)	3 (1)
Rash pruritic	2 (1)	2 (1)
Urticaria	2 (1)	2 (1)
Rash morbilliform	2 (1)	0
Blister	0	2 (1)
Angioedema	1 (<1)	0
Drug hypersensitivity ^a	1 (<1)	0
Eosinophilic pustular folliculitis	1 (<1)	0
Generalised erythema	1 (<1)	0
Prurigo	1 (<1)	0
Rash erythematous	1 (<1)	0
Rash follicular	0	1 (<1)
Skin exfoliation	0	1 (<1)

a) For the adverse event of 'drug hypersensitivity', the drug specified was "study drug" (Subject 1541-8255; Study GS-US-216-0114).

Source: ADAE dataset for Integrated Summary of Safety (ISS)

Of the 206 rash events, only four were considered serious in nature; all four occurred in Study GS-US-216-0114 and three of the four were reported in the ATV/co group (but none was considered related to study drug). No subject permanently discontinued study drug for a serious rash event. There were no cases consistent with Stevens-Johnson syndrome or erythema multiforme (toxic epidermal necrolysis). Narratives for the four serious rash events are as follows:

- Subject 0661-8042** (ATV/co): 26-year-old Hispanic male developed Grade 2 AE of 'rash' ("vasculitis-like rash on hands and feet") on Study Day 71, in conjunction with flu-like symptoms and cough for which he had been taking brompheniramine/dextromethorphan/guaifenesin, azithromycin, and diphenhydramine. The subject had also recently started taking health supplements including proteins and vitamins. Study drug was interrupted on Study Day 72.. Skin biopsy on Study Day 74 revealed "focal vacuolar interface changes and occasional necrotic keratinocytes", leading to a diagnosis of interface dermatitis. Drug eruption could not be ruled out. Methylprednisolone, fexofenadine, and clobetasol were initiated that same date. Azithromycin and diphenhydramine were stopped on Study Day 75. The event was not considered related to study drug by the investigator, but possibly related to brompheniramine/dextromethorphan/guaifenesin or azithromycin. The event resolved by Study Day 88. Study drugs were restarted sequentially over the next four days and rash did not recur. Given the results of the re-challenge, this reviewer concurs with the investigator's assessment of causality.
- Subject 3614-8420** (ATV/co): 25-year-old white male, randomized to ATV/co, developed Grade 2 AE of rash papular ("erythematopapular rash of both legs") on Study Day 161 with no systemic complaints or symptoms. He had recently been treated with intravenous acyclovir for herpes zoster on his left shoulder. On

Study Day 162, he was hospitalized and restarted on intravenous acyclovir for the lower extremities rash. Findings from a cutaneous biopsy were consistent with a cutaneous infection and ruled out a hypersensitivity reaction. After reevaluation, acyclovir was discontinued on Study Day 163. The following day, the subject was discharged with oral clindamycin as well as topical antibiotics and prednisolone cream. The event was not considered related to study drug by the investigator and did not result in study drug interruption. The event was considered resolved by Study Day 187. Given the resolution of the rash with ongoing study drug treatment and the results of the skin biopsy, this reviewer concurs with the investigator's assessment.

- **Subject 4140-8516** (ATV/co): a 52 year-old Hispanic male developed Grade 2 'angioedema' on Study Day 364. That day, the subject presented to the emergency department intoxicated, complaining of "allergies" as well as a "swollen throat and itchy tongue", possibly secondary to sunflower seeds he had eaten. The subject was noted to have mild drooling, stridor, dysarthria, and edema of the base of the tongue and epiglottis. He was brought to the operating room for possible intubation, but since he was more awake and responsive, the plan to intubate was abandoned. The subject was hospitalized to monitor his airway. No other details were provided. The event was not considered related to study drug by the investigator and was considered resolved by the next day. Study drug was continued without interruption throughout the event. Given the sequence of events and alternative possible etiologies, this reviewer concurs with the investigator's assessment.
- **Subject 4169-8476** (ATV/r): a 32-year-old Asian female developed a Grade 2 AE of 'rash', associated with fever, on Study Day 10 that resulted in hospitalization and study drug interruption for two days. The event was considered related to study drug by the investigator. The rash AE resolved with medication treatment. The subject subsequently reported a nonserious (Grade 1) rash on Study Day 13 that continued despite study drug interruption and resolved later while subject was still receiving study drug. This subject eventually discontinued study medications on Study Day 225 for SAE of renal impairment (see Table 16). Causality in this case is confounded by the recurring/remitting nature of the rash; however, given the early onset of the rash, the reviewer is inclined to agree with the investigator's assessment.

The majority of rash AEs in the pooled analysis were mild and not considered related to the study drugs by the investigators. However, the proportion of subjects with Grade 2-3 rash AEs was numerically greater in the ATV/co group (30/77 [39%]) compared with the ATV/r group (23/79 [29%]), as was the proportion of subjects with Grade \geq 2 drug-related rash events (ATV/co 20/77 [26%], ATV/r 15/79 [19%]). No Grade 4 rash events were reported. The median time to rash AE in the pooled analysis was slightly shorter in the ATV/co group: 13 days (Q1- Q3: 9-128 days) versus 20 days (Q1-Q3: 10-209 days)

in the ATV/r group. Overall, more than half of the rash events (53%) occurred within 30 days of randomization, with a similar percentage of subjects in each treatment group experiencing early-onset rash; no obvious differences were noted between the groups with respect to the types and frequencies of early rash events.

In the pooled safety analysis of the STRIBILD Phase 3 clinical trials, a significantly lower percentage of subjects receiving STRIBILD had rash events compared with the ATRIPLA group (21% vs. 31%, respectively; P -value < 0.001). There was no statistical difference in the incidence of rash events between the STRIBILD and ATV/r + TVD groups (21% vs. 23%, respectively; P -value = 0.64).

In Study GS-US-236-0118, the open-label trial in HIV-infected subjects with mild to moderate renal impairment, four subjects (two in each cohort) had rash events while taking STRIBILD or COBI. All rash AEs were Grade 1 and none was considered study drug-related by the investigators; however, there is no comparator group in this trial.

In summary, based on the pooled analysis of COBI Phase 2 and 3 trials, and supportive data from the STRIBILD trials, there does not appear to be an increased risk of rash events with a COBI-containing regimen compared with ATV/r.

7.4 Supportive Safety Results

This section provides an overall summary of common AEs and laboratory findings in the COBI development program, with focus on the pooled safety analysis set of Studies GS-US-216-0105 and GS-US-216-0114. Data are provided for general laboratory abnormalities and for laboratory assessments related to hematology, pancreatic enzymes, and lipid parameters. Please refer to Sections 7.3.5.1 for discussion of renal laboratory abnormalities, Section 7.3.5.2 for creatinine kinase abnormalities, and Section 7.3.5.4 for liver-related laboratory abnormalities.

Thyroid and immunoglobulin assessments are also summarized as nonclinical studies have shown that COBI affects thyroid in rats (secondary to species-specific microsomal hepatic enzyme induction and thyroid hormone imbalance) and decreases T-cell dependent immunoglobulin G (IgG) antibody response in female rats.

7.4.1 Common Adverse Events

Table 32 provides a broad overview of treatment-emergent AEs observed in the pooled double-blind safety analysis of COBI Phase 2 and 3 trials. As shown in the table, the overall frequency of AEs was comparable between the two treatment groups (92%). The incidence rates for Grade 3-4 AEs, SAEs, and Grade 2-4 drug-related AEs (or adverse drug reactions [ADR]) were slightly higher in the ATV/co group; however, a similar percentage of subjects in each treatment group discontinued study drug due to an AE.

Table 32: Summary of Treatment-Emergent Adverse Events in Phase 2 and 3 Trials Double-Blind Treatment Period (Pooled Analysis GS-US-216-0105 and -0114)

Treatment-Emergent Adverse Events	Number of Subjects (%)	
	ATV/co (N=394)	ATV/r (N=377)
Any AE	361 (92)	347 (92)
Any AE Grade 2-4	236 (60)	213 (57)
Any AE Grade 3-4	70 (18)	50 (13)
Any study drug-related AE	224 (57)	216 (57)
Any study drug-related AE Grade 2-4	98 (25)	79 (21)
Any study drug-related AE Grade 3-4	27 (7)	17 (5)
Any SAE	38 (10)	25 (7)
Any study drug-related SAE	5 (1)	6 (2)
Any AE leading to study drug discontinuation	27 (7)	27 (7)
Death	0	0

Abbreviations: AE = adverse event; SAE = serious adverse event

Source: ADAE dataset for Integrated Summary of Safety (ISS)

Table 33 summarizes the most common AEs reported in the pooled safety analysis (occurring in $\geq 4\%$ in the ATV/co group). With the exception of 'diarrhea' and 'nasopharyngitis', where the ATV/r group had a greater percentage of subjects with these events, there were no significant between-group differences in the frequencies or types of AEs by MedDRA Preferred Term.

Table 33: Treatment-Emergent Adverse Events (Any Grade, Any Causality) in Phase 2 and 3 Trials Double-Blind Treatment Period (Pooled Analysis GS-US-216-0105 and -0114)

MedDRA Preferred Term	Number of Subjects (%)	
	ATV/co (N=394)	ATV/r (N=377)
<i>Any Adverse Event</i>	361 (92)	347 (92)
Jaundice	74 (19)	55 (15)
Ocular icterus	68 (17)	68 (18)
Nausea	66 (17)	59 (16)
Diarrhea	59 (15)	80 (21)
Hyperbilirubinemia	43 (11)	34 (9)
Headache	41 (10)	54 (14)
Upper respiratory tract infection	40 (10)	30 (8)
Nasopharyngitis	37 (9)	56 (15)
Fatigue	30 (8)	29 (8)
Dizziness	27 (7)	22 (6)

Vomiting	27 (7)	17 (5)
Cough	26 (7)	23 (6)
Flatulence	25 (6)	15 (4)
Rash	24 (6)	23 (6)
Sinusitis	23 (6)	18 (5)
Pyrexia	21 (5)	25 (7)
Depression	21 (5)	20 (5)
Bronchitis	20 (5)	20 (5)
Insomnia	19 (5)	17 (5)
Abdominal pain	18 (5)	18 (5)
Back pain	17 (4)	26 (7)
Lymphadenopathy	14 (4)	20 (5)
Urinary tract infection	14 (4)	20 (5)
Pruritus	14 (4)	18 (5)

Source: ADAE dataset for Integrated Summary of Safety (ISS)

7.4.2 Laboratory Findings

In the pooled safety analysis, most subjects had at least one treatment-emergent laboratory abnormality. Unless otherwise noted, the discussions below describe laboratory analyte assessments (i.e., not AE reports).

Table 34 summarizes the overall incidence of treatment-emergent laboratory abnormalities by maximum toxicity grade, and specifically the incidence of hematologic and pancreatic laboratory abnormalities. For each laboratory abnormality, individual subjects are counted once and the maximum severity grade for each subject is reported. In general, the overall incidence of laboratory abnormalities was similar between the two treatment groups; however, the incidence of Grade 3-4 laboratory abnormalities was higher in the ATV/co group (75%) compared with the ATV/r group (64%). For hematologic and pancreatic laboratory tests, there were no notable between-group differences. The incidence of Grade 3-4 amylase and lipase abnormalities was numerically greater in the ATV/co group, but the total number of subjects with these abnormalities was small in each case.

Table 34: Treatment-Emergent Hematologic and Pancreatic Laboratory Abnormalities in Phase 2 and 3 Trials Double-Blind Treatment Period (Pooled Analysis GS-US-216-0105 and -0114)

Maximum Post-Baseline Toxicity Grade	Number of Subjects (%)	
	ATV/co (N=393)	ATV/r (N=375)
Any Laboratory Abnormality		
<i>Any Grade</i>	386 (98)	371 (99)
Grade 1	9 (2)	20 (5)
Grade 2	82 (21)	112 (30)
Grade 3	212 (54)	175 (47)
Grade 4	83 (21)	64 (17)

White Blood Cells (x10 ³ /μL)		
<i>Any Grade</i>	14 (4)	16 (4)
Grade 1 (2000 to 2500/mm ³)	12 (3)	14 (4)
Grade 2 (1500 to <2000/mm ³)	1 (<1)	2 (1)
Grade 3 (1000 to <1500/mm ³)	1 (<1)	0
Neutrophils (x10 ³ /μL)		
<i>Any Grade</i>	51 (13)	45 (12)
Grade 1 (1000 to 1300/mm ³)	27 (7)	27 (7)
Grade 2 (750 to <1000/mm ³)	18 (5)	14 (4)
Grade 3 (500 to <750/mm ³)	4 (1)	3 (1)
Grade 4 (<500/mm ³)	2 (1)	1 (<1)
Hemoglobin (g/dL)		
<i>Any Grade</i>	11 (3)	8 (2)
Grade 1 (8.5 to 10.0 g/dL)	7 (2)	7 (2)
Grade 2 (7.5 to <8.5 g/dL)	1 (<1)	1 (<1)
Grade 3 (6.5 to <7.5 g/dL)	2 (1)	0
Grade 4 (<6.5 g/dL)	1 (<1)	0
Platelets (x10 ³ /μL)		
<i>Any Grade</i>	11 (3)	9 (2)
Grade 1 (100,000 to <125,000/mm ³)	8 (2)	7 (2)
Grade 2 (50,000 to <100,000/mm ³)	1 (<1)	2 (1)
Grade 3 (25,000 to <50,000/mm ³)	1 (<1)	0
Grade 4 (<25,000/mm ³)	1 (<1)	0
Amylase (U/L)		
<i>Any Grade</i>	76 (19)	77 (21)
Grade 1 (>1.0 to 1.5x ULN)	42 (11)	55 (15)
Grade 2 (>1.5 to 3.0x ULN)	20 (5)	14 (4)
Grade 3 (>3.0 to 5.0x ULN)	11 (3)	6 (2)
Grade 4 (>5.0x ULN)	3 (1)	2 (1)
Lipase (U/L) ^a		
<i>Any Grade</i>	10 (23)	4 (12)
Grade 1 (>1.0 to 1.5x ULN)	2 (5)	1 (3)
Grade 2 (>1.5 to 3.0x ULN)	4 (9)	1 (3)
Grade 3 (>3.0 to 5.0x ULN)	3 (7)	2 (6)
Grade 4 (>5.0x ULN)	1 (2)	0

a) Subjects with serum amylase > 1.5 x upper limit of normal also had serum lipase test performed.
Source: ADLB dataset for Integrated Summary of Safety (ISS)

Lipid Assessments

In the COBI Phase 2 and 3 trials, subjects had fasting lipids measured at baseline and every 24 weeks. In the pooled analysis, a total of 59 subjects were taking lipid modifying agents at baseline (start date on or before Study Day 1), with comparable percentages in each treatment group (ATV/co 28 [7%], ATV/r 31 [8%]). Lipid modifying agents (e.g. medication class code C10) included HMG-CoA reductase inhibitors (pravastatin, atorvastatin, rosuvastatin, and simvastatin), fish oils, omega-3 fatty acids, nicotinic acid, fenofibrate and lecithin. Among these 59 subjects, only two subjects, both in the COBI treatment group, experienced Grade > 2 hyperlipidemia during treatment despite therapy with a lipid lowering agent (i.e., an HMG-CoA reductase inhibitor in each case):

- **Subject 0031-5584** (Study -0105): switched from simvastatin to pravastatin on Study Day 1, but developed Grade 3 hypertriglyceremia as early as Study Day 7 and had progressive hypercholesterolemia recorded during the course of treatment with ATV/co, with maximum fasting total cholesterol of 303 mg/dL (Grade 3) noted on Study Day 161.
- **Subject 0031-8161** (Study -0114): had been on rosuvastatin for more than three years prior to starting treatment with ATV/co and remained on rosuvastatin during study drug treatment; this subject had Grade 3 hypercholesterolemia reported at the Week 48 study visit (fasting total cholesterol 361 mg/dL).

Among subjects not taking lipid modifying agents at baseline, and who had both baseline and follow-up lipid laboratory tests (N=672), the percentage of subjects who developed Grade > 2 lipid laboratory toxicities during study drug treatment was small (1%) and comparable between treatment groups (Table 35). No cases of Grade 4 lipid laboratory toxicities were reported during the double-blind treatment period.

Table 35: Treatment-Emergent Fasting Lipid Test Abnormalities in Phase 2 and 3 Trials Double-Blind Treatment Period (Pooled Analysis GS-US-216-0105 and -0114)^a

Maximum Post-Baseline Toxicity Grade	Number of Subjects (%)	
	ATV/co (N=343)	ATV/r (N=329)
Any Fasting Lipid Laboratory Test		
<i>Any Grade</i>	65 (19)	73 (22)
Grade 1	42 (12)	42 (13)
Grade 2	19 (6)	27 (8)
Grade 3	4 (1)	4 (1)
Fasting Total Cholesterol (mg/dL)		
<i>Any Grade</i>	59 (17)	64 (19)
Grade 1 (200 to 239 mg/dL)	42 (12)	42 (13)
Grade 2 (<239 to 300 mg/dL)	15 (4)	21 (6)
Grade 3 (>300 mg/dL)	2 (1)	1 (<1)
Fasting Triglycerides (mg/dL)		
<i>Any Grade</i>	6 (2)	9 (3)

Grade 1 (N/A)	0	0
Grade 2 (500 to 750 mg/dL)	4 (1)	6 (2)
Grade 3 (>750 to 1200 mg/dL)	2 (1)	3 (1)

a) Analysis excludes subjects taking lipid modifying agents at baseline

Abbreviations: N/A = Not Available

Source: ADLB dataset for Integrated Summary of Safety (ISS)

Among subjects not taking lipid modifying agents at baseline, and who had both baseline and Week 48 laboratory results, the mean changes from baseline to Week 48 in fasting total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides are shown in Table 36. In brief, the mean changes in lipid parameters from baseline were not substantially different between the two treatment groups throughout study treatment or at Week 48.

Table 36: Mean Changes in Fasting Lipid Parameters (mg/dL) from Baseline to Week 48 in Phase 2 and 3 Trials Double-Blind Treatment Period (Pooled Analysis GS-US-216-0105 and -0114)^a

Fasting Lipid Parameter	Study Visit	ATV/co			ATV/r		
		N	Mean Value	SD	N	Mean Value	SD
Total Cholesterol (mg/dL)	Baseline	305	164.5	35.9	294	165.2	35.9
	Week 48		169.4	37.0		173.8	39.1
<i>Mean Change</i>			+ 4.8	27.2		+ 8.6	30.5
HDL Cholesterol (mg/dL)	Baseline	304	44.3	12.5	294	43.3	12.8
	Week 48		47.4	13.1		46.9	12.1
<i>Mean Change</i>			+ 3.1	10.2		+ 3.7	10
LDL Cholesterol (mg/dL)	Baseline	306	102.6	31	295	102.9	31.1
	Week 48		108.2	33.1		110.3	33.5
<i>Mean Change</i>			+ 5.6	24.2		+ 7.3	26.9
Triglycerides (mg/dL)	Baseline	305	121.2	67.3	294	129.6	95.7
	Week 48		142.6	86.1		157.6	104.4
<i>Mean Change</i>			+ 21.1	71.8		+ 28.0	98.5

a) Analysis excludes subjects taking lipid modifying agents at baseline and only includes subjects with both baseline and Week 48 laboratory values.

Abbreviations: SD = standard deviation

Source: ADLB dataset for Integrated Summary of Safety (ISS), CM datasets for Studies GS-US-26-0105 and -0114

The Applicant conducted an ITT analysis of mean lipid changes from baseline that included all subjects regardless of lipid modifying agent status and reported no significant differences between the two treatment groups, with the exception of mean change from baseline at Week 48 for fasting triglycerides (ATV/co +16 mg/dL [SD 96.9], ATV/r +30 mg/dL [SD 103.8]; *P*-value = 0.043). FDA reviewers conducted a sensitivity analysis that censored subjects on HMG-CoA reductase inhibitors and arrived at similar conclusions as the Applicant. The clinical significance of these intra-group differences, however, is not clear. Results of the FDA analysis will be reported in labeling.

Among the 712 subjects not taking lipid modifying agents at baseline, six subjects initiated therapy with an HMG-CoA reductase inhibitor during study drug treatment (ATV/co 2/366 [1%], ATV/r 4/346 [1%]). In addition, one subject in each treatment group (in Study -0114) had their lipid lowering medication switched during the course of treatment for unspecified reasons.

Thyroid Assessments

Thyroid function was assessed in Study GS-US-216-0105 because of nonclinical findings in rats with COBI, including microsomal hepatic enzyme induction and thyroid hormone imbalance, which the Applicant maintains are species-specific. In Study -0105, no clinically relevant changes from baseline in mean values for thyroid stimulating hormone (TSH), T3, or T4 were observed in either treatment group during the randomized or open-label phase with ATV/co. Similar results were noted in Study GS-US-236-0104, the Phase 2b trial with STRIBILD.

Immunoglobulin Assessments

Immunoglobulin assessments were also performed in Study GS-US-216-015 because nonclinical studies showed that COBI decreases T-cell dependent immunoglobulin G (IgG) antibody response in female rats only. In Study -0105, there were small decreases in median values for IgG and immunoglobulin M (IgM) in both groups during the randomized phase and in the open-label phase with ATV/co, but median values remained within the normal range throughout. Similar findings were noted in Study GS-US-236-0104 with STRIBILD.

7.4.3 Vital Signs

Vital signs other than height and weight were not collected in Study GS-US-216-0105 or GS-US-216-0114. Mean weight change from baseline was similar at Week 48 between the two treatment groups in the pooled analysis: +1.4 kg (SD 5) in the ATV/co group and +1.7 kg (SD 4.8) in the ATV/r group. Please see Section 7.3.5.6 (Cardiovascular Events) for adverse events related to blood pressure and heart rate. Any other vital sign changes considered clinically important were reported as AEs and discussed as such in the appropriate sections of this review.

7.4.4 Electrocardiograms (ECGs)

Because COBI demonstrated a potential to prolong the PR interval and decrease left ventricular function in isolated rabbit hearts, and a tendency to slightly prolong the PR interval in dogs, additional echocardiogram (ECHO) and electrocardiogram (ECG) data were collected in Phase 1 trials with COBI and in the Phase 2 and 3 trials of COBI and STRIBILD.

Phase 1 Trials

- **Study GS-US-216-0107** was a Phase 1, partially-blinded, randomized, placebo- and positive-controlled trial to evaluate the effects of COBI on the QT/QTc interval in healthy volunteers. Results from this trial were reviewed by the FDA Interdisciplinary Review Team-QT Consult group who concluded that no significant QTc prolongation effect of COBI (250 mg and 400 mg) was detected. The single suprathreshold dose (400 mg) produced mean C_{max} values of 2.7-fold higher than the mean C_{max} for the therapeutic dose (150 mg) at steady state. These concentrations are likely to be above those for the predicted worst case scenario (double dosing or drug interaction). At these concentrations there would be no prolongations of the QT-interval.

In the same trial, COBI prolonged the PR interval with a mean effect (placebo corrected) of 20.2 msec at the 400 mg dose and of 9.5 msec at the 250 mg dose at 3.5 hours post-dose. Five subjects in the 400 mg arm (N=48) and two in the 250 mg arm (N=48) had an asymptomatic absolute PR >200 msec post-baseline. This effect may be significant in the elderly, patients with sick sinus syndrome, conduction defects due to various causes, patients with atrial fibrillation with a slow ventricular response and concomitant medications that prolong the PR interval, e.g. verapamil, lopinavir, or atazanavir. That said, no subject had an absolute PR interval greater than 250 msec and no clinically significant AEs or changes in physical exams or vital signs were observed in Study -0107.

- **Study GS-216-0116** was a Phase 1 trial with a primarily PK-related objective comparing two formulations of COBI, but also included a substudy to explore the effect of COBI (150 mg) at steady state on left ventricular function using ECHO and ECG. This was a two cohort study; however, only Cohort 1, consisting of 34 evaluable subjects, participated in the two time-matched ECG and ECHO assessments of left ventricular function occurring at baseline and repeated one time in the Study Day 14-19 window. In summary, the two time-matched (baseline and on-treatment) ECGs showed that all subjects had normal absolute PR (< 210 msec) and QTcF (<450 msec) intervals at both time points. The time-matched ECHO assessments of left ventricular function (end systolic volume, end diastolic volume, and ejection fraction) were normal at both time points. Nonparametric comparisons of the mean change between baseline and post-dose measures for each of the three left ventricular function parameters revealed a non-clinically significant increase in left ventricular end-systolic volume (3.72 mL, P -value = 0.017).

Phase 2 and 3 Trials

In the Phase 2 Study GS-US-216-0105, there were no clinically relevant changes from baseline in median values for ECG parameters (PR, QRS, QT, or QTcF intervals, or heart rate) during the randomized phase or open label phase with ATV/co. One subject in the ATV/co group and two subjects in the ATV/r group had clinically significant ECG findings reported:

- **Subject 1966-5525** (ATV/co): probable anteroseptal myocardial infarction, age indeterminate, consider left atrial enlargement. This subject was a 47-year-old white male who had chest pain reported as an AE with onset the same day as the abnormal ECG findings (Study Day 337). The subject also had Grade 3 pericarditis of unknown cause reported as an SAE with onset on Day 648, with resolution on Study Day 679. No action was taken with study drug and the AEs were not considered related to study drug by the investigator.
- **Subject 0744-5504** (ATV/r): possible left ventricular hypertrophy/possible left atrial enlargement
- **Subject 2003-5512** (ATV/r): PR interval out of range.

In the Phase 3 Study GS-US-216-0114, there were no notable differences between treatment groups in the percentages of subjects with ECG abnormalities. For the majority of subjects, no ECG abnormalities were observed. Two subjects (1%) in each treatment group with normal ECGs at baseline developed clinically significant abnormal ECGs by Week 48:

- **Subject 0986-8250** (ATV/co): developed sinus bradycardia with sinus arrhythmia and extensive ST elevation suggestive of pericarditis on Study Day 44. Study drug was discontinued due to an SAE of rhabdomyolysis on Day 60. ECG normalized on Day 108.
- **Subject 0986-8272** (ATV/co): nonspecific ST changes; no concomitant AE was reported that was related to the ECG findings.
- **Subject 1480-8039** (ATV/r): sinus arrhythmia and first degree AV block. This subject had an AE of Grade 2 symptomatic cardiac arrhythmia reported at the time of the abnormal ECG finding that resolved on the same day.
- **Subject 3697-8684** (ATV/r): possible inferior infarct. This subject had an AE of Grade 2 hypertensive crisis at the time of the abnormal ECG finding.

Given the totality of the clinical data, labeling of ECG changes is not warranted; however, the results of the thorough QTc study will be reported.

7.4.5 Special Safety Studies/Clinical Trials

Cardiac Safety

Please see Section 7.4.4 for a discussion of Study GS-216-0116, the Phase 1 trial exploring the effect of COBI on left ventricular function using echocardiograms and ECGs.

Renal Safety

- **Study GS-US-216-0121** was a Phase 1 randomized, blinded, placebo-controlled trial evaluating the effect of COBI and RTV on renal function as assessed by markers of glomerular filtration. The PK/PD of COBI was evaluated in non-HIV-1 infected subjects with mild to moderate renal impairment (eGFR 50–79 mL/min), with an additional cohort of subjects with normal renal function (eGFR \geq 80 mL/min). In terms of safety, both COBI and RTV were found to be well tolerated in both renal function cohorts, and the overall safety profile of COBI was consistent with that observed in other trials. No deaths, SAEs, premature discontinuation of study drug, or AEs of interest (renal events or fractures) were reported in either treatment cohort. Please see Section 4.4.2 for discussion of the pharmacodynamic findings from this trial.
- **Study GS-US-216-0124** was a Phase 1, open-label, parallel-design, multiple dose trial designed to evaluate the PK of COBI-boosted EVG in non-HIV-1 infected subjects with severe renal impairment (eGFR < 30 mL/min), with a matching cohort of subjects with normal renal function (eGFR \geq 90 mL/min). No clinically relevant changes in COBI PK were observed in subjects with severe renal impairment compared with matched control subjects following once-daily administration of COBI + EVG. Study drug was well tolerated in this trial and the safety findings were consistent with those of other clinical trials, including those of non-renally impaired subjects in Studies -0105 and -0114, in which the eligibility criteria for eGFR were \geq 80 mL/min and \geq 70 mL/min, respectively. All AEs in this trial were Grade 1 and no subject in either renal function group prematurely discontinued study drug treatment because of an AE. Since clinically meaningful differences in the PK or clinical safety of COBI were not observed at the extremes of renal function, the Applicant proposes, and the review team agrees, that no dose adjustment of COBI is warranted in patients with renal impairment.

Reviewer's Comment:

The review team agrees that renal dosing of COBI is not needed; however, FDA recommends that labeling also point out that dosing recommendations for concomitant medications that rely on eGFR for renal dosing are not available for these drugs when coadministered with COBI. Because of COBI's effect on serum creatinine and eGFR, dosing of such medications in renally-impaired patients cannot be done with certainty.

- **Study GS-US-236-0118** is an ongoing Phase 3, multicohort trial designed to evaluate the safety of COBI-containing antiretroviral regimens in HIV-1 infected adults with mild to moderate renal impairment. Please see Section 7.3.5.1 for a discussion of the interim safety results from this trial as reported in the Safety Update to this NDA.

Hepatic Safety

As noted in Section 4.4.3, COBI is primarily metabolized and eliminated by the liver.

- **Study GS-US-183-0133** was a Phase 1 trial that assessed the PK of EVG and COBI in non-HIV-1 infected subjects with normal hepatic function and moderate hepatic impairment (Child-Pugh-Turcotte [CPT] Classification B). No clinically relevant differences in COBI PK were observed between subjects with moderate impairment and healthy subjects. Exploratory analyses conducted by the Applicant indicated no clinically relevant correlations between COBI exposures versus CPT scores or individual liver function laboratory parameters (i.e., albumin, total bilirubin, prothrombin time, and international normalized ratio [INR]) for subjects with moderate hepatic impairment. Based on a similar percentage free fraction (unbound concentration) for COBI between the normal matched control subjects and the moderate hepatic impairment subjects, there appears to be no effect of hepatic impairment on COBI protein binding. Based on these data, the review team agrees with the Applicant that no dosage adjustment of COBI is necessary for patients with mild to moderate hepatic impairment. Labeling will refer prescribers to the individual ATV and DRV labels for dosing recommendations of those drugs in patients with hepatic impairment. The effect of severe hepatic impairment (Child-Pugh-Turcotte Class C) on the PK of COBI has not been studied.

7.4.6 Immunogenicity

Cobicistat is a small molecule and not a peptide. As such, immunogenicity effects were not anticipated and therefore not specifically assessed for during the COBI clinical trials.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The Phase 2 and 3 clinical trials of COBI used the same 150 mg tablet formulation, therefore an assessment for true dose dependency for AEs using these datasets was not possible.

Limited clinical experience from Phase 1 trials of COBI at doses greater than the 150 mg once-daily therapeutic dose suggests a dose dependency for PR interval increases.

- **Study GS-US-216-0113** was a Phase 1 study to evaluate the PK, safety and tolerability of COBI in 24 healthy volunteers. Cobicistat tablets administered at two supratherapeutic doses (single dose of 400 mg [N=12] or 7 daily doses of 300 mg [N=12]) were generally well tolerated. A total of nine mild AEs unrelated to study drug occurred. Time-matched ECGs showed evidence of asymptomatic, dosing-related PR interval increases in nine subjects between 3 and 6 hours after dosing following both single- and multiple-dose administration of COBI 300 mg (three subjects) and single-dose administration of COBI 400 mg (six subjects). Absolute PR intervals remained within the normal range (120 to 210 msec) in all but two subjects, who each had a single asymptomatic Grade 1 PR interval increase. In all 24 subjects, QTcF intervals remained normal at all assessed time points.
- **Study GS-US-216-0119** (N = 48) was a Phase 1, partially randomized, open-label, multiple-dose, multicohort, crossover study designed to evaluate the PK and safety of twice-daily administration of COBI 150 mg alone and that of twice-daily administration of COBI-boosted DRV or tipranavir (TPV) versus twice-daily administration of RTV-boosted DRV or TPV. In brief, COBI total daily exposures (AUC) were approximately 4-fold higher following twice-daily administration alone relative to historical data for once-daily administration. Twice-daily administration of COBI 150 mg for 10 days was well tolerated. With twice-daily administration, the addition of COBI as a CYP3A inhibitor to DRV or TPV administration was not associated with increased adverse safety findings versus RTV-boosted DRV or TPV. No subject developed a graded abnormality in serum creatinine or a renal AE during any treatment. Tipranavir exposures, however, were markedly lower following twice-daily administration of TPV/co versus TPV/r.

7.5.2 Time Dependency for Adverse Events

Based on Kaplan-Meier (KM) estimates for time to premature study drug discontinuation, there was no significant difference between the ATV/co and ATV/r treatment groups in the percentage of subjects who discontinued study drug early (see Figure 1). The percentage of subjects who discontinued study drug early was the same for each treatment group at Week 2 (3%) and Week 4 (5%). The KM estimate for time to premature study drug discontinuation at Week 48 was 14% in the ATV/co group and 12% in the ATV/r group, but per the Applicant the difference was not statistically significant (overall *P*-value = 0.35).

Please refer to Section 7.3.5.1 (Renal Safety) for a detailed time dependency assessment of changes in renal parameters (e.g. serum creatinine and creatinine clearance).

7.5.3 Drug-Demographic Interactions

Sex

Based on population PK analyses, no relevant differences in the PK of COBI and thus its activity as a pharmacoenhancer are expected based on sex.

In the COBI Phase 2 and 3 clinical trials, only 16% of the pooled safety population was female and so firm conclusions regarding drug-demographic interactions in this subpopulation cannot be made. Table 37 provides a top-line summary of AEs and laboratory abnormalities reported in the pooled analysis by gender. The overall incidence of treatment-emergent AEs in the ATV/co group was similar between men and women (91% and 95%, respectively) and comparable with the rates observed in the ATV/r group (92% for both sexes). Numerically, women in the ATV/co group had a higher incidence of moderate to severe AEs, including study drug-related AEs, than men in the same treatment group, but the rates by gender were consistent with the rates observed in the ATV/r comparator group. In general, small differences in the types of AEs were observed between the sexes in both treatment groups, but these were consistent with those expected (e.g., women having higher incidences of anemia, reproductive system and breast disorders). For nearly all AEs, regardless of MedDRA hierarchy level, the difference between the sexes was <2% in both treatment groups. Moreover, no pattern indicative of a gender treatment effect was noted between the two treatment groups.

Table 37: Summary of Treatment-Emergent Adverse Events and Laboratory Abnormalities by Gender in Phase 2 and 3 Trials Double-Blind Treatment Period (Pooled Analysis GS-US-216-0105 and -0114)

Treatment-Emergent Adverse Events or Laboratory Abnormalities	Number of Subjects (%)			
	ATV/co		ATV/r	
	Men (N=334)	Women (N=60)	Men (N=312)	Women (N=65)
Any AE	304 (91)	57 (95)	287 (92)	60 (92)
Any AE Grade 2-4	197 (59)	39 (65)	167 (53)	46 (71)
Any AE Grade 3-4	59 (18)	11 (18)	40 (13)	10 (15)
Any study drug-related AE	186 (56)	38 (63)	175 (56)	41 (63)
Any study drug-related AE Grade 2-4	78 (23)	20 (33)	58 (19)	21 (32)
Any study drug-related AE Grade 3-4	23 (7)	4 (7)	14 (4)	3 (5)
Any SAE	33 (10)	5 (6)	20 (6)	5 (8)
Any study drug-related SAE	3 (1)	2 (3)	4 (1)	2 (3)
Any AE leading to study drug discontinuation	22 (7)	5 (6)	21 (7)	6 (9)
Any Laboratory Abnormality	327 (98)	59 (98)	308 (99)	63 (97)
Any Laboratory Abnormality Grade 3-4	255 (76)	40 (67)	200 (64)	39 (60)

Source: ADAE and ADLB datasets for Integrated Summary of Safety (ISS)

No drug-demographic interactions based on sex were noted in the STRIBILD Phase 3 clinical trials, although women made up only 10% of the subject population in those trials.

Race

Based on population PK analyses, no relevant differences in the PK of COBI and thus its activity as a pharmacoenhancer are expected based on race.

In the pooled COBI Phase 2 and 3 clinical trials, 58% of subjects in the ATV/co group were white, 21% were black or African American, 11% were Asian, 9% were “other”, and <1% were either American Indian or Alaska Native, native Hawaiian or Pacific Islander, or undetermined (due to collection of race information not being permitted by local authorities) (see Table 2). In the pooled analysis, similar percentages of white and nonwhite subjects in each treatment group reported any treatment-emergent AE (ATV/co: white 90%, nonwhite 95%; ATV/r: white 93%, nonwhite 91%). Overall, no differences indicative of a treatment effect between white and nonwhite subjects were apparent in the pattern of AEs reported. Similarly, no differences based on ethnicity (Hispanic or non-Hispanic) were noted in either treatment group in the pooled analysis. Similar findings were observed in the Phase 3 clinical trials of STRIBILD.

Age

The PK, safety, and effectiveness of COBI in children less than 18 years have not been established. The proposed labeling recommends that COBI not be administered to patients under the age of 18 years.

Pharmacokinetic studies have not been performed with COBI in the elderly (i.e., those 65 years of age or older). Insufficient numbers of elderly subjects have been evaluated in clinical studies of COBI to determine whether they respond differently than younger subjects. In the pooled Phase 2 and 3 trials of COBI, only three subjects were ≥ 65 years old at randomization, and all three were randomized to the ATV/r treatment group. The proposed labeling recommends caution with use of COBI in elderly patients, keeping in mind the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

In the pooled analysis of COBI Phase 2 and 3 trials, 60% of subjects in each treatment group were <40 years of age. The percentage of subjects with treatment-emergent AEs was similar in subjects <40 and ≥ 40 years of age within and across treatment groups (ATV/co: <40 years 93%, ≥ 40 years 89%; ATV/r: < 40 years 93%, ≥ 40 years 90%). Within the ATV/co group, the percentage of subjects < 40 and ≥ 40 years of age with SAEs was the same (10%), including SAEs considered related to study drug (1%). Also, no significant difference was noted in the percentage of subjects reporting AEs leading

to study drug discontinuation (ATV/co: < 40 years 8%, ≥ 40 years 5%; ATV/r: < 40 years 7%, ≥ 40 years 7%). However, among subjects who discontinued study drug due to renal AEs (see Table 16), two-thirds in the ATV/co group and three-fourths in the ATV/r group were ≥ 40 years of age. Indeed, the incidence of renal AEs of interest (see Table 14) in the ATV/co group was higher among subjects ≥ 40 years (14/154 [9%]) than among subjects < 40 years (13/240 [5%]), but this age difference was also seen in the comparator treatment group (ATV/r: ≥ 40 years 18/151 [12%]), <40 years 18/226 [8%]). Otherwise, no differences indicative of a treatment effect were apparent between age groups in the overall pattern of AEs reported.

7.5.4 Drug-Disease Interactions

Baseline HIV Disease Characteristics

In the pooled safety analysis, similar percentages of subjects with baseline HIV-1 RNA ≤ 100,000 copies/mL or > 100,000 copies/mL in each treatment group reported any AE (ATV/co: ≤ 100,000 copies/mL 91%, > 100,000 copies/mL 93%; ATV/r: ≤ 100,000 copies/mL 93%, > 100,000 copies/mL 90%). Overall, no differences indicative of a treatment effect between HIV-1 RNA subgroups were apparent in the pattern of AEs reported. Within the ATV/co group, a higher percentage of subjects with HIV-1 RNA ≤ 100,000 copies/mL had AEs in the MedDRA SOC 'Psychiatric Disorders' compared to subjects with HIV-1 RNA > 100,000 copies/mL (6/250 [2.4%] vs. 0/194 [0.0%], respectively), but the majority of these AEs were deemed unrelated to study drug by the investigators. Moreover, by lower MedDRA hierarchy levels (e.g. HLGT, HLT, or PT) there were no AEs with a difference > 2% between subgroups defined by HIV-1 RNA.

With respect to baseline CD4 cell count, similar percentages of subjects with baseline CD4 cell count ≤ 350 cells/μL or > 350 cells/μL in each group reported any treatment-emergent AE (ATV/co: ≤ 350 cells/μL 93%, > 350 cells/μL 90%; ATV/r: ≤ 350 cells/μL 93%, > 350 cells/μL 91%). Within the ATV/co group, subjects with CD4 cell count > 350 cell/ μL tended to have higher incidence of diarrhea, jaundice (including ocular icterus), nausea, fatigue, and dizziness than subjects with CD4 cell count ≤ 350 cells/μL. With the exception of jaundice, these subgroup differences were the opposite of what was observed in the corresponding ATV/r subgroups. Nonetheless, no discernible AE pattern indicative of a possible treatment effect between CD4 cell count subgroups was noted.

Hepatitis B and/or C Virus Co-Infection

In the pooled safety analysis, a small number of subjects were coinfecting with HBV (25 subjects [3%]) or HCV (37 subjects [5%]) based on baseline HBV surface antigen serology and HCV antibody testing (see Table 2). Because of differing eligibility criteria between the Phase 2 and 3 trials, all co-infected subjects were in Study -0114. Two subjects (one in each treatment group) were co-infected with both HBV and HCV.

Of the 60 subjects co-infected with HBV or HCV, 22 (37%) had hepatobiliary AEs, a finding that was comparable to the general HIV-1 study population (Table 27) and to the subgroup of subjects without co-infection (276/711 [38%]). However, a greater number of these co-infected subjects with hepatobiliary events were in the ATV/co group (ATV/co 14/36 [39%], ATV/r 8/24 [33%]). Within the ATV/co group, the hepatic AE profile in co-infected subjects was consistent with underlying viral hepatitis infection and, as would be expected in this population, the incidence of treatment-emergent AST and ALT elevations was higher among these subjects (58%) than in the general HIV-1 infected population without co-infection (24%).

Renal Impairment

Study GS-US-236-0118 is an ongoing Phase 3, multicohort trial designed to evaluate the safety of COBI-containing antiretroviral regimens in HIV-1 infected adults with mild to moderate renal impairment. Please see Section 7.3.5.1 for discussion of the interim safety results from this trial as reported in the Safety Update to this NDA.

Please see Section 7.3.5.1 (Renal Safety) for discussion of renal safety in a subgroup of subjects with baseline eGFR \leq 90mL/min and $<$ 70 mL/min in the pooled Phase 2 and 3 COBI trials.

7.5.5 Drug-Drug Interactions

Please refer to the Clinical Pharmacology Review by Dr. Stanley Au for detailed discussion of the drug-drug interaction studies.

Please refer to Sections 4.4.2 and 4.4.3 for discussion of the PD and PK properties of COBI.

Cobicistat is a potent mechanism-based inhibitor of cytochrome P450 3A and may increase plasma concentrations of agents that are primarily metabolized by CYP3A. Drugs that are extensively metabolized by CYP3A and have high first-pass metabolism are most susceptible to large increases in exposure when coadministered with COBI. As such, coadministration of COBI with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated; e.g., alfuzosin, dronedarone, irinotecan (with ATV/co only), ergot derivatives, cisapride, HMG-CoA reductase inhibitors (particularly lovastatin & simvastatin), phosphodiesterase-5 inhibitors (sildenafil for the treatment of pulmonary arterial hypertension), and sedative hypnotics (particularly orally administered midazolam and triazolam).

Coadministration of COBI with drugs that induce CYP3A may result in decreased plasma concentration of COBI and consequently that of the COBI-boosted product,

leading to loss of therapeutic effect and possible development of resistance. As such, the following agents are contraindicated or not recommended for coadministration with COBI: rifampin, rifabutin, rifapentine, St John's wort (*Hypericum perforatum*), systemic dexamethasone, carbamazepine, oxcarbazepine, phenobarbital, and phenytoin.

The potential for interactions with drugs not previously evaluated will need to be addressed by the Applicant. For example, drug interaction information was not provided for anti-addiction drugs methadone or buprenorphine/naloxone or the HCV direct-acting antiviral drugs boceprevir or telaprevir.

Final FDA labeling recommendations regarding drug-drug interactions between COBI and non-ARV drugs will be based on the results of drug interaction trials or the expected changes in the concentrations of COBI and/or the co-administered drug based on the metabolic properties of the individual drugs.

Coadministration with Hormonal Contraceptives

Coadministration of COBI-containing STRIBILD with hormonal contraceptives was evaluated in Study GS-US-236-0106 (N=21), a Phase 1, open-label, single-center, multiple-dose, fixed-sequence trial designed to evaluate the effect of STRIBILD on the PK of a representative hormonal contraceptive medication, Ortho Tri-Cyclen® Lo (norgestimate [NGM] 0.180 mg/0.215 mg/0.250 mg/ethinyl estradiol [EE] 0.025 mg), in healthy adult women of childbearing potential. Subjects who had not taken Ortho Tri-Cyclen Lo or a generic equivalent for one full menstrual cycle enrolled into Part A, a lead-in period consisting of dosing with Ortho Tri-Cyclen Lo for one full menstrual cycle. Otherwise, subjects enrolled directly into Part B, which consisted of two 28-day menstrual cycles. The treatment scheme in Part B was as follows:

- Part B Cycle 1: Ortho Tri-Cyclen Lo, administered orally once daily in the morning on Days 1 to 28
- Part B Cycle 2: Ortho Tri-Cyclen Lo, administered orally once daily in the morning on Days 29 to 56, plus STRIBILD tablet coadministered orally once daily in the morning on Days 40 to 49

In this trial, the mean C_{max} , C_{tau} , and AUC_{tau} of NGMN (pharmacologically active metabolite of NGM) increased by 108%, 167%, and 126%, respectively, after co-administration of NGM/EE with STRIBILD relative to NGM/EE administered alone. The mean C_{tau} and AUC_{tau} of EE decreased by 43% and 25% after co-administration of NGM/EE with STRIBILD as compared to NGM/EE administered alone. There was no significant change in the C_{max} of EE. Comparison of Day 0 to Day 21 changes in pharmacodynamics after administration of NGM/EE with STRIBILD versus NGM/EE alone revealed a similar decrease in serum follicle-stimulating hormone after both treatments and a greater reduction in serum luteinizing hormone after NGM/EE with STRIBILD than after NGM/EE alone. No changes in serum progesterone were

observed. Although the decreased exposure to EE is considered unlikely to lead to contraceptive failure, the potential risk of increased exposure to NGM is presently unclear. In this trial, taking NGM/EE as an oral contraceptive concurrent with COBI was shown to be safe and well tolerated. Results from this drug interaction trial, however, cannot be extrapolated to other oral contraceptives, and because no data are available regarding the use of ATV/co or DRV/co with oral hormonal contraceptives (i.e., NGM/EE), the Applicant recommends that alternative forms of contraceptive be considered.

In the pooled Phase 2 and 3 trials of COBI, 26 subjects (25 women and 1 transgender woman) were taking hormonal therapy, either for contraception or replacement therapy, in conjunction with study drugs (ATV/co 7, ATV/r 19). Review of their AE findings did not reveal any obvious drug interaction safety issues between COBI and hormonal therapy in these women, although the assessment is limited by the small sample size.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The overall incidence of neoplasm in the COBI Phase 2 and 3 clinical trials was similar between treatment groups (ATV/co 13 [3%], ATV/r 12 [3%]). Over half of the neoplasms were benign (predominantly skin neoplasms). One subject in each treatment group of Study GS-US-216-0114 reported lymphoma (Subject 5126-8346 with Burkitt's lymphoma on Study Day 3 in the ATV/co group and Subject 1021-8499 with Hodgkin's disease on Study Day 76 in the ATV/r group). In addition, one subject in the ATV/co group (Subject 0986-8216) had a nonserious thyroid nodule reported on Study Day 107. None of the neoplasms was considered related to study drug by the investigators and, with the exception of the two cases of lymphoma, none was assessed as serious. With the exception of the subject with Burkitt's lymphoma in the ATV/co group, none of the neoplasms required study drug discontinuation.

Please refer to Section 4.3 for information related to nonclinical studies assessing carcinogenesis and mutagenesis.

7.6.2 Human Reproduction and Pregnancy Data

Animal studies do not indicate direct or indirect harmful effects of COBI with respect to pregnancy, embryonal and fetal development, parturition, or postnatal development. Nonclinical reproductive toxicology studies of COBI are discussed in Section 4.3.

Pregnancy and breastfeeding were exclusion criteria for all clinical trials with COBI. In addition, pregnancy was a pre-defined stopping criterion for discontinuation of study drug. Therefore, no adequate and well-controlled evaluation of COBI in pregnant women has been conducted.

Five pregnancies were reported in Phase 1 studies with COBI, but only two involved women receiving COBI, including one pregnancy reported in a subject who received COBI in Study GS-US-201-0101, a first-in-human trial of GS-8374, an investigational PI no longer in development, and COBI. Details of these two pregnancies are as follows:

- In Study GS-US-216-0101, **Subject 2006** (COBI 100 mg) had a positive pregnancy test result on [REDACTED] (b) (6) from the study start). Cobicistat was discontinued, and the subject was discontinued from the trial for a protocol violation. A healthy baby was born [REDACTED] (b) (6) (40 weeks gestation) via Cesarean section with no delivery complications.
- In Study GS-US-201-0101, **Subject 4955-1025** had a confirmed pregnancy reported on [REDACTED] (b) (6) after the last dose of study drug). She had received one oral dose of GS-8374 600 mg + COBI 150 mg under fed conditions on Day 1, followed by an oral dose of study drugs once daily under fed conditions for 10 days. The outcome of the pregnancy was a live birth.

No pregnancies were reported in Study GS-US-216-0105 in either the double-blind treatment phase or in the open-label phase with ATV/co.

In Study GS-US-216-0114, six subjects (Subjects 1609-8162, 2728-8382, and 2822-8570 in the ATV/co group; and Subjects 0369-8360, 0986-8249, and 5217-8504 in the ATV/r group) had confirmed pregnancies during the trial and study drug was discontinued in four subjects. Brief narratives for the three COBI cases are as follows:

- **Subject 2728-8382** (ATV/co): 33-year-old woman experienced a spontaneous abortion on [REDACTED] (b) (6), the same day the pregnancy was confirmed. The spontaneous abortion was considered related to study drug by the investigator. The event was considered resolved on Day 350 and no action was taken with study drug.
- **Subject 2822-8570** (ATV/co): 19-year-old woman had pregnancy confirmed on Study [REDACTED] (b) (6) (contraceptive failure – subject had not used her Depo-Provera for 3 months); subject had an induced abortion on an unknown date shortly thereafter and remained on study drug.
- **Subject 1609-8162** (ATV/co): 35-year-old woman had pregnancy confirmed on Study [REDACTED] (b) (6) (contraceptive failure – condom and spermicide use). Study drugs were discontinued on Study Day 61 and subject had an elective abortion on Study [REDACTED] (b) (6).

Per the Safety Update Report, three additional pregnancies were reported in Study - 0114 since the original NDA (Subject 0687-8661 [abortion elective] in the ATV/co group; Subjects 0986-8273 [continuing] and 2822-8526 [abortion spontaneous] in the ATV/r group). The event of abortion spontaneous in the ATV/r group was in a 44-year-old

woman (Subject 2822-8526); the event was reported as serious but not related to study drug.

Cobicistat falls under Category B for use in pregnancy and the Applicant recommends that COBI should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

7.6.3 Pediatrics and Assessment of Effects on Growth

The safety, PK and effectiveness of COBI have not been established in pediatrics. The Applicant expects similar COBI exposures will provide similar boosting activity in pediatrics as in adults; however, the dose needed to achieve those exposures (PK) and adequate level of CYP3A inhibition (PD) are likely to be different and possibly higher (on a mg/kg basis) in children than adults and higher in younger versus older children.

The Applicant is planning to characterize the PK, safety, and activity of COBI in pediatric patients and is proposing an integrated development plan with EVG and STRIBILD. The anticipated indication for COBI in pediatrics, however, is as a CYP3A inhibitor of ATV and DRV. The Applicant plans to initially study COBI only with approved pediatric doses of ATV and DRV, which for DRV traditionally consists of twice-daily administration. Before that, however, development of age-appropriate pediatric COBI formulations (reduced-strength tablets and powder for oral suspension) are required for use in children <12 years of age.

If formulation development is successful, the relative bioavailability of the COBI age-appropriate formulations will be compared to the adult COBI tablet in a randomized, open-label, single-center, single-dose, crossover trial in 60 healthy adult volunteers (Study GS-US-216-0127).

Once bioavailability has been established, an open-label trial to evaluate the PK, safety, and antiviral activity of the COBI age-appropriate formulations (administered with ATV or DRV and a background regimen) will be evaluated in HIV-1 infected, treatment-experienced pediatric subjects 3 months to <18 years of age with viral suppression on a regimen including ATV/r or DRV/r (Study GS-US-216-0128); because the trial is being conducted in suppressed, treatment-experienced pediatric subjects, it would not be possible to enroll subjects younger than 3 months of age. The PK data from Study GS-US-216-0128 will serve as a bridge between the adolescent and younger children and adult data that demonstrate COBI pharmacoenhancement of ATV and DRV (in both healthy and HIV-1 infected adult subjects). Data from Study GS-US-216-0128 will support the registration of COBI, in combination with either ATV or DRV, for patients <18 years of age.

The Applicant does not plan to evaluate any additional PI/COBI combinations for use in pediatrics (or adults).

Table 38 summarizes the proposed trials in the COBI pediatric development plan.

Table 38: COBI Pediatric Development Plan Clinical Trials

Study ID	Study Design	Study Type	Age Ranges (years)	Estimated Evaluable Subjects	Status
GS-US-216-0127	A relative bioavailability study of age-appropriate formulations of COBI in healthy adults (for use in pediatric subjects < 18 years of age)	Pharmacokinetics and safety	18 to 45 years (inclusive)	60 (30 per cohort)	Planned
GS-US-216-0128 ^a	An open-label, multicenter, multi-cohort, 2-part study of once-daily ATV/co or twice-daily DRV/co administered with a background regimen in HIV-1 infected, antiretroviral treatment-experienced subjects 3 months to <18 years of age	Pharmacokinetics, safety, and antiviral activity	3 months to <18 years	100	Planned

^a Appropriateness of this study will be determined pending the development and assessment of the relative bioavailability of age-appropriate pediatric formulations.

Source: Proposed Pediatric Study Request for IND 101283

To support the planned coadministration of COBI with DRV twice-daily (BID) in pediatric subjects, the Applicant is relying on PK and short-term (10 days) safety data from 24 subjects in Study GS-US-216-0119 (see Section 7.5.1). That trial demonstrated adequate boosting with DRV plus COBI BID relative to DRV plus RTV BID in adults. COBI total daily exposures (AUC) were ~4-fold higher following twice-daily administration alone relative to historical data for once-daily administration. Relative to twice-daily administration of COBI alone, twice-daily administration of DRV/co resulted in ~50% lower COBI exposure (AUC), but well above exposures associated with its pharmacoenhancing effects based on DRV exposures in this study and historical data for COBI and its effects on CYP3A activity. Darunavir plasma exposures were bioequivalent following twice-daily administration of DRV/co versus DRV/r, and were in the range associated with robust and durable antiviral efficacy. Twice-daily COBI 150 mg for 10 days was well tolerated. With twice-daily administration, the addition of COBI to DRV was not associated with increased adverse safety findings versus RTV-boosted DRV. Mean [SD] increases from baseline in serum creatinine after 9 days of dosing were small but numerically larger in subjects receiving DRV/co versus DRV/r (0.3 [0.09] mg/dL versus 0.1 [0.11] mg/dL, respectively), resulting in decreases in mean estimated

creatinine clearance. No subject, however, developed a graded abnormality in serum creatinine and no renal AEs were reported.

Reviewer's Comment:

It is unlikely that the limited safety data from the small bioequivalence Study -0119 will suffice to support pediatric development of twice-daily DRV/co. A full development program for twice-daily COBI would be required to support such a pediatric indication. At the pre-NDA meeting, the Applicant was informed of the option of directly evaluating once-daily DRV/co for a pediatric indication, but in this submission the Applicant has indicated their plans to initially study COBI only with the currently approved doses of DRV in pediatric patients. However, since the submission of the original COBI NDA, once-daily dosing of DRV has been approved in treatment-naïve pediatric patients 3 to <12 years of age and in treatment-experienced patients 3 to <18 years of age with no DRV resistance-associated substitutions.

Darunavir tablets, coadministered with low-dose RTV, are currently approved in the United States for children 3 to <18 years of age; a full pediatric waiver has been granted for pediatric patients < 3 years of age due to potential toxicity issues. ATV capsules, coadministered with low-dose RTV, are currently approved in the United States for children \geq 6 years of age. The Pediatric Written Request for ATV includes a waiver for pediatric patients < 3 months of age due to risk of kernicterus and a deferral of pediatric studies for patients 3 months to 6 years of age to determine safe and appropriate dosing. The final report for pediatric studies of ATV capsules in subjects 3 months to 18 years of age is still pending, but the Applicant anticipates that the requested ATV pediatric study will be concluded prior to the initiation of the proposed COBI pediatric study (Study GS-US-216-0128), which will include two cohorts with ATV/co in patients < 6 years of age.

Reviewer's Comment:

Submission of a pediatric NDA supplement for ATV capsules is anticipated by Q3 2013.

As part of this NDA, the Applicant is requesting a partial waiver to conduct pediatric studies with COBI in pediatric subjects birth to < 3 months of age as enrollment of these subjects into studies evaluating COBI as a CYP3A inhibitor of ATV and DRV will be impractical based on the current labeling and pediatric waivers granted for ATV and DRV.

In addition, the Applicant is requesting a deferral of pediatric studies required under Section 2 of the Pediatric Research Equity Act (PREA) for subjects 3 months to <18 years of age, since COBI tablets are ready for approval for use in adults before pediatric studies are complete. Further, the bioavailability results for COBI age-appropriate tablets and liquid formulation from Study GS-US-216-0127 are necessary for initiation of Study GS-US-216-0128 in subjects 3 months to <18 years.

The review team for this NDA will meet with the FDA Pediatric Review Committee (PeRC) on April 3, 2013 to review the proposed pediatric plan and draft a Written Request for pediatric studies. The outcome of the meeting will be reported in the CDTL memorandum to this NDA.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

In the pooled analysis of COBI Phase 2 and 3 trials, four subjects reported one overdose each during the trial (ATV/co 3 [1%], ATV/r 1 [$<1\%$]). All four overdoses were reported in Study GS-US-216-0114. For the three overdoses for which onset dates were available, only the subject in the ATV/r group had an associated AE (ocular icterus in Subject 1000-8671). Otherwise, there was no clear association with clinical symptoms or sequelae per the Applicant.

In the STRIBILD Phase 3 trials, a total of 18 subjects in the STRIBILD group reported an overdose. Per the Applicant, most of these overdoses were not associated with clinical symptoms or sequelae.

Limited clinical experience is also available from the two trials that assessed supratherapeutic doses of COBI (Studies GS-US-216-0107 and -0113). In these trials, a single dose of cobicistat 400 mg was administered to a total of 60 healthy subjects. In addition, 12 subjects were administered COBI 150 mg twice-daily for 7 days in Study -0113 (see Section 7.5.1). No severe adverse reactions were reported in either of these trials.

If an overdose with COBI occurs, the Applicant recommends monitoring for evidence of toxicity and initiating general supportive measures. As COBI is highly bound to plasma proteins, it is unlikely to be significantly removed by hemodialysis or peritoneal dialysis.

No data are available regarding the potential for abuse of COBI. However, no safety issues concerning the abuse or misuse of COBI tablets are anticipated from the available data.

No specific studies have been conducted to evaluate the effects of subjects being withdrawn from treatment with COBI.

8 Postmarket Experience

No prior application for marketing approval or registration has been made for COBI tablets. No postmarketing data are available with COBI tablets as a stand-alone product.

The first postmarketing Periodic Adverse Drug Experience Report (PADER) for STRIBILD tablets was submitted to NDA 203100 on December 12, 2012, covering the reporting period of August 27, 2012 through November 26, 2012. A total of 15 adverse experience reports, describing 22 events, were included in the PADER. No new safety issues for STRIBILD were apparent from the data presented in the PADER that affected the overall benefit-risk of the product. No regulatory actions concerning safety were taken anywhere in the world where the product is marketed.

The Applicant's Company Core Data Sheet for STRIBILD tablets was updated to include the following adverse drug reactions based on pooled Week 96 data from Studies GS-US-236-0102 and -0103 and Week 96 data from Study GS-US-183-0145:

- suicidal ideation and suicide attempt in patients with a pre-existing history of depression or psychiatric illness with a frequency of "uncommon"
- the frequency of depression and insomnia was updated from "common" to "very common" and the frequency of renal failure and blood creatinine increased was updated to from "uncommon" to "common" based on an update from Week 48 to Week 96 data
- a statement was added that no additional proximal renal tubular dysfunction cases were reported from Week 48 to Week 96

9 Appendices

9.1 Literature Review/References

1. Josephson F. Drug-drug interactions in the treatment of HIV infection: focus on pharmacokinetic enhancement through CYP3A inhibition. *J Intern Med* 2010; 268:530-9.
2. Hamada, Y, Nishijima T, Watanabe K, et al. High incidence of renal stones among HIV-infected patients on ritonavir-boosted atazanavir than in those receiving other protease inhibitor-containing antiretroviral therapy. *Clin Infect Dis* 2012; 55:1262-9.

9.2 Labeling Recommendations

Final labeling is being negotiated with the Applicant at the time of this writing. The following important revisions to the proposed labeling were made by the review team:

Applicant's Proposed Language	FDA Recommended Revision
1 INDICATIONS AND USAGE	
<div style="background-color: #cccccc; height: 70px; width: 100%;"></div>	<p>(b) (4) [TRADENAME] is indicated in adults as a CYP3A inhibitor of atazanavir and darunavir (once daily dosing regimen) [See Dosage and Administration (2)];</p> <p>This indication is based on Week 48 clinical trial data [See Clinical Studies (14)] and supported by pharmacokinetic data.</p> <p>The following points should be considered when initiating therapy with [TRADENAME]:</p> <ul style="list-style-type: none"> • [TRADENAME] is not recommended for use with darunavir 600 mg twice daily, or with other HIV-1 protease inhibitors, including fosamprenavir, lopinavir/ritonavir, ritonavir, saquinavir or tipranavir [See Warnings and Precautions (5.3)]. • Use caution when administering [TRADENAME] with other concomitant medications because the drug interaction profile of [TRADENAME] may differ from ritonavir [See Warnings and Precautions

	(5.2), Drug Interactions (7), and Clinical Pharmacology (12.3)]. <ul style="list-style-type: none">• There are no comparative pharmacokinetic or clinical data evaluating elvitegravir and cobicistat as single entities relative to STRIBILD.
--	--

Rationale: This section was extensively revised to emphasize the correct use of COBI as a CYP3A inhibitor of ATV and DRV once daily and provide the basis for the indication. The review team also considered it important to make prominent the information that COBI is not to be used with PI s other than ATV or DRV and that caution is warranted when COBI is used with concomitant medications given the potential for drug-drug interactions that cannot always be predicted by RTV.

2 DOSAGE AND ADMINISTRATION

(b) (4)	[TRADENAME] must only be administered with atazanavir or darunavir (once daily dosing regimen), and in combination with other antiretroviral agents. [TRADENAME] must be administered with food. The recommended dose of [TRADENAME] and atazanavir or darunavir are presented in Table 1. Also consult the prescribing information for atazanavir or darunavir. 2.2 Renal Impairment No dosage adjustment of [TRADENAME] is required in patients with renal impairment, including those with severe renal impairment [See Clinical Pharmacology (12.3)]. [TRADENAME] has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function. Consider this effect when [TRADENAME] is coadministered with a drug that has dosing adjustment recommendations guided by estimated creatinine clearance [See Warnings and Precautions (5.1), Adverse Reactions (6.1), and Clinical Pharmacology (12.2)].
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Rationale:

. The renal impairment section was made more prominent by creating its own subsection

Lastly, Table 1

(not shown) was expanded to include the treatment populations for each PI/co combination:

- ATV/co: treatment-naive and -experienced
- DRV/co: treatment-naive and -experienced with no DRV resistance associated substitutions

4 CONTRAINDICATIONS

The Applicant's proposal for this section included a list of contraindicated drugs

FDA recommends a table (not shown) of contraindicated drugs, by drug class and with clinical comment for each.

5 WARNINGS AND PRECAUTIONS

(b) (4)

5.1 New Onset or Worsening Renal Impairment

*Use with Tenofovir Disoproxil Fumarate
 Use with Other Renally Eliminated Drugs*

5.1 Use with Concomitant Medications

5.3 Use with Antiretrovirals

Coadministration with Darunavir and Other Protease Inhibitors

Rationale: This section was extensively revised.

(b) (4)

(b) (4)

6 ADVERSE REACTIONS

(b) (4)

FDA recommends including pooled safety data from the Phase 2 and 3 trials (Studies -0105 and -0114) in this section, lowering the cut-off criterion for the ADR and laboratory abnormality tables to 2%, and revising the lipid table to include pooled data but also to exclude subjects on HMG-CoA reductase inhibitors (mITT analysis). Also, a statement regarding the unknown clinical significance of these lipid changes was included since the differences between the two treatment groups were mostly not significant.

7 DRUG INTERACTIONS

This reviewer defers to the Clinical Pharmacology reviewer to describe the revisions made to this section. A key revision, however, was to shift the emphasis in the drug-drug interaction table away from the effect of concomitant medications on COBI concentrations and instead focus on the effect of concomitant medications on the concentrations of COBI and the boosted

<i>PI (and vice versa).</i>	
14 CLINICAL STUDIES	
(b) (4)	HIV-1 RNA < 50 copies/mL HIV-1 RNA ≥ 50 copies/mL
<i>Rationale: In the table of virologic outcomes, (b) (4) FDA recommends revising the categories according to the primary endpoint as defined in the snapshot algorithm.</i>	

9.3 Advisory Committee Meeting

Although a dedicated Advisory Committee meeting for this NDA was not convened, safety issues related to COBI were discussed at an Advisory Committee meeting for NDA 203100 for STRIBILD tablets on May 11, 2012. Please refer to the transcript for full details of the committee discussion.

In brief, the committee recommended approval of STRIBILD but had concerns with limitations of the data regarding renal safety and recommended longer term follow-up and additional studies to address renal abnormalities and drug-drug interactions with use of STRIBILD.

With respect to renal safety as it pertains to COBI, the committee had the following recommendations:

- ❖ Education for prescribers on tubulopathy, specifically on the various tests that available (e.g., urine protein, urine glucose, serum creatinine, and calculated creatinine clearance) and how to analyze renal laboratory data in efforts to detect potential tubulopathy early. The possible use of less widely available tests to assess for tubulopathy (e.g., B2-microglobulin) was also discussed.
- ❖ Use of the Chronic Kidney Disease Epidemiology Collaboration formula (CKD-EPI) to measure kidney function. It was noted that this formula has the least bias in the normal range but is not well validated in HIV-infected patients. Alternative methods to estimate GFR (e.g. use of cystatin C) were also discussed.
- ❖ Heightened vigilance in patients with known risk factors for renal disease (i.e. diabetes, hypertension, family history).
- ❖ Additional laboratory monitoring to potentially improve renal safety. There was general agreement that urine dipstick testing would be inexpensive, simple to perform, and would not constitute a burden to practicing physicians. It was noted that other modalities, such as baseline protein quantification (via a 24-hour urine

collection) and monitoring of patients' urine protein-creatinine ratio might be helpful. There was no specific discussion related to the use of STRIBILD in patients with baseline glycosuria and proteinuria.

- ❖ Use of laboratory cutoffs to help distinguish the effect of COBI on serum creatinine and creatinine clearance from genuine renal dysfunction. There was general agreement with the Applicant and the Agency's suggestion of using a confirmed serum creatinine increase of greater than or equal to 0.4 mg/dL from baseline. One of the renal experts on the committee also suggested use of percent increase in serum creatinine as an adjunctive measure.

Additionally, the committee recommended postmarketing studies to address the following:

- STRIBILD use in women
- Longer-term safety monitoring focusing on renal and bone parameters
- Alternate methods and optimal markers for early detection of tubulopathy and appropriate timing of monitoring
- Pharmacodynamic/pharmacokinetic interactions between CYP3A inhibitors (i.e., COBI) and tenofovir
- Drug-drug interactions (e.g., antiretrovirals for "salvage therapy", hepatitis C protease inhibitors, oral contraceptives, methadone)
- Drug resistance, including but not limited to the development of resistance to HIV protease inhibitors associated with the use of COBI.

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

/s/

PETER S MIELE
03/22/2013

KIMBERLY A STRUBLE
03/22/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 203094 Applicant: Gilead Sciences Stamp Date: June 28, 2012
Drug Name: cobicistat NDA/BLA Type: 505 (b) (1)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	✓			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	✓			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	✓			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	✓			
5.	Are all documents submitted in English or are English translations provided when necessary?	✓			
6.	Is the clinical section legible so that substantive review can begin?	✓			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	✓			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	✓			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	✓			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	✓			
11.	Has the applicant submitted a benefit-risk analysis for the product?	✓			COBI should not be initiated as part of a regimen containing FTC, 3TC, TDF, or ADV in patients who have an estimated CrCl < 70 mL/min because dose adjustment of these drugs is required below 50 mL/min, and such dose adjustments have not been established in combination with COBI.
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to	✓			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	✓			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		✓		Although the applicant has not submitted a rationale, the submitted trials are international and over 50% of the submitted clinical efficacy and safety data are from U.S. subjects.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	✓			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	✓			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	✓			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	✓			N= 394 at 48 weeks with ATV/COBI. Supportive safety data from the Stribild (EVG/COBI/FTC/TDF) development program, which includes one Phase 2 trial and two large Phase 3 trials, will also be used (N=749 for COBI 150 mg QD exposure, pooled analysis).
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?				
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	✓			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	✓			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	✓			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	✓			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?				
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	✓			<p>Deferral to conduct pediatric studies with COBI is being requested - reason: studies conducted in adults are completed and the drug is ready for approval for use in adults.</p> <p>Partial waiver to conduct pediatric studies with COBI in pediatric subjects birth < 3 months of age is being request – reason: studies are impossible and highly impracticable.</p>
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	✓			
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		✓		Although the applicant has not submitted a rationale, the submitted trials are international and over 50% of the submitted clinical efficacy and safety data are from U.S. subjects.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	✓			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	✓			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	✓			
34.	Are all datasets to support the critical safety analyses available and complete?	✓			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	✓			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	✓			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	✓			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	✓			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	✓			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____YES__

If the Application is not fileable from the clinical 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.

None at this time.

Peter S. Miele, M.D.

August 15, 2012

Reviewing Medical Officer

Date

Kimberly A. Struble, Pharm. D.

August 15, 2012

Clinical Team Leader

Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

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

/s/

PETER S MIELE
08/15/2012

KIMBERLY A STRUBLE
08/15/2012