CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	203-100
Priority or Standard	Standard
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Division / Office	Division of Anti-Viral Products/ Office of Antimicrobial Products
Reviewer Name(s)	Adam Sherwat
Review Completion Date	July 2, 2012
Established Name	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate
(Proposed) Trade Name	Stribild
Therapeutic Class	Integrase inhibitor, Pharmacokinetic enhancer, Nucleoside reverse transcriptase inhibitor, Nucleotide reverse transcriptase inhibitor
Applicant	Gilead
Formulation(s)	Fixed-dose combination regimen containing elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate
Dosing Regimen	One tablet taken once daily with food
Indication(s)	Treatment of HIV-1 Infection
Intended Population(s)	HIV-1 infected treatment naïve adults

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends approval of the Elvitegravir/ Cobicistat/ Emtricitabine /Tenofovir Disoproxil Fumarate (E/C/F/T) fixed-dose combination (FDC) for use in HIV-1 infected treatment naïve adults. This recommendation is based on the data contained in the NDA submission 203-100. In the two pivotal Phase 3 trials, GS-US-236-0102 and GS-US-236-0103, E/C/F/T was demonstrated to be non-inferior to Atripla® (efavirenz/emtricitabine/tenofovir disoproxil fumarate [ATR]) and to ritonavir-boosted atazanavir (ATV/r) + Truvada® (emtricitabine/tenofovir disoproxil fumarate [TVD]) respectively in suppressing HIV RNA. The demonstrated safety profile of E/C/F/T is acceptable and no deficiencies preclude approval.

1.2 Risk Benefit Assessment

Benefits

Single tablet, once-daily regimens offer patient convenience and the potential for increased compliance and less patient-related dosing errors. The two single tablet regimens that are currently approved for once-daily administration in the treatment of HIV-1 infection and are considered preferred or alternative regimens respectively in treatment naïve patients[14] are ATR and Complera™ (emtricitabine/rilpivirine/tenofovir disoproxil fumarate). The E/C/F/T formulation would be the first single tablet regimen without a non-nucleotide reverse transcriptase inhibitor (NNRTI) component, and therefore could be used in patients who are either intolerant to NNRTIs, have a relative contraindication to NNRTI use, or have virologic resistance that precludes their use. In addition, the E/C/F/T formulation is pregnancy class B while ATR (due to the efavirenz [EFV] component) is pregnancy class D, allowing for potential use of E/C/F/T in women of childbearing potential. It is also notable that the E/C/F/T formulation does not contain ritonavir and could therefore be used in patients who are intolerant to ritonavir containing regimens.

In the two pivotal Phase 3 trials, as well as a supportive Phase 2 trial (GS-US-236-0104), E/C/F/T was shown to be non-inferior to the comparator groups with respect to efficacy. Both comparator groups (ATR and ATV/r + TVD) used in these trials are considered preferred regimens for use in HIV-1 treatment naïve patients per 2012 Department of Health and Human Services Guidelines[14]. Immunologic benefit, as gauged by improvement in CD4+ cell count from baseline, was demonstrated by the E/C/F/T group and was similar to that noted in the comparator groups. Rates of virologic

failure were low in the E/C/F/T group and similar to rates demonstrated in the comparator groups.

The safety profile of E/C/F/T was acceptable. In the pivotal Phase 3 studies, there was a lesser incidence of premature study drug discontinuation due to adverse events (AEs) in the E/C/F/T group compared to either control group. The incidence of any treatment-emergent AEs, moderate to severe AEs, and serious adverse events (SAEs) judged related to study drug by the investigator was similar between groups. No safety signals related to skin and soft tissue or hepatobiliary AEs (including Hy's Law cases) were identified in the E/C/F/T group.

Risks

The following safety-related issues were identified in the review of the pooled data from the pivotal Phase 3 studies:

Musculoskeletal AEs were more common in the E/C/F/T group (21.3%) than in either of the comparator groups (ATR 15.6%, ATV/r + TVD 15.5%). 'Back pain' and a constellation of AEs related to muscle pain, stiffness and spasms all were reported at a higher rate in the E/C/F/T group than in either of the control arms. However, the vast majority of musculoskeletal AEs were of mild or moderate severity (i.e. grade 1 or 2) and rarely lead to study drug discontinuation.

With respect to sleep disorders and disturbances, E/C/F/T fared favorably when compared to ATR (which was not unexpected given the known side-effect profile of ATR), but unfavorably when compared to ATV/r + TVD. However, virtually all of the AEs related to sleep disorders and disturbances in the E/C/F/T group were of mild or moderate severity and none led to the discontinuation of E/C/F/T.

A constellation of renal AEs (e.g. renal failure, Fanconi's syndrome, and increased blood creatinine) led to subject discontinuation more frequently in the E/C/F/T group than in either of the comparator groups (all of which included tenofovir [TDF]). Of particular concern were four cases consistent with proximal tubulopathy. All of these cases led to study drug discontinuation, and all occurred in the E/C/F/T group. This frequency of proximal tubulopathy leading to study drug discontinuation was greater in the E/C/F/T group than would generally be expected with the use of TDF, based on results of previous clinical trials[1-3,6,7,9,10,13].

Also of note, a higher overall frequency of graded creatinine elevations and graded proteinuria was reported in the E/C/F/T group compared to either of the control arms. The Applicant maintains that a modest elevation in creatinine levels and decrease in estimated creatinine clearance and estimated GFR (eGFR) are to be expected with the

E/C/F/T formulation due to a cobicistat-related inhibition of tubular creatinine secretion, but that actual GFR (aGFR) is not affected. However, the disproportionate number of renal adverse events and discontinuations and the higher incidence of graded creatinine and urine protein laboratories raise the question as to whether two discrete processes may be at work, a non-pathologic increase in eGFR as the Applicant contends and a bona fide increased risk of renal adverse events of concern.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for Postmarket Risk Evaluation and Mitigation Strategies related to this NDA submission.

1.4 Recommendations for Postmarket Requirements and Commitments

Considerations at this time include the following:

- A randomized, controlled trial in women assessing safety and efficacy
- A study (or studies) evaluating renal safety, particularly assessing for an increase in proximal tubular dysfunction with study regimens including both COBI and TDF.
- Additional drug-drug interaction studies (e.g. oral contraceptives, telaprevir, (b) (4) methadone)
- Longer-term virology assessments including: 1) continued sequencing of the protease in order to assess for disproportionate numbers of amino acid substitutions in the E/C/F/T arm (b) (4)

2 Introduction and Regulatory Background

2.1 Product Information

Generic Name: Elvitegravir (EVG)/Cobicistat (COBI)/Emtricitabine (FTC)/Tenofovir Disoproxil Fumarate (TDF)

Trade Name: Stribild

Chemical Class: New fixed-dose combination antiviral product including two new molecular entities (EVG and COBI)

Pharmacological Class: EVG (integrase strand-transfer inhibitor or INSTI), COBI (pharmacoenhancer devoid of anti-HIV activity), FTC (nucleoside reverse transcriptase inhibitor or NRTI), and TDF (nucleotide reverse transcriptase inhibitor or NtRTI)

Proposed Indication: Treatment of HIV-1 infection in treatment naïve adults

Dosage: E/C/F/T (150/150/200/300 mg) tablet once daily

Age Group: Adults

E/C/F/T is a fixed-dose combination tablet. EVG is an INSTI that prevents integration of HIV-1 genetic material into the host-cell genome. COBI is a new chemical entity and structural analogue of ritonavir devoid of ARV activity. It is a mechanism-based cytochrome P450 3A (CYP3A) inhibitor that enhances or "boosts" the exposure of CYP3A substrates, including EVG. 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. EVG and COBI have been developed to be used within a new 4-drug fixed-dose combination tablet (the E/C/F/T FDC) that also contains the approved dual nucleoside/nucleotide reverse transcriptase inhibitor (NRTI/NtRTI) backbone FTC/TDF (Truvada® [TVD]).

2.2 Tables of Currently Available Treatments for Proposed Indications

There are currently 26 drugs approved for the treatment of HIV-1 infection (excluding fixed dose combinations or different formulations). Based on the mechanism of action on the life cycle of the human immunodeficiency virus, the drugs are classified into 6 HIV-1 drug classes: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion/entry inhibitors, CCR5 antagonists, and integrase inhibitors. Table 1 summarizes the approved anti-retroviral drugs.

Table 1: Approved Antiretroviral Drugs

Drug Class	Generic Name	Trade Name
NRTI	Zidovudine (AZT)	Retrovir®
	Didanosine (ddI)	Videx®/Videx EC®
	Stavudine (d4T)	Zerit®
	Lamivudine (3TC)	Epivir®
	Abacavir	Ziagen®
	Tenofovir (TDF)	Viread®
	Emtricitabine (FTC)	Emtriva®
NNRTI	Delavirdine	Rescriptor®

	Nevirapine	Viramune®
	Efavirenz (EFV)	Sustiva®
	Etravirine	Intelence®
	Rilpivirine	Edurant®
PI	Indinavir	Crixivan®
	Ritonavir	Norvir®
	Saquinavir, hard gel	Invirase®
	Saquinavir, soft gel	Fortavase®
	Nelfinavir	Viracept®
	Amprenavir	Agenerase®
	fos-amprenavir	Lexiva®
	Atazanavir (ATV)	Reyataz®
	Lopinavir/ritonavir (LPV/r)	Kaletra®
	Tipranavir (TPV)	Aptivus®
	Darunavir (DRV)	Prezista®
Fusion/Entry Inhibitor	Enfuvirtide (ENF)	Fuzeon®
CCR5 receptor antagonist	Maraviroc	Selzentry®
Integrase Inhibitor	Raltegravir	Isentress®

2.3 Availability of Proposed Active Ingredient in the United States

Neither COBI nor EVG are currently available either as single agents or as components of a combination product.

FTC was first approved for treatment of HIV-1 in the United States (US) on 02 July 2003 and is currently available for use.

TDF was first approved for treatment of HIV-1 in the US on 26 October 2001 and is currently available for use.

TVD was first approved for treatment of HIV-1 in the US on 02 August 2004 and is currently available for use.

2.4 Important Safety Issues With Consideration to Related Drugs

Initially approved in the US in 2007, Raltegravir (Isentress®) is the only integrase inhibitor currently available for use. The following is a summary of the known safety

issues related to this drug drawn from the licensing trials and from postmarket experience:

In the licensing trials, headache and insomnia occurred with a greater incidence in subjects receiving raltegravir than in the control subjects. There was also a greater incidence, in at least one of the licensing trials, of the following grade 2-4 laboratory abnormalities in the raltegravir group compared to the control group: thrombocytopenia, and an elevation of fasting serum glucose, amylase, lipase, creatine kinase, AST, ALT, alkaline phosphatase, and bilirubin.

Severe, potentially life-threatening, and fatal skin reactions have been reported. These include cases of Stevens-Johnson syndrome and toxic epidermal necrolysis. Hypersensitivity reactions have also been reported and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including hepatic failure.

The following adverse drug reactions (ADRs) occurred in <2% of treatment-naïve or treatment-experienced subjects receiving Isentress in a combination regimen. These events were included in the product insert because of their seriousness, increased incidence with Isentress as compared to efavirenz or placebo, or investigator's assessment of a potential causal relationship. The ADRs included the following: abdominal pain, gastritis, dyspepsia, vomiting, nausea, fatigue, asthenia, hepatitis, hypersensitivity, genital herpes, herpes zoster, dizziness, depression (particularly in subjects with a pre-existing history of psychiatric illness, including suicidal ideation and behaviors), nephrolithiasis, and renal failure.

The following ADRs were identified during post-approval use: thrombocytopenia, diarrhea, hepatic failure (with and without associated hypersensitivity) in patients with underlying liver disease and/or concomitant medications, rhabdomyolysis, cerebellar ataxia, anxiety, and paranoia.

Currently, no products pharmacologically related to COBI (i.e. CYP3A inhibitors devoid of ARV activity) have received FDA approval. However, ritonavir, a protease inhibitor, is commonly used at sub-therapeutic doses to boost other protease inhibitors. The mechanism of action (i.e. inhibition of CYP3A) and drug-drug interaction profile is similar to that of COBI in this regard.

Please see Section 8 (Post-Market Experience) for a discussion of FTC and TDF.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

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This section will summarize and focus only on those notable events which had a direct bearing on the current submission, i.e. those events directly related to the E/C/F/T formulation.

End of Phase 2 meeting (EOP2) for IND (b) (4): This meeting was scheduled for 6 February 2007, but was cancelled by the Applicant subsequent to receiving the Agency's written responses to their queries. There were no issues directly related to the E/C/F/T development program provided in the written comments.

End of Phase 2 meeting (EOP2) for IND (b) (4): This meeting occurred on 12 March 2010. The following issues relevant to the E/C/F/T development program were discussed with the Applicant:

- There was agreement that the Phase 3 clinical studies of COBI as part of the E/C/F/T formulation may proceed.
- There was agreement that the proposed development plan would support the registration of COBI as a pharmacoenhancer of EVG tablets.
- There was agreement with the possible plan for staggered filing of the COBI tablet NDA relative to the NDAs for EVG tablets and E/C/F/T tablet
- There was a discussion related to the plan 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
- Given the observed increase in serum creatinine with COBI, and the observed renal toxicities with tenofovir, the Agency inquired how the Applicant plans to monitor for early signs of renal toxicity during the course of the trial. The Applicant responded that estimated creatinine clearance will be assessed on a regular basis.
- The Agency requested an assessment of COBI's safety in the setting of renal impairment and the Applicant agreed to conduct a dedicated renal impairment study.
- With respect to the thorough QT study of COBI, the Agency requested a table comparing the C_{max} of COBI observed in all the pharmacokinetic and clinical studies conducted to date with the C_{max} observed at the supratherapeutic dose in the QT study. This was requested to determine whether the C_{max} adequately encompassed the maximum concentrations COBI that may be observed clinically.
- The Agency queried the Applicant on COBI's effect on PR prolongation and bilirubin levels. The Applicant responded that they have not seen an effect on

PR prolongation in Phase 2 studies of COBI, nor have they noted an increase in bilirubin, liver enzymes, or PR prolongation with the E/C/F/T tablet in the Phase 2 trials.
- There was agreement with the Applicant's proposed plan for submission of study analysis datasets, CRFs, and laboratory data for the E/C/F/T NDA submission.

Pre-NDA meeting for IND 103093 (E/C/F/T): This meeting occurred on 13 July 2011. Key issues addressed included the following:

- The Agency agreed to the Applicant's proposal to submit the NDA for the E/C/F/T tablet in December 2011, followed by the NDAs for EVG and COBI tablets in the March-April 2012 timeframe.
- The Agency requested that the Applicant streamline the proposed NDA for the E/C/F/T tablet to include only the trials considered essential for the efficacy and safety review of the fixed-dose combination product under consideration.
- The Agency was queried as to whether an Advisory Committee (AC) meeting was anticipated in regards to this submission and responded in the affirmative.

2.6 Other Relevant Background Information

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

A routine consultation to be performed by the Division of Scientific Investigation (DSI) was requested at the filing of the NDA. Please refer to Antoine El-Hage's review for further details. Four domestic sites were inspected. The data from these sites were deemed acceptable in support of Gilead's NDA application for the E/C/F/T formulation.

3.2 Compliance with Good Clinical Practices

The clinical trials were conducted in accordance with the ICH Good Clinical Practice guidelines. The trial protocols and amendments were reviewed and approved by Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs). Written informed consent was obtained from all subjects prior to any trial-related procedures. Inspections of selected clinical sites by DSI found the data provided by the sites to be acceptable (refer to section 3.1 for additional detail).

3.3 Financial Disclosures

Of the investigators or sub-investigators involved (b) (6) sixteen investigators or sub-investigators accepted payments greater than $25,000 and four investigators or sub-investigators had an equity interest of greater than $50,000 with Gilead Sciences, Inc. These investigators and sub-investigators were responsible for enrolling (b) (6) of the (b) (6) subjects enrolled in these studies. (b) (6) an investigator in the above mentioned category, enrolled (b) (6) of total subjects in studies (b) (6) combined. No other site was responsible for enrolling (b) (6) of subjects in the combined studies. Given the relatively small percentage of subjects enrolled by any individual site, and given the use of blinding and randomization in these clinical trials, it is unlikely that inclusion of these subjects will bias the study results.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

EVG is a white to yellowish white powder with very low aqueous solubility. The chemical (CAS) name for EVG is 6-(3-Chloro-2-fluorobenzyl)-1-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

COBI on silicon dioxide is a white powder soluble in water at a rate of 0.075 mg/mL. The chemical (CAS) name for COBI is 2,7,10,12-Tetraazatridecanoic acid, 12-methyl-13-[2-(1-methylethyl)-4-thiazolyl]-9-[2-(4-morpholinyl)ethyl]-8,11-dioxo-3,6 bis(phenylmethyl), 5-thiazolylmethyl ester, (3*R*,6*R*,9*S*).

Please refer to the original NDA reviews of FTC and TDF for a description of their chemical properties.

E/C/F/T tablets contain 150 mg of EVG, 150 mg of COBI, 200 mg of FTC, and 300 mg of TDF (as 245 mg tenofovir disoproxil). The tablets are capsule-shaped, film-coated green, and debossed with “GSI” on one side and “1” on the other side. The E/C/F/T tablet is a bilayer tablet, with one layer containing EVG/COBI and the other layer containing FTC/TDF. Each tablet contains the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, indigo carmine (FD&C Blue #2) aluminum lake (E132), lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, polyethylene glycol, silicon dioxide, sodium lauryl sulfate, talc (b) (4), titanium dioxide (b) (4), and yellow iron oxide (b) (4). The E/C/F/T tablet is an immediate-release, solid oral dosage form. The dissolution profiles for the proposed commercial tablet formulation showed that greater than (b) (4) of all the active ingredients were dissolved within 30 minutes.

Inspections of the production facilities are still on-going at the time of this review. Please see the CMC Review by Dr. Celia Cruz, Dr. Fuqiang Liu, and Dr. Milton Sloan for further details.

4.2 Clinical Microbiology

Please refer to the Virology Review by Dr. Takashi Komatsu and Dr. Sung Rhee for details.

EVG is an HIV-1 integrase (IN) strand transfer inhibitor. It prevents the integration of HIV-1 DNA made by reverse transcription of the viral genomic RNA into the host cell chromosome. Integrated viral DNA (provirus) is required for productive HIV-1 infection. Using recombinant HIV-1 integrase, EVG was shown to inhibit the DNA strand transfer reaction with an IC_{50} value of 8.8 nM. COBI is a specific inhibitor of CYP3A, the body's major drug-metabolizing enzyme, to increase the systemic levels of co-administered agents metabolized by this enzyme system.

The antiviral activity of EVG was shown against laboratory isolates of HIV-1, T- and M-tropic viruses, with EC_{50} values ranging from 0.1 to 0.7 nM. In addition, EVG had antiviral activity against multiple clinical isolates of HIV including clades A, B, C, D, E, F, G, and O isolates (EC_{50} values ranged from 0.1 to 1.3 nM) and a single HIV-2 clinical isolate (EC_{50} value of 0.53 nM). Cobicistat has no detectable antiviral activity against laboratory and clinical isolates of HIV-1 in cell culture.

EVG-resistant isolates of HIV-1 have been isolated during serial passage of $HIV\text{-}1_{IIIB}$ in the presence of increasing concentrations of EVG. Genotypic analysis of the IN-coding region in passaged virus showed emergence of an E92Q substitution, followed by S147G, H51Y, and E157Q substitutions. These substitutions persisted until the end of the selection. These mutant viruses showed reduced susceptibility to EVG (9- to 449-fold). In other selection experiments, D10E, S17N, T66I/K, F121Y, Q148R, S153Y, D232N, and R263K substitutions were selected and viruses harboring these substitutions showed reduced susceptibility to EVG (5- to 109-fold).

In a pooled resistance analysis of Studies 236-0102, 236-0103, and 236-0104 (a small Phase 2 study of E/C/F/T versus ATR) in treatment-naïve subjects, genotypic and phenotypic resistance to the individual components of E/C/F/T was monitored in isolates from subjects with virologic failure who were treated with E/C/F/T and had HIV-1 RNA ≥400 copies/mL at the time of virologic failure (or later while still on treatment). HIV-1 variants harboring EVG-treatment emergent amino acid substitutions in the HIV-1 IN protein were detected in failure isolates from 20 of the 24 evaluated subjects. These failure isolates had reductions in susceptibility to EVG ranging from 1 to >198-fold that of wild-type HIV-1. IN substitutions previously identified in clinical trials or in cell culture

as conferring reduced susceptibility to EVG were detected in 11 subjects' isolates (45.8% of evaluated E/C/F/T-treatment failures). These substitutions included T66I, E92Q, Q148R, and N155H (EVG resistance-associated substitutions) and H51Y, I68I/V, G140C, S153A, E157Q, and V165I IN substitutions. Isolates harboring these substitutions had reduced susceptibility to EVG (6- to >198-fold compared to wild-type HIV-1). The remaining 9 subjects' failure isolates harbored one or more treatment-emergent IN substitutions that have not been identified as associated with EVG resistance and had ≤2.1-fold reduced susceptibility to EVG.

As illustrated in Table 2, of the 11 subjects with primary EVG resistance-associated IN substitutions, 10 subjects were also evaluated for FTC/TDF resistance. All 10 of these subjects developed M184I/V ± K65R substitutions in RT in addition to the EVG resistance-associated IN substitutions. The RT M184I/V ± K65R substitutions were also detectable in 2 subjects whose failure isolates showed no detectable EVG resistance-associated substitutions. All 12 isolates with the RT M184I/V substitution showed reduced susceptibility to FTC (42 to >152-fold). Two of the 4 isolates with the RT K65R substitution in addition to M184I/V demonstrated reduced susceptibility both to tenofovir (1.5- to 1.6-fold) and FTC (>84 to >88-fold). Concurrent emergence of RT substitutions conferring reduced susceptibility to both EFV and FTC were less frequently (25%, 2/8) observed in virologic failures in the ATR treatment group.

Table 2: Genotypic and Phenotypic Resistance in Evaluable Virologic Failure (VF) Isolates in the Censored, As-Treated Subject Populations (Pooled from Studies 102, 103, and 104)

QUAD Treatment (24 VFs)					
EVG^R-associated substitutions in IN	# subjects	FTC^R- and TDF^R-associated substitutions in RT	Drug susceptibility (fold-change)		
			EVG	FTC	TFV
YES, n=11	3	K65R, M184V	111 - >198	84 - 109	1.1 - 1,6
	7	M184I/V	6 - 51	75 - >152	0.5 - 0.7
	1	not determined	20 - 54[1]	-	-
NO, n=13	1	K65R, M184I	2	42 - 116[1]	0.8
	1	M184V	1	>88	0.4
	10	NONE	1 - 2	1 - 2	0.6 - 1.1
	1	not determined	1	-	-
ATR Treatment (15 VFs)					
EFV^R-associated substitutions in RT	# subjects	FTC^R- and TDF^R-associated substitutions in RT	Drug susceptibility (fold-change)		
			EFV	FTC	TFV
YES, n=8	2	K65R, M184I/V	19 - >70	42 - >129	1.4 - 1.8
	6	NONE	1 - 68	1	0.5 - 1.1
NO, n=7	7	NONE	1 - 2	1	0.7 - 1.2

EVG^R = primary elvitegravir resistance; EFV^R = Efavirenz resistance; FTC^R = FTC resistance; TDF^R = TDF resistance
[1]Two isolates evaluated for this subject.
Source: FDA Virology Reviewer's Analysis

Preliminary clonal genotypic analyses of failure isolates from only 2 of the 10 subjects with primary EVG resistance-associated IN substitutions and NRTI resistance data have been completed. This analysis revealed linkage of the observed IN and RT substitutions associated with EVG and FTC resistance on the same viral genome. Thus, these two subjects experienced virologic failure with simultaneous emergence of HIV-1 variants resistant to at least 2 antiviral components of the single-tablet regimen of E/C/F/T.

Since COBI is structurally similar to the HIV-1 protease inhibitor RTV, possible protease inhibitory activity *in vivo* was assessed by comparing the protease sequences in failure isolates from the E/C/F/T and ATR treatment arms of 236-0102. A disproportionate number of substitutions in the protease sequence developed on-treatment in the E/C/F/T treatment arm (9 substitutions/14 subjects) compared to the ATR arm (4 substitutions/15 subjects). Three of the 9 protease substitutions in isolates from the E/C/F/T arm have been associated with resistance to protease inhibitors (M36I, D60E, and V77I). However, none of these protease substitutions are considered primary resistance mutations. The clinical relevance of this observation is unclear at this time as the number of subjects was small; however, this issue will require careful follow up.

Cross-resistance between EVG and raltegravir was observed when drug susceptibilities of virologic failure isolates collected in subjects treated with E/C/F/T in the 3 clinical trials described above were assessed. All EVG-resistant, subject-derived, recombinant HIV-1 variants with ≥2.5-fold reduced susceptibility to EVG (biological cutoff for EVG) also showed >1.5-fold reduced susceptibility to raltegravir (biological cutoff for raltegravir). EVG-resistant viruses showed varying degrees of cross-resistance to raltegravir depending on the type and number of substitutions. Primary EVG resistance-associated substitutions T66K, E92Q, Q148H/K/R, and N155H conferred reduced susceptibility both to EVG (5- to 108-fold) and to raltegravir (6- to 34-fold). Viruses expressing the T66I substitution that was identified in 2 E/C/F/T-treated subjects conferred 15- to 31-fold reduced susceptibility to EVG but only 1-2-fold reduced susceptibility to raltegravir.

In summary, the 3 clinical trials submitted help to characterize emergence of IN and RT resistance in treatment naïve subjects receiving E/C/F/T. Patients failing treatment with E/C/F/T are likely to also be cross-resistant to raltegravir and other IN inhibitors and some patients failing E/C/F/T will fail with resistance to two classes of drugs. Although the COBI component of E/C/F/T has no direct antiviral effect, the suggestion of higher proportion of failure isolates with protease substitutions will require further evaluation.

4.3 Preclinical Pharmacology/Toxicology

Please refer to the Pharmacology/Toxicology Reviews by Dr. Laine Myers and Dr. Pritam Verma for additional details related to EVG and COBI. Please refer to the original NDA reviews of FTC and TDF for information related to these agents.

General Toxicology Studies

Single dose and repeat dose nonclinical studies with EVG demonstrated no adverse target-organ toxicity. Treatment-related effects included changes in cecum weights, dilation of the cecum, and the presence of lipid vacuoles in the lamina propria of the upper small intestines of rats and dogs.

Repeat dose nonclinical studies with COBI identified target organ toxicity involving the liver (mouse, rat, and dog) and thyroid (rat). Slight hematological changes were noted in rats and slight clinical chemistry changes were observed in mice, rats, and dogs, with urinalysis changes noted primarily 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 and/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, association with remarkable serum chemistry, or histopathological correlates. Other potential toxicities related to COBI that were observed in nonclinical studies include PR interval prolongation in the 4-week dog toxicity study and decreases in left ventricular function in isolated rabbit hearts.

Carcinogenesis and Mutagenesis

Elvitegravir was negative for mutagenic potential in a bacterial reverse mutation test, equivocal in a chromosomal aberration test in Chinese hamster lung (CHL) cells, and negative in 2 rat micronucleus assays. Long-term 2-year carcinogenicity studies in mice and rats with EVG showed no carcinogenic potential at exposures 14- to 20-fold greater than the exposure observed in humans at the therapeutic dose.

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 a rat micronucleus assay. Two-year mouse and rat carcinogenicity studies are ongoing.

Reproductive Toxicology Studies and Studies in Juvenile Rats

Elvitegravir did not have any effects on rat fertility, embryo-fetal viability or development in rats or rabbits, or on perinatal or postnatal development in rats. Elvitegravir was well tolerated in juvenile rats up to 2000 mg/kg/day.

Cobicistat demonstrated no adverse effects on fertility or embryo-fetal viability in a fertility study in male and female rats, and no teratogenic effects in rat and rabbit developmental toxicity studies. In rats, at 125 mg/kg/day, increases in post-implantation loss and decreased fetal weights were associated with significant maternal toxicity. There were no significant effects on perinatal or postnatal development in rats. 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

Elvitegravir was not phototoxic or immunotoxic and was negative for delayed-type hypersensitivity. It was considered neither a skin irritant nor a strong eye irritant.

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 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. Vikram Arya for additional details.

4.4.1 Mechanism of Action

EVG is an integrase strand-transfer inhibitor that functions by preventing integration of HIV-1 genetic material into the host cell genome.

COBI is a mechanism-based cytochrome P450 3A (CYP3A) inhibitor that enhances the exposure of CYP3A substrates, including EVG. It is a structural analogue of ritonavir but devoid of anti-viral activity.

FTC and TDF (a nucleoside analogue of cytidine and nucleotide analogue of adenosine monophosphate respectively) function by inhibiting the HIV-1 reverse transcriptase.

4.4.2 Pharmacodynamics

EVG

In vitro, EVG showed no detectable inhibition of human hepatic microsomal CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, or CYP2E1 activity and weak inhibition of CYP3A. At clinically relevant concentrations, EVG is a weak inducer of CYP3A activity.

Elvitegravir is a potent inhibitor of human organic anion transporting polypeptide 1B3 (OATP1B3), and a weak inhibitor of human Pgp and organic anion transporting polypeptide 1B1 (OATP1B1).

COBI

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

At high concentrations, COBI is a weak activator of human pregnane X receptor and increases hepatocyte CYP3A4 mRNA and protein.

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

COBI inhibits the organic cation transporter 2 (OCT2), the renal efflux transporters OCTN1, and the multidrug and toxin extrusion protein 1 (MATE1), which may effect the tubular secretion of endogenous substrates of these transporters (e.g. creatinine)

COBI, at very high concentrations, is a weak inhibitor or MDR1 and breast cancer resistance protein.

4.4.3 Pharmacokinetics

EVG

Absorption: Absorption of EVG is unaffected by local gastrointestinal (GI) pH. It is, however, subject to chelating in the GI tract by high concentrations of di- and tri-valent cations (e.g. high-strength antacids). Peak concentrations are observed ~ 3 to 4 hours following oral dosing.

Distribution: EVG is highly protein bound (98% to 99% with preferential binding to albumin over AAG) and predominantly distributed to plasma relative to the cellular

components of the blood. The distribution of EVG into peripheral compartments (e.g., cerebrospinal fluid or genital tract secretions) has not been evaluated in humans.

Metabolism: The biotransformation of EVG is primarily via CYP-mediated aromatic and aliphatic hydroxylation and/or primary or secondary glucuronidation. Two primary metabolites are observed following unboosted administration: (1) M1 (GS-9202), produced by CYP3A4, and whose formation is almost completely inhibited when administered with RTV or COBI, and (2) M4 (GS-9200), produced by uridine diphosphate glucuronosyltransferase (UGT) 1A1/3, whose plasma exposure (AUC_{tau}) is very low and not affected by boosting. Potent UGT1A1 inhibition can result in increased EVG exposure.

Elimination: Following administration of boosted [^{14}C]EVG, 94.8% of the radioactive dose was recovered in feces, consistent with hepatobiliary excretion; 6.7% was recovered in urine, primarily as glucuronide metabolites, with no unchanged EVG observed. In plasma, EVG was the predominant species, representing ~ 93% of circulating radioactivity. All observed metabolites, including several minor metabolites, constitute < 10% relative systemic exposure (AUC_{tau}) to parent drug in humans.

COBI

Absorption: Absorption is not influenced by local GI pH. 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: COBI is highly protein bound (97-98%) and excluded from the cellular components of the blood. The distribution of COBI into peripheral compartments (e.g., cerebrospinal fluid or genital tract secretions) has not been evaluated in humans.

Metabolism: COBI is extensively metabolized in vitro via CYP3A (major) and CYP2D6 (minor) mediated oxidation. Therefore, COBI exposures are decreased when COBI is co-administered 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 [^{14}C]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.

E/C/F/T (in HIV-1 uninfected subjects)

Elvitegravir C_{max} and AUC were comparable between single and multiple doses of E/C/F/T, indicating substantial inhibition of EVG metabolism by COBI after a single dose. EVG T_{max} was similar following single- or multiple-dose administration. In comparison, EVG mean C_{tau} was ~ 43% higher following multiple-dose administration relative to single-dose administration. Per Applicant, these results are consistent with ongoing inhibition of CYP3A activity and the consequent reduction in the systemic clearance of EVG by COBI with multiple dosing due to mechanism-based inhibition of CYP3A.

Cobicistat mean AUC and C_{max} were 40% and 23% higher upon multiple dosing relative to single dosing, while T_{max} was comparable.

Tenofovir mean AUC and C_{max} were ~ 25% to 30% higher upon multiple dosing compared to single dosing, with comparable T_{max} values. Steady-state mean TDF AUC_{tau} was modestly higher (~ 26%) when administered as the E/C/F/T formulation compared with TDF 300-mg tablets, but within the range of values observed when TDF is co-administered with boosted PIs. The sponsor attributes these findings to an inhibitory effect of COBI on Pgp (MDR1)-mediated secretory (efflux) transport of TDF in the intestine.

FTC mean AUC, C_{max}, and T_{max} estimates were comparable after single or multiple dosing and versus FTC 200-mg capsules alone.

E/C/F/T (in HIV-1 infected subjects)

PK sub-studies were performed in HIV-infected subjects and results were compared to HIV-1 uninfected subjects. EVG AUC_{tau}, C_{max}, and C_{trough} were comparable between the two populations. COBI AUC_{tau} and C_{max} were approximately 25% lower while T_{max} and $T_{½}$ were comparable in HIV-1 infected subjects compared with healthy subjects. The exposures and overall PK of FTC and TDF were comparable between the two populations.

Food Effect

COBI exposure parameters AUC_{inf}, AUC_{last}, and C_{max} were bioequivalent under light meal and fasted conditions. Modest decreases in exposure parameters ranging from 19% to 27% were observed with a high-calorie/high-fat meal relative to the fasted state.

EVG, presumably due to its low aqueous solubility, had maximum increases in exposure (AUC_{inf} 87%, AUC_{last} 91%, and C_{max} 56%) following a high-calorie/high-fat meal compared to a fasted state. Modest increases were noted in EVG exposure (AUC_{inf} 34%, AUC_{last} 36%, and C_{max} 22%) when administered with a light meal compared to a fasted state. Emtricitabine and TDF exposures in the presence of food were consistent with their established PK profiles. The proposed product labeling recommends the E/C/F/T FDC be taken with food.

5 Sources of Clinical Data

The two pivotal phase 3 trials, GS-US-236-0102 and GS-US-236-0103, provided the primary data for characterization of the tolerability, safety and effectiveness of the E/C/F/T formulation in HIV-infected, treatment naïve subjects. Both trials were multicentered, randomized, double-blind, double-dummy studies designed to assess the safety and efficacy of the E/C/F/T formulation. The two studies were identical in design except in their choice of active control. The active control for study 236-0102 was efavirenz/emtricitabine/tenofovir disoproxil fumarate (Atripla®, ATR), while trial 236-0103 utilized ritonavir-boosted atazanavir (ATV/r) plus emtricitabine/tenofovir disoproxil fumarate (Truvada®, TVD) as the active control.

In addition to the two phase 3 pivotal trials, a small phase 2 study, GS-US-236-0104, provided supportive data in the evaluation of the safety and efficacy of the E/C/F/T formulation.

'High level' safety data from a phase 2 and phase 3 trial with EVG (GS-US-183-0130 and GS-US-183-0145 respectively) and a phase 2 and phase 3 trial with COBI (GS-US-216-0105 and GS-US-216-0114 respectively) were provided by the sponsor and included in this review when deemed appropriate.

5.1 Tables of Studies/Clinical Trials

The two pivotal phase 3 trials and the supportive phase 2 trial, all conducted in HIV-1 infected, treatment naïve subjects, are summarized in Table 3. In addition, a large number of phase 1 clinical pharmacology trials have been submitted by the Applicant. Please refer to Dr. Vikram Arya's Clinical Pharmacology Review for further details.

Table 3 Summary of Pivotal Phase 3 and Supportive Phase 2 Trials

Trial Name	Study Design	Active Control	# Randomized/ # Treated	Primary Efficacy Endpoint
GS-US-236-0102	Randomized, double-blinded, double-dummy, active-control	EFV/TDF/FTC	707/700 (1:1 randomization)	% subjects with HIV-1 RNA < 50 copies/ml at Week 48

GS-US-236-0103	Randomized, double-blinded, double-dummy, active-control	TDF/FTC/ATV/r	715/708 (1:1 randomization)	% subjects with HIV-1 RNA < 50 copies/ml at Week 48
GS-US-236-0104	Randomized, double-blinded, double-dummy, active-control	EFV/TDF/FTC	71/71 (2:1 randomization favoring study drug)	% subjects with HIV-1 RNA < 50 copies/ml at Week 24

5.2 Review Strategy

The clinical review for this NDA was based primarily on the data from the two Phase 3 trials, GS-US-236-0102 and GS-US-236-0103. The safety analysis was conducted by integrating safety data from these two trials. In addition, data from the Phase 2 trial, GS-US-236-0104 were reviewed for key safety analyses. The Safety Update Report (SUR) containing safety data up to the cutoff date of 21 November 2011 for studies 236-0102, 236-0103, and 236-0104 was also reviewed. Review of efficacy was conducted in collaboration with Dr. Wen Zeng, the statistical reviewer from the Division of Biometrics.

5.3 Discussion of Individual Studies/Clinical Trials

GS-US-236-0102: An ongoing, Phase 3, randomized, double-blind, double-dummy, active controlled trial in the U.S. and Puerto Rico to evaluate the safety and efficacy of the E/C/F/T formulation versus ATR in HIV-1 infected, antiretroviral treatment (ART) naïve adults.

Subjects were enrolled in a total of 102 study sites; 97 in the U.S. and 5 in Puerto Rico.

The primary objective was to demonstrate non-inferiority of treatment with the E/C/F/T formulation compared to the control (ATR) as determined by the achievement of HIV-1 RNA < 50 copies/ml at Week 48, and assuming a non-inferiority margin of 12%. The choice of the non-inferiority margin was based on earlier clinical trials of antiretroviral drugs and follows our standard recommendation for trials in this patient population.

The primary efficacy endpoint was the percentage of subjects with virologic success (i.e. HIV-1 RNA < 50 copies/ml) at Week 48 using the FDA-defined snapshot analysis. HIV viral load is an established endpoint for assessment of treatment effect, as cited in the FDA Guidance, “Antiretroviral Drugs Using Plasma HIV RNA Measurements-Clinical Considerations for Accelerated and Traditional Approval”.

Subjects were randomized in a 1:1 fashion and randomization was stratified based on HIV-1 RNA level (≤ 100,000 copies/ml or > 100,000 copies/ml) at screening.

Major inclusion criteria included plasma HIV-1 RNA levels ≥ 5000 copies, estimated glomerular filtration rate (eGFR) > 70 ml/min, no prior use of ART, and sensitivity to EFV, FTC, and TDF, as demonstrated by genotypic testing.

Notable exclusion criteria included a new AIDS-defining condition diagnosed within the 30 days prior to screening. Included under AIDS defining conditions were CD4+ T-lymphocyte count < 200/µl and CD4+ T-lymphocyte percent < 14.

Evaluations for subject safety (physical examination, safety laboratories) and efficacy (HIV-1 RNA, CD4+ lymphocyte count) were performed at the following scheduled visits: Week 2, 4, 8, 12, 16, 24, 32, 40, 48, 60, 72, 84, and 96. Subjects were closely monitored for virologic failure (i.e. suboptimal virologic response or virologic rebound) and were managed according to clearly defined algorithms. An external Independent Data Monitoring Committee was established to monitor subject safety and evaluate efficacy data while the study is ongoing.

A total of 700 subjects were randomized and received at least one dose of study medication: 348 in the E/C/F/T group and 352 in the ATR group. Subjects will be treated for 192 weeks in the randomized, double-blinded phase.

GS-US-236-0103: An ongoing, Phase 3, randomized, double-blind, double-dummy, active controlled, international trial to evaluate the safety and efficacy of the E/C/F/T formulation versus ATV/r + TVD as the active control in HIV-1 infected, ART naïve adults.

Subjects were enrolled in a total of 146 study sites; 88 in the U.S. and Puerto Rico, 11 in France, 8 in Germany, 8 in Australia, 7 in Canada, 6 in United Kingdom, 3 in Belgium, 3 in Italy, 3 in Austria, 2 in Thailand, 2 in Netherlands, 1 in Portugal, 1 in Mexico, 1 in Denmark, 1 in Switzerland, and 1 in Sweden.

The study design of GS-US-236-0103 is virtually identical to GS-US-0102 with the exception of the active control arm (ATV/r + TVD). As such, the genotypic inclusion criterion includes sensitivity to ATV, FTC, and TDF.

A total of 708 subjects were randomized and received at least one dose of study medication: 353 in the E/C/F/T group and 355 in the ATV/r + TVD group. Subjects will be treated for 192 weeks in the randomized, double-blinded phase.

GS-US-236-0104: An ongoing, Phase 2, randomized, double-blind, double-dummy, active controlled trial in the U.S. to evaluate the safety and efficacy of the E/C/F/T formulation versus ATR in HIV-1 infected, ART naïve adults.

Subjects were enrolled in a total of 30 study sites in the U.S.

The primary objective was to assess the efficacy of the E/C/F/T formulation compared to the control (ATR) as determined by the achievement of HIV-1 RNA < 50 copies/ml at Week 24.

The primary efficacy endpoint was the percentage of subjects with virologic success (i.e. HIV-1 RNA < 50 copies/ml) at Week 24.

Subjects were randomized in a 2:1 fashion (E/C/F/T:ATR) and randomization was stratified based on HIV-1 RNA level (≤ 100,000 copies/ml or > 100,000 copies/ml) at screening.

Major inclusion criteria included plasma HIV-1 RNA levels ≥ 5000 copies, CD4 count > 50 copies/ml, estimated glomerular filtration rate (eGFR) > 80 ml/min, negative hepatitis B and C serology, no prior use of ART, and absence of NRTI, NNRTI, or PI resistance mutations by genotypic analysis.

Consistent with the two Phase 3 studies discussed above, subjects were excluded for a new AIDS-defining condition diagnosed within the 30 days prior to screening. Included under AIDS defining conditions were CD4+ T-lymphocyte count < 200/µl and CD4+ T-lymphocyte percent < 14.

Evaluations for subject safety (physical examination, safety laboratories) and efficacy (HIV-1 RNA, CD4+ lymphocyte count) were performed at the following scheduled visits: Week 2, 4, 8, 12, 16, 24, 32, 40, 48, and 60. Subjects were closely monitored for virologic failure (i.e. suboptimal virologic response or virologic rebound) and were managed according to clearly defined algorithms. An external Independent Data Monitoring Committee was established to monitor subject safety and evaluate efficacy data while the study was ongoing.

A total of 71 subjects were randomized and received at least one dose of study medication: 48 in the E/C/F/T group and 23 in the ATR group. Subjects were treated for 60 weeks in the randomized, double-blinded phase. At Week 60, all subjects were unblinded and given the option to receive the E/C/F/T formulation in an open-label rollover study.

6 Review of Efficacy

Efficacy Summary

In the two pivotal Phase 3 trials, E/C/F/T was shown to be non-inferior to the comparator groups with respect to efficacy. In trial 236-0102, 87.6% of E/C/F/T subjects had virologic success compared to 84.1% of subjects in the ATR group. In trial 236-0103, 89.5% of E/C/F/T subjects had virologic success compared to 86.8% of subjects in the ATR group. In both studies, the E/C/F/T group met the pre-specified NI margin of 12%. Rates of virologic failure were low in the E/C/F/T group and similar to rates demonstrated in the comparator groups.

6.1 Indication

E/C/F/T is indicated for the treatment of HIV-1 infection in treatment-naïve adults. The Applicant also requested that the indication include the treatment of HIV-1 infection in treatment-experienced adults with no resistance to the component drugs. However, in our view, the data do not support that broader indication (please see Section 9.2 for further details).

6.1.1 Methods

The indication is based on the 48 week data from GS-US-236-0102 and GS-US-236-0103. The Phase 2b trial, GS-US-236-0104, provided additional efficacy data supporting the indication. All data tables in this section were generated by the primary clinical reviewer using JReview unless otherwise specified.

6.1.2 Demographics

The intent to treat population (ITT) included 1408 subjects. 701 subjects received E/C/F/T, 352 subjects received ATR and 355 subjects received ATV/r + TVD. Baseline characteristics, including gender, race, ethnicity and age, were comparable between the E/C/F/T and control arms (Table 4). The majority of study participants in all arms were male (88-92%) and Caucasian (62-78%). All subjects in GS-US-236-0102, and the majority of subjects in GS-US-236-0103 (54%) were recruited in the U.S.

The median baseline viral load, percentage of participants with viral load < 100,000, and median CD4+ count were well balanced between the E/C/F/T group and control arms.

Table 4: Demographics and Baseline Characteristics

	GS-US-236-0102		GS-US-236-0103		Pooled 0102 and 0103
	E/C/F/T	ATR N=352	E/C/F/T	ATV/r + TVD	E/C/F/T N=701

	N=348		N=353	N= 355	
Gender n (%)					
Male	307 (88.2%)	316 (89.8%)	324 (91.8%)	316 (89.0%)	631 (90.0%)
Female	41 (11.8%)	36 (10.2%)	29 (8.2%)	39 (11.0%)	70 (10.0%)
Race n (%)					
White	214 (61.5%)	227 (64.5%)	250 (70.8%)	277 (78.0%)	464 (66.2%)
Black or African American	106 (30.5%)	91 (25.9%)	72 (20.4%)	47 (13.2%)	178 (25.4%)
Asian	6 (1.7%)	10 (2.8%)	17 (4.8%)	17 (4.8%)	23 (3.3%)
American Indian or Alaska Native	2 (0.6%)	4 (1.1%)	2 (0.6%)	3 (0.8%)	4 (0.6%)
Native Hawaiian or other Pacific Islander	4 (1.1%)	1 (0.3%)	1 (0.3%)	2 (0.6%)	5 (0.7%)
Other	16 (4.6%)	19 (5.4%)	11 (3.1%)	9 (2.5%)	27 (3.9%)
Ethnicity n (%)					
Hispanic or Latino	82 (23.6%)	85 (24.1%)	64 (18.1%)	47 (13.2%)	146 (20.8%)
Not Hispanic or Latino	266 (76.4%)	267 (75.9%)	284 (80.5%)	298 (83.9%)	550 (78.5%)
Not Reported	0 (0.0%)	0 (0.0%)	5 (1.4%)	10 (2.8%)	5 (0.7%)
Age (years)					
Median (min, max)	37 (18-63)	38 (18-67)	37 (19-72)	39 (19-69)	37 (18-72)
Geographical Region n (%)					
North America	348 (100%)	352 (100%)	219 (62%)	209 (58.9%)	567 (81.0%)
Europe	0 (0 %)	0 (0 %)	97 (27.5%)	110 (31.0%)	97 (13.8%)
Australia	0 (0 %)	0 (0 %)	30 (8.5%)	32 (9.0%)	30 (4.3%)
Asia	0 (0 %)	0 (0 %)	7 (2.0%)	4 (1.1%)	7 (1.0%)
Plasma HIV-1 RNA					
Median (min, max)	55,600 (436-2,620,000)	60,900 (1080-3,500,000)	75,300 (49-3,760,000)	72,100 (950-4,230,000)	60,400 (49-3,760,000)
< 100,000, n (%)	230 (66.1%)	236 (67.0%)	203 (57.5%)	214 (60.3%)	433 (61.8%)
100k-500k, n (%)	101 (29.0%)	99 (28.1%)	126 (35.7%)	121 (34.1%)	227 (32.4%)
> 500,000, n (%)	17 (4.9%)	17 (4.8%)	24 (6.8%)	20 (5.6%)	41 (5.8%)
CD4+ Cell Count (/uL)					
Median (min, max)	375.5 (14-1348)	383 (3-1003)	351 (5-1132)	366 (10-963)	360 (5-1348)
< 200	41 (11.8%)	49 (13.9%)	50 (14.2%)	37 (10.4%)	91 (13.0%)
HIV Clinical Stage					
AIDS	28 (8.0%)	24 (6.8%)	32 (9.1%)	24 (6.8%)	60 (8.6%)
Asymptomatic HIV Infection	290 (83.3%)	295 (83.8%)	285 (80.7%)	293 (82.5%)	575 (82.0%)
Symptomatic HIV Infection	30 (8.6%)	33 (9.4%)	36 (10.2%)	38 (10.7%)	66 (9.4%)

6.1.3 Subject Disposition

The percentage of subjects continuing study treatment at the time of the Week 48 analysis was similar between the E/C/F/T group and the comparator groups in the Phase 3 studies. Similarly, the distribution reasons that subjects discontinued study treatment was similar between the E/C/F/T group and the comparator groups (please refer to Table 5 below).

Table 5: Reasons for Prematurely Discontinuing Study Drugs in Studies 236-0102 and 236-0103

	GS-US-236-0102		GS-US-236-0103	
Number of subjects, n(%)	E/C/F/T N=348	ATR N=352	E/C/F/T N=353	ATV/r + TVD N=355
Subjects still on Study Treatment up to the Analysis Data Cut Date, n (%)	311 (89.4%)	306 (86.9%)	320 (90.7%)	315 (88.7%)
Reasons for Prematurely Discontinuing Study Treatment, n (%)				
Adverse Event	12 (3.4%)	18 (5.1%)	13 (3.7%)	18 (5.1%)
Death	1 (0.3%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Lack of Efficacy	5 (1.4%)	4 (1.1%)	4 (1.1%)	1 (0.3%)
Lost to Follow-Up	10 (2.9%)	12 (3.4%)	7 (2.0%)	7 (2.0%)
Non-Compliance with Study Drug	3 (0.9%)	6 (1.7%)	5 (1.4%)	5 (1.4%)
Physician Decision	1 (0.3%)	0 (0.0%)	1 (0.3%)	3 (0.8%)
Pregnancy	1 (0.3%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Protocol Violation	1 (0.3%)	0 (0.0%)	1 (0.3%)	0 (0.0%)
Withdrawal by Subject	3 (0.9%)	5 (1.4%)	1 (0.3%)	6 (1.7%)

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint for the pivotal Phase 3 trials was the percentage of subjects with virologic success (HIV-1 RNA < 50 copies/ml at Week 48) using the FDA-defined snapshot analysis algorithm. In trial 236-0102, 87.6% of E/C/F/T subjects had virologic success compared to 84.1% of subjects in the ATR group. In trial 236-0103, 89.5% of E/C/F/T subjects had virologic success compared to 86.8% of subjects in the ATR group. In both studies, the E/C/F/T group met the pre-specified NI margin of 12%. Please refer to table 6 for details.

Table 6: Primary Efficacy Endpoint Results (using the ITT analysis population)

	Study 236-0102		Study 236-0103	
	E/C/F/T* (N=348)	ATR (N=352)	E/C/F/T (N=353)	ATV/r + TVD (N=355)
Virologic Success (HIV-1 RNA < 50 copies/mL) at Week 48	305 (87.6%)	296 (84.1%)	316 (89.5%)	308 (86.8%)
Treatment Difference	3.6% (-1.6%, 8.8%)		3.0% (-1.9%, 7.8%)	
Overall Failure	43 (12.4%)	56 (15.9%)	37 (10.5%)	47 (13.2%)
Virologic Failure at Week 48	25 (7.2%)	25 (7.1%)	19 (5.4%)	19 (5.4%)
HIV-1 RNA ≥ 50 copies/mL	13 (3.7%)	11 (3.1%)	7 (2.0%)	8 (2.3%)
Discontinued Study Drug Due to Lack of Efficacy	4 (1.1%)	2 (0.6%)	4 (1.1%)	0 (0.0%)
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL	8 (2.3%)	12 (3.4%)	8 (2.3%)	11 (3.1%)
No Virologic Data in Week 48 Window	18 (5.2%)	31 (8.8%)	18 (5.1%)	28 (7.9%)
Discontinued Study Drug Due to AE/Death	10 (2.9%)	19 (5.4%)	11 (3.1%)	18 (5.1%)
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL	8 (2.3%)	11 (3.1%)	7 (2.0%)	9 (2.5%)
Missing Data During Window but on Study Drug	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.3%)

6.1.5 Analysis of Secondary Endpoints(s)

Change in CD4+ Cells from Baseline

There was no clinically relevant difference apparent with respect to the change in CD4+ cells (in cells/uL) from baseline through Week 48 between E/C/F/T and the comparator groups. In Study GS-US-236-0102, the mean +/- SD change in CD4+ cells from baseline at Week 48 for E/C/F/T was 236.1 +/- 168.3 and for ATR it was 205.0 +/- 153.3. In Study GS-US-236-0103, the mean +/- SD change in CD4+ cells from baseline at Week 48 for E/C/F/T was 207.4 +/- 164.0 and for ATV/r + TVD it was 212.6 +/- 163.1.

6.1.6 Other Endpoints

6.1.7 Subpopulations

A number of subgroup analyses were performed on the primary efficacy endpoint (see Table 7 below). No substantive differences in efficacy based on gender, race, age, region, baseline HIV-1 RNA level or baseline CD4 count were appreciated.

Subjects with baseline viral load >500,000 copies/mL were less likely to achieve virologic success than those <500,000 copies/mL; however, the number of patients in this subgroup was small and the overall response exceeded the response observed in the comparator arms of the Phase 3 trials.

As was previously noted, the percentage of women enrolled across study arms was low (8-12%).

Table 7: Subgroup Analyses on the Primary Efficacy Endpoint for Studies 236-0102 and 236-0103 (ITT Population)

	Study 236-0102		Study 236-0103	
	E/C/F/T N=348)	ATR (N=352)	E/C/F/T N=353)	ATV/r + TVD (N=355)
Overall Virologic Success (HIV-1 RNA < 50 copies/mL) at Week 48	305 (87.6%)	296 (84.1%)	316 (89.5%)	308 (86.8%)
Gender				
Male	270/307 (87.9%)	266/316 (84.2%)	292/324 (90.1%)	276/316 (87.3%)
Female	35/41 (85.4%)	30/36 (83.3%)	24/29 (82.8%)	32/39 (82.1%)
Race				
White	191/214 (89.3%)	199/227 (87.7%)	225/250 (90.0%)	240/277 (86.6%)
Non-White	114/134 (85.1%)	97/125 (77.6%)	91/103 (88.3%)	68/78 (87.2%)
Age				
≤40	179/208 (86.1%)	179/209 (85.6%)	191/216 (88.4%)	173/205 (84.4%)
>40	126/140 (90.0%)	117/143 (81.8%)	125/137 (91.2%)	135/150 (90.0%)
Region				
USA	305 (87.6%)	296 (84.1%)	172/197 (87.3%)	155/185 (83.8%)
Non-USA	N/A	N/A	144/156 (92.3%)	153/170 (90.0%)
Baseline HIV-1 RNA				
≤ 100,000 copies/mL	206/230 (89.6%)	201/236 (85.2%)	188 /203 (92.6%)	192 /214 (89.7%)
> 100,000 copies/mL	99/118 (83.9%)	95/116 (81.9%)	128 /150 (85.3%)	116 /141 (82.3%)
Baseline CD4+ Cell Count				
≤ 200 cells/uL	32/43 (74.4%)	42/51 (82.3%)	43/54 (79.6%)	33/39 (84.6%)
> 200 cells/uL	273/305 (89.5%)	254/301 (84.3%)	273/299 (91.3%)	275/316 (87.0%)

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The Applicant conducted a large number of dose ranging PK studies assessing COBI and EVG both as single agents, in combination, and with approved ARV drugs.

Study GS-US-236-0101 was a key dose-finding study. This was a phase 1 study to evaluate the relative bioavailability of EVG (150 mg), FTC (200 mg), TDF (300 mg) and COBI (100 mg or 150 mg) as a fixed-dose combination tablet versus ritonavir-boosted EVG (EVG/r) at 150/100 mg, FTC (200 mg), and TDF (300 mg) given as individual agents. This study indicated that COBI, at a dose of 150 mg, boosted EVG exposure to levels similar to those obtained after administration of EVG/r. It also demonstrated clinically equivalent exposures to TDF and FTC compared to co-administration of the individual agents, although the C_{max} and C_{tau} for TDF and the AUC_{tau}, C_{max} and C_{tau} for FTC was higher with E/C/F/T.

The identical formulation of E/C/F/T used in this study (with COBI at 150 mg) was carried forward into the Phase 2 study GS-US-236-0104. Identical doses of the E/C/F/T components were also used in the pivotal Phase 3 studies (b) (4) Study GS-US-236-0110 evaluated the relative bioavailability of this new E/C/F/T formulation and confirmed that the EVG and COBI exposures were bioequivalent between the two E/C/F/T formulations and that clinically equivalent exposures of TDF and FTC were obtained.

Please refer to the Clinical Pharmacology Review by Dr. Vikram Arya for additional details.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The FDA Guidance, “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 Division 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). The Phase 3 trials are designed to continue for a minimum of 192 Weeks. As such, additional efficacy and safety data will be generated by the Applicant and reviewed by the Division.

6.1.10 Additional Efficacy Issues/Analyses

EVG exposure-response analysis for efficacy in treatment naïve HIV-1 infected patients was based on intensive and sparse pharmacokinetic data available from 373 subjects who received E/C/F/T in GS-US-236-0102 and GS-US-236-0103. A relatively flat exposure-response relationship was identified across the EVG exposures (EVG AUC (min-max) was 4358-69754 ng·hr/mL; C_{tau} (min-max) was 58-2341 ng/mL). Patients with baseline viral load >500,000 copies/mL were less likely to achieve virologic success; however, no dose adjustment is recommend in patients with higher baseline viral load as the overall response in patients with high baseline viral load exceeded that observed in the comparator arms of the Phase III trials. Exposure-response efficacy analyses were not performed for COBI because the primary role of COBI is to increase the exposure of EVG and COBI is not expected to have antiviral activity.

Please refer to the Clinical Pharmacology Review by Dr. Vikram Arya and the Pharmacometrics Review by Dr. Jeffry Florian for additional details.

7 Review of Safety

Safety Summary

The most common adverse events identified during the Phase 3 trials included gastrointestinal disorders (primarily diarrhea and nausea) and infections and infestations (led by upper respiratory tract infections). The overall incidence of gastrointestinal adverse events by MedDRA system organ class was less in the E/C/F/T group (53.8%) than in the ATV/r + TVD group (56.6%), but greater than that of the ATR group (45.7%). Five subjects (0.7%) discontinued E/C/F/T due to gastrointestinal disorders (the majority related to diarrhea and/or nausea). This was less than the incidence of discontinuation in the ATV/r + TVD group (1.4%), but greater than that of the ATR group (0.0%). With respect to infections and infestations, no substantive difference in incidence was noted when comparing the E/C/F/T group to either of the control groups at the System Organ Class or Preferred Term level. A higher incidence of SAEs in the category of 'infections and infestations' was noted, however, none of these adverse events were judged by the investigator as related to study drug.

Musculoskeletal adverse events were more common in the E/C/F/T group (21.3%) than in either of the comparator groups (ATR 15.6%, ATV/r + TVD 15.5%). 'Back pain' and a constellation of adverse events related to muscle pain, stiffness and spasms all were reported at a higher rate in the E/C/F/T group than in either of the control arms. However, the vast majority musculoskeletal adverse events were of mild or moderate severity (i.e. grade 1 or 2) and rarely lead to study drug discontinuation or were deemed serious adverse events.

Adverse psychiatric events in the E/C/F/T group were primarily related to sleep disorders and disturbances, depressed mood disorders and disturbances and anxiety disorders and symptoms. With respect to sleep disorders and disturbances, E/C/F/T fared favorably when compared to ATR, but less favorably when compared to ATV/r + TVD. However, virtually all of these adverse events in the E/C/F/T group were of mild or moderate severity and none led to the discontinuation of E/C/F/T. E/C/F/T fared favorably when compared to ATR with respect mood disorders, but had a slightly higher incidence of 'mood disorders' when compared to ATV/r + TVD. Most of the mood disorder related AEs in the E/C/F/T group were of mild to moderate severity. There were two discontinuations in the E/C/F/T group related to the mood disorder AEs, 'completed suicide' (judged unrelated by investigator) and 'depression' (judged related by investigator). There was no notable difference in incidence of anxiety disorders when comparing E/C/F/T to ATR or ATV/r + TVD.

The notable AEs which led to subject discontinuation more frequently in the E/C/F/T group than in either of the comparator groups included a constellation of renal AEs (e.g. renal failure, Fanconi's syndrome, and increased blood creatinine). Of particular interest are four cases that appear consistent with proximal tubular dysfunction. All of these cases led to study drug discontinuation and all of them occurred in the E/C/F/T group. This frequency of proximal tubulopathy leading to study drug discontinuation was greater in the E/C/F/T group than expected with the use of TDF based on results of previous clinical trials using TDF as a component of a study regimen[1-3, 6,7,9,10,13].

Of note, a higher overall incidence of graded creatinine elevations and graded proteinuria was reported in the E/C/F/T group compared to either of the control arms. The sponsor maintains that a modest elevation in creatinine levels and decrease in estimated creatinine clearance and estimated GFR (eGFR) are to be expected with the E/C/F/T formulation due to a cobicistat-related inhibition of tubular creatinine secretion, but that actual GFR (aGFR) is not affected. This is supported by the results of the Study GS-US-216-0121 where actual GFR was measured by clearance of iohexol, as well as the results for cysGFR in the pooled safety analysis set of Studies GS-US-236-0102, GS-US-236-0103, & GS-US-236-0104. However, the disproportionate number of renal adverse events and discontinuations and the higher incidence of graded creatinine and urine protein laboratories raise the question as to whether two discrete processes are at work, a non-pathologic increase in eGFR as the sponsor contends and a bona fide increased risk of renal adverse events of concern. These renal AEs and laboratory abnormalities will be discussed in detail in Section 7.3.5.

There were no safety signals of concern with respect to skin and soft tissue or hepatobiliary adverse events. No Hy's Law cases of drug-induced hepatotoxicity were identified. There was no evidence of clinically relevant changes in thyroid function or

clinically relevant declines in serum immunoglobulin G as was suggested in pre-clinical testing.

7.1 Methods

As discussed previously, the Phase 3 trials, GS-US-236-0102 and GS-US-236-0103 are double-blind, double-dummy, active controlled trials with a 1:1 randomization scheme. The two trials are identical in design and patient population (i.e. treatment naïve) with the exception of the control arm used (ATR in GS-US-236-0102 and ATV/r + TVD in GS-US-236-0103). Pooled AE data from these trials were reviewed from 1408 subjects who received at least one dose of study drug to identify clinical adverse events and laboratory toxicities associated with E/C/F/T use. In addition, selected safety data from the Phase 2 trial (GS-US-236-0104) was reviewed.

The Applicant identified specific adverse events of interest based on the cumulative safety data from the non-clinical studies, Phase 1 through Phase 3 clinical trials, and the known safety profile of FTC and TDF. This cumulative data, in addition to adverse events of interest identified during the course of this review, was used to create a specific safety analysis section, 'Submission Specific Primary Safety Concerns' (Section 7.3.5).

Review of this original NDA included safety data through Week 48 for trials 236-0102 and 236-0103, as well as follow-up safety data as provided in the Safety Update Report (SUR). As these clinical trials were not powered to detect statistically significant differences in AEs, when differences in frequency of AEs are noted in the following sections, it does not necessarily imply that these differences are statistically significant.

Overall, the FDA's pooled Phase 3 safety data analyses replicated the Applicant's findings with few exceptions. The exceptions did not lead to a clinically meaningful difference, and were due to methods used in identifying the specific subject population of interest, pooling preferred terms outside of the MedDRA classification scheme or differences in attribution of treatment-relatedness.

All data tables in this section were generated by the primary clinical reviewer from the ISS datasets using JReview unless otherwise specified.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The Applicant's analysis for summary of clinical safety in support of E/C/F/T for the treatment of HIV-1 infection in treatment-naïve adult patients relied primarily on safety data from two Phase 3 trials (GS-US-236-0102 and GS-US-236-0103) and one Phase 2 trial (GS-US-236-0104). The Applicant also included high-level safety data from a

Phase 2 and a Phase 3 clinical trial with EVG (GS-US-183-0130 and GS-US-183-0145 respectively), and a Phase 2 and Phase 3 clinical trial with COBI (GS-US-216-0105 and GS-US-216-0114 respectively).

This NDA review focuses on the safety data from the two Phase 3 trials (236-0102 and 236-0103) with periodic use of additional supportive data from the Phase 2 trial (236-0104). As mentioned above, safety data from both non-clinical studies and Phase 1 through Phase 3 clinical trials were considered for identification of specific adverse events of interest.

7.1.2 Categorization of Adverse Events

The sponsor coded AEs using MedDRA 14.0. An assessment of the Applicant's coding of events was carried out with attention given to assuring proper agreement between the investigators' verbatim terms and the selected MedDRA Preferred terms. Particular attention was given to adverse events that led to study drug discontinuation and serious adverse events judged related to study drug. Additionally, a random check of adverse events without respect to severity or causality of adverse events was performed. No issues of concern were identified.

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

The Phase 3 trials were identical in design with the exception of the control group used. Therefore, the safety data were pooled for estimating and comparing safety incidence.

7.2 Adequacy of Safety Assessments

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

The dose and formulation selected for marketing is the E/C/F/T (150/150/200/300 mg) tablet. This was the dose used throughout the two pivotal Phase 3 studies (236-0102 & 236-0103) and the supportive Phase 2 study (236-0104). Therefore, the use of these studies to assess the safety of the proposed dose and formulation intended for marketing is appropriate. A total of 749 subjects from the pivotal Phase 3 trials and supportive Phase 2 trial received at least one dose of E/C/F/T. Of these 749 subjects, 707 subjects have been exposed to E/C/F/T for 24 weeks, 509 subjects have been exposed for 48 weeks and 164 subjects have been exposed for 60 weeks. Please refer to Section 6.1.2 for demographic information.

7.2.2 Explorations for Dose Response

Exposure-safety relationships were evaluated by the Applicant and FDA.

The exposure-safety analyses for EVG evaluated whether there was a potential relationship between predicted EVG AUC_{tau} and C_{tau} and the most common adverse events observed during the Phase III trials (e.g., headache, diarrhea, and nausea). For all EVG analyses, no relationship was observed between predicted AUC_{tau} or C_{tau} and the adverse event of interest.

Exposure-safety analyses for COBI assessed both associations with common adverse events observed during Phase III trials (e.g., headaches, diarrhea, and nausea) and changes in calculated creatinine clearance. COBI exposure-response analysis was based on intensive PK sampling in 61 subjects. Similar COBI exposures (AUC_{tau} and C_{tau}) were observed between subjects with and without the key adverse events of interest.

An exposure-response analysis on changes in renal function versus COBI concentrations was also conducted as elevations in serum creatinine and subsequently, reduced estimated glomerular filtration rate (eGFR), was observed in the E/C/F/T treatment arms. No relationship between COBI exposures and change in eGFR were observed based on the available COBI pharmacokinetic data.

Please refer to Dr. Jeff Florian's Pharmacometrics Review for further details.

7.2.3 Special Animal and/or In Vitro Testing

Comprehensive programs of non-clinical studies with EVG, COBI, FTC, and TDF have been conducted. Full data from the studies using EVG and COBI in support of this NDA were provided with this submission. Please refer to Section 4.3 and the Pharmacology-Toxicology Reviews by Dr. Laine Myers and Dr. Pritam Verma for additional details. The data from to the studies of the FTC and TDF components of E/C/F/T were provided by the sponsor in support of the original NDA submission for these products.

No non-clinical safety studies were performed with the E/C/F/T formulation. The Applicant asserts that there are no anticipated relevant pharmacokinetic or toxicological interactions expected in the E/C/F/T combination beyond the anticipated pharmacokinetic boosting of EVG by COBI. This reviewer considers the non-clinical studies performed in support of this submission to be adequate.

7.2.4 Routine Clinical Testing

Routine clinical evaluations for safety (through Week 48) in studies GS-US-236-0102 and GS-US-236-0103 included medical history taking for assessment of adverse events and changes in concomitant medications at all scheduled visits (Weeks 2, 4, 8, 12, 16, 24, 32, 40, & 48), a complete physical exam at Weeks 24 and 48 and symptom-directed physical exams as needed at the other scheduled visits, safety laboratory assessments at all scheduled visits and ECG assessment at screening and Week 48. Subjects with serious adverse events were followed through the last day of study and/or until the investigator and/or sponsor 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 the PD profile of EVG and COBI, and Section 4.4.3 for a discussion of the PK profile of EVG, COBI, and E/C/F/T. Please refer to Section 7.5.5 for a discussion of drug-drug interactions.

Please refer to the Clinical Pharmacology Review by Dr. Vikram Arya for additional details.

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

The known safety profiles of the NRTIs (including the TDF and FTC components of this FDC) and of raltegravir were taken into consideration in the safety evaluation.

7.3 Major Safety Results

7.3.1 Deaths

In the pooled Phase 3 analysis, 6 subjects, 1 in the E/C/F/T group, 2 in the ATR group and 3 in the ATV/r + TVD group, died during the 48 week treatment period. The events are summarized in the table below.

Table 8: Deaths Listing

Subject ID	Treatment Group	Age	Sex	Race	Date of First Dose	Date of Last Dose	Date of Death	Cause of Death
Protocol 236-0102								
0659-6676	ATR	43	M	White	8/11/2010	8/15/2010	(b) (6)	Suicide, Death by Hanging
2140-6687	ATR	51	M	Black or African American	8/16/2010	6/14/2011		Metastatic Carcinoma
2480-6165	E/C/F/T	46	M	White	5/5/2010	10/28/2010		Suicide

Protocol 236-0103								
0444-7106	ATV/r + TVD	29	M	Black or African American	7/2/2010	9/19/2010	(b) (6)	Septic Shock related to Hodgkin's Lymphoma
1407-7116	ATV/r + TVD	32	M	White	7/6/2010	7/25/2010		Pneumocystis Jiroveci Pneumonia
1978-7529	ATV/r + TVD	25	M	White	9/9/2010	5/15/2011		Cardiopulmonary Arrest related to an overdose of recreational drugs

The suicide of Subject 0659-6676 was considered related to study drug (ATR) by the investigator. No other deaths were considered related to study drug by the investigator.

The subject (2480-6165) who received the E/C/F/T formulation was a 46 year old white male with a history significant for major depression, bipolar disorder, insomnia, and amphetamine abuse. The subject was receiving bupropion, clonazepam, and zolipedem prior to randomization and started aripiprazole on the day of randomization. The subject's baseline CD4 count and viral load were 296 cells/mm^3 and 119,000 copies/ml respectively. His depression was reported as stable at the beginning of the study. Worsening depression, reported as mild in severity, was diagnosed on Study Day (SD) 169. The subject committed suicide (b) (6).

No deaths were reported in the Phase 2 study, GS-236-0104, or in any of the Phase I studies with the E/C/F/T formulation.

7.3.2 Nonfatal Serious Adverse Events (SAEs)

In the pooled Phase 3 analysis, a total of 67 subjects receiving E/C/F/T (9.6%) had SAEs. The incidence of SAEs in the E/C/F/T group was greater than that of either comparator group (ATR, 6.8%; ATV/r + TVD, 8.7%). The most common SAE (by System Organ Class) was 'infection and infestation' occurring in 4.7% of subjects in the E/C/F/T group compared to 1.7% in the ATR group and 3.7% in the ATV/r + TVD group. The only other SAE occurring with > 1% incidence in the E/C/F/T group was 'gastrointestinal disorders,' which occurred in 1.3% of E/C/F/T recipients compared to 0.3% of ATR recipients and 0.6% of ATV/r + TVD recipients. Table 9 summarizes all treatment-emergent SAEs that occurred during the Phase 3 trials. Multiple AEs were counted only once per subject for each system organ class.

Table 9: Treatment-Emergent Serious Adverse Events in the Phase 3 Trials

	E/C/F/T	ATR	ATV/r + TVD
Studies (Number of Subjects)	236-0102, 0103	236-0102	236-0103

	(N=701)	(N=352)	(N=355)
Number of Subjects Experiencing Any Treatment-Emergent SAE	67 (9.6%)	24 (6.8%)	31 (8.7%)
Number of Subjects Experiencing Any Treatment-Emergent SAE by Body System or Organ Class n (%)			
INFECTIONS AND INFESTATIONS	33 (4.7%)	6 (1.7%)	13 (3.7%)
GASTROINTESTINAL DISORDERS	9 (1.3%)	1 (0.3%)	2 (0.6%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	7 (1.0%)	3 (0.9%)	3 (0.8%)
PSYCHIATRIC DISORDERS	6 (0.9%)	4 (1.1%)	6 (1.7%)
NERVOUS SYSTEM DISORDERS	5 (0.7%)	4 (1.1%)	1 (0.3%)
VASCULAR DISORDERS	5 (0.7%)	0 (0.0%)	0 (0.0%)
HEPATOBILIARY DISORDERS	4 (0.6%)	0 (0.0%)	1 (0.3%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	4 (0.6%)	2 (0.6%)	2 (0.6%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	4 (0.6%)	0 (0.0%)	4 (1.1%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	3 (0.4%)	3 (0.9%)	0 (0.0%)
RENAL AND URINARY DISORDERS	3 (0.4%)	0 (0.0%)	0 (0.0%)
INVESTIGATIONS	2 (0.3%)	0 (0.0%)	1 (0.3%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2 (0.3%)	0 (0.0%)	1 (0.3%)
IMMUNE SYSTEM DISORDERS	1 (0.1%)	3 (0.9%)	0 (0.0%)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	1 (0.1%)	0 (0.0%)	0 (0.0%)
CARDIAC DISORDERS	0 (0.0%)	2 (0.6%)	0 (0.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0 (0.0%)	1 (0.3%)	1 (0.3%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0 (0.0%)	1 (0.3%)	1 (0.3%)
METABOLISM AND NUTRITION DISORDERS	0 (0.0%)	2 (0.6%)	1 (0.3%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0 (0.0%)	1 (0.3%)	0 (0.0%)

Table 10 summarizes the treatment-emergent SAEs that occurred and are related (per investigator) to at least one of the study drugs (i.e. E/C/F/T or ATR or ATV/r + TVD). Multiple AEs were counted only once per subject for each system organ class and preferred term. The numbers of events (5 in total in the E/C/F/T group) were too small to discern an adverse safety trend with respect to E/C/F/T in this analysis. No related SAE was reported in more than 1 subject (per System Organ Class) in the E/C/F/T

group. Two subjects in the ATR group had more than 1 related SAE by preferred term. Subject 1603-6327 had dyspnea exertional, dyspnea, and syncope. Subject 0729-6443 had pyrexia and abdominal pain.

Table 10: Treatment-Emergent Serious Adverse Events at Least Related to E/C/F/T or ATR or ATV/r + TVD by System Organ Class and Preferred Term n (%)

	E/C/F/T	ATR	ATV/r + TVD
Studies (Number of Subjects)	236-0102, 0103 (N=701)	236-0102 (N=352)	236-0103 (N=355)
Number (%) of Subjects Experiencing Any Treatment-Emergent Related SAE	5 (0.7%)	7 (2.0%)	2 (0.6%)
PSYCHIATRIC DISORDERS	1 (0.1%)	2 (0.6%)	0 (0.0%)
DEPRESSION	1 (0.1%)	0 (0.0%)	0 (0.0%)
COMPLETED SUICIDE	0 (0.0%)	1 (0.3%)	0 (0.0%)
SUICIDE ATTEMPT	0 (0.0%)	1 (0.3%)	0 (0.0%)
IMMUNE SYSTEM DISORDERS	1 (0.1%)	0 (0.0%)	0 (0.0%)
DRUG HYPERSENSITIVITY	1 (0.1%)	0 (0.0%)	0 (0.0%)
HEPATOBILIARY DISORDERS	1 (0.1%)	0 (0.0%)	0 (0.0%)
LIVER INJURY	1 (0.1%)	0 (0.0%)	0 (0.0%)
NERVOUS SYSTEM DISORDERS	1 (0.1%)	3 (0.9%)	0 (0.0%)
HEADACHE	1 (0.1%)	1 (0.3%)	0 (0.0%)
SYNCOPE	0 (0.0%)	1 (0.3%)	0 (0.0%)
GRAND MAL CONVULSION	0 (0.0%)	1 (0.3%)	0 (0.0%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (0.1%)	0 (0.0%)	0 (0.0%)
BURKITT'S LYMPHOMA	1 (0.1%)	0 (0.0%)	0 (0.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0 (0.0%)	1 (0.3%)	0 (0.0%)
DYSPNEA EXERTIONAL	0 (0.0%)	1 (0.3%)	0 (0.0%)
DYSPNEA	0 (0.0%)	1 (0.3%)	0 (0.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0 (0.0%)	1 (0.3%)	1 (0.3%)
RASH MACULO-PAPULAR	0 (0.0%)	1 (0.3%)	0 (0.0%)
DRUG ERUPTION	0 (0.0%)	0 (0.0%)	1 (0.3%)
INFECTIONS AND INFESTATIONS	0 (0.0%)	0 (0.0%)	1 (0.3%)
IMPETIGO	0 (0.0%)	0 (0.0%)	1 (0.3%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0 (0.0%)	1 (0.3%)	0 (0.0%)
PYREXIA	0 (0.0%)	1 (0.3%)	0 (0.0%)
GASTROINTESTINAL DISORDERS	0 (0.0%)	1 (0.3%)	0 (0.0%)
ABDOMINAL PAIN	0 (0.0%)	1 (0.3%)	0 (0.0%)

An SAE of Burkitt's lymphoma was reported which was judged related to E/C/F/T by the investigator. This occurred in Subject 1021-7348, a 41 year old male with an unremarkable medical history and a baseline HIV-1 RNA of 76,700 copies/ml and CD4 count of 393 cells/ml. On SD 344 he was diagnosed with Burkitt's lymphoma and on SD 350, E/C/F/T was discontinued due to this SAE. He initiated chemotherapy and the event is continuing at the time of this submission.

An SAE of 'lymphoma' judged unrelated to E/C/F/T by the investigator was also reported. This occurred in Subject 0315-6335, a 34 year old male diagnosed with large cell lymphoma on SD 80.

The SUR documented an additional SAE of 'left testicular mass, Burkitt's lymphoma' judged unrelated to E/C/F/T by the investigator. This occurred in subject 0659-6511, a 40 year old Latin American male, diagnosed with EBV-positive Burkitt's lymphoma based on pathology from an orchiectomy performed on SD 490.

Of note, in the ATR group there was an unrelated (per investigator) SAE for disseminated large cell lymphoma and in the ATV/r + TVD group there was 1 unrelated SAE for Hodgkin's disease and 1 unrelated SAE for B-cell lymphoma.

Please see Section 7.3.5, Submission Specific Primary Safety Concerns, for further details with respect to subjects with renal disorders, neurologic and psychiatric disorders, musculoskeletal disorders, hepatobiliary disorders, gastrointestinal and skin disorders.

7.3.3 Dropouts and/or Discontinuations

Overall, 26 subjects (3.7%) in the E/C/F/T group, 18 subjects (5.1%) in the ATR group, and 18 subjects (5.1%) in the ATV/r + TVD group had at least 1 AE leading to discontinuation. The most common AEs (by System Organ Class) leading to discontinuation in the E/C/F/T group included Psychiatric Disorders (0.7%) and Gastrointestinal Disorders (0.7%). Table 11 summarizes the number (%) of subjects who experienced any treatment-emergent adverse event that led to premature study discontinuation. Multiple AEs were counted only once per subject for each System Organ Class.

Table 11: Number (%) of Subjects Experiencing Any Treatment-Emergent AE Leading to Premature Study Drug Discontinuation by System Organ Class

	E/C/F/T	ATR	ATV/r + TVD
Studies (Number of Subjects)	236-0102, 0103 (N=701)	236-0102 (N=352)	236-0103 (N=355)

Number (%) of Subjects Experiencing Any TEAE Leading to Premature Study Drug Discontinuation	26 (3.7%)	18 (5.1%)	18 (5.1%)
PSYCHIATRIC DISORDERS	5 (0.7%)	6 (1.7%)	1 (0.3%)
GASTROINTESTINAL DISORDERS	5 (0.7%)	0 (0.0%)	5 (1.4%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	4 (0.6%)	3 (0.9%)	2 (0.6%)
INVESTIGATIONS	4 (0.6%)	0 (0.0%)	0 (0.0%)
NERVOUS SYSTEM DISORDERS	3 (0.4%)	3 (0.9%)	2 (0.6%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	3 (0.4%)	5 (1.4%)	4 (1.1%)
RENAL AND URINARY DISORDERS	3 (0.4%)	0 (0.0%)	1 (0.3%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2 (0.3%)	0 (0.0%)	0 (0.0%)
INFECTIONS AND INFESTATIONS	2 (0.3%)	0 (0.0%)	2 (0.6%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	2 (0.3%)	1 (0.3%)	1 (0.3%)
HEPATOBILIARY DISORDERS	1 (0.1%)	0 (0.0%)	2 (0.6%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.1%)	1 (0.3%)	0 (0.0%)
IMMUNE SYSTEM DISORDERS	1 (0.1%)	1 (0.3%)	0 (0.0%)
VASCULAR DISORDERS	1 (0.1%)	1 (0.3%)	0 (0.0%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0 (0.0%)	1 (0.3%)	1 (0.3%)
EYE DISORDERS	0 (0.0%)	0 (0.0%)	4 (1.1%)

Table 12 summarizes the AEs that occurred in more than 1 subject (by preferred term) in the E/C/F/T group and that led to premature discontinuation. Multiple AEs were counted only once per subject for each preferred term.

Table 12: Treatment-Emergent Adverse Events Leading to Premature Study Drug Discontinuation and Occurring in More Than 1 Subject in the Combined E/C/F/T Arms.

	E/C/F/T	ATR	ATV/r + TVD
Studies (Number of Subjects)	236-0102, 0103 (N=701)	236-0102 (N=352)	236-0103 (N=355)
DIARRHEA	2 (0.3%)	0 (0.0%)	1 (0.3%)
NAUSEA	2 (0.3%)	0 (0.0%)	4 (1.1%)
FATIGUE	2 (0.3%)	1 (0.3%)	2 (0.6%)
PYREXIA	2 (0.3%)	1 (0.3%)	0 (0.0%)
HEPATITIS C	2 (0.3%)	0 (0.0%)	0 (0.0%)

BLOOD CREATININE INCREASED	3 (0.4%)	0 (0.0%)	0 (0.0%)
RENAL FAILURE	2 (0.3%)	0 (0.0%)	0 (0.0%)

The following adverse events leading to discontinuation do not appear in Table 12 as each occurred in only 1 subject in the E/C/F/T group. Although each is a discrete Preferred Term, these AEs are closely related to other AEs leading to discontinuation and therefore should be noted. Under 'Neoplasms', 1 subject discontinued for lymphoma and 2 subjects discontinued for 'Burkitt's lymphoma' (one of which was included in the SUR). These three cases are discussed in Section 7.3.2 (Non-Fatal Serious Adverse Events). Under 'Psychiatric Disorders', 1 subject discontinued due to depression and 1 subject discontinued due to a completed suicide. Also under 'Psychiatric Disorders', 1 subject discontinued due to paranoia and another due to schizophrenia. Finally, under 'Renal and Urinary Disorders', in addition to the subjects who discontinued due to 'renal failure' and 'blood creatinine increased', 1 subject discontinued due to 'Fanconi's syndrome'.

In summary, the notable AEs which led to subject discontinuation more frequently in the E/C/F/T group than in either of the comparator groups included a constellation of renal AEs (e.g. 'renal failure', 'Fanconi's syndrome', and 'increased blood creatinine').

Please see Section 7.3.5, Submission Specific Primary Safety Concerns, for further details with respect to subjects with renal disorders, neurologic and psychiatric disorders, musculoskeletal disorders, hepatobiliary disorders, gastrointestinal and skin disorders.

7.3.4 Significant Adverse Events

56% of subjects in the E/C/F/T group experienced any treatment-emergent AE of at least moderate severity compared to 55% in the ATR group, and 62% in the ATV/r + TVD group. Table 13 summarizes the treatment-emergent adverse events of at least moderate severity reported in at least 2% of subjects in the E/C/F/T group. Multiple AEs were counted only once per subject for each Preferred Term.

Table 13: Treatment-Emergent Adverse Events of at Least Moderate Severity (Grades 2-4) Reported in at Least 2% of Subjects Receiving E/C/F/T

	E/C/F/T	ATR	ATV/r + TVD
Studies (Number of Subjects)	236-0102, 0103 (N=701)	236-0102 (N=352)	236-0103 (N=355)
MedDRA Preferred Term, n (%)			
DIARRHEA	40 (5.7%)	15 (4.3%)	27 (7.6%)
NAUSEA	20 (2.9%)	9 (2.6%)	9 (2.5%)
UPPER RESPIRATORY TRACT INFECTION	27 (3.9%)	11 (3.1%)	12 (3.4%)

BRONCHITIS	25 (3.6%)	9 (2.6%)	10 (2.8%)
HEADACHE	29 (4.1%)	5 (1.4%)	9 (2.5%)
BACK PAIN	15 (2.1%)	7 (2.0%)	7 (2.0%)
ARTHRALGIA	14 (2.0%)	2 (0.6%)	6 (1.7%)
DEPRESSION	24 (3.4%)	26 (7.4%)	12 (3.4%)
FATIGUE	14 (2.0%)	14 (4.0%)	14 (3.9%)

The vast majority of the events summarized in Table 13 were of moderate (grade 2) severity in all treatment groups. There were 85 (12.1%) subjects in the E/C/F/T group, 37 (10.5%) subjects in the ATR group, and 45 (12.7%) subjects in the ATV/r + TVD group with grade 3 events. There were 5 (0.7%) subjects in the E/C/F/T group, 6 (1.7%) subjects in the ATR group, and 4 (1.1%) subjects in the ATV/r + TVD group with grade 4 events.

Table 14 summarizes the grade 3 and grade 4 treatment-emergent adverse events that occurred in ≥ 2 subjects in the E/C/F/T group. Multiple AEs were counted only once per subject for each Preferred Term. The System Organ Classes most commonly involved included 'Gastrointestinal Disorders', 'Infections and Infestations', and 'Investigations'.

Table 14: Grade 3 and 4 treatment emergent AEs occurring in ≥ 2 subjects in the E/C/F/T group

	E/C/F/T	ATR	ATV/r + TVD
Studies (Number of Subjects)	236-0102, 0103 (N=701)	236-0102 (N=352)	236-0103 (N=355)
MedDRA Preferred Term, n(%)			
NEUTROPENIA	3 (0.4%)	0 (0.0%)	0 (0.0%)
ABDOMINAL PAIN	6 (0.9%)	2 (0.6%)	3 (0.8%)
NAUSEA	4 (0.6%)	1 (0.3%)	2 (0.6%)
DIARRHOEA	3 (0.4%)	0 (0.0%)	4 (1.1%)
CONSTIPATION	2 (0.3%)	0 (0.0%)	0 (0.0%)
PANCREATITIS	2 (0.3%)	0 (0.0%)	0 (0.0%)
FATIGUE	3 (0.4%)	0 (0.0%)	3 (0.8%)
APPENDICITIS	5 (0.7%)	1 (0.3%)	1 (0.3%)
PNEUMONIA	3 (0.4%)	1 (0.3%)	0 (0.0%)
CELLULITIS	2 (0.3%)	0 (0.0%)	2 (0.6%)
GASTROENTERITIS	2 (0.3%)	1 (0.3%)	0 (0.0%)
URINARY TRACT INFECTION	2 (0.3%)	1 (0.3%)	0 (0.0%)
ALT INCREASED	5 (0.7%)	0 (0.0%)	0 (0.0%)
AST INCREASED	3 (0.4%)	1 (0.3%)	0 (0.0%)
BLOOD CREATININE INCREASED	2 (0.3%)	0 (0.0%)	0 (0.0%)
BACK PAIN	2 (0.3%)	0 (0.0%)	1 (0.3%)
HEADACHE	3 (0.4%)	1 (0.3%)	0 (0.0%)
DEPRESSION	5 (0.7%)	6 (1.7%)	2 (0.6%)
PANIC ATTACK	2 (0.3%)	0 (0.0%)	0 (0.0%)
NEPHROLITHIASIS	2 (0.3%)	0 (0.0%)	0 (0.0%)

7.3.5 Submission Specific Primary Safety Concerns

Renal Assessment

COBI and Change in Estimated GFR:

The Applicant maintains that a modest elevation in serum creatinine levels and decrease in estimated creatinine clearance and estimated GFR (eGFR) is to be expected with the E/C/F/T formulation due to a cobicistat-related inhibition of tubular creatinine secretion, but that actual GFR (aGFR) is not affected. This position is supported by the following: 1) Study GS-US-216-0121 in which aGFR was measured using iohexol after administration of either COBI or ritonavir and where no statistically significant differences were observed at Day 7 or Day 14 (relative to Day 0); and 2) a comparison of creatinine clearance calculated by Cockcroft-Gault with eGFR measured by cystatin C in the pooled safety analysis set of studies 236-0102 and 236-0103. Cystatin C is a low molecular weight protein that is produced at a constant rate by all nucleated cells and is freely filtered by the glomerulus, reabsorbed and catabolized, but not secreted by the renal tubules.

GS-US-216-0121 was a randomized, blinded, placebo-controlled phase 1 study evaluating the effect of COBI and ritonavir on renal function as assessed by markers of glomerular filtration rate. The study consisted of two cohorts; Cohort 1 comprised of 36 healthy subjects with estimated GFR by Cockcroft-Gault ($eGFR_{CG}$) ≥ 80 mL/min, and Cohort 2 comprised of 18 subjects with stable mild-to-moderate renal impairment ($eGFR_{CG}$ 50-79 mL/min). Renal function was assessed on Days 0 (baseline), 7, and 14 in subjects in Cohorts 1 and 2 using $eGFR_{CG}$, estimated GFR by MDRD ($eGFR_{MDRD}$), direct measurement using iohexol clearance (aGFR), cystatin C clearance (cysGFR), and measurement of 24-hour urinary creatinine excretion (mGFR). Statistically significant decreases were observed at Day 7 relative to Day 0 in GFR estimated using serum and/or urinary creatinine to assess renal function ($eGFR_{CG}$, $eGFR_{MDRD}$ and mGFR) in subjects in both cohorts receiving COBI. These decreases were reversible and eGFR (Cohorts 1 and 2) and mGFR (Cohort 1) values had reverted to baseline levels at Day 14. No statistically significant differences relative to Day 0 were observed at Day 7 or Day 14 in aGFR or cysGFR. The Applicant asserts that the time to onset, magnitude, and resolution of the changes in $eGFR_{CG}$, $eGFR_{MDRD}$, and mGFR, together with the absence of statistically significant changes in aGFR and cysGFR, are consistent with inhibition of proximal tubular secretion of creatinine by COBI.

The presence of decline in $eGFR_{CG}$ and the absence of decline in cysGFR in 236-0102 and 236-0103 provide additional support for this assertion. Figure 1a displays the mean

calculated creatinine clearance values by Cockcroft-Gault (in mL/min) from baseline through Week 48 in 236-0102 and 236-0103. The numerical changes from baseline at Week 48 were as follows: E/C/F/T group (mean ± SD change from baseline = -14 ml/min ± 15); ATV/r + TVD group (-9 ml/min ± 16); ATR group (-2 ml/min ± 16). Figure 1b displays eGFR (mL/min) over time from baseline through Week 48 as measured by the cystatin C derived method. Using this method, no mean decline in eGFR in the E/C/F/T group is evident through Week 48 (baseline eGFR = 98.2 mL/min, eGFR at Week 48 = 107.2 mL/min).

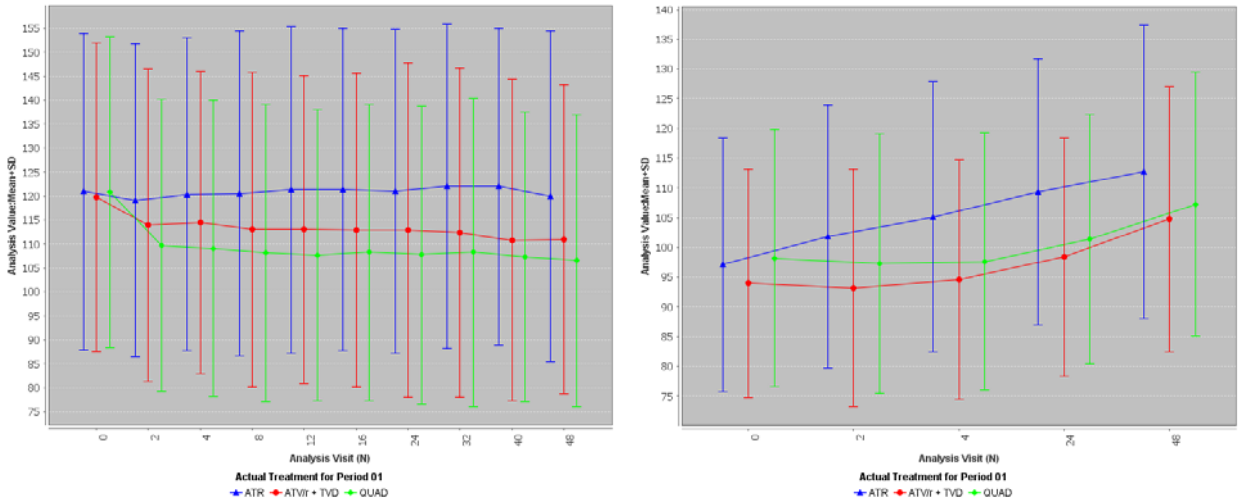

Figure 1a: Creatinine Clearance (mL/min) by Cockcroft-Gault Method over time, mean analysis values with standard deviation; Figure 1b: eGFR (mL/min) by cystatin C-derived Method over time, mean analysis values with standard deviation

Analogous findings to those for $eGFR_{CG}$ were demonstrated for serum creatinine (see Figure 2 below). The changes in mean values (from baseline) at Week 48 were as follows: E/C/F/T group (mean ± SD change = 0.14 mg/dl ± 0.13); ATV/r + TVD group (mean ± SD change = 0.09 mg/dl ± 0.13); ATR group (mean ± SD change = 0.02 mg/dl ± 0.12).

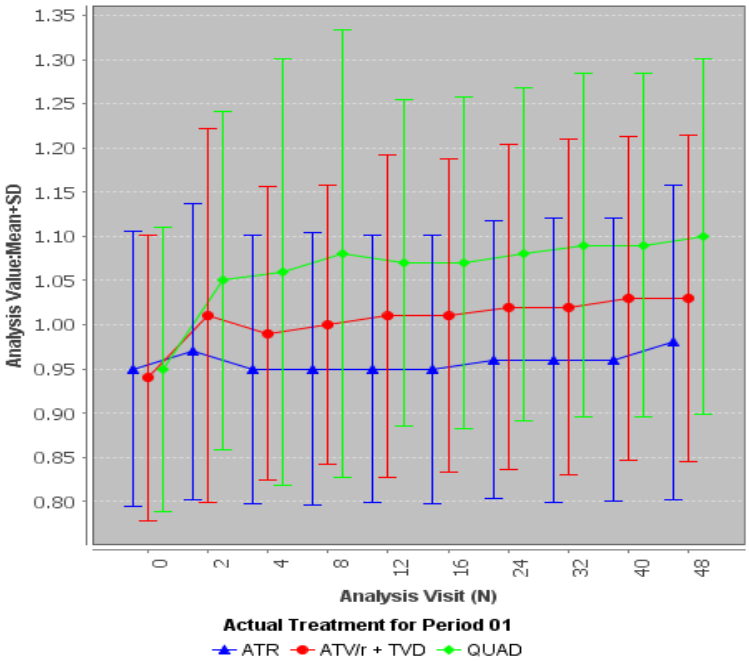

Figure 2: Serum creatinine (mg/dL) over time, mean analysis values with standard deviation

Tenofovir Nephrotoxicity:

Tenofovir, one of the four components of the E/C/F/T FDC tablet, is an acyclic nucleotide analogue reverse transcriptase inhibitor. It is structurally similar to adefovir and cidofovir, both of which have been shown to be nephrotoxic. These two drugs cause acute kidney injury (AKI) such as acute tubular necrosis (ATN) and Fanconi's syndrome, by disrupting proximal tubular mitochondrial function. However, in the case of tenofovir, randomized clinical trials in generally healthy HIV-positive subjects failed to reveal significant renal injury. However, with more widespread use of tenofovir, including patients with other co-morbid conditions, evidence of nephrotoxicity began to appear.[12,17] These reports described AKI including toxic ATN, Fanconi's syndrome and rare cases of nephrogenic diabetes insipidus.

Most reported cases of tenofovir-associated nephropathy identified a partial or complete Fanconi syndrome, with or without a reduction in GFR. Fanconi syndrome is a generalized proximal tubulopathy; in its complete form it includes renal tubular acidosis, glycosuria with normoglycemia, aminoaciduria, hypophosphatemia, hypouricemia, and tubular proteinuria. Tubular dysfunction may precede the decline of renal function. Other manifestations of proximal tubulopathy in individual patients include osteomalacia and decreased bone mass due to phosphate wasting and/or calcitriol deficiency[5].

Tenofovir is eliminated by a combination of glomerular filtration and proximal tubular secretion. It is transported via organic anion transporter (OAT-1) and OAT-3 (to a more limited degree) from the basolateral circulation into the proximal tubular cells, where it is eventually translocated into the urine through apical efflux transporters such as multi-drug resistance protein-2 (MRP-2) and MRP-4. Renal impairment with decreased glomerular filtration rate (GFR) will increase the amount of tenofovir that is secreted, increasing trafficking through the proximal tubular cells. Increasing activity of OAT-1 may increase the amount of tenofovir entering the proximal tubular cells and impaired MRP driven efflux activity can reduce tenofovir secretion and increase intracellular tenofovir concentration[5]. Of note, a single nucleotide polymorphism in the MRP-2 efflux transporter gene (ABCC2) has been documented in HIV-positive patients who developed tenofovir induced nephrotoxicity[19]

Increased tenofovir trafficking and/or increased intracellular concentrations of tenofovir may lead to mitochondrial (mt) DNA depletion and mitochondrial dysfunction. Herlitz et al[8] presented a renal biopsy series of 13 patients with tenofovir nephrotoxicity. The duration of tenofovir therapy at the time of biopsy ranged from 3 weeks to 8 years (median 8 months) with tenofovir being discontinued at the time of biopsy in all patients. The histological and ultrastructural findings demonstrated a distinct pattern of proximal tubular injury characterized by severe mitochondrial damage. Clinical follow-up was available for 11 of the 13 patients. Complete recovery of renal function occurred in 6 patients (including one who required dialysis for 4 months). The five additional patients exhibited partial recovery but did not return to baseline. Three of these five patients required dialysis, each for approximately 1 month. Of note, glycosuria was found in 5 out of 7 non-diabetic patients biopsied for tenofovir nephrotoxicity with increased serum creatinine and residual diuresis. The renal recovery rate described by Herlitz et al was very similar to that described by Malik et al[17] in an earlier case series in which 9 patients out of 19 had their serum creatinine return to baseline after discontinuation of TDF treatment after diagnosis of Fanconi's syndrome.

A number of studies have attempted to assess the risk of renal disease associated with exposure to TDF. In a recent metaanalysis[4], the risk difference for AKI (variably defined in each study) for tenofovir compared to control subjects was estimated to be 0.7% (95% CI 0.2-1.2%). For this specific analysis, Cooper et al surveyed eight studies totaling 7496 participants. No significant risk differences were found for chronic kidney failure (0.2%; 95% CI, -1.5 to 0.2) or end-stage kidney failure requiring long-term dialysis (0.2%; 95% CI, -0.3 to 0.7). A separate study[11] involving a 4-year follow-up of 10,343 tenofovir-treated patients (3700 person-years) in an expanded access program (EAP) disclosed a serious renal adverse event in 0.5%, the SAE 'renal failure' in 0.3%, and an SAE in the category of 'Fanconi / renal tubular disorder / hypophosphatemia / glycosuria' in < 0.1%. However, this analysis had several limitations. First, it was limited by the relatively brief duration of treatment in the EAP, which was a mean of 13

weeks in the US, 24 weeks in the European Union/Australia and 29 weeks in Canada. Second, AE reporting was considered voluntary in some of the country-specific EAPs. Third, only SAEs were assessed, not renal events leading to drug discontinuation or non-serious renal AEs. Any of these factors may have led to an underestimation of the true incidence of renal events of interest. In the same article, the authors assessed the TDF post-marketing safety database (which included 455,392 person-years of TDF exposure) for serious adverse drug reactions (SADR). They found a reporting rate of 43.3/100,000 person years for any renal SADR, 24.2/100,000 person years for 'renal failure' and a rate of 22.4/100,000 person years for a SADR in the category of 'Fanconi / renal tubular disorder / hypophosphatemia / glycosuria'. However, this study was limited by the voluntary nature of adverse drug reaction reporting. A recently published study[20] assessed 10,841 HIV-infected patients from the Veterans Health Administration, and reported that each year of exposure to tenofovir was associated with a 34% increased risk of proteinuria (95% CI 25–45%, p<0.0001), an 11% increased risk of rapid decline in renal function (3–18%, p<0.0033), and a 33% increased risk of chronic kidney disease (18–51%; p<0.0001). In this study, proteinuria was defined as two consecutive urine dipstick measurements ≥30 mg/dL, rapid decline in kidney function was defined as an annual decline in eGFR ≥3 ml/ min/1.73m^2, and chronic kidney disease (CKD) was defined as an eGFR < 60 ml/ min/1.73m^2.

Multivariate analysis of postmarketing clinical data has shown that advanced age, low body weight, higher serum creatinine levels before starting tenofovir treatment, comorbidities (diabetes, hypertension, HCV coinfection) concomitant nephrotoxic medications, advanced HIV infection (low CD4 counts, AIDS), and, in some studies, male sex were risk factors for tenofovir induced GFR reduction[5]. The odds of developing significant renal function reduction were 3.7 times higher for patients receiving tenofovir plus ritonavir-boosted protease inhibitor regimes than for those receiving tenofovir plus non-nucleoside reverse transcriptase inhibitor-based therapy, even adjusting for HIV viral load[21]. It is notable that ritonavir is transported by MRP-2 and co-administration increases tenofovir concentration. It should be noted that a recent study assessing 10,841 HIV-infected patients from the Veterans Health Administration found no significant interactions between TDF renal toxicity and baseline co-morbidities such as advanced HIV disease, pre-existing chronic kidney disease, diabetes and hypertension[20].

The Infectious Diseases Society of America (IDSA) provides the following guidance for renal monitoring of patients receiving TDF: Patients who have a GFR <90 mL/min per 1.73 m^2, patients receiving other medications eliminated via renal secretion (e.g., adefovir, acyclovir, ganciclovir, or cidofovir), patients with other comorbid diseases (e.g., diabetes or hypertension), or patients receiving ritonavir-boosted protease inhibitor regimens should be monitored at least biannually for measurements of renal function, serum phosphorus, and urine analysis for proteinuria and glycosuria.[15] IDSA rates this

guidance as “B-III” indicating that there is moderate evidence to support this recommendation based on opinions of respected authorities, clinical experience, descriptive studies, or reports of expert committees. Of note, other experts in the field have advocated for more frequent laboratory monitoring (i.e. at least every 3 months). These authors argue that a permanent decline in renal function could potentially be avoided by such a screening schedule.[16] The current Department of Health and Human Services guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents recommends renal monitoring for all patients receiving TDF. Specific monitoring recommendations include the following: serum creatinine & calculated creatinine clearance every 3-6 months, serum phosphate every 3-6 months (suggested by some experts), and urinalyses every 6 months. More frequent urinalyses may be indicated for patients with increased risk of renal insufficiency such as patients with diabetes and hypertension.[14]

A review of the literature was performed to assess the frequency of proximal tubulopathy leading to study drug discontinuation in previous clinical trials using tenofovir as a component of a study regimen in treatment-naive patients. In the trials used to support the approval of tenofovir in treatment-naïve patients (Study 903[7] and 934[6]) and the trials used to support the approval of rilpivirine in treatment naïve patients (the ECHO[10] and THRIVE[3] trials), a total of 1,652 treatment naïve subjects received a study regimen which included tenofovir (plus FTC or 3TC). No discontinuations of tenofovir due to Fanconi’s syndrome (or due to any other renal adverse event) were reported through 48 weeks. Long-term follow-up identified no discontinuations due to renal adverse events through 144 weeks[1] in Study 934 and 288 weeks[2] in Study 903.

Treatment Emergent Renal Adverse Events in the Phase 3 Trials:

Table 15 summarizes selected treatment-emergent renal adverse events in the Phase 3 E/C/F/T trials by Preferred Term. These AEs appear under the MedDRA SOCs ‘Renal and Urinary Disorders’ except where noted otherwise. Multiple AEs were counted only once per subject for each preferred term. The notable adverse events that occurred with a higher incidence in the E/C/F/T group than in either of the comparator groups included the following: ‘Fanconi syndrome acquired’, ‘renal failure’, ‘blood creatinine increased’, ‘microalbuminuria’, ‘proteinuria’, ‘nocturia’ and ‘polyuria’.

Table 15: Renal Adverse Events by Preferred Term in Studies 236-0102 and 236-0103

Study Drug(s) Studies (Number of Subjects)	E/C/F/T 236-0102, 0103 (N=701)	ATR 236-0102 (N=352)	ATV/r + TVD 236-0103 (N=355)
Fanconi syndrome acquired	1 (0.1%)	0 (0.0%)	0 (0.0%)
Nephropathy toxic	0 (0.0%)	0 (0.0%)	1 (0.3%)
Renal Failure	4 (0.6%)	1 (0.3%)	0 (0.0%)
Blood creatinine increased[a]	7 (1.0%)	1 (0.3%)	1 (0.3%)
Nephrolithiasis	4 (0.6%)	6 (1.7%)	3 (0.8%)
Hydronephrosis	1 (0.1%)	0 (0.0%)	0 (0.0%)
Nocturia	10 (1.4%)	2 (0.6%)	1 (0.3%)
Polyuria	3 (0.4%)	0 (0.0%)	1 (0.3%)
Renal colic	1 (0.1%)	1 (0.3%)	1 (0.3%)
Hematuria[b]	9 (1.2%)	9 (2.6%)	4 (1.1%)
Leukocyturia	1 (0.1%)	0 (0.0%)	2 (0.6%)
Microalbuminuria	1 (0.1%)	0 (0.0%)	0 (0.0%)
Proteinuria[c]	10 (1.4%)	3 (0.9%)	3 (0.8%)
Pyuria	1 (0.1%)	0 (0.0%)	0 (0.0%)

a. The MedDRA Preferred Term (PT) 'blood creatinine increased' is found in the SOC 'investigation'. None of the subjects with this AE have also reported the AEs 'renal failure', 'fanconi syndrome acquired' or 'nephropathy toxic'.
b. The AE 'hematuria' includes the PTs 'hematuria', plus the terms 'blood urine', 'red blood cells urine positive', and 'blood urine present' which are found in the SOC 'investigations' under the HLT 'urinalysis NEC'. Subjects were counted only once in the event that more than one of these AEs was reported for the same subject.
c. The AE 'proteinuria' includes the PTs 'proteinuria', and the term 'protein urine' found in the SOC 'investigations' under the HLT 'urinalysis NEC'. Subjects were counted only once in the event that more than one of these AEs was reported for the same subject.

Most of the renal AEs summarized in Table 15 were grade 1 or 2 in severity. The following AEs listed in the E/C/F/T group in Table 15 were severity grade 3: 'Fanconi syndrome acquired', 1 of the AEs for 'renal failure', 2 of the AEs for 'blood creatinine increased', 2 of the AEs for 'nephrolithiasis', the AE for 'hydronephrosis', and 1 of the AEs for 'hematuria'. There were no grade 4 AEs reported in this table.

There were four renal related SAEs in the E/C/F/T group. These included 'alcohol poisoning, renal failure, transaminases increased' in Subject 0033-6466 (discussed below), nephrolithiasis in Subject 1236-7114, and two SAEs in Subject 1965-7155 ('congenital ureteric anomaly, hydronephrosis' and 'urinary tract infection'). All of these SAEs were considered unrelated to study drug per investigator and the FDA clinical reviewer agrees with the investigators' causality assessments.

In the pooled Phase 3 studies, 8 subjects in the E/C/F/T group discontinued study drug due to a renal AE (3 subjects with 'renal failure', 1 subject with 'Fanconi syndrome

acquired', 3 subjects with 'blood creatinine increased', and 1 subject with 'increased serum creatinine'). One subject in the ATV/r + TVD group discontinued study drug due to a renal AE ('nephropathy toxic') judged as related to study drug(s) by the investigator and Applicant. Four of the subjects who received E/C/F/T developed proximal renal tubular dysfunction leading to study drug discontinuation. For the FDA safety assessment, 'proximal tubular dysfunction' was defined primarily by the presence of ≥ 2 of the following criteria: 1) normoglycemic glycosuria (≥ 1+), 2) new onset or substantive increase (compared to baseline) in proteinuria, and 3) hypophosphatemia and/or increase (compared to baseline) in fractional excretion of phosphate. In addition, the clinical circumstances surrounding the laboratory abnormalities, the time course and persistence of these abnormalities, and the presence of improvement after discontinuation of study drug(s) were factors applied in judging cases. Using these review criteria, no subjects in the ATR or ATV/r + TVD groups developed proximal tubular dysfunction leading to study drug discontinuation. The laboratory characteristics of the four subjects in the E/C/F/T group with renal tubular dysfunction leading to study drug discontinuation are summarized in Table 16.

Table 16: Subjects with Proximal Tubular Dysfunction Leading to Study Drug Discontinuation in the Studies 236-0102 and 236-0103

Subject Number and Group	Serum Creatinine[b] Creatinine Clearance[e] (Study Date)			Serum PO_4[a,c]	Urine Protein (by dipstick)[a]	Urine Glucose (by dipstick)[a,g]	Fractional Excretion of PO_4 (%)[a]
	Base-line	At Drug d/c[d]	At Last Available Visit				
0663-6049 E/C/F/T	1.26 70.9 (1)	**2.86** 31.8 (66)	**1.70** 55.7 (590)	3.2, 3.4, 3.1	(-), 2+, (-)	(-), (-), (-)	9.8, 29.7, NA[f]
0754-6242 E/C/F/T	1.13 126.9 (1)	**1.78** 80.0 (323)	**1.54** 90.9 (381)	3.5, **1.8**, 3.7	(tr), 2+, 2+	(-), 4+, (tr)	21.9, 64.1, 28.3
0698-6222 E/C/F/T	1.0 82.3 (1)	**1.65** 49.4 (411)	**1.31** 73.2 (505)	3.6, 3.0, 4.8	(tr), 2+, (-)	(-), 2+, (-)	4.8, 25.6, NA
2003-6267 E/C/F/T	**1.52** 68.3 (1)	**4.33** 24.6 (37)	**1.82** 61.3 (512)	3.1, 3.0, **1.9**	(-), 2+, (-)	(-), 2+, (-)	26.5, 73.9, NA

Results in **bold** indicate values outside of the normal range. Laboratory normal ranges were not provided for creatinine clearance, urine protein, urine glucose or fractional excretion of PO_4.
a. The laboratory values listed represent the baseline value, followed by the value reported at the visit on the day of (or most closely preceding) study drug discontinuation, followed by the value at the last available visit.
b. Laboratory normal range for serum creatinine: 0.45-1.35 mg/dL (for 0663-6049 and 2003-6267) and 0.45-1.24 mg/dL (for 0754-6242 and 0698-6222).
c. Laboratory normal range for serum phosphate: 2.2-5.1 mg/dL
d. The laboratory values listed represent the reported value at the visit on the day of or most closely preceding study drug discontinuation. The study date is the exact date of study drug discontinuation.

e. Creatinine Clearance in mL/min as calculated using the Cockcroft-Gault equation.
f. NA = Not Available
g. All positive values documented on the day of or most closely preceding study drug discontinuation were normoglycemic (simultaneous serum glucose ≤ 100 mg/dL)

The mean age of the four subjects was 41 years (range 20-60 years of age) and all were enrolled in U.S. sites. The mean baseline CD4 count was 363 cells/uL (range 263-489). Both Subject 0663-6049 and Subject 2003-6267 were over age 50 (56 and 60 years old respectively), had a past medical history of hypertension, were receiving anti-hypertensive medications, and had a creatinine clearance less than 70 mL/min at either a screening or baseline visit. Both of these subjects had very early onset proximal tubulopathy with renal failure leading to drug discontinuation (at Study Day 66 and 37 respectively). Subject 0754-6242 received oral acyclovir from Day 224 until Day 260; documented NSAID use among these subjects was minimal.

An additional four subjects in the E/C/F/T group and a single subject in the ATV/r + TVD group discontinued study drug due to a renal AE, but did not meet the review definition of proximal tubular dysfunction. The renal AEs included 'renal failure' in 2 subjects, 'blood creatinine increased' in 2 subjects and 'nephropathy toxic' in 1 subject. The laboratory characteristics of these five subjects are summarized in Table 17.

Table 17: Subjects Who Did Not Meet the Review Definition of Proximal Tubular Dysfunction but Developed Renal AEs Leading to Study Drug Discontinuation in Studies 236-0102 and 236-0103

Subject Number and Group	Serum Creatinine[b] Creatinine Clearance[e] (Study Date)			Serum PO_4[a,c]	Urine Protein (by dipstick)[a]	Urine Glucose (by dipstick)[a]	Fractional Excretion of PO_4 (%)[a]
	Base-line	At Drug d/c[d]	At Last Available Visit				
0663-6014 E/C/F/T	0.98 184.0 (1)	**1.54** 120.2 (513)	1.35 135.3 (589)	3.0, 2.8, 3.4	(tr), 1+, (-)	(-), (-), (-)	5.8, 13.3, NA[f]
1602-7555 E/C/F/T	1.15 106.5 (1)	**1.53** 76.0 (422)	**1.39** 86.7 (445)	3.0, 3.5, 3.4	(tr), (tr), (tr)	(-), (-), (-)	4.7, 19.2, NA
0663-6517 E/C/F/T	1.04 91.3 (1)	**1.30** 79.2 (198)	1.01 79.8 (507)	3.4, 3.7, 3.5	(-), (tr), 1+	(-), (-), (-)	9.3, 10.9, NA
1021-7599 E/C/F/T	0.92 111.3 (1)	**1.29** 77.5 (120)	**1.45** 71.8 (417)	3.1, 3.5, 2.7	3+, 2+, 2+	(-), (-), (-)	7.0, 14.6, NA
0663-7308 ATV/r + TVD	0.88 108.1 (1)	**1.43** 63.2 (262)	0.89 107.3 (420)	3.3, 4.3, 3.3	(tr), 1+, 1+	(-), (-), (-)	5.7, 18.0, NA

Results in **bold** indicate values outside of the normal range. Laboratory normal ranges were not provided for creatinine clearance, urine protein, urine glucose or fractional excretion of PO_4.

a. The laboratory values listed represent the baseline value, followed by the value reported at the visit on the day of (or most closely preceding) study drug discontinuation, followed by the value at the last available visit.
b. Laboratory normal range for serum creatinine: 0.45-1.35 mg/dL (for 0663-6014); 0.45-1.24 mg/dL (for 1602-7555, 0663-6517, 1021-7599); 0.35-1.14 mg/dL (for 0663-7308)
c. Laboratory normal range for serum phosphate: 2.2-5.1 mg/dL
d. The laboratory values listed represent the reported value at the visit on the day of or most closely preceding study drug discontinuation. The study date is the exact date of study drug discontinuation.
e. Creatinine Clearance in mL/min as calculated using the Cockcroft-Gault equation.
f. NA = Not Available

In support of this application, the Applicant also provided renal safety data from the Week 48 analysis of Study GS-US-216-0114, an ongoing Phase 3 study in HIV-1 infected treatment naïve subjects to evaluate the safety and efficacy of TVD + ATV boosted with COBI (ATV/COBI) versus TVD + ATV boosted with RTV. A total of 692 subjects received at least one dose of study drug (ATV/COBI + TVD 344, ATV/r + TVD 348). The Applicant identified 14 subjects who experienced a renal AE of interest or discontinued study drug due to renal causes; 6 in the COBI group and 8 in the ritonavir group. We analyzed each case using our review criteria and identified five cases in the ATV/COBI + TVD group and 2 cases in the ATV/r + TVD group as being consistent with proximal tubulopathy. The laboratory characteristics of those 7 subjects are summarized in Table 18.

Table 18: Subjects with Proximal Renal Tubular Dysfunction Leading to Study Drug Discontinuation in GS-US-216-0114

Subject Number	Serum Creatinine[b] Cr Clearance[e] (Study Date)			Serum PO_4[a,c]	Urine Protein (by dipstick)[a]	Urine Glucose (by dipstick)[a,g]	Fractional Excretion of PO_4 (%)[a]
	Base-line	At Drug d/c[d]	At Last Available Visit				
ATV/COBI + TVD							
4142-8361	1.06 87.7 (1)	**5.07** 16.6 (176)	**2.19** NA[f] (211)	4.4, 2.8, NA	(-), 2+, NA	(-), 3+, NA	6.6, 80.8, NA
0691-8292	0.70 97.2 (1)	0.94 70.6 (118)	0.79 85.8 (344)	4.1, **1.9,** 4.2	(tr), 3+, (-)	(-), 3+, (-)	6.8,13.5, 6.6
0986-8283	1.02 100.0 (1)	**3.58** 26.7 (345)	**1.93** 50.9 (378)	3.4, **2.0,** 3.3	(-), 2+, (-)	(-), 1+, (-)	NA, 47.6, NA
4127-8204[i]	0.68 77.4 (1)	0.98 50.4 (364)	0.94 52.6 (426)	3.7, 3.4, 3.6	(tr), 2+, 1+	(-), 1+, (-)	NA, 11.0, NA
2840-8066	1.03 122.4 (1)	**1.79** 76.0 (450)	**1.79** 76.0 (450)	3.1, 2.2, 2.2	(-), 2+, 2+	(-), (-), (-)	4.2, 16.8. 16.8
ATV/r + TVD							
1978-8016	0.91 73.9 (1)	**1.3** 55.1 (237)	1.17 56.7 (498)	2.6, **2.1,** 2.6	(-), 2+, (tr)	(-), 2+, (-)	11, 19.2, NA
3976-8058[h]	1.0 102.0 (1)	**1.56** 70.4 (396)	**1.48** 75.5 (421)	2.6, **1.6,** 2.9	(-), 2+, (tr)	(-), 3+, (tr)	5.2, 33.2, NA

Results in **bold** indicate values outside of the normal range. Laboratory normal ranges were not provided for creatinine clearance, urine protein, urine glucose or fractional excretion of PO_4.
a. The laboratory values listed represent the baseline value, followed by the value reported at the visit on the day of (or most closely preceding) study drug discontinuation, followed by the value at the last available visit.
b. Laboratory normal range for serum creatinine: 0.45-1.35 mg/dL (for 0986-8283); 0.45-1.24 mg/dL (for 4142-8361, 2840-8066, 1978-8016, 3976-8058); 0.35-1.14 mg/dL (for 0691-8292, 4127-8204)
c. Laboratory normal range for serum phosphate: 2.2-5.1 mg/dL
d. The laboratory values listed represent the reported value at the visit on the day of or most closely preceding study drug discontinuation. The study date is the exact date of study drug discontinuation.
e. Creatinine Clearance in mL/min as calculated using the Cockcroft-Gault equation.
f. NA = Not Available
g. All positive values documented on the day of or most closely preceding study drug discontinuation were normoglycemic (simultaneous serum glucose ≤ 100 mg/dL) except for Subject 4142-8361 who had a simultaneous serum glucose of 137 mg/dL and Subject 4127-8204 who had a simultaneous serum glucose of 103 mg/dL.
h. Discontinuation values for this subject are from study day 397.
i. Discontinuation values for this subject are from study day 365.

In the five cases consistent with proximal tubulopathy in the ATV/COBI + TVD group in study 216-0114, the mean age of subjects was 44 years of age (range 30-51 years old). Two subjects were female and three were male. The mean baseline CD4 count was 324 cells/uL (range 145-478), and only 1 subject had a baseline CD4 count < 200 (145 cells/uL). One subject had a history of type 2 diabetes mellitus. No subjects had a history of hypertension or were receiving concomitant nephrotoxic agents. In the two cases consistent with proximal tubulopathy in the ATV/r + TVD group, both subjects were male and 48 years of age. Their mean baseline CD4 count was 432 (range 292-571). One subject had a baseline CrCl < 90 mL/min, but neither subject had a significant past medical history or was receiving concomitant nephrotoxic medications.

Table 19 summarizes the timing of onset of proteinuria and glycosuria in the 11 subjects who discontinued study drug with evidence of proximal tubular dysfunction in studies 236-0102, 236-0103 and 216-0114. All 11 of these subjects developed urinary glucose and/or protein abnormalities that preceded discontinuation of study drug. Eight of these subjects had a change in serum creatinine of < 0.4 mg/dL at the time of the 1st documented urinary abnormality.

Table 19: Timing of Onset of Proteinuria & Glycosuria (Studies 236-0102, 236-0103 and 216-0114)

Subject #, Group	Study Day of Drug d/c	Study Day of 1st Urine Protein ≥ 1+ (actual value)	Study Day of 1st Urine Glucose ≥ 1+ (actual value)[a]	Δ Serum Cr from baseline[c] at the 1st reported Urine Protein and/or Urine Glucose[a] ≥ 1+
Studies 236-0102 and 236-0103				
0663-6049 E/C/F/T	66	16 (1+)	NG[b]	0.63
0754-6242 E/C/F/T	323	15 (1+)	52 (2+)	0.23
0698-6222 E/C/F/T	411	84 (1+)	279 (1+)	0.23
2003-6267 E/C/F/T	37	16 (2+)	16 (2+)	0.95
Study 216-0114				
4142-8361 ATV/c + TVD	176	29 (1+)	170 (3+)	0.37
0691-8292 ATV/c + TVD	118	29 (1+)	113 (3+)	0.22
0986-8283 ATV/c + TVD	345	225 (1+)	337 (1+)	0.62
4127-8204[i] ATV/c + TVD	364	110 (1+)	229 (3+)	0.13
2840-8066 ATV/c + TVD	450	114 (1+)	226 (1+)	0.33
1978-8016 ATV/r + TVD	237	84 (1+)	167 (1+)	0.20

3976-8058[h] ATV/r + TVD	396	281 (2+)	225 (1+)	0.32

a. All positive values documented were normoglycemic (simultaneous serum glucose ≤ 100 mg/dL) except for Subject #5 who had simultaneous serum glucose of 137 mg/dL, Subject #8 who had simultaneous serum glucose of 130 mg/dL, Subject #10 who had a simultaneous serum glucose of 118 mg/dL, and Subject #11 who had a simultaneous serum glucose of 103 mg/dL.
b. NG = subject did not develop glycosuria
c. Serum creatinine was reported in mg/dL

Table 20 summarizes these subjects' baseline serum creatinine values, their peak serum creatinine levels while receiving study drug, and their nadir serum creatinine levels following study drug discontinuation. The final column summarizes the number of days between discontinuation of study drug and the reported nadir serum creatinine value. Ten of these 11 subjects had laboratory follow-up information available after study drug discontinuation. Subject 2840-8066 did not have follow-up laboratory data. In 8 of those 10 subjects with available follow-up data, serum creatinine has not returned to the subjects' baseline values at the time of this analysis. Of note, in some cases the change in serum creatinine may not be the best reflection of change in renal function. As an example, Subject 4127-8204 whose serum creatinine value always remained within normal limits, had a baseline creatinine clearance of 77 mL/min, a nadir of 44, and a maximal recovery to 53 mL/min. This table illustrates that although all subjects showed improvement (and often substantive improvement) in serum creatinine after discontinuing study drug, the majority of subjects have not returned to their baseline values. However, the follow-up of many of the subjects is still ongoing.

Table 20: Renal Recovery Following Study Drug Discontinuation (Studies 236-0102, 236-0103 and Study 216-0114)

Subject Number, Group	Baseline sCr (Study Day 1)	Peak sCr on Study Drug	Nadir sCr after Study Drug d/c	Number of Days Between Study Drug d/c and Nadir sCr
Studies 236-0102 and 236-0103				
0663-6049, E/C/F/T	1.3	2.9	1.5	439
0754-6242, E/C/F/T	1.1	2.0	1.5	58
0698-6222, E/C/F/T	1.0	1.7	1.3	94
2003-6267, E/C/F/T	1.5	4.3	1.4	384
Study 216-0114				
4142-8361, ATV/c + TVD	1.1	5.1	2.1	31
0691-8292, ATV/c + TVD	0.7	0.9	0.7	51
0986-8283, ATV/c + TVD	1.0	3.6	1.9	33
4127-8204[i],ATV/c + TVD	0.7	1.2	0.9	62
2840-8066, ATV/c + TVD	1.0	1.8	1.8	0
1978-8016, ATV/r + TVD	0.9	1.3	1.0	48
3976-8058[h],ATV/r + TVD	1.0	1.6	1.5	25

Laboratory Abnormalities Related to Renal Function in Studies 236-0102 and 236-0103:

Serum Creatinine, Serum Phosphate, and Serum Magnesium

Table 21 summarizes the serum creatinine, phosphate, and magnesium laboratory abnormalities by severity grade. 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 post-baseline maximum severity for each laboratory test. Of note, there was a higher overall incidence of graded creatinine abnormalities in the E/C/F/T group (7.1%) than in either the ATR group (1.2%) or the ATV/r + TVD group (4.3%). These differences were primarily driven by grade 1 events.

Table 21: Graded Serum Creatinine Elevations and Graded Hypophosphatemia and Hypomagnesemia

Study Drug(s) Studies (Number of Subjects)	E/C/F/T 236-0102, 0103 (N=701)	ATR 236-0102 (N=352)	ATV/r + TVD 236-0103 (N=355)
# of Subjects used in this Analysis	699	351	352
Serum Creatinine, maximum toxicity grade, n (%)			
Grade 1 (> 1.5 to 2 mg/dL)	47 (6.7%)	3 (0.9%)	14 (4.0%)
Grade 2 (> 2 to 3 mg/dL)	2 (0.3%)	1 (0.3%)	1 (0.3%)
Grade 3 (> 3 to 6 mg/dL)	1 (0.1%)	0 (0.0%)	0 (0.0%)
All Grades	50 (7.1%)	4 (1.2%)	15 (4.3%)
Serum Phosphate, maximum toxicity grade, n (%)			
Grade 1 (2.0 mg/dL to < LLN)	33 (4.7%)	11 (3.1%)	13 (3.7%)
Grade 2 (1.5 to < 2.0 mg/dL)	12 (1.7%)	5 (1.4%)	7 (2.0%)
Grade 3 (1.0 to < 1.5 mg/dL)	1 (0.1%)	0 (0.0%)	2 (0.6%)
All Grades	46 (6.5%)	16 (4.5%)	22 (6.3%)
Serum Magnesium, maximum toxicity grade, n (%)			
Grade 1 (1.45 mg/dl to < LLN)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Grade 2 (1.09 to < 1.45 mg/dL)	2 (0.3%)	1 (0.3%)	0 (0.0%)
All Grades	3 (0.4%)	1 (0.3%)	0 (0.0%)

Urine Glucose, Urine Protein, and Hematuria:

Table 22 summarizes proteinuria and glycosuria by toxicity grade. 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 post-baseline maximum severity for each laboratory test. There was a higher overall incidence of proteinuria in the E/C/F/T group (38.7%) than in either the ATR group (28.7%) or the ATV/r + TVD group (24.2%). This

was driven primarily by an increased incidence of both grade 1 and grade 2 proteinuria in the E/C/F/T group compared to the control arms. The incidence of glycosuria in the E/C/F/T group was not increased compared to the ATR or ATV/r + TVD groups.

Table 22: Proteinuria and Glycosuria

Study Drug(s) Studies (Number of Subjects)	E/C/F/T 236-0102, 0103 (N=701)	ATR 236-0102 (N=352)	ATV/r + TVD 236-0103 (N=355)
# of Subjects used in this Analysis	699	351	352
Urine Protein			
Grade 1 (1+ proteinuria)	225 (32.2%)	97 (27.6%)	69 (19.6%)
Grade 2 (2-3+ proteinuria)	43 (6.2%)	4 (1.1%)	15 (4.3%)
Grade 3 (4+ proteinuria)	2 (0.3%)	0 (0.0%)	1 (0.3%)
All Grades	270 (38.7%)	101 (28.7%)	85 (24.2%)
Urine Glucose			
Grade 1 (2+ glycosuria)	4 (0.6%)	0 (0.0%)	8 (2.3%)
Grade 2 (3+ glycosuria)	6 (0.9%)	3 (0.9%)	7 (2.0%)
Grade 3 (4+ glycosuria)	6 (0.9%)	2 (0.6%)	5 (1.4%)
All Grades	16 (2.4%)	5 (1.5%)	20 (5.7%)

We performed an analysis of the data from the pooled Phase 3 E/C/F/T group (N = 699) in which normoglycemic glycosuria was defined as urine glucose ≥ 1+ with concurrent blood glucose levels ≤ 100 mg/dL, and proteinuria as urine protein ≥ 1+. In that analysis, only 10 subjects (1.4%) developed normoglycemic glycosuria, and of those 10 subjects, 3 (0.4%) developed proximal tubulopathy leading to discontinuation of study drug. Using the same analysis criteria, only 6 subjects (0.9%) developed concurrent proteinuria and normoglycemic glycosuria, and 3 (0.4%) of those 6 subjects developed proximal tubulopathy leading to discontinuation of study drug.

In study 216-0114, 7 subjects (including 5 subjects in the ATV/COBI + TVD arm and 2 subjects in the ATV/r + TVD arm) discontinued study drug with evidence of proximal tubular dysfunction. Five of these 7 subjects had documented normoglycemic glycosuria (simultaneous serum glucose ≤ 100 mg/dL), and all 7 of these subjects had concurrent proteinuria and glycosuria (with normoglycemia in 5 of the subjects) documented at one or more study visits.

There was a slightly higher overall incidence of graded hematuria in the E/C/F/T group (13.6%) compared to the ATR group (10.8%) or the ATV/r + TVD group (12.8%). This included a higher incidence of grade 3 (the highest grade reached) events in the E/C/F/T group (3.0%) compared to the ATR group (1.4%) or the ATV/r + TVD group (2.3%).

Assessment of Potential Renal Toxicity:

The disproportionate number of renal adverse events leading to study drug discontinuation (including proximal tubulopathies) in the E/C/F/T group combined with a higher frequency of graded serum creatinine and urine protein abnormalities raise a question as to whether two discrete processes may be at work: a non-pathologic decrease in eGFR as the Applicant maintains and a bona fide increased risk of renal dysfunction. The difficulty arises in assessing for and rapidly discriminating between these two events, as a modest elevation in creatinine and modest decline in eGFR is anticipated with the use of E/C/F/T, but prolonged use in the setting of renal injury should be avoided.

The Applicant proposes the following renal safety measures in the draft label with respect to the use of E/C/F/T: 1) assess CrCl before initiating treatment with E/C/F/T and do not initiate treatment in patients with a CrCl < 70 mL/min; 2) discontinue E/C/F/T if the estimated CrCl declines below 50 mL/min; 3) perform routine monitoring of estimated CrCl and serum phosphorus in patients with renal impairment or at risk of renal impairment; 4) avoid administration of E/C/F/T with concurrent or recent use of nephrotoxic drugs.

In addition to the Applicant's suggested renal safety monitoring plan the following measures should also be considered: 1) extending renal monitoring to all E/C/F/T recipients; 2) monitoring urine protein and urine glucose and; 3) providing a creatinine threshold to distinguish the effect of COBI on serum creatinine from genuine renal dysfunction.

Renal monitoring is currently recommended for all patients receiving tenofovir per DHHS guidelines[14]. In the Phase 3 studies, 236-0102, 236-0103 and 216-0114, it was not possible to wholly predict who would develop proximal tubulopathy based solely on their risk factors. Eleven subjects discontinued study drug with evidence of proximal tubular dysfunction in these studies. Four of these 11 subjects had a CrCl > 90 mL/min at baseline, had no history of either hypertension or diabetes mellitus, and were not receiving a ritonavir-boosted protease inhibitor. The only potential risk factors for these subjects were a baseline CD4 count of 145 cells/uL in one subject and receipt of oral acyclovir for 36 days in another subject. However the latter subject had new onset normoglycemic glycosuria, worsening proteinuria, and a serum creatinine increase from 1.1 to 2.0 prior to starting acyclovir.

Urine dipstick testing for protein and glucose is a non-invasive, inexpensive, and widely available method. It is currently recommended every six months for all patients receiving tenofovir (per DHHS guidelines) and more frequently for patients with

increased risk of renal insufficiency. Unlike serum creatinine and creatinine clearance, urinary protein and glucose measurements would not be confounded by COBI's impact on creatinine secretion. In the Phase 3 studies, abnormal urinary protein and glucose findings were shown to pre-date drug discontinuation due to tubulopathy in all subjects, and pre-date appreciable increases in serum creatinine (for example greater than 0.4 mg/dL) in the majority of subjects who discontinued study drug due to tubulopathy.

Providing health care professionals with laboratory thresholds to help distinguish the expected effect of COBI on serum creatinine and creatinine clearance from that of genuine renal dysfunction would serve two important functions. It would aid health care providers in identifying patients with true renal dysfunction and prevent prolonged exposure to drug in this setting, and it could also help prevent unnecessary discontinuations of E/C/F/T related to anticipated laboratory changes. Judging a patient as intolerant to tenofovir due to presumed renal toxicity and thereby losing tenofovir as a future treatment option is of considerable importance. The selection of appropriate thresholds would require balancing these two important considerations. Based on a review of the data, a confirmed change in serum creatinine ≥ 0.4 mg/dL from baseline might be an appropriate threshold **to trigger more intensive renal safety monitoring**. We define confirmed change as a change that was documented on two consecutive visits. The value of 0.4 mg/dL is equal to the mean change in serum creatinine + 2 standard deviations measured at week 48 in the E/C/F/T subjects in the pooled Phase 3 trials. In these pooled trials, only 17 subjects (or 2.4%) of the E/C/F/T group had a change in serum creatinine ≥ 0.4 mg/dL on two consecutive visits. These 17 subjects included all 4 E/C/F/T subjects who discontinued due to proximal tubulopathy. It appears, therefore, that 0.4 mg/dL may be a reasonable threshold to discriminate the anticipated effect of COBI from genuine renal dysfunction in subjects receiving E/C/F/T and to trigger more intensive renal safety monitoring.

Psychiatric Adverse Events

Adverse psychiatric events in the E/C/F/T group were primarily related to sleep disorders and disturbances, depressed mood disorders and disturbances, and anxiety disorders and symptoms.

Table 23 summarizes the treatment-emergent mood disorders by a derived group term and MedDRA Preferred Term. For this analysis, the following MedDRA High Level Group Terms were grouped together under the non-MedDRA category of "mood disorders": depressed mood disorders and disturbances, mood disorders and disturbances NEC, manic and bipolar mood disorders and disturbances, suicidal and self-injurious behaviors NEC (which included the preferred terms 'completed suicide,' 'suicide attempt,' and 'suicidal ideation'), and adjustment disorders (including subtypes). However adjustment disorders (including subtypes) was limited to the Preferred Terms

'adjustment disorder with mixed anxiety and depressed mood' and 'adjustment disorder with depressed mood' and did not include the Preferred Term 'adjustment disorder.' Multiple AEs were counted only once per subject for the derived term "mood disorders" and for each Preferred Term.

Table 23: Treatment-Emergent Mood Disorders by Derived Group Term and Preferred Term

	E/C/F/T	ATR	ATV/r + TVD
Studies (Number of Subjects)	236-0102, 0103 (N=701)	236-0102 (N=352)	236-0103 (N=355)
Derived Grouped Term n (%) and Preferred Term n (%)			
MOOD DISORDERS	67 (9.6%)	49 (13.9%)	29 (8.2%)
ANHEDONIA	1 (0.1%)	0 (0.0%)	0 (0.0%)
DEPRESSED MOOD	1 (0.1%)	2 (0.6%)	2 (0.6%)
DEPRESSION	53 (7.6%)	39 (11.1%)	23 (6.5%)
MAJOR DEPRESSION	4 (0.6%)	0 (0.0%)	0 (0.0%)
AFFECT LABILITY	1 (0.1%)	1 (0.3%)	1 (0.3%)
AFFECTIVE DISORDER	0 (0.0%)	1 (0.3%)	0 (0.0%)
ANGER	2 (0.3%)	0 (0.0%)	0 (0.0%)
ELEVATED MOOD	0 (0.0%)	1 (0.3%)	0 (0.0%)
EMOTIONAL DISORDER	1 (0.1%)	0 (0.0%)	0 (0.0%)
EUPHORIC MOOD	1 (0.1%)	2 (0.6%)	0 (0.0%)
MOOD SWINGS	2 (0.3%)	2 (0.6%)	1 (0.3%)
BIPOLAR DISORDER	4 (0.6%)	0 (0.0%)	1 (0.3%)
BIPOLAR I DISORDER	0 (0.0%)	1 (0.3%)	0 (0.0%)
HYPOMANIA	0 (0.0%)	0 (0.0%)	1 (0.3%)
COMPLETED SUICIDE	1 (0.1%)	1 (0.3%)	0 (0.0%)
SUICIDAL IDEATION	2 (0.3%)	0 (0.0%)	1 (0.3%)
SUICIDE ATTEMPT	0 (0.0%)	2 (0.6%)	1 (0.3%)
ADJUSTMENT DISORDER WITH DEPRESSED MOOD	1 (0.1%)	0 (0.0%)	0 (0.0%)
ADJUSTMENT DISORDER WITH MIXED ANXIETY AND DEPRESSED MOOD	0 (0.0%)	0 (0.0%)	1 (0.3%)

E/C/F/T fared favorably when compared to ATR with respect to the derived term "mood disorders," but had a slightly higher incidence of "mood disorders" when compared to ATV/r + TVD. All of the AEs related to "mood disorders" in the E/C/F/T group were of mild to moderate severity (grade 1 or 2), except for 7 subjects who had grade 3 adverse events (5 with depression, 1 with major depression, & 1 with anger), and 1 death (completed suicide).

Table 24 summarizes the treatment-emergent sleep disorders by MedDRA HLGTs and Preferred terms. Multiple AEs were counted only once per subject for the HLGT and for each Preferred Term.

Table 24: Treatment-Emergent Sleep Disorders by MedDRA HLGT and Preferred Term

	E/C/F/T	ATR	ATV/r + TVD
Studies (Number of Subjects)	236-0102, 0103 (N=701)	236-0102 (N=352)	236-0103 (N=355)
MedDRA HLGT and Preferred Terms n (%)			
SLEEP DISORDERS AND DISTURBANCES	119 (17%)	130 (36.9%)	35 (9.9%)
ABNORMAL DREAMS	65 (9.3%)	95 (27.0%)	14 (3.9%)
INITIAL INSOMNIA	0 (0.0%)	1 (0.3%)	0 (0.0%)
INSOMNIA	59 (8.4%)	49 (13.9%)	18 (5.1%)
NIGHTMARE	4 (0.6%)	7 (2.0%)	3 (0.8%)
SLEEP DISORDER	7 (1.0%)	4 (1.1%)	3 (0.8%)

Although E/C/F/T fared favorably when compared to ATR, the comparison of E/C/F/T to ATV/r + TVD was less favorable with respect to sleep disorders and disturbances. However, all of these adverse events in the E/C/F/T group were of mild or moderate (grade 1 or 2) severity except for 1 subject with grade 3 insomnia. Also, no subject in the E/C/F/T group discontinued study drug due to sleep disturbances.

There was no notable difference in incidence of anxiety disorders and symptoms (by MedDRA HLGT) when comparing E/C/F/T (4.9%) to ATR (5.1%) or ATV/r + TVD (4.8%).

With respect to treatment-emergent sexual dysfunctions and disturbances E/C/F/T compared favorably against ATV/r + TVD (incidence of 1.3% versus 3.1% respectively) but less favorably when compared to ATR (incidence of 1.3% versus 0.6% respectively). The great majority of the AEs in all study groups related to decreased libido, with an incidence of 1.1% in the E/C/F/T group compared to 2.8% in the ATV/r + TVD group and 0.6% in the ATR group.

Five subjects had psychiatric AEs that led to discontinuation of E/C/F/T. These AEs included the following: 'completed suicide,' 'depression,' 'paranoia,' 'schizophrenia,' and 'self-esteem decreased.' The AEs of 'paranoia' and 'depression' were judged related to study drugs by the investigator. This reviewer agrees with the investigator assessment with respect to 'paranoia' as the subject experienced resolution of the AE rapidly upon discontinuation of the study drug. The relationship of E/C/F/T to the case of depression is less strong given the subject's underlying history of depression and concomitant

changes in psychiatric medication that preceded the event. The event of 'schizophrenia' was judged not related to E/C/F/T by the investigator. Although the subject (0407-7528) does have a pre-existing history of depression and bipolar disorder, the subject's unremarkable psychiatric assessment at study day 29, followed by onset of the adverse event relatively early after initiation of study drug (study day 32) argues for the possible relationship of E/C/F/T to the event. Please see Section 7.3.1 (Deaths) for further details on the AE 'completed suicide.'

In summary, E/C/F/T fared favorably when compared to ATR with respect "mood disorders", but had a slightly higher incidence of "mood disorders" when compared to ATV/r + TVD. Most of the mood disorder-related AEs in the E/C/F/T group were of mild to moderate severity. There were two discontinuations in the E/C/F/T group related to the mood disorder AEs, 'completed suicide' and 'depression'. With respect to sleep disorders and disturbances, E/C/F/T fared favorably when compared to ATR, but less favorably when compared to ATV/r + TVD. However, virtually all of these adverse events in the E/C/F/T group were of mild or moderate severity and none led to the discontinuation of E/C/F/T.

Musculoskeletal Adverse Events

Overall, musculoskeletal adverse events (by MedDRA SOC) were more common in the E/C/F/T group (21.3%) than in either of the comparator groups (ATR 15.6%, ATV/r + TVD 15.5%). The majority of these events were of mild or moderate severity (i.e. grade 1 or 2). Four grade 3 adverse events occurred in subjects receiving E/C/F/T (2 for back pain, 1 for synovitis and 1 for osteitis). One grade 4 event, rhabdomyolysis, occurred in the E/C/F/T group.

Table 25 summarizes the treatment-emergent musculoskeletal events by the MedDRA HLGTs 'Musculoskeletal and Connective Tissue Disorders NEC' and 'Muscle Disorders.' Multiple AEs were counted only once per subject for each MedDRA High Level Group Term and Preferred Term. The E/C/F/T group had a greater incidence of adverse events than either comparator group when assessing AEs by these HLGTs. Adverse events by Preferred Term that occurred in ≥ 1% of E/C/F/T subjects included 'back pain', 'musculoskeletal pain', 'pain in extremity', 'muscle spasms' and 'myalgias'. The incidences of these AEs were higher in the E/C/F/T group than in either of the comparator groups.

Table 25: Treatment-Emergent Musculoskeletal Adverse Events by Selected MedDRA HLGTs (Musculoskeletal and Connective Tissue Disorders NEC and Muscle Disorders) and Preferred Terms

	E/C/F/T	ATR	ATV/r + TVD
Studies (Number of Subjects)	236-0102,	236-0102	236-0103

	0103 (N=701)	(N=352)	(N=355)
MedDRA High Level Group Term & Preferred Terms, n (%)			
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS NEC	81 (11.6%)	34 (9.7%)	25 (7.0%)
BACK PAIN	37 (5.3%)	14 (4.0%)	13 (3.7%)
FLANK PAIN	3 (0.4%)	1 (0.3%)	1 (0.3%)
GROIN PAIN	1 (0.1%)	0 (0.0%)	1 (0.3%)
LIMB DISCOMFORT	1 (0.1%)	1 (0.3%)	0 (0.0%)
MUSCULOSKELETAL CHEST PAIN	3 (0.4%)	2 (0.6%)	0 (0.0%)
MUSCULOSKELETAL DISCOMFORT	1 (0.1%)	0 (0.0%)	0 (0.0%)
MUSCULOSKELETAL PAIN	7 (1.0%)	1 (0.3%)	3 (0.8%)
MUSCULOSKELETAL STIFFNESS	6 (0.9%)	1 (0.3%)	0 (0.0%)
NECK MASS	1 (0.1%)	0 (0.0%)	0 (0.0%)
NECK PAIN	3 (0.4%)	5 (1.4%)	3 (0.8%)
PAIN IN EXTREMITY	27 (3.9%)	13 (3.7%)	9 (2.5%)
PLANTAR FASCIITIS	2 (0.3%)	1 (0.3%)	0 (0.0%)
SENSATION OF HEAVINESS	1 (0.1%)	0 (0.0%)	1 (0.3%)
MUSCLE DISORDERS	35 (5.0%)	12 (3.4%)	14 (3.9%)
COMPARTMENT SYNDROME	0 (0.0%)	0 (0.0%)	1 (0.3%)
MUSCLE SPASMS	13 (1.9%)	4 (1.1%)	1 (0.3%)
MUSCLE TIGHTNESS	0 (0.0%)	0 (0.0%)	1 (0.3%)
MUSCLE TWITCHING	1 (0.1%)	0 (0.0%)	0 (0.0%)
MUSCULAR WEAKNESS	1 (0.1%)	0 (0.0%)	0 (0.0%)
MYALGIA	19 (2.7%)	8 (2.3%)	9 (2.5%)
MYOSITIS	0 (0.0%)	1 (0.3%)	2 (0.6%)
RHABDOMYOLYSIS	2 (0.3%)	0 (0.0%)	1 (0.3%)

The E/C/F/T group had a higher incidence of muscle injury (0.4%) and muscle rupture (0.3%) compared to the control groups who reported neither adverse event. These events were of grade 1 or 2 in severity.

The E/C/F/T group had a greater incidence of adverse events than either comparator group when assessing AEs by the HLGTs of 'Joint Disorders' and 'Tendon, Ligament, and Cartilage Disorders'. Adverse events by Preferred Term occurring in ≥ 1% of E/C/F/T subjects included 'arthralgias' and 'tendonitis'. 'Arthalgias' occurred in 4.1% of subjects in the E/C/F/T group, 2.6% of subjects in the ATR group, and 3.4% of subjects in the ATV/r + TVD group. 'Tendonitis' occurred in 1.0% of subjects in the E/C/F/T group, 0.3% of subjects in the ATR group, and 0.8% of subjects in the ATV/r + TVD group. There were no reports of 'tendon rupture' in the E/C/F/T group and only 1 subject with the adverse event, 'tendon injury'.

Table 26 summarizes the treatment-emergent musculoskeletal events by the MedDRA HLGTs 'Bone Disorders'. Multiple AEs were counted only once per subject for each High Level Group Term and Preferred Term. E/C/F/T fared favorably when compared to ATV/r + TVD with respect to 'bone disorders,' but had a slightly higher incidence of 'bone disorders' when compared to ATR. However, the total number of events was small and no adverse events by Preferred Term occurred in ≥ 1% of E/C/F/T subjects. The combined incidence of 'osteopenia' and 'osteoporosis' was 1.3% in the E/C/F/T group compared to 0.0% in the ATR group and 2.2% in the ATV/r + TVD group.

Table 26: Treatment-Emergent Musculoskeletal Adverse Events by MedDRA HLGT (Bone Disorders) and Preferred Terms

	E/C/F/T	ATR	ATV/r + TVD
Studies (Number of Subjects)	236-0102, 0103 (N=701)	236-0102 (N=352)	236-0103 (N=355)
MedDRA High Level Group Term & Preferred Term n (%)			
BONE DISORDERS (EXCL CONGENITAL AND FRACTURES)	13 (1.9%)	1 (0.3%)	8 (2.3%)
BONE PAIN	2 (0.3%)	0 (0.0%)	0 (0.0%)
EXOSTOSIS	0 (0.0%)	0 (0.0%)	1 (0.3%)
MEDIAL TIBIAL STRESS SYNDROME	1 (0.1%)	0 (0.0%)	0 (0.0%)
OSTEITIS	1 (0.1%)	0 (0.0%)	0 (0.0%)
OSTEOPENIA	4 (0.6%)	0 (0.0%)	4 (1.1%)
OSTEOPOROSIS	5 (0.7%)	0 (0.0%)	4 (1.1%)
PAIN IN JAW	0 (0.0%)	1 (0.3%)	0 (0.0%)

The overall frequency of bone fractures was 1.3% in the E/C/F/T group compared to 1.7% in the ATR group and 1.7% in the ATV/r + TVD group. Table 27 summarizes the treatment-emergent bone fractures, focusing on the anatomic sites particularly associated with osteoporotic fractures including the vertebrae, hip, pelvis, humerus, and wrist. No substantive difference in incidence was apparent in the E/C/F/T group when compared to the control arms. Multiple AEs were counted only once per subject for each Preferred Term. The majority of these adverse events were grade 1 or 2 in severity. There were two grade 3 AEs in the E/C/F/T group (femur fracture & lumbar vertebral fracture), and no grade 4 AEs. Trauma was a component in several of these AEs.

Table 27: Treatment-Emergent Bone Fractures at Anatomic Sites Associated with Osteoporotic Fractures

	E/C/F/T	ATR	ATV/r + TVD
Studies (Number of Subjects)	236-0102, 0103 (N=701)	236-0102 (N=352)	236-0103 (N=355)

MedDRA Preferred Terms, n (%)			
FEMUR FRACTURE	1 (0.1%)	0 (0.0%)	0 (0.0%)
LUMBAR VERTEBRAL FRACTURE	2 (0.3%)	0 (0.0%)	0 (0.0%)
THORACIC VERTEBRAL FRACTURE	0 (0.0%)	0 (0.0%)	1 (0.3%)
UPPER LIMB FRACTURE	0 (0.0%)	2 (0.6%)	2 (0.6%)
WRIST FRACTURE	0 (0.0%)	1 (0.3%)	0 (0.0%)

The Applicant conducted a DEXA substudy in a subset of 120 subjects (E/C/F/T 54, ATV/r + TVD 66) in GS-US-236-0103. Table 28 summarizes the results of the bone mineral density (BMD) findings at Week 48 compared to baseline. There was a decline in lumbar spine and hip BMD in both treatment groups with no statistically significant difference in the percentage change from baseline to Week 48 between the treatment groups.

Table 28: Percentage Change from Baseline in Bone Mineral Density (G/CM^2) of the Lumbar Spine and Hip (Femur) at Week 48

Treatment Group	% Change from Baseline [Mean (SD)]	% Change from Baseline [Min, Max]	Week 48 Value [Mean]	Baseline Value [Mean]	Analysis Subject Count at Baseline, Week 48
Lumbar Spine					
E/C/F/T	-2.63 (3.31)	-11.41, 6.44	1.04	1.06	53, 51
ATV/r + TVD	-3.33 (3.08)	-12.76, 4.32	1.07	1.11	63, 60
Hip (Femur)					
E/C/F/T	-3.06 (2.60)	-10.41, 0.63	0.97	1.00	51, 51
ATV/r + TVD	-3.88 (2.80)	-15.50, 0.84	0.99	1.03	65, 61

Only subjects with non-missing spine or hip BMD for the baseline visit and at least one post-baseline visit were included in the DEXA substudy analysis set.

Two subjects had musculoskeletal AEs that led to the discontinuation of E/C/F/T. No subjects had musculoskeletal AEs that led to discontinuation in either of the control arms. The AEs that led to discontinuation were 'Limb Discomfort' (Subject 1541-7705) and the SAE (and only grade 4 musculoskeletal AE) 'Rhabdomyolysis' (Subject 0959-7110).

- Subject 1541-7705, a 35 year old male, developed fatigue and lower extremity discomfort on Study Day 241 judged related to E/C/F/T by the investigator. E/C/F/T was discontinued on Study Day 247, and the lower extremity discomfort resolved on Study Day 262. Peak CPK value was 292 U/L on Study Day 227.

- Subject 0959-7110, a 30 year old white male, was hospitalized on Study Day 342 with aspiration pneumonia related to binge drinking and substance abuse, C5 radiculopathy, rhabdomyolysis, and right deltoid pressure ischemia. Study drugs were discontinued on Study Day 342 due to the events listed. The investigator

assessed the adverse events as unrelated to study drugs and this reviewer concurs with that assessment.

Musculoskeletal SAEs occurred in two subjects receiving E/C/F/T: Subject 0959-7110 with 'rhabdomyolysis' (discussed above) and Subject 0637-6051 with grade 3 synovitis. Subject 0637-6051, a 50 year old black male with a history of arthritis since 1999, was hospitalized on Study Day 251 with severe pain in his neck, shoulders and knees. He was initially diagnosed with polymyalgia rheumatica, a diagnosis that was later changed to post-viral arthritis. The event, assessed as unrelated to study drugs by the investigator, was considered resolved on Study Day 278.

In summary, musculoskeletal adverse events were more common in the E/C/F/T group (21.3%) than in either of the comparator groups (ATR 15.6%, ATV/r + TVD 15.5%). 'Back pain' and a constellation of adverse events related to muscle pain, stiffness and spasms all were reported at a higher rate in the E/C/F/T group than in either of the control arms. However, the vast majority musculoskeletal events were of mild or moderate severity (i.e. grade 1 or 2) and rarely lead to study drug discontinuation. The combined incidence of 'osteopenia' and 'osteoporosis' was 1.3% in the E/C/F/T group compared to 0.0% in the ATR group and 2.2% in the ATV/r + TVD group. There was no evidence of an increased risk of osteoporotic fractures in the E/C/F/T group compared to the control groups. The DEXA substudy performed in a subset of GS-US-236-0103 subjects demonstrated a decline in lumbar spine and hip BMD in both treatment groups with no statistically significant difference in the percentage change from baseline to Week 48 between the treatment groups.

Laboratory: Creatine Kinase

Table 29 summarizes the creatine kinase laboratory values by toxicity grade. No substantive difference in overall incidence was apparent in the E/C/F/T group when compared to the control arms.

Table 29: Creatine Kinase Laboratory Toxicities

	E/C/F/T	ATR	ATV/r + TVD
Studies (Number of Subjects)	236-0102, 0103 (N=701)	236-0102 (N=352)	236-0103 (N=355)
# of Subjects used in this Analysis	699	351	352
Creatine Kinase (U/L), Maximum toxicity grade, n (%)			
Grade 1 (3 to <6 x ULN)	66 (9.4%)	25 (7.1%)	26 (7.4%)
Grade 2 (6 to < 10 x ULN)	25 (3.6%)	17 (4.8%)	16 (4.5%)
Grade 3 (10 to < 20 x ULN)	23 (3.3%)	14 (4.0%)	10 (2.8%)
Grade 4 (≥ 20 x ULN)	13 (1.9%)	25 (7.1%)	16 (4.5%)
All Grades	127 (18.2%)	81 (23.1%)	68 (19.3%)

Gastrointestinal Adverse Events

The overall incidence of gastrointestinal adverse events by MedDRA system organ class was less in the E/C/F/T group (53.8%) than in the ATV/r + TVD group (56.6%), but greater than that of the ATR group (45.7%). There were a total of nineteen grade 3 events (2.7%) in the E/C/F/T group. The most common grade 3 events included abdominal pain (0.9%), nausea (0.6%), diarrhea (0.4%), constipation (0.3%) and pancreatitis (0.3%). There were no grade 4 events. The other events in the E/C/F/T group were either grade 1 or 2 in severity.

Table 30 summarizes the treatment-emergent gastrointestinal adverse events which occurred in ≥ 1% of the subjects in the E/C/F/T group. Multiple AEs were counted only once per subject for each Preferred Term. 'Diarrhea' and 'nausea' accounted for the majority of gastrointestinal adverse events in the E/C/F/T group.

Table 30: Treatment-Emergent Gastrointestinal Disorders Occurring in ≥ 1% of Subjects in the E/C/F/T Group

	E/C/F/T	ATR	ATV/r + TVD
Studies (Number of Subjects)	236-0102, 0103 (N=701)	236-0102 (N=352)	236-0103 (N=355)
MedDRA Preferred Term, n (%)			
DIARRHEA	157 (22.4%)	66 (18.8%)	97 (27.3%)
NAUSEA	142 (20.3%)	48 (13.6%)	69 (19.4%)
VOMITING	39 (5.6%)	14 (4.0%)	24 (6.8%)
ABDOMINAL PAIN	32 (4.6%)	10 (2.8%)	17 (4.8%)
CONSTIPATION	27 (3.9%)	9 (2.6%)	9 (2.5%)
FLATULENCE	25 (3.6%)	4 (1.1%)	29 (8.2%)
DYSPEPSIA	19 (2.7%)	6 (1.7%)	11 (3.1%)
HEMORRHOIDS	19 (2.7%)	10 (2.8%)	7 (2.0%)
GASTROESOPHAGEAL REFLUX DISEASE	16 (2.3%)	8 (2.3%)	10 (2.8%)
ABDOMINAL DISTENSION	13 (1.9%)	3 (0.9%)	11 (3.1%)
ABDOMINAL PAIN UPPER	13 (1.9%)	3 (0.9%)	4 (1.1%)
ABDOMINAL DISCOMFORT	11 (1.6%)	6 (1.7%)	5 (1.4%)
TOOTHACHE	9 (1.3%)	6 (1.7%)	5 (1.4%)
DRY MOUTH	8 (1.1%)	6 (1.7%)	5 (1.4%)
RECTAL HAEMORRHAGE	8 (1.1%)	1 (0.3%)	2 (0.6%)
APHTHOUS STOMATITIS	7 (1.0%)	2 (0.6%)	1 (0.3%)
CHEILITIS	7 (1.0%)	2 (0.6%)	3 (0.8%)
PROCTALGIA	7 (1.0%)	2 (0.6%)	1 (0.3%)

Five subjects (0.7%) discontinued E/C/F/T due to gastrointestinal disorders. These included one subject with diarrhea and nausea, one subject with nausea, one subject with diarrhea, one subject with abdominal discomfort and vomiting and one subject with oral hypoesthesia.

Nine subjects (1.3%) had gastrointestinal SAEs, however, none of these events were judged to be related to E/C/F/T by the investigators.

Hepatobiliary Adverse Events

Table 31 summarizes the treatment-emergent hepatobiliary adverse events. The overall incidence of hepatobiliary adverse events was less in the E/C/F/T group than in either of the control groups. No adverse hepatobiliary events by Preferred Term occurred in ≥ 1% of E/C/F/T subjects. There were four grade 3 events in the E/C/F/T group ('bile duct stone', 'cholecystitis', 'cholelithiasis', and 'hepatomegaly') and one grade 4 event ('hepatitis alcoholic'). The other events in the E/C/F/T were either grade 1 or 2 in severity.

Table 31: Treatment-Emergent Hepatobiliary Disorders by MedDRA HLGT and Preferred Terms

	E/C/F/T	ATR	ATV/r + TVD
Studies (Number of Subjects)	236-0102, 0103 (N=701)	236-0102 (N=352)	236-0103 (N=355)
HEPATOBILIARY DISORDERS (by MedDRA System Organ Class), n (%)	8 (1.1%)	7 (2.0%)	38 (10.7%)
MedDRA High Level Group Term & Preferred Term n (%)			
BILE DUCT DISORDERS	1 (0.1%)	0 (0.0%)	1 (0.3%)
BILE DUCT STONE	1 (0.1%)	0 (0.0%)	1 (0.3%)
GALLBLADDER DISORDERS	4 (0.6%)	2 (0.6%)	2 (0.6%)
CHOLECYSTITIS	1 (0.1%)	0 (0.0%)	0 (0.0%)
CHOLELITHIASIS	3 (0.4%)	1 (0.3%)	2 (0.6%)
GALLBLADDER DISORDER	0 (0.0%)	1 (0.3%)	0 (0.0%)
HEPATIC AND HEPATOBILIARY DISORDERS	4 (0.6%)	5 (1.4%)	36 (10.1%)
HEPATIC CIRRHOSIS	0 (0.0%)	0 (0.0%)	1 (0.3%)
HEPATIC STEATOSIS	1 (0.1%)	1 (0.3%)	2 (0.6%)
HEPATITIS	0 (0.0%)	1 (0.3%)	0 (0.0%)
HEPATITIS ALCOHOLIC	1 (0.1%)	1 (0.3%)	0 (0.0%)
HEPATOMEGALY	2 (0.3%)	0 (0.0%)	0 (0.0%)
HYPERBILIRUBINEMIA	0 (0.0%)	1 (0.3%)	3 (0.8%)
JAUNDICE	0 (0.0%)	1 (0.3%)	31 (8.7%)
LIVER INJURY	1 (0.1%)	0 (0.0%)	0 (0.0%)
PORTAL HYPERTENSION	0 (0.0%)	0 (0.0%)	1 (0.3%)

Four subjects in the E/C/F/T group (0310-6674, 0933-7385, 4142-7608, & 0989-6311) had liver-related adverse events that led to study drug discontinuation. All of these subjects had either a history of chronic hepatitis C infection or evidence of acute hepatitis C infection. Their narratives follow:

Subject 0310-6674 was a 52 year old white female with a history of hepatitis C and abnormal baseline laboratory values. Her baseline hepatic panel follows: ALT 77 U/L (2.3x ULN), AST 82 U/L (2.4x ULN), alkaline phosphatase 252 U/L (2 x ULN), GGT 1159 (23.7x ULN) and total bilirubin 1.5 mg/dl. 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. Her hepatic panel on Study Day 35 follows: ALT 24 U/L, AST 63 U/L, alkaline phosphatase 379 U/L (3.1 x ULN), GGT 742 (15.1x ULN) and total bilirubin 4.2 mg/dl (3.5x ULN). Peak bilirubin was 5.4 mg/dl recorded on Study Day 30, with ALT 30 U/L and AST 60 U/L. An MRI cholangiogram on Study Day 38 revealed fatty liver, no evidence of any intrahepatic biliary duct dilatation, a mildly dilated common bile duct (8 mm), no obstructing lesion and a normal gallbladder. The last available hepatic panel is from Study Day 67 which yielded the following results ALT 18 U/L, AST 53 U/L, alkaline phosphatase 165 U/L, GGT 194 (4x ULN) and total bilirubin 1.0 mg/dl. This subject did not meet Hy's Law criteria (see below).

Subject 0933-7385 was a 36 year old white male with a history of hepatitis C and mildly elevated baseline transaminases (ALT 60, 1.4x ULN & AST 53, 1.5x ULN). The subject developed an increase in transaminases beginning on SD64 and peaking on SD91 with ALT = 710 (16.5x ULN) and AST = 515 (14.3 x ULN). Bilirubin and alkaline phosphatase remained within normal limits throughout the study. Hepatitis C RNA was 13,000,000 on SD90. The subject discontinued E/C/F/T on SD91 due to the increases in ALT and AST and the event was judged related to study drug by the investigator.

Subject 4142-7608 had a history of hepatitis C since 2009 and markedly abnormal baseline transaminases (ALT 673, 15.7x ULN, and AST 282, 7.8x ULN) with normal bilirubin and alkaline phosphatase levels. This subject discontinued E/C/F/T on SD 127 for 'hepatitis C' which the investigator judged as probable re-infection or less likely re-activation. However, this subject had no appreciable worsening of his liver function parameters from baseline through the date of study drug discontinuation. Therefore, if this was a new hepatitis C infection or re-activation, it appears unrelated to and unaffected by study drug.

Subject 0989-6311 developed well documented acute hepatitis C (please refer to 'Hy's Law' below for a description of the case).

Four subjects in the E/C/F/T group had hepatobiliary SAEs. These included 'cholecystitis' (Subject 1609-1628), 'cholelithiasis' (Subject 0698-6206), 'hepatitis alcoholic' (Subject 2058-6709), and 'liver injury' (Subject 0310-6674) as discussed above. One subject in the E/C/F/T group had an SAE reported under the system organ code 'investigations' with the Preferred Terms 'elevated ALT' and 'elevated AST'. The adverse events 'elevated ALT' and 'elevated AST' resolved with the subject remaining on study medication. Only the SAE 'liver injury' was judged related to study drug by the investigator.

Hy's Law

Hy's Law refers to the observation made by Dr. Hy Zimmerman that drug induced hepatocellular injury (i.e. aminotransferase elevation) accompanied by jaundice had a poor prognosis. Hepatocellular injury sufficient to impair bilirubin excretion has been used at the FDA to identify drugs likely to cause severe liver injury. The definition used by the FDA as indicator of clinical concern for drug-induced liver injury includes: ALT or AST > 3x ULN, total bilirubin > 2x ULN without an initial increase in alkaline phosphatase, and no other explanations for the increases in liver enzymes (e.g. viral hepatitis, pre-existing or acute liver disease, another drug capable of causing the observed injury).

To help identify hepatic adverse events which may be treatment related, the above criteria were applied to both the Phase 3 and the Phase 2b trials. In summary, no unconfounded case meeting the definition of Hy's Law (e.g. FDA's definition of drug induced liver injury) was identified. From the E/C/F/T group, 2 subjects met the laboratory criteria for Hy's Law. However, the events were cofounded by alcohol abuse and abnormal baseline laboratory parameters in subject 2058-6709 and acute hepatitis C in the subject 0989-6311.

Subject 2058-6709 was a 39 year old black male with a history of alcoholism and baseline ALT = 74 U/L, AST = 200 U/L, and total bilirubin = 0.2 mg/dL. He was admitted to the hospital on Study Day 238 with alcoholic hepatitis. On Study Day 247, he had the following laboratory results: ALT 39 U/L, AST 114 U/L (3.2x ULN), total bilirubin 2.8 mg/dl (2.3x ULN), and alkaline phosphatase 127. Study drug was continued without reduction throughout the event and on Study Day 333, he had the following laboratory results: ALT 28 U/L, AST 79 U/L (2.2x ULN), total bilirubin 0.5 mg/dl.

Subject 0989-6311 was a 48 year old white male who discontinued E/C/F/T on Study Day 401 due to an AE of severe acute hepatitis C. The subject was hepatitis C seronegative at screening with AST, ALT and total bilirubin all within normal limits. On Study Day 402, he had the following laboratory results: ALT 587 U/L (13.2x ULN), AST

202 U/L (5.6x ULN), total bilirubin 9.1 mg/dl (7.6x ULN), and alkaline phosphatase 166 (<1.5x ULN). He was also noted to be hepatitis C antibody positive (repeatedly positive on 2 separate samples) with detectable hepatitis C viral RNA.

In summary, the hepatic safety profile of E/C/F/T appears acceptable. There were four liver-related adverse events in the E/C/F/T group that led to study drug discontinuation, two of which were judged to be related to study drug by the investigator. This reviewer agrees with the investigators' causality assessment. Three of these events occurred in subjects with chronic hepatitis C and one of these events was directly related to acute hepatitis C. There were no unconfounded cases that met the criteria of Hy's Law in the E/C/F/T group. Based on the totality of data, including the laboratory results (Section 7.4.2), a warning, precaution, or special monitoring for hepatotoxicity or hepatobiliary disorders is not warranted.

Skin and Soft Tissue Adverse Events

Overall, there was a lower incidence of skin and soft tissue disorders in the E/C/F/T group (21.7%) than in the ATR group (31.8%) and the same incidence in the E/C/F/T group as compared to the ATV/r + TVD group (21.7%). The difference in incidence of skin and soft tissue AEs in the ATR group compared to the E/C/F/T and ATV/r + TVD groups was primarily due to an increase in AEs under the MedDRA HLGT 'Rashes, Eruptions, and Exanthems NEC' (ATR 17%, E/C/F/T 7.1%, ATV/r + TVD 7.9%). No concerning trends were noted in the E/C/F/T group when compared with either of the control groups.

Three subjects (0.4%) discontinued E/C/F/T due to skin and subcutaneous tissue adverse events (exfoliative dermatitis, rash, and abnormal skin odor) as compared to 1.4% of subjects in the ATR group and 1.1% of subjects in the ATV/r + TVD group. Subject 0684-7454 developed exfoliative dermatitis on his hands and feet on SD10 and E/C/F/T was discontinued on SD19. There was no evidence of concurrent elevation of LFTs (compared to baseline) or eosinophilia. The adverse event was considered to be related to E/C/F/T by the investigator. Subject 5130-7614 developed a rash involving his upper extremities, neck, truck and buttocks on SD156. There was no associated fever, concurrent LFT abnomalities, or eosinophilia. The subject was treated with prednisolone and E/C/F/T was discontinued on SD159. The adverse event was considered to be related to E/C/F/T by the investigator.

One additional subject discontinued E/C/F/T due to the Immune System Disorder AE 'drug hypersensitivity.' Subject 2434-7653, a 47 year old white male, developed high grade fever on SD 8 and was hospitalized for evaluation of antiretroviral allergy on SD 15 at which point study drug was discontinued. Laboratory data from SD 15 demonstrated a leukocytosis (16 x 10^3 cells/mL), an elevation in serum creatinine (1.38

mg/dL), mild proteinuria (1+), and an elevated C-reactive protein level (129 mg/l). There was no evidence of eosinophilia or LFT abnormalities. A thoracoabdominal CT was preformed which revealed hilar, lumboaortic, and perirectal adenpathy (<15 mm). Blood cultures were negative. High grade fevers persisted through SD 18 at which point the subject developed a grade 1 eruption localized to his trunk. Fevers abated by SD 19. The AE 'drug hypersensitivity' was judged related to study drug by the investigator.

Cardiac Adverse Events

Overall, there was a lower incidence of cardiac disorders in the E/C/F/T group (1.7%) than in the ATR group (2.3%) and a greater incidence than that seen in the ATV/r + TVD group (1.4%). Table 32 summarizes the treatment-emergent cardiac disorders by selected HLGTs and Preferred Terms. Multiple AEs were counted only once per subject for each MedDRA High Level Term and Preferred Term. There was a higher incidence of 'myocardial disorders' in the E/C/F/T group compared to the control groups, but the overall incidence in all groups was very low. No SAEs related to cardiac disorders or discontinuations due to cardiac disorders occurred in the E/C/F/T group.

Table 32: Treatment-Emergent Cardiac Disorders by MedDRA HLGT and Preferred Terms

	E/C/F/T	ATR	ATV/r + TVD
Studies (Number of Subjects)	236-0102, 0103 (N=701)	236-0102 (N=352)	236-0103 (N=355)
MedDRA High Level Group Term & Preferred Term, n (%)			
CARDIAC ARRHYTHMIAS	7 (1.0%)	5 (1.4%)	3 (0.8%)
ARRHYTHMIA	0 (0.0%)	0 (0.0%)	1 (0.3%)
ATRIAL FIBRILLATION	1 (0.1%)	0 (0.0%)	0 (0.0%)
BRADYCARDIA	1 (0.1%)	0 (0.0%)	0 (0.0%)
BUNDLE BRANCH BLOCK RIGHT	0 (0.0%)	1 (0.3%)	0 (0.0%)
CONDUCTION DISORDER	1 (0.1%)	0 (0.0%)	0 (0.0%)
EXTRASYSTOLES	1 (0.1%)	1 (0.3%)	0 (0.0%)
SINUS BRADYCARDIA	2 (0.3%)	1 (0.3%)	0 (0.0%)
SINUS TACHYCARDIA	0 (0.0%)	0 (0.0%)	1 (0.3%)
TACHYCARDIA	1 (0.1%)	2 (0.6%)	0 (0.0%)
VENTRICULAR EXTRASYSTOLES	0 (0.0%)	0 (0.0%)	1 (0.3%)
CARDIAC DISORDER SIGNS AND SYMPTOMS	1 (0.1%)	2 (0.6%)	1 (0.3%)
INTRACARDIAC MASS	0 (0.0%)	1 (0.3%)	0 (0.0%)
PALPITATIONS	1 (0.1%)	1 (0.3%)	1 (0.3%)
CORONARY ARTERY DISORDERS	1 (0.1%)	1 (0.3%)	1 (0.3%)
ACUTE MYOCARDIAL INFARCTION	0 (0.0%)	1 (0.3%)	0 (0.0%)
ANGINA PECTORIS	1 (0.1%)	0 (0.0%)	0 (0.0%)
MYOCARDIAL INFARCTION	0 (0.0%)	0 (0.0%)	1 (0.3%)
MYOCARDIAL DISORDERS	3 (0.4%)	0 (0.0%)	0 (0.0%)
DILATATION VENTRICULAR	1 (0.1%)	0 (0.0%)	0 (0.0%)
LEFT ATRIAL DILATATION	1 (0.1%)	0 (0.0%)	0 (0.0%)
LEFT VENTRICULAR HYPERTROPHY	1 (0.1%)	0 (0.0%)	0 (0.0%)
RIGHT ATRIAL DILATATION	1 (0.1%)	0 (0.0%)	0 (0.0%)

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

93% of subjects in the E/C/F/T group experienced any treatment-emergent AE compared to 95% of subjects in the ATR group, and 94% of subjects in the ATV/r + TVD group. Table 33 summarizes all AEs that occurred in at least 3% of subjects (by preferred term) in the E/C/F/T group, regardless of causality. Multiple AEs were counted only once per subject for each preferred term.

Table 33: Treatment-Emergent Adverse Events that Occurred in at Least 3% of Subjects Receiving E/C/F/T

	E/C/F/T	ATR	ATV/r + TVD
Studies (Number of Subjects)	236-0102, 0103 (N=701)	236-0102 (N=352)	236-0103 (N=355)
MedDRA Preferred Term n (%)			
DIARRHEA	157 (22.4%)	66 (18.8%)	97 (27.3%)
NAUSEA	142 (20.3%)	48 (13.6%)	69 (19.4%)
VOMITING	39 (5.6%)	14 (4.0%)	24 (6.8%)
ABDOMINAL PAIN	32 (4.6%)	10 (2.8%)	17 (4.8%)
CONSTIPATION	27 (3.9%)	9 (2.6%)	9 (2.5%)
FLATULENCE	25 (3.6%)	4 (1.1%)	29 (8.2%)
UPPER RESPIRATORY TRACT INFECTION	102 (14.6%)	38 (10.8%)	58 (16.3%)
NASOPHARYNGITIS	51 (7.3%)	19 (5.4%)	28 (7.9%)
BRONCHITIS	43 (6.1%)	20 (5.7%)	18 (5.1%)
SINUSITIS	39 (5.6%)	28 (8.0%)	18 (5.1%)
ANOGENITAL WARTS	28 (4.0%)	8 (2.3%)	6 (1.7%)
URINARY TRACT INFECTION	22 (3.1%)	13 (3.7%)	12 (3.4%)
FOLLICULITIS	21 (3.0%)	9 (2.6%)	11 (3.1%)
INFLUENZA	21 (3.0%)	8 (2.3%)	11 (3.1%)
ABNORMAL DREAMS	65 (9.3%)	95 (27.0%)	14 (3.9%)
INSOMNIA	59 (8.4%)	49 (13.9%)	18 (5.1%)
DEPRESSION	53 (7.6%)	39 (11.1%)	23 (6.5%)
ANXIETY	23 (3.3%)	14 (4.0%)	14 (3.9%)
HEADACHE	102 (14.6%)	34 (9.7%)	44 (12.4%)
DIZZINESS	42 (6.0%)	86 (24.4%)	25 (7.0%)
FATIGUE	90 (12.8%)	45 (12.8%)	45 (12.7%)
PYREXIA	25 (3.6%)	17 (4.8%)	14 (3.9%)
BACK PAIN	37 (5.3%)	14 (4.0%)	13 (3.7%)
ARTHRALGIA	29 (4.1%)	9 (2.6%)	12 (3.4%)
PAIN IN EXTREMITY	27 (3.9%)	13 (3.7%)	9 (2.5%)
COUGH	40 (5.7%)	14 (4.0%)	28 (7.9%)
OROPHARYNGEAL PAIN	29 (4.1%)	25 (7.1%)	18 (5.1%)
RASH	47 (6.7%)	43 (12.2%)	22 (6.2%)
LYMPHADENOPATHY	27 (3.9%)	13 (3.7%)	10 (2.8%)
DECREASED APPETITE	23 (3.3%)	12 (3.4%)	16 (4.5%)

The most common AEs in the E/C/F/T group by System Organ Class included 'gastrointestinal disorders' and 'infections and infestations'. The reader is referred to Section 7.3.5 for detailed information on the gastrointestinal events. With respect to infections and infestations, no substantive difference in incidence was noted when

comparing the E/C/F/T group to either of the control groups at the System Organ Class or Preferred Term level. A higher incidence of SAEs in the category of 'infections and infestations' was noted, however, none of these adverse events were judged by the investigator as related to study drug.

There were notable differences in the incidence of adverse events in the categories of psychiatric disorders, musculoskeletal and connective tissue disorders, and skin and subcutaneous tissue disorders between the E/C/F/T group and one or both of the control groups. These are discussed in detail in their respective sub-sections in Section 7.3.5.

Under the System Organ Class, 'nervous system disorders,' the AE 'headache' was more common in the E/C/F/T group (14.6%) than in either the ATR group (9.7%) or the ATV/r + TVD group (12.4%). Most of the headaches were grade 1 in severity. Grade 2 headaches occurred in 4% of subjects in the E/C/F/T group, 1.1% of subjects in the ATR group, and 2.5% of subjects in the ATV/r + TVD group. Grade 3 headaches occurred in 0.4% of subjects in the E/C/F/T group, 0.3% of subjects in the ATR group and none of the subjects in the ATV/r group. There were no grade 4 headaches in any group. There was one discontinuation for headache in the E/C/F/T group (Subject 0659-6573) that was judged related to study drug by the investigator. This was considered an SAE by the investigator based on the criteria of "important medical event". There was one additional SAE of headache in the E/C/F/T group which was associated with new onset hypertension and judged unrelated to study drug.

Hypertension was also a relatively common adverse event occurring in 2.7% of subjects in the E/C/F/T group, 2.0% of subjects in the ATR group and 1.1% of subjects in the ATV/r + TVD group.

7.4.2 Laboratory Findings

Table 34 summarizes the hepatic and pancreatic laboratory abnormalities by severity grade. 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 post-baseline maximum severity for each laboratory test. There is no evidence of a concerning trend with respect to hepatic or pancreatic laboratory findings in the E/C/F/T group compared to the ATR or the ATV/r + TVD group.

Table 34: Hepatobiliary and Pancreatic Laboratory Toxicities

	E/C/F/T	ATR	ATV/r + TVD
Studies (Number of Subjects)	236-0102, 0103 (N=701)	236-0102 (N=352)	236-0103 (N=355)
Total Number of Subjects used in this Analysis	699	351	352

Maximum toxicity grade, n(%)			
Aspartate Aminotransferase (U/L)			
Grade 1 (1.25 to 2.5 x ULN)	93 (13.3%)	66 (18.8%)	49 (13.9%)
Grade 2 (>2.5 to 5 x ULN)	16 (2.3%)	31 (8.8%)	14 (4.0%)
Grade 3 (>5 to 10 x ULN)	9 (1.3%)	8 (2.3%)	11 (3.1%)
Grade 4 (>10 x ULN)	6 (0.9%)	4 (1.1%)	3 (0.9%)
Alanine Aminotransferase (U/L)			
Grade 1 (1.25 to 2.5 x ULN)	84 (12.0%)	86 (24.5%)	52 (14.8%)
Grade 2 (>2.5 to 5 x ULN)	13 (1.9%)	22 (6.3%)	16 (4.5%)
Grade 3 (>5 to 10 x ULN)	4 (0.6%)	8 (2.3%)	6 (1.7%)
Grade 4 (>10 x ULN)	6 (0.9%)	3 (0.9%)	2 (0.6%)
Bilirubin (mg/dL)			
Grade 1 (>1 to 1.5 x ULN)	10 (1.4%)	2 (0.6%)	26 (7.4%)
Grade 2 (>1.5 to 2.5 x ULN)	10 (1.4%)	1 (0.3%)	108 (30.7%)
Grade 3 (>2.5 to 5 x ULN)	3 (0.4%)	0 (0.0%)	169 (48.0%)
Grade 4 (>5 x ULN)	1 (0.1%)	0 (0.0%)	36 (10.2%)
Alkaline Phosphatase (U/L)			
Grade 1 (1.25 to 2.5 x ULN)	28 (4.0%)	18 (5.1%)	15 (4.3%)
Grade 2 (>2.5 to 5 x ULN)	3 (0.4%)	3 (0.9%)	1 (0.3%)
Grade 3 (>5 to 10 x ULN)	0 (0.0%)	1 (0.3%)	1 (0.3%)
Gamma Glutamyl Transferase (U/L)			
Grade 1 (1.25 to 2.5 x ULN)	52 (7.4%)	63 (17.9%)	20 (5.7%)
Grade 2 (>2.5 to 5 x ULN)	12 (1.7%)	20 (5.7%)	11 (3.1%)
Grade 3 (>5 to 10 x ULN)	5 (0.7%)	12 (3.4%)	2 (0.6%)
Grade 4 (>10 x ULN)	3 (0.4%)	5 (1.4%)	3 (0.9%)
Amylase (U/L)			
Grade 1 (>1 to 1.5 x ULN)	103 (14.7%)	63 (17.9%)	37 (10.5%)
Grade 2 (>1.5 to 2.0 x ULN)	24 (3.4%)	17 (4.8%)	10 (2.8%)
Grade 3 (>2.0 to 5 x ULN)	14 (2.0%)	6 (1.7%)	10 (2.8%)
Grade 4 (>5 x ULN)	2 (0.3%)	2 (0.6%)	3 (0.9%)
Lipase (U/L)[1]			
Grade 1 (>1 to 1.5 x ULN)	1 (1.7%)	2 (6.1%)	2 (6.1%)
Grade 2 (>1.5 to 3.0 x ULN)	8 (13.8%)	5 (15.2%)	3 (9.1%)
Grade 3 (>3.0 to 5 x ULN)	5 (8.6%)	4 (12.1%)	6 (18.2%)
Grade 4 (>5 x ULN)	2 (3.4%)	1 (3.0%)	1 (3.0%)

1. The 'Lipase' assessment was only performed in subjects with serum amylase > 1.5 x ULN. Therefore the denominator differs for this test (58 subjects in the E/C/F/T group, 33 subjects in the ATR group, and 33 subjects in the ATV/r + TVD group)

Table 35 summarizes the hematologic laboratory abnormalities by severity grade. 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 post-baseline maximum severity for each laboratory test. There is no evidence of a concerning trend with respect to hematologic laboratory findings in the E/C/F/T group compared to the ATR or the ATV/r + TVD group.

Table 35: Hematologic Laboratory Toxicities

	E/C/F/T	ATR	ATV/r + TVD
Studies (Number of Subjects)	236-0102, 0103 (N=701)	236-0102 (N=352)	236-0103 (N=355)
Total Number of Subjects used in this Analysis	699	351	352
Maximum toxicity grade, n(%)			
Hemoglobin (g/dL)			
Grade 1 (8.5-10 g/dL)	6 (0.9%)	2 (0.6%)	6 (1.7%)
Grade 2 (7.5 to < 8.5 g/dL)	1 (0.1%)	2 (0.6%)	0 (0.0%)
Leukocytes (x10^3/uL)			
Grade 1 (2000-2500/mm^3)	16 (2.3%)	12 (3.4%)	10 (2.8%)
Grade 2 (1500 to < 2000/mm^3)	2 (0.3%)	2 (0.6%)	2 (0.6%)
Grade 3 (1000 to < 1500/mm^3)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Platelets (x10^3/uL)			
Grade 1 (100,000 to < 125,000/mm^3)	7 (1.0%)	5 (1.4%)	4 (1.1%)
Grade 2 (50,000 to < 100,000/mm^3)	6 (0.9%)	2 (0.6%)	2 (0.6%)
Grade 3 (25,000 to < 50,000/mm^3)	1 (0.1%)	1 (0.3%)	0 (0.0%)
Grade 4 (< 25,000/mm^3)	1 (0.1%)	0 (0.0%)	1 (0.3%)

Table 36 summarizes the mean changes in fasting lipid values in studies 236-0102 and 236-0103. This assessment was limited to subjects with available baseline and Week 48 fasting lipid values. The differences in lipid parameters between the E/C/F/T group and the control groups were generally small and of uncertain clinical significance.

Table 36: Fasting Lipid Values, Mean Change from Baseline

Treatment Group, Studies, (Numbers of Subjects)	Parameters (in mg/dL)	Mean Baseline Value	Mean Change from Baseline at Week 48	Number of Subjects With Both Baseline and Week 48 Values
E/C/F/T 236-0102, 0103 (N=701)				
	Fasting Cholesterol	166.2	+10.7	606
	Fasting HDL Cholesterol	43.1	+5.9	605
	Fasting LDL Cholesterol	101.1	+10.1	606
	Fasting Triglycerides	122.3	+13.3	606
ATR 236-0102 (N=352)				
	Fasting Cholesterol	163	+18.8	298
	Fasting HDL Cholesterol	42.6	+7.8	298

	Fasting LDL Cholesterol	97.7	+17	298
	Fasting Triglycerides	125.3	+13.6	298
ATV/r + TVD 236-0103 (N=355)				
	Fasting Cholesterol	169.2	+9.5	287
	Fasting HDL Cholesterol	41.8	+5.3	286
	Fasting LDL Cholesterol	102.6	+11.2	288
	Fasting Triglycerides	134.9	+31.5	287

Table 37 summarizes the cholesterol and triglyceride values by severity grade. 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 post-baseline maximum severity for each laboratory test. There were no clinically meaningful differences in cholesterol severity grades in any of the study groups. The highest incidence of graded hypertriglyceridemia was seen in the ATV/r + TVD group. Overall incidences of hypertriglyceridemia were equivalent in the E/C/F/T and ATR groups.

Table 37: Cholesterol and Triglyceride Laboratory Toxicities

	E/C/F/T	ATR	ATV/r + TVD
Studies (Number of Subjects)	236-0102, 0103 (N=701)	236-0102 (N=352)	236-0103 (N=355)
Total Number of Subjects used in this Analysis	699	351	352
Maximum toxicity grade, n(%)			
Fasting Cholesterol (mg/dL)			
Grade 1 (200-239 mg/dL)	115 (16.5%)	58 (16.5%)	63 (17.9%)
Grade 2 (<239-300 mg/dL)	39 (5.6%)	26 (7.4%)	25 (7.1%)
Grade 3 (> 300 mg/dL)	5 (0.7%)	5 (1.4%)	0 (0.0%)
Fasting Triglycerides (mg/dL)			
Grade 1 (N/A)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Grade 2 (500-750 mg/dL)	11 (1.6%)	4 (1.1%)	8 (2.3%)
Grade 3 (>750-1200 mg/dL)	1 (0.1%)	0 (0.0%)	4 (1.1%)
Grade 4 (> 1200 mg/dL)	0 (0.0%)	2 (0.6%)	0 (0.0%)

There was no clinically meaningful difference between E/C/F/T and the comparator groups with respect to the incidence of hyperglycemia, hypoglycemia, hyperkalemia, hypokalemia, hypernatremia or hyponatremia in the Phase 3 studies.

Thyroid function was assessed in study GS-US-236-0104 because of pre-clinical findings in rats with COBI including microsomal hepatic enzyme induction and thyroid hormone imbalance which the Applicant maintains are species-specific findings. No clinically significant changes in thyroid parameters (TSH, T3, or T4) were appreciated in the Phase 2b study.

Immunoglobulin G (IgG) levels were also assessed in GS-US-236-0104 because of pre-clinical findings in rats with COBI including decreases in IgG in female rats. A similar decline in IgG from baseline levels was noted in both the E/C/F/T (from 940 to 760 mg/dL) and ATR groups (from 907 to 709 mg/dL). This may be related to anti-retroviral treatment with subsequent improvement in B-cell dysregulation and reduction in polyclonal gammopathy.

Please see Section 7.3.5 (Submission Specific Primary Safety Concerns) for a discussion of the following laboratory parameters: serum creatinine, creatinine clearance, serum phosphate and magnesium, urine glucose and protein, and blood creatine kinase.

7.4.3 Vital Signs

Vital signs other than height and weight were not collected in Studies GS-US-236-0102, GS-US-236-0103 or GS-US-236-0104. The AE 'hypertension' was reported in 2.7% of E/C/F/T subjects, 2.0% of ATR subjects, and 1.1% of ATV/r + TVD subjects. All AE's of 'hypertension' in the E/C/F/T group were either grade 1 or 2 in severity, only 1 event (0.1%) was deemed related to E/C/F/T by the investigator, and no events led to discontinuation of E/C/F/T. No AEs of 'hypertensive crisis', 'hypotension' or 'orthostatic hypotension' were reported in the E/C/F/T group. Please see Section 7.3.5 for a discussion of cardiac adverse events.

7.4.4 Electrocardiograms (ECGs)

In non-clinical testing, COBI showed the 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. Due to these findings, additional echocardiogram and ECG data was collected in the Phase 1 study GS-US-216-0116 (see Section 7.4.5) and additional ECG data collected in the Phase 2 and 3 E/C/F/T studies. No increased incidence of ECG findings consistent with PR prolongation or AV abnormality was apparent in the E/C/F/T group in the Phase 3 trials.

The sponsor performed two QT studies in support of this submission, GS-US-183-0128 and GS-US-216-0107.

GS-US-183-0128 was a phase 1, double-blind, randomized, comparative, positive and placebo controlled, parallel group study of the effects of ritonavir-boosted EVG at therapeutic and supratherapeutic doses on the QT/QTc interval in healthy subjects. The Interdisciplinary Review Team (IRT) for QT studies provided the following assessment: Two doses of EVG were evaluated in this "thorough QT/QTc study": 125

mg EVG and 250 mg EVG (both doses were administered with 100 mg ritonavir). The mean steady-state C_{max} from the supratherapeutic dose (250 mg EVG) was 3663 ng/mL, which is 1.6 fold higher than the mean C_{max} from the proposed therapeutic dose group (125 mg EVG). The largest upper bounds of the two-sided 90% CI for the time-matched, baseline adjusted mean difference of QTcF between the two treatment groups of EVG/r and placebo in this study were 7.3 msec and 8.1 msec, both less than 10 msec, the level suggested as the threshold for regulatory concern in ICH E14. The largest mean differences were less than 5 msec for both EVG/r treatment groups. In addition, the results from similar analyses conducted for differing methods for QT correction, QTcB, QTcI, and QTcN, were consistent with those for QTcF. Exposure-response analysis does not reveal a significant relationship between QT interval and plasma EVG concentrations.

IRT noted that the supratherapeutic dose used in the study provided only a 60% increase in mean C_{max}. The sponsor provided follow-up information confirming that the drug concentrations achieved in the thorough QTc Study, GS-US-183-0128, are higher than those that can be reasonably expected after administration of the highest therapeutic dose. IRT was provided this data and found it satisfactory in addressing their concern.

GS-US-216-0107 was a phase 1, partially-blinded, randomized, placebo- and positive-controlled study to evaluate the effects of COBI on the QT/QTc interval in healthy subjects. The IRT for QT studies provided the following assessment: No significant QTc prolongation effect of COBI (250 mg and 400 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference of QTcI between COBI (250 mg and 400 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcI for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time was adequately demonstrated, indicating that assay sensitivity was established. The single supratherapeutic dose (400 mg) produced mean C_{max} values of 2.7-fold higher than the mean C_{max} for the therapeutic dose at steady state (150 mg). 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.

COBI prolonged the PR interval with a mean effect (placebo corrected) of 20.2 ms at the 400-mg dose and of 9.5 ms at the 250-mg dose at 3.5 hours post-dose. Five subjects in the 400-mg arm and 2 in the 250-mg arm had an asymptomatic absolute PR >200 ms post-baseline. This 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, atazanavir.

7.4.5 Special Safety Studies/Clinical Trials

Cardiac Safety

GS-US-216-0116 was a phase 1 study with primarily PK-related objectives, but also included a secondary objective of exploring the effect of two formulations of COBI (dosed at 150 mg) at steady state on left ventricular function using echocardiograms (ECHO) and ECGs. This was a two cohort study, however, only cohort 1, consisting of 34 evaluable subjects, participated in the 2 time-matched ECGs and ECHO assessments of left ventricular function occurring at baseline and repeated one time in the SD14-19 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 postdose measures for each of the 3 left ventricular function parameters revealed a non-clinically significant increase in left ventricular end-systolic volume (3.72 mL, p = 0.017).

Renal Safety

GS-US-216-0121 was a randomized, blinded, placebo-controlled phase 1 study evaluating the effect of COBI and ritonavir on renal function as assessed by markers of glomerular filtration rate (please refer to Section 7.3.5 for a detailed discussion of this study).

GS-US-216-0124 assessed the PK of EVG and of COBI in non-HIV-1 infected subjects with severe renal impairment ($eGFR_{CG}$ < 30 mL/min) and subjects with normal renal function (eGFR ≥ 90 mL/min). For EVG, the AUC_{tau}, C_{max}, and C_{tau} following once-daily administration of EVG boosted with COBI for 7 days were approximately 25%, 33%, and 31% lower in subjects with severe renal impairment than in matched controls. For COBI, the AUC_{tau}, C_{max}, and C_{tau} were approximately 25%, 22%, and 13% higher in subjects with severe renal impairment than in matched control subjects. The differences in exposures between subjects with severe renal impairment and those with normal renal function were not deemed to be clinically relevant by the Applicant. No differences in EVG or COBI plasma protein binding were observed between the 2 groups. The sponsor concluded, based on these results that dose adjustment of EVG or COBI would not be warranted in subjects with renal impairment. However, the FTC and TDF components of E/C/F/T do require adjustment in the setting of renal impairment (creatinine clearance < 50 mL/min) and this cannot be achieved with the fixed-dose E/C/F/T tablet.

GS-US-236-0118 is an ongoing Phase 3, open-label, multicenter, multiple-cohort study evaluating the safety of COBI-containing highly active antiretroviral regimens in HIV-1 infected adults with mild to moderate renal impairment (eGFR 50-89 mL/min). Cohort 1 is enrolling treatment naïve subjects and subjects will receive E/C/F/T. Cohort 2 is enrolling treatment-experienced subjects and subjects will be switched to a regimen of ATV/co or COBI-boosted darunavir plus 2 NRTIs upon enrolling. The Applicant has provided data through 21 November 2011 in the SUR, and as of that date, 8 subjects have been enrolled in Cohort 1 and 15 subjects have been enrolled in Cohort 2. No deaths or SAEs have been reported. One subject in Cohort 2 discontinued drug due to the AE 'affect lability.' There have been no renal AEs of interest or bone fracture AEs of interest reported through 21 November 2011.

Hepatic Safety

Study GS-US-183-0133 assessed the PK of EVG and COBI in non-HIV-1 infected subjects with normal hepatic function and moderate hepatic impairment (Child-Pugh-Turcotte Classification B). The steady-state plasma exposure of EVG was higher (AUC_{tau}, C_{tau}, and C_{max} were 35%, 80%, and 41% higher, respectively) in the subjects with moderate hepatic impairment relative to matched control subjects with normal hepatic function. Per protocol, a clinically significant increase of EVG AUC_{tau} or C_{max} was defined as 50% for subjects with moderate hepatic impairment compared to normal matched control subjects. The AUC_{tau} and C_{max} of COBI were relatively comparable in the subjects with moderate hepatic impairment relative to normal matched control subjects with normal hepatic function, with the exception of COBI C_{tau} (geometric least-squares mean ratio 208%), which was not considered clinically relevant by the Applicant.

FTC and TDF have a primarily renal route of elimination and do not require dose adjustment in patients with hepatic impairment

Based on these data, we agree with the Applicant's conclusion that the E/C/F/T fixed dose formulation may be used in patients with mild or moderate hepatic impairment. There is currently no data in subjects with severe hepatic impairment, therefore the E/C/F/T formulation is not recommended for use in this population.

7.4.6 Immunogenicity

As all of the components of the E/C/F/T pill, including the two NMEs (COBI and EVG), are small molecules and not peptides, immunogenicity effects were not anticipated and therefore not specifically assessed for during the clinical trials.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The two pivotal Phase 3 trials and the supportive Phase 2 trial all used the E/C/F/T fixed dose formulation, therefore assessing for true dose dependency for AEs using these datasets was not possible.

For a discussion of exposure-response safety analyses, please refer to Section 7.2.2.

7.5.2 Time Dependency for Adverse Events

The Applicant provided a Kaplan-Meier (KM) plot of the time to premature discontinuation of study drug which revealed a lower percentage of subjects in the E/C/F/T group discontinuing prematurely at Week 2 (1%) and Week 48 (9%) compared to the ATR group (3% at Week 2 and 13% at Week 48) and the ATV/r + TVD group (3% at Week 2 and 13% at Week 48). However, the difference among groups was not statistically significant.

Please refer to Section 7.3.5 for a detailed time dependency assessment of changes in renal parameters (e.g. serum creatinine & creatinine clearance).

7.5.3 Drug-Demographic Interactions

Only 10% of subjects in the E/C/F/T group, in the pooled Phase 3 studies (GS-US-236-0102 and GS-US-236-0103), were female. Therefore, making conclusive statements related to drug-demographic interactions for this population is not possible. The overall incidence of treatment-emergent AEs in the E/C/F/T group was similar in men and women (93% of women and 92.7% of men); however the incidence of SAEs and discontinuations due to AEs differed. 14% of women and 9% of men in the E/C/F/T group had SAEs. SAEs were judged as related by the investigator in 2.9% of women and 0.5% of men. 5.7% of women and 3.5% of men discontinued E/C/F/T due to an adverse event. However, a unique and consistent pattern with respect to reasons for discontinuation or related SAEs in women was not apparent.

In the E/C/F/T group, in the pooled Phase 3 studies, 66% of subjects were White, 25% were Black or African American, 3% were Asian, 0.6% were American Indian or Alaska native, 0.7% were native Hawaiian or other Pacific islander, and 3.9% were 'Other'. The overall incidence of treatment-emergent AEs in the E/C/F/T group was similar in Whites, Blacks, and Asians (94%, 90%, and 87% respectively). 10.3% of Whites, 8.4% of Blacks, and 4.3% of Asians in the E/C/F/T group had an SAE. SAEs were judged as related by the investigator in 0.9% of Whites, 0.6% of Blacks and 0.0% of Asians. 5.0% of Whites, 1.1% of Blacks and 4.3% of Asians discontinued E/C/F/T due to an adverse event. It should be noted that due to the limited number of Asian subjects enrolled,

conclusive statements on drug-demographic interactions cannot be made for this subpopulation.

With respect to ethnicity, 21% of the E/C/F/T subjects in the pooled Phase 3 studies were Hispanic or Latino. The overall incidence of treatment-emergent AEs in the E/C/F/T group was similar in Hispanic and non-Hispanic subjects (89% and 94% respectively). 11% of Hispanic subjects and 9.1% of non-Hispanic subjects in the E/C/F/T group had an SAE. SAEs were judged as related by the investigator in 0.7% of Hispanic subjects and 0.7% of non-Hispanic subjects. 2.7% of Hispanic subjects and 4% of non-Hispanic subjects discontinued E/C/F/T due to an adverse event.

7.5.4 Drug-Disease Interactions

Hepatitis B and C Co-Infection

In the pooled Phase 3 studies, a limited number of subjects were infected with both HIV-1 and hepatitis B or C: 44 subjects in the E/C/F/T group, 23 subjects in the ATR group, and 17 subjects in the ATV/r + TVD group. The overall incidence of adverse events in co-infected subjects was similar between study groups (E/C/F/T 95.7%, ATR 95.8%, ATV/r +TVD 100%), as was the incidence of AEs assessed by MedDRA System Organ Class. Discontinuation of study drug due to an AE occurred in 13% of the co-infected subjects in the E/C/F/T group, 4.2% of subjects in the ATR group, and 11.8% of subjects in the ATV/r + TVD group. Three co-infected subjects discontinued study drug for liver related AEs in the E/C/F/T group (Subject 0310-6674 with 'Liver Injury', Subject 4142-7608 with 'Hepatitis C' and Subject 0933-7385 with AST and ALT elevation), compared to 0 subjects in the ATR group and 1 subject in the ATV/r + TVD group ('jaundice'). Please refer to Section 7.3.5 under 'Hepatobiliary Adverse Events' for the subject narratives of the E/C/F/T discontinuations.

Baseline Renal Insufficiency

This reviewer assessed the subset of subjects in the Phase 3 trials with a calculated (Cockroft-Gault) creatinine clearance < 70 ml/min at baseline. This accounted for only 20 subjects in total (10 E/C/F/T subjects, 6 ATR subjects, and 4 ATV/r + TVD subjects), as an exclusion criterion for these studies included a calculated CrCl < 70 ml/min. Four subjects (20% of this subset) discontinued study drug due to an AE. There was one discontinuation in the ATV/r + TVD group and three discontinuations in the E/C/F/T group. Of note, 2 of the discontinuations in the E/C/F/T group were due to renal AEs ('renal failure' in subject 0663-6049 and 'blood creatinine increased' in subject 2003-6267). These subjects both developed proximal tubulopathies and their clinical courses are discussed in detail in Section 7.3.5.

7.5.5 Drug-Drug Interactions

Please refer to the Clinical Pharmacology Review by Dr. Vikram Arya for a detailed discussion of the drug-drug interaction studies.

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

E/C/F/T should not be administered with other ARV drugs or with Hepsera (adefovir dipivoxil).

Administration with antacids should be separated from E/C/F/T by at least 2 hours to prevent lower absorption of EVG due to chelation by antacids.

With respect to oral contraceptives, a drug-drug interaction (DDI) study with E/C/F/T and a representative oral contraceptive (Ortho Tri-Cyclen® Lo, norgestimate [NGM] and ethinyl estradiol [EE]) was performed. In this study, 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 E/C/F/T as compared 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 E/C/F/T as compared to NGM/EE administered alone. There was no significant change in the C_{max} of EE. 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. Results from this DDI trial cannot be extrapolated to other oral contraceptives

COBI (and therefore EVG) measures decrease when co-administered with moderate-to-strong CYP3A inducers. Because it may result in loss of therapeutic activity of the EVG component, the following agents are not recommended for co-administration with E/C/F/T: rifampin, rifabutin, rifapentine, St. John's wort, systemic dexamethasone, carbamazepine, oxcarbazepine, phenobarbital, and phenytoin.

By inhibiting CYP3A, COBI substantially increases systemic exposure of CYP3A substrates [e.g. alfozosin, ergot derivatives, cisapride, HMG CoA reductase inhibitors (particularly lovastatin & simvastatin), phosphodiesterase-5 inhibitors, sedative hypnotics (particularly midazolam and triaolam)].

The Applicant recommends that co-administration of E/C/F/T with the following drugs be contraindicated due to the potential for serious and/or life-threatening events or loss of virologic response and development of resistance: alfuzosin, rifabutin, rifampin, rifapentine, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, St. John's wort (*Hypericum perforatum*), lovastatin, simvastatin, pimozide, sildenafil and

tadalafil (for the treatment of pulmonary arterial hypertension), and orally administered midazolam & triazolam.

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

FDA's final recommendations pertaining to drug-drug interactions between E/C/F/T and non-antiretroviral drugs will be based on either the results of drug-drug interaction trials (with either E/C/F/T, EVG and COBI administered together, or EVG and ritonavir administered together) or the expected change in the concentration of EVG, COBI, and the co-administered drug based on the metabolic properties of the individual drugs.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The overall incidence of neoplasm in the Phase 3 trials was similar in the E/C/F/T group (5%) compared to the ATR group (4%) and the ATV/r + TVD group (7.3%). There was one SAE (Burkitt's lymphoma) in the neoplasm category that was judged related to E/C/F/T by the investigator. Please see Section 7.3.2 for further details related to this SAE.

Please refer to Section 4.3 for information related to non-clinical studies assessing carcinogenesis and mutagenesis.

7.6.2 Human Reproduction and Pregnancy Data

Non-clinical reproductive toxicology studies of EVG and COBI are discussed in Section 4.3.

Pregnancy and breastfeeding were exclusion criteria for all clinical trials. In addition, pregnancy was a predefined condition triggering discontinuation of study drug. Therefore, the use of E/C/F/T in the setting of pregnancy has not been studied.

There were a total of four pregnancies reported in subjects receiving E/C/F/T (1 in GS-US-236-0102 and 3 in GS-US-236-0103). The pregnancy in trial 236-0102 was terminated due to an elective abortion and study drug was discontinued. Of the three subjects with a reported pregnancy in 236-0103, one subject delivered a healthy baby, one subject's pregnancy was continuing as of 15 November 2011, and for one subject the outcome of the pregnancy is unknown.

E/C/F/T falls under Category B for use in pregnancy. E/C/F/T should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

7.6.3 Pediatrics and Assessment of Effects on Growth

The safety and efficacy of the E/C/F/T formulation have not been established in pediatrics.

The Applicant has proposed a pediatric plan encompassing three clinical studies:

The Applicant has requested a (b) (4) waiver of pediatric studies for pediatric subjects less than 6 years of age.

The Applicant has requested a deferral for studies in subjects 6 to < 12 years of age pending possible approval of E/C/F/T in adults. Additionally, the availability of the safety, efficacy and pharmacokinetic data for E/C/F/T in subjects 12 to < 18 years (b) (4) (b) (4) and the individual components (EVG and COBI) in subjects 6 to < 12 years of age will be required for development of an E/C/F/T reduced strength FDC intended for administration in subjects ages 6 to <12 (b) (4)

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

If an overdose of E/C/F/T occurs, the Applicant recommends monitoring for evidence of toxicity and initiating general supportive measures including close clinical assessment. EVG and COBI are highly protein bound and unlikely to be removed by hemodialysis or peritoneal dialysis. Up to 30% of the FTC dose and approximately 10% of the TFV dose can be removed by hemodialysis.

No SAEs were reported in studies assessing supratherapeutic doses of EVG, COBI, FTC, or TDF as individual agents; however, clinical data is limited. In the E/C/F/T Phase 3 trials, a total of 18 subjects in the E/C/F/T group reported an overdose. Per Applicant, most of these overdoses were not associated with clinical symptoms or sequelae.

Of note, there have been post-marketing reports of flares of hepatitis B (HBV) following withdrawal of FTC and TDF (both components of E/C/F/T) in patients co-infected with HIV-1 and HBV.

7.7 Additional Submissions / Safety Issues

8 Postmarket Experience

No post-marketing data are available for E/C/F/T or for its COBI or EVG components. Large bodies of safety data are available for emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF). Please refer to their FDA approved product labels for additional details not discussed below.

Truvada® (TVD) was first approved in the US on 02 August 2004 and is currently approved in 137 countries. Since initial approval, the Applicant estimates the cumulative exposure to be 1,662,156 patient-years of treatment. Please refer to the safety issues identified below for the individual components of TVD, namely FTC and TDF.

Emtricitabine (FTC) was initially approved in the US on 02 July 2003 and is currently approved in 38 countries. Since initial approval, the Applicant estimates the cumulative exposure to be 116,638 patient-years of treatment. The product label states that more than 2,000 adult patients with HIV-1 infection have been treated with FTC alone or in combination with other antiretroviral agents for periods of 10 days to 200 weeks in clinical trials.

The most common adverse reactions (incidence ≥10%, any severity) identified from any of the 3 large controlled clinical trials include headache, diarrhea nausea, fatigue, dizziness, depression, insomnia, abnormal dreams, rash, abdominal pain, asthenia, increased cough, and rhinitis. Specific “post-marketing” or “post-approval” safety data is not available in the product label.

Tenofovir DF (TDF) was first approved for treatment of HIV-1 in the US on 26 October 2001 and is currently approved in 149 countries for treatment of HIV-1 infection in adults. TDF was first approved for treatment of HBV in Turkey on 28 March 2008 and is currently approved in 43 countries for treatment of HBV infection. Since initial approval,

the Applicant estimates the cumulative exposure to Viread® in HIV-1 or HBV infected patients to be 1,713,841 patient-years of treatment.

The following adverse reactions, by body system heading, have been identified during post-approval use of TDF:

Immune System Disorders: allergic reaction, including angioedema

Metabolism and Nutrition Disorders: lactic acidosis, hypokalemia, hypophosphatemia

Respiratory, Thoracic, *and Mediastinal Disorders*: dyspnea

Gastrointestinal Disorders: pancreatitis, increased amylase, abdominal pain

Hepatobiliary Disorders: hepatic steatosis, hepatitis, increased liver enzymes (most commonly AST, ALT gamma GT)

Skin and Subcutaneous Tissue Disorders: rash

Musculoskeletal and Connective Tissue Disorders: rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy

Renal and Urinary Disorders: acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria. See section 7.3.5 for additional details.

General Disorders and Administration Site Conditions: asthenia

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia.

The following significant safety issues have been associated with both FTC and TDF and are discussed in their respective FDA approved product labels:

Lactic acidosis and severe hepatomegaly with steatosis

Fat redistribution including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance"

Immune Reconstitution Syndrome

Severe acute exacerbations of Hepatitis B, including cases of liver decompensation and liver failure

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

The following important revisions are recommended by this reviewer:

Indications and Usage (Section 1):

Applicant's Proposed Language: *[TRADENAME] is indicated as a complete regimen for the treatment of HIV-1 infection in adults who are antiretroviral treatment-naïve or who have no known substitutions associated with resistance to the individual components of [TRADENAME].*

Recommended Revision: *[TRADENAME] is indicated as a complete regimen for the treatment of HIV-1 infection in adults who are antiretroviral treatment-naïve and who have no known substitutions associated with resistance to the individual components of [TRADENAME].*

Rationale: The revised indication is supported by the pivotal Phase 3 trials which were performed in a treatment naïve population. There is currently not enough data to extend this indication (as proposed by the Applicant) to treatment-experienced patients who have no known substitutions associated with resistance to the individual components of E/C/F/T as such a population may have archived resistance mutations to component(s) of E/C/F/T.

Warnings and Precautions (Section 5.3):

Summary of FDA recommendations:

- Monitor for the presence of urine glucose and protein as a potential early indicator of proximal renal tubular dysfunction.
- Monitor serum creatinine and creatinine clearance in all patients, not just in 'patients at risk.'
- Specify that renal impairment has been reported with the use of E/C/F/T as well as with tenofovir DF.
- Provide laboratory thresholds to help distinguish the expected effect of COBI on serum creatinine from that of genuine renal dysfunction.

Adverse Reactions (Section 6.1):

Summary of FDA recommendations:

- Provide additional details related to the cases of proximal tubulopathy, including clarification of clinical outcomes.
- Recommend providing the mean ± SD change in serum creatinine at week 48 (compared to baseline) for E/C/F/T and the control groups (as was done for estimated GFR).
- Recommend including language related to the increased rates of proteinuria in the E/C/F/T group (38.7%) compared to the control arms (ATR 28.7%, ATV/r + TVD 24.2%). As the grading scale for proteinuria was limited to grades 1-3, proteinuria does not appear on Table 2 which is limited to grade 3 and 4 laboratory abnormalities occurring in ≥ 2% of subjects.
- Recommend adding arthralgias to Table 1, as arthralgias occurred at a rate of 2.0% in the E/C/F/T group in the pooled Phase 3 studies.
- Recommend removing Table 3 ('Lipid Values, Mean Change from Baseline, Reported in Subjects Receiving [TRADENAME] or Comparator in Studies 102 and 103'), as the differences in impact on lipid parameters between E/C/F/T and the control groups do not appear to be clinically meaningful.

Pharmacodynamics, Effects on Electrocardiogram (Section 12.2)

- Recommend including language (based on input from IRT) related to findings of PR prolongation in Study GS-US-216-0107.

Additional areas of the label may also be revised after further review.

9.3 Advisory Committee Meeting

The Antiviral Drugs Advisory Committee met on May 11, 2012, to discuss new drug application (NDA) 203100, for a fixed-dose combination tablet of EVG/COBI/FTC/TDF, submitted by Gilead Sciences, Inc. The application proposes an indication for the treatment of HIV-1 infection in adults who are antiretroviral naïve or have no known substitutions associated with resistance to the individual components.

The Committee was asked to address a number of questions with respect to NDA 203100. The questions are listed below followed by the summary of discussion points in italics. Please refer to the transcript for details of the committee discussion.

1) Please comment on the safety profile of elvitegravir/cobicistat/emtricitabine/ tenofovir disoproxil fumarate, focusing on proximal tubulopathy and other renal adverse events leading to subject discontinuation.

Committee Discussion: *Overall, the committee was concerned with the limitations of the current study data and recommended longer term follow-up and additional studies to address renal abnormalities and drug-drug interactions with E/C/F/T use.*

Additional recommendations included:

- *Education for prescribers on tubulopathy, specifically on the various tests that are 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.*
- *The 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-positive 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).*
- *Further studies assessing the safety profile of E/C/F/T in women.*

2) VOTE**:** Considering the overall risks and benefits, do the available data support approval of E/C/F/T as a complete regimen for treatment of HIV-1 infection in treatment-naïve adults?

YES: 13 NO: 1 ABSTAIN: 0

a. If no, what additional studies are recommended?

b. If yes, proceed with the remaining questions *(questions #3 and #4)*:

Committee Discussion: *The majority of the committee agreed that the available data support approval of E/C/F/T as a complete regimen for treatment of HIV-1 infection in treatment-naïve adults. Those who voted "Yes" stated that there was positive efficacy data demonstrated and a favorable risk-benefit profile with E/C/F/T use. The panel member who voted "No" expressed concerns relating to the E/C/F/T potential effects on kidney function and the limited amount of data involving women participating in the clinical trials to date. In addition, the panel member noted that there are alternatives to E/C/F/T available for treatment of HIV-1 infection in treatment-naïve adults and recommended that the Agency wait to make a decision on approval until the ongoing studies on E/C/F/T are complete. Overall, the committee stressed the need for further studies.*

3) Please comment on whether there are additional measures needed to improve renal safety in patients receiving elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate. As part of your discussion, please comment on the following:

a. Would additional laboratory monitoring (e.g. urine dipstick testing for protein and glucose) potentially improve renal safety? Does use in patients with baseline glycosuria and proteinuria warrant separate recommendations?

Committee Discussion: *Overall, the committee agreed that additional laboratory monitoring would 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 E/C/F/T in patients with baseline glycosuria and proteinuria.*

b. Would renal safety be enhanced by monitoring renal function in all patients as opposed to only patients with renal impairment or at risk of renal impairment?

Committee Discussion: *The committee agreed that additional monitoring would potentially improve renal safety, and that renal safety would be enhanced by monitoring renal function in all patients as opposed to only patients with renal impairment or at risk for renal impairment.*

c. Should laboratory cutoffs be provided to help distinguish the effect of cobicistat on serum creatinine and creatinine clearance from genuine renal dysfunction? If yes,

please comment on specific parameters, including, but not limited to the Applicant's current proposal.

Committee Discussion: *Overall, the committee agreed that there should be laboratory cutoffs provided to help distinguish the effect of cobicistat on serum creatinine and creatinine clearance from genuine renal dysfunction. There was general agreement with the Applicant and 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 panel also suggested the use of percent increase in serum creatinine as an adjunctive measure.*

4) Please discuss any post marketing studies needed to further define risks or optimal use of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate.

Committee Discussion: *The committee recommended post marketing studies to address the following:*

- *E/C/F/T 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 PK enhancers (e.g. 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.*
- *Metabolic profile changes while on therapy*

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

/s/

ADAM I SHERWAT
07/02/2012

LINDA L LEWIS
07/02/2012

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 203-100 **Applicant:** Gilead **Stamp Date:** October 27th, 2011

Drug Name: QUAD **NDA/BLA Type:** Original NDA submission; 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.	X			eCTD format
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
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)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
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?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			Yes, a Clinical Overview, and Clinical Efficacy and Safety Summaries have been provided.
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			Yes, under 5.3.5.3 with a link to 2.7.4.
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			Yes, under 5.3.5.3 with a link to 2.7.3.
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			The Clinical Overview contains a "Benefits and Risks Conclusions" section.
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?	X			505 (b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: GS-US-236-0101 Study Title: A Phase 1 Multiple Dose Study to Evaluate Relative Bioavailability of Elvitegravir, Emtricitabine, and Tenofovir DF plus Pharmacoenhancer GS-9350 Fixed-Dose Combination Tablet vs. the Individual Components	X			Although the sponsor has performed numerous PK studies on the individual QUAD components, Study GS-US-236-0101 appears to have been one of the pivotal dose finding studies

	Content Parameter	Yes	No	NA	Comment
	Ritonavir Boosted Elvitegravir, Emtricitabine, and Tenofovir DF Sample Size: 44 Arms: • EVG 150 mg + RTV 100 mg, QD PO (A) • STR containing EVG 150 mg/ COBI 100 mg/ FTC 200 mg/ TDF 300 mg QD PO (B) • FTC 200 mg + TDF 300 mg, QD PO (C) • STR containing EVG 150 mg/ COBI 150 mg/ FTC 200 mg/ TDF 300 mg QD PO (D) Location in submission: Section 5.3.3.1				for the QUAD formulation proper. One of the sponsor's conclusions related to this study was the following: *The FDC tablet containing EVG/FTC/TDF/GS-9350 150 mg was selected for further evaluation in subsequent Phase 2 and 3 trials.*
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? <u>Pivotal Study #1</u> GS-US-236-0102: Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Elvitegravir/Emtricitabine/Tenofovir Disoproxil Fumarate/GS-9350 Versus Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate in HIV-1 Infected, Antiretroviral Treatment-Naive Adults Sample Size: 700 Subjects Randomized Sponsor's Proposed Indication: The QUAD pill is indicated as a complete regimen for the treatment of HIV-1 infection in adults who are antiretroviral treatment-naïve or who have no known substitutions associated with resistance to the individual components of the QUAD pill. <u>Pivotal Study #2</u> GS-US-236-0103: A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Elvitegravir/Emtricitabine/Tenofovir Disoproxil Fumarate/GS-9350 Versus Ritonavir-Boosted Atazanavir Plus Emtricitabine/Tenofovir Disoproxil Fumarate in HIV-1 Infected, Antiretroviral Treatment-Naive Adults Sample Size: 715 Subjects Randomized Sponsor's Proposed Indication: The QUAD pill is indicated as a complete regimen for the treatment of HIV-1 infection in adults who are antiretroviral treatment-naïve or who have no known substitutions associated with resistance to the individual components of the QUAD pill.	X			
15.	Do all pivotal efficacy studies appear to be adequate and	X			Yes, however the

	Content Parameter	Yes	No	NA	Comment
	well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	(see comments)			sponsor's proposed indication would appear to allow use in a treatment experienced population. The use in a treatment experienced population is not supported by the submitted efficacy studies which were only performed in a treatment naïve population.
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.	X			Primary Endpoint: % of subjects with HIV-1 RNA < 50 copies/ml at week 48 using the FDA-defined snapshot analysis Secondary Endpoint: Virologic outcomes at week 48 using the FDA-defined TLOVR analysis with HIV-1 RNA cutoff at 50 copies/ml
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	This is not applicable as adequate U.S. data have been provided. As background GS-US-236-0102 was conducted entirely in the U.S and Puerto Rico (681 subjects enrolled in the U.S. and 26 enrolled in PR). GS-US-236-0103 was conducted almost entirely in North America and Western Europe (376 patients were enrolled in the U.S., the rest were enrolled in N. America or W. Europe except for 11 patients enrolled in Thailand).
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner	X			

	Content Parameter	Yes	No	NA	Comment
	previously requested by the Division?				
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			GS-US-183-0128: A Phase 1, Double-Blind, Randomized, Comparative, Positive and Placebo Controlled, Parallel Group Study of the Effects of Ritonavir-boosted GS-9137 at Therapeutic and Supratherapeutic Doses on the QT/QTc Interval in Healthy Subjects GS-US-216-0107: A Phase 1, Partially-Blinded, Randomized, Placebo- and Positive-Controlled Study to Evaluate the Effects of GS-9350 on the QT/QTc Interval in Healthy Subjects
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			The sponsor has provided a Post-marketing section (5.3.6) which includes safety reports and summaries related to tenofovir, FTC and Truvada.
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?	X			In pooling data from the 749 subjects enrolled in studies 236-0102, 236-0103, and 236-0104, 707 subjects have been exposed to QUAD for 24 weeks, 509 subjects have been exposed for 48 weeks and 164 subjects have been exposed for 60 weeks.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	

[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.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?		X		I am unable to locate this document and plan to notify the sponsor.
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?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			Yes, narrative summaries for all deaths, AE leading to dropout and SAEs have been provided within the body of study reports 0102, 0103 and 0104.
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			The sponsor has submitted the following: A request for waiver of pediatric studies, a request for deferral of pediatric studies, and a Pediatric Plan. The sponsor has requested a deferral of pediatric studies for subjects 6 to < 18 years of age. The sponsor has requested a (b) (4) waiver of pediatric studies for the following pediatric populations under 6 years of age: (b) (4)

[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).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					(b) (4) [redacted] See Section 1.9 for additional details.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	See comment in #17 above.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			See Comment in #15 above
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			The sponsor submitted all CRFs for participants with SAEs (including death) 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?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			Section 1.3.4
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?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___Yes_X____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant. N/A

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

1. Please request that the sponsor provide a "coding dictionary" or, if already provided, indicate its location in the submission. 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).

2. We note that women only comprised 10% of the study population in the pivotal phase 3 trials (GS-US-236-0102 & GS-US-236-0103). This may need to be reflected in product labeling or may need to be addressed in PMC.

Reviewing Medical Officer	Date
Adam Sherwat	16 December 2011

Clinical Team Leader	Date
Linda Lewis	16 December 2011

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

/s/

ADAM I SHERWAT
12/16/2011

LINDA L LEWIS
12/16/2011