U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA:	NDA 208215
Drug Name:	Emtricitabine/tenofovir alafenamide (b) (4) and 200/25 mg oral fixed-dose combination tablets
Indication(s):	Treatment of adults and children 12 years of age and older with human immunodeficiency virus type 1 infection
Applicant:	Gilead Sciences, Inc.
Date(s):	Stamp date: April 7, 2015
	Date assigned to reviewer: October 2, 2015
Review Priority:	Standard
Biometrics Division:	Division of Biometrics IV
Statistical Reviewer:	Daniel Rubin, PhD
Concurring Reviewers:	Statistical team leader: Thamban Valappil, PhD
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1 EXECUTIVE SUMMARY

In this submission the Applicant, Gilead Sciences, Inc., seeks to provide evidence that emtricitabine/tenofovir alafenamide (F/TAF) is safe and effective when used as an oral tablet in combination with other agents as antiretroviral therapy for HIV-1 infection. Emtricitabine and tenofovir alafenamide are nucleoside reverse transcriptase inhibitor, and the latter is an oral prodrug of tenofovir.

F/TAF was previously FDA-approved under NDA 207561 as a component in a fixed dose combination tablet with the integrase strand transfer inhibitor elvitegravir and pharmacoenhancer cobicistat (E/C/F/TAF). This approval was based on evidence of safety and efficacy from two Phase 3, randomized, double-blind trials GS-US-292-0104 and GS-US-292-0111, which demonstrated non-inferiority to the active control regimen of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (STB).

In the current submission, the Applicant has not presented results of standalone adequate and well-controlled Phase 3 trials. Rather, safety and efficacy of F/TAF for use in various combinations is to be based on extrapolation from the E/C/F/TAF trials, bioequivalence bridging studies, and results of a Phase 2 trial.

This Phase 2 trial US-GS-299-0102 was a double-blind, non-inferiority study conducted over years 2012-2014 that randomized treatment-naïve adults with HIV-1 infection to the daily fixed-dose combination tablet D/C/F/TAF of darunavir (800 mg), cobicistat (150 mg), emtricitabine (200 mg), and tenofovir alafenamide (10 mg), or to the comparator daily regimen DRV+COBI+TVD of darunavir (800 mg), cobicistat (150 mg), emtricitabine (200 mg), and tenofovir disoproxil fumarate (300 mg). The primary efficacy endpoint was virologic success at Week 24, defined by HIV-1 RNA <50 copies/mL, based on the FDA "snapshot algorithm" to classify certain outcomes with discontinuations or missing data. The pre-specified non-inferiority margin for this Week 24 endpoint was 12% on the risk difference scale. Subjects were randomized in a 2:1 ratio to D/C/F/TAF (n = 103 subjects) or the DRV+COBI+TVD control group (n = 50 subjects). Baseline demographics and disease characteristics were similar between the randomized D/C/F/TAF and DRV+COBI+TVD groups in the reviewed Phase 2 trial. Subjects were enrolled in the United States, had a median age of 33 years, were over 90% male, were 60% White and 35% Black, and 84% had the risk factor of homosexual sex. Baseline HIV-1 RNA was >100,000 copies/mL in 20% of subjects, CD4 count was <200 cells/µL in 14% of subjects, and 90% of subjects had asymptomatic infection at baseline.

The efficacy results in the following table show that D/C/F/TAF met the 12% non-inferiority margin for the Week 24 virologic success primary efficacy endpoint. However, the previous and current FDA guidances on drug development for HIV-1 infection recommend a primary endpoint of Week 48 virologic success. For this longer term endpoint, D/C/F/TAF did not meet the guidance-recommended 12% non-inferiority margin. Thus, this trial did not provide standalone substantial evidence of efficacy for the D/C/F/TAF regimen. In addition, this was a single Phase 2 trial without replicated evidence for the same regimen, and in fact the statistical analysis plan stated that the

sample size "was chosen to estimate the response rate of HIV-1 RNA < 50 copies/mL at Week 24 for the regimen to allow for the planning of Phase 3 studies."

Table 1: Virologic success rates for D/C/F/TAF in GS-US-299-0102

Virologic success	D/C/F/TAF (n = 103)	DRV+COBI+TVD (n = 50)	Difference (95% CI)	P-value
Week 24	77/103 (75%)	37/50 (74%)	3.3% (-11% to 18%)	0.64
Week 48	79/103 (77%)	42/50 (84%)	-6.2% (-20% to 7%)	0.35

Source: GS-US-299-0102 Clinical Study Report, Tables 9-1 and 9-2.

Results within the Phase 2 trial did not provide a statistical basis for concern regarding lack of efficacy for D/C/F/TAF. While numeric trends for the Week 48 endpoint favored the DRV+COBI+TVD control group the results were inconclusive, and did not approach statistical inferiority.

The small sample size of this trial limited exploratory subgroup analyses, and no quantitative or qualitative treatment interactions were identified for further investigation.

Before results of the reviewed Phase 2 trial were analyzed, the FDA clinical reviewer had recommended increased vigilance for the ocular safety of F/TAF. The trial results added to this signal, as eye disorder adverse events occurred in 6/103 (6%) of subjects randomized to D/C/F/TAF and 0/50 (0%) subjects in the DRV+COBI+TVD group. The Applicant has suggested that tenofovir alafenamide may have superior bone safety or renal safety relative to tenofovir disoproxil fumarate. No fracture events occurred in this trial, and one adverse event of proximal renal tubulopathy occurred in the control group.

Prior to this reviewer's involvement, the FDA sent a mid-cycle communication to the Applicant expressing concern that the success rates in the above table were lower than those in the Phase 3 trials of E/C/F/TAF, in which Week 48 virologic success rates in the pooled trials were 800/866 (92%) in the E/C/F/TAF group and 784/867 (90%) in the STB group. This communication suggested that reduced efficacy may be due to lower TAF exposure when F/TAF is combined with darunavir/cobicistat. Although this was a cross-study comparison, the relevant trials were conducted by the same sponsor over a similar time period, with similar entry criteria, procedures, endpoints, and relatively similar patient characteristics. The Applicant presented several alternative explanations for the observed efficacy differences, including greater discontinuation rates seen in the reviewed Phase 2 trial of D/C/F/TAF and worse adherence in this trial due to the number of pills required to maintain blinding. These explanations could not fully account for the cross-study differences in outcomes, as the difference persisted under a best/worst analysis in which discontinuations were handled as favorably as possible for D/C/F/TAF and as unfavorably as possible for E/C/F/TAF. However, due to the inherent limitations of non-randomized comparisons, only a randomized trial comparing D/C/F/TAF to E/C/F/TAF in treatment-naïve adults with HIV-1 infection could definitively confirm or refute a signal for reduced efficacy.

2 INTRODUCTION

2.1 Overview

This review considers evidence submitted by the Applicant, Gilead Sciences, Inc., for the safety and efficacy of oral fixed-dosed combination emtricitabine/tenofovir alafenamide (F/TAF) for antiretroviral therapy, in combination with other agents, in treatment-naïve adults with human immunodeficiency virus (HIV)-1 infection. Specifically, this review focuses on the Phase 2 randomized trial GS-US-299-0102, which evaluated the regimen of darunavir, cobicistat, and emtricitabine/tenofovir alafenamide (D/C/F/TAF).

Although the Applicant submitted results this Phase 2 for this NDA, the pivotal trials for the F/TAF combination were actually reviewed in the previously approved New Drug Application (NDA) 207561. In the prior application F/TAF was combined with elvitegravir and cobicistat (E/C/F/TAF) and evaluated in the replicated Phase 3 trials GS-US-292-0104 and GS-US-292-0111. Therefore, the Applicant proposes that the safety and efficacy of D/C/F/TAF is to be based on results of bioequivalence studies, the aforementioned Phase 2 study, and bridging from the pivotal trial results for E/C/F/TAF.

During the application review, but prior to this reviewer's involvement, the Division of Antiviral Products expressed concern in a mid-cycle communication to the Applicant that efficacy appeared lower for the D/C/F/TAF regimen in its Phase 2 trial than was seen in the separate Phase 3 trials of E/C/F/TAF, and noted based on clinical pharmacology considerations that this may be due TAF achieving lower exposures when combined with darunavir than when combined with elvitegravir. Consequently, this review also considers the statistical evidence supporting this potential signal for decreased efficacy.

Due to the number of different trials, antiretroviral drugs, and regimens already mentioned in the preceding paragraphs, the following tables may provide a useful key.

Table 2: Trials reviewed or discussed in this NDA statistical review

Study	Design	Treatment arms	Sample size	Comments
GS-US-299-0102	A Phase 2, randomized, double-blind trial in treatment-naïve adults with HIV-1 infection.	1:1 randomization to D/C/F/TAF versus DRV+COBI+TVD.	D/C/F/TAF: N = 103 DRV+COBI+DRV: N = 50	Statistical review conducted for the current NDA.
GS-US-292-0104 and GS-US-299-0111	Two identically designed, Phase 3, randomized, double-blind, non-inferiority trials in treatment-naïve adults with HIV-1 infection.	1:1 randomization to E/C/F/TAF versus STB.	E/C/F/TAF: N = 866 (pooled trials) STB: N = 867 (pooled trials)	Previously reviewed under NDA 207561. Cross-study comparisons are discussed using these trials in the current statistical review.

Table 3: List of drugs discussed in this statistical review

Drug name	Description and mechanism of action
Darunavir	A protease inhibitor used in combinations for HIV-1 antiretroviral therapy
Cobicistat	A pharmacokinetic enhancer that does not itself possess antiretroviral activity, but may enhance other drugs such as darunavir by increasing exposure
Emtricitabine	A nucleoside reverse transcriptase inhibitor used in combinations for HIV-1 antiretroviral therapy
Tenofovir alafenamide	A prodrug of the nucleoside reverse transcriptase inhibitor tenofovir; proposed in the application for use in combinations for HIV-1 antiretroviral therapy
Elvitegravir	An integrase strand transfer inhibitor used in combinations for HIV-1 antiretroviral therapy
Tenofovir disoproxil fumarate	A prodrug of the nucleoside reverse transcriptase inhibitor tenofovir; used in combinations for HIV-1 antiretroviral therapy

Table 4: Regimen abbreviations used for this statistical review

Abbreviation	Regimen
F/TAF	Emtricitabine/tenofovir alafenamide
D/C/F/TAF	Darunavir/cobicistat/emtricitabine/tenofovir alafenamide
DRV+COBI+TVD	Cobicistat-boosted darunavir given with emtricitabine coformulated with tenofovir disoproxil fumarate
E/C/F/TAF	Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
STB	Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate

The regulatory history and timeline of events for this NDA are summarized in the table below. A statistical review was requested by the Division approximately 6 months after receipt of the application. During the course of the review, the FDA approved E/C/F/TAF under a different NDA and released a revised guidance document.

Table 5: Timeline of events

April 7, 2014	This application, NDA 208215, is received by the FDA (i.e., the stamp date). This is a standard review, meaning the PDUFA goal is to complete the review in 12 months by April 7, 2016.
September 29, 2015	The mid-cycle communication is sent by the FDA to the Applicant expressing concern regarding the efficacy of D/C/F/TAF based on cross-study comparisons with E/C/F/TAF.
October 2, 2015	This reviewer is asked to provide a statistical review for this NDA.
November 2, 2015	The FDA releases its revised guidance document on developing antiretroviral drugs for treatment of HIV-1 infection.
November 5, 2015	E/C/F/TAF is given FDA approval under NDA 207561.

2.1.1 HIV-1 infection and antiretroviral therapy

Background on HIV-1 infection, antiretroviral therapy, regulatory history, and development pathways recommended by the Division of Antiviral Products are discussed in the most recent FDA guidance document[1] for this indication.

HIV-1 infection is a serious and life-threatening disease caused by the human immunodeficiency virus, which is a type of retrovirus that replicates in human host cells through reverse transcription. If untreated, the disease progressively damages the immune system. This can lead to acquired immunodeficiency syndrome (AIDS), in which opportunistic infections can be fatal. The virus is most commonly spread as a sexually transmitted disease. It is estimated that tens of millions of people worldwide have been infected and/or killed by HIV-1 infection.

In the United States, combinations of antiretroviral therapies are recommended for chronic treatment of HIV-1 infection as soon as a diagnosis is made. Therapies operate through different mechanisms, and antiretroviral drugs include fusion inhibitors, integrase inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, CCR5 inhibitors, and protease inhibitors. This review focuses on therapies for treatment-naïve patients, meaning those who have not already been treated.

The guidance document mentioned above (as well as guidance documents written at the time of trial design) recommend that for traditional approval clinical trials evaluate antiretroviral drugs for treatment-naïve subjects using the primary efficacy endpoint of virologic success after 48 weeks of therapy, meaning a measurement of viral load. The Phase 2 trial GS-US-299-0102 reviewed in this application used a primary endpoint defined by virologic success at Week 24, which will be described in detail in Section 3.2.1.

2.1.2 Emtricitabine/tenofovir alafenamide

Oral pills are already marketed in the United States for emtricitabine/tenofovir disoproxil fumarate. Emtricitabine is a nucleoside reverse transcriptase inhibitor. Tenofovir disoproxil fumarate is a nucleoside reverse transcriptase inhibitor that is an oral prodrug of the nucleotide analog tenofovir. Tenofovir alafenamide, which is the new component evaluated in this application, is a different oral prodrug of tenofovir. Please refer to the clinical virology review for additional details regarding antiviral mechanisms.

In the reviewed Phase 2 trial GS-US-299-0102, subjects were given a once daily fixed dose combination tablet containing 800 mg darunavir (a protease inhibitor), 150 mg cobicistat (a pharmacoenhancer intended to increase darunavir exposure), 200 mg emtricitabine, and 10 mg tenofovir alafenamide. (b) (4)

[1] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment. Guidance for Industry. November 2015. Revision 1. Available online at http://www fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm355128.pdf

(b) (4)

2.1.3 Scope of statistical review

This review focuses on the following two specific issues identified by the Division as requiring statistical input:

- The statistical evidence for the safety and efficacy of D/C/F/TAF, based on the Phase 2 trial GS-US-299-0102.
- The statistical evidence for the potential of reduced D/C/F/TAF efficacy relative to E/C/F/TAF, based on a cross-study comparison of the Phase 2 trial GS-US-299-0102 and the Phase 3 trials GS-US-292-0104 and GS-US-292-0111.

Several statistical issues are considered beyond the scope of this review, but are discussed in the aforementioned FDA guidance document:

- The appropriateness of the specific virologic success endpoint definitions, cutoffs, and handling of missing data and treatment discontinuations using the "snapshot algorithm" described in the guidance, and the validity of this viral load endpoint as a surrogate for preventing disease progression and mortality.
- The appropriateness of the 12% non-inferiority margin used for the primary efficacy analysis of Week 24 virologic success endpoint in the reviewed Phase 2 trial. For this trial of D/C/F/TAF versus DRV+COBI+TVD, demonstrating the contribution of the F/TAF regimen component through a non-inferiority comparison requires an argument that the DRV+COBI+TVD comparator would have a large effect relative to a hypothetical DRV+COBI regimen.

In addition, this reviewer defers to other respective review disciplines regarding a number of other issues in this application, including the use, labeling, and dose of F/TAF in combinations with agents other than darunavir/cobicistat, primary review of safety, review of hypothesis generating data such as *in vitro* studies and animal studies, and review of bioequivalence studies.

2.2 Data Sources

Materials reviewed for the Phase 2 trial GS-US-299-0102 of D/C/F/TAF included the clinical study report, protocol, statistical analysis plan, and patient-level datasets. The link in the FDA Electronic Document Room to the datasets used is as follows: \\CDSESUB1\evsprod\NDA208215\0000\m5\datasets\gs-us-299-0102\

For the cross-study comparisons involving Phase 3 studies GS-US-292-0104 and GS-US-292-0111 of E/C/F/TAF, clinical study reports were reviewed. Datasets for the respective trials can be found in the following locations of the FDA Electronic Document Room:

- \\CDSESUB1\evsprod\NDA207561\0000\m5\datasets\gs-us-292-0104
- \\CDSESUB1\evsprod\NDA207561\0000\m5\datasets\gs-us-292-0111

3 STATISTICAL EVALUATION

3.1 Data Analysis and Quality

The quality of the submitted data for the Phase 2 trial GS-US-299-0102, which compared the D/C/F/TAF and DRV+COBI+TVD regimens, was generally sufficient for this review. This reviewer was able to reproduce the major efficacy results from the submitted datasets, including results the Week 24 and Week 48 virologic success endpoints. Furthermore, the analyses conducted by the Applicant appeared generally consistent with the pre-specified statistical analysis plan.

For a discussion of the data analysis and quality in the Phase 3 trials GS-US-292-0104 and GS-US-292-0111 comparing E/C/F/TAF to STB, please refer to Section 3.1.1 of the statistical review of NDA 207561 by Thomas Hammerstrom, PhD, who reported that he was "able to reproduce the applicant's results nearly exactly" and that the "overall conclusion of clinical and statistical non-inferiority are the same for both the FDA and the applicant's analyses."

3.2 Evaluation of Efficacy

This section of the review focuses on evidence for the efficacy of the D/C/F/TAF regimen obtained in the Phase 2 trial GS-US-299-0102. The subsequent Section 3.3 then briefly discusses the safety results in this Phase 2 trial.

3.2.1 Study design and endpoints for GS-US-299-0102

GS-US-299-0102 was a Phase 2, double-blind, multicenter, controlled trial in which treatment-naïve adult subjects with HIV-1 infection were randomized to D/C/F/TAF or DRV+COBI+TVD regimens.

The trial enrolled a total of 153 subjects, of whom 150 were enrolled at 37 study centers in the United States and 3 were enrolled at a study center in Puerto Rico. The first subject was screened in April 2012 and the last subject observation was in February 2014.

Inclusion criteria required subjects to be >18 years old and to sign a written informed consent form. Diagnosis required plasma HIV-1 RNA levels ≥5,000 copies/mL and CDR+ cell count >50 cells/μL. Subjects were to be treatment-naïve, meaning no prior use of any approved or experimental anti-HIV drug. Subjects were to have normal electrocardiograms, adequate renal function, normal hepatic transaminases and total bilirubin levels, normal serum amylase levels, adequate hematologic function, and normal thyroid-stimulating hormone.

Exclusion criteria disallowed subjects with a newly acquired AIDS-defining condition diagnosed within the 30 days prior to screening, Hepatitis B, Hepatitis C, a history of decompensated cirrhosis, current alcohol or substance abuse, a previous or recent malignancy, an implanted defibrillator or pacemaker, or a recent or ongoing serious

infection other than HIV-1 requiring parenteral antibiotic or antifungal therapy. Also excluded were subjects receiving ongoing therapy with a variety of other medications, including drugs known not to be used with darunavir or cobicistat, which included certain alpha adrenergic receptor antagonists, analeptics, anticonvulsants, antihistamines, antimycobacterials, calcium channel blockers, ergot derivatives, GI motility agents, herbal supplements, HMG-CoA reductase inhibitors, neuroleptics, sedatives/hypnotics, and systemic corticosteroids. Please refer to the protocol for further details and specific definitions used for inclusion and exclusion criteria.

The two randomized treatment intervention groups were as follows:

- D/C/F/TAF group:
    - A once daily fixed dose combination tablet of 800 mg darunavir, 150 mg cobicistat, 200 mg emtricitabine, and 10 mg tenofovir alafenamide.
    - Two daily placebos tablets were given to match 400 mg darunavir tablets in the comparator group.
    - A placebo tablet was given daily to match a 150 mg cobicistat tablet in the control group.
    - A placebo tablet was given daily to match a tablet containing emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg in the comparator group.
- DRV+COBI+TVD group:
    - Two daily tablets of 400 mg darunavir.
    - One daily tablet of 150 mg cobicistat.
    - One daily tablet containing emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg.
    - One daily placebo tablet to match the darunavir/cobicistat/ emtricitabine/ tenofovir alafenamide in the comparator group.

Overall, subjects required 5 daily tablets to maintain the blinding.

Subjects were randomized in a 2:1 ratio to D/C/F/TAF or to DRV+COBI+TVD arms, such that n=103 and n=50 subjects were assigned to the respective groups. The randomization was stratified at screening by HIV-1 RNA level (≤100,000 or >100,000 copies/mL) and by race (Black or non-Black).

Subjects were treated for 48 weeks, and were given dosing diaries to record adherence. Afterwards, depending on the calendar time of trial enrollment. Subjects could continue on blinded study medication, return for an unblinding visit, or enroll in an open-label extension phase. This review will not focus on efficacy outcomes defined after post-randomization Week 48.

Post-baseline assessments were to occur at the end of Weeks 2, 4, 8, 12, 16, 24, 3, 40 and 48. Evaluations at the baseline and post-baseline visits included a review of adverse events, concomitant medications, complete physical examinations, 12-lead electrocardiograms, urine collection for laboratory procedures, and blood sample collection for laboratory analyses including HIV-1 RNA levels, CDR+ cell counts.

Study medication could be discontinued due to intercurrent illness affecting clinical status, toxicity, lack of efficacy, subject request to discontinue, noncompliance, or pregnancy during the study. Study medication could also be discontinued in favor of an alternative antiretroviral regimen in case of suboptimal virologic response or virologic rebound with reverse transcriptase or protease resistance detected from viral genotype/phenotype analysis results. Suboptimal virologic response was defined by HIV-1 RNA < 1 $\log_{10}$ reduction from baseline and ≥ 50 copies/mL at the Week 8 visit confirmed at the next (scheduled or unscheduled) visit. Virologic rebound was defined by a rebound in HIV-1 RNA to ≥400 copies/mL at two consecutive scheduled or unscheduled visits at after previously achieving <50 copies/mL, or having a >1 $\log_{10}$ increase in HIV-1 RNA from the nadir at consecutive scheduled or unscheduled visits.

The protocol distinguished between criteria for discontinuation of study treatment and criteria for premature discontinuation from study assessments, and stated that every attempt was to be made to continue study assessments for subjects who discontinued study medication. However, if this was not possible the subject was to return for an Early Study Drugs Discontinuation Visit followed by a 30-day follow-up visit.

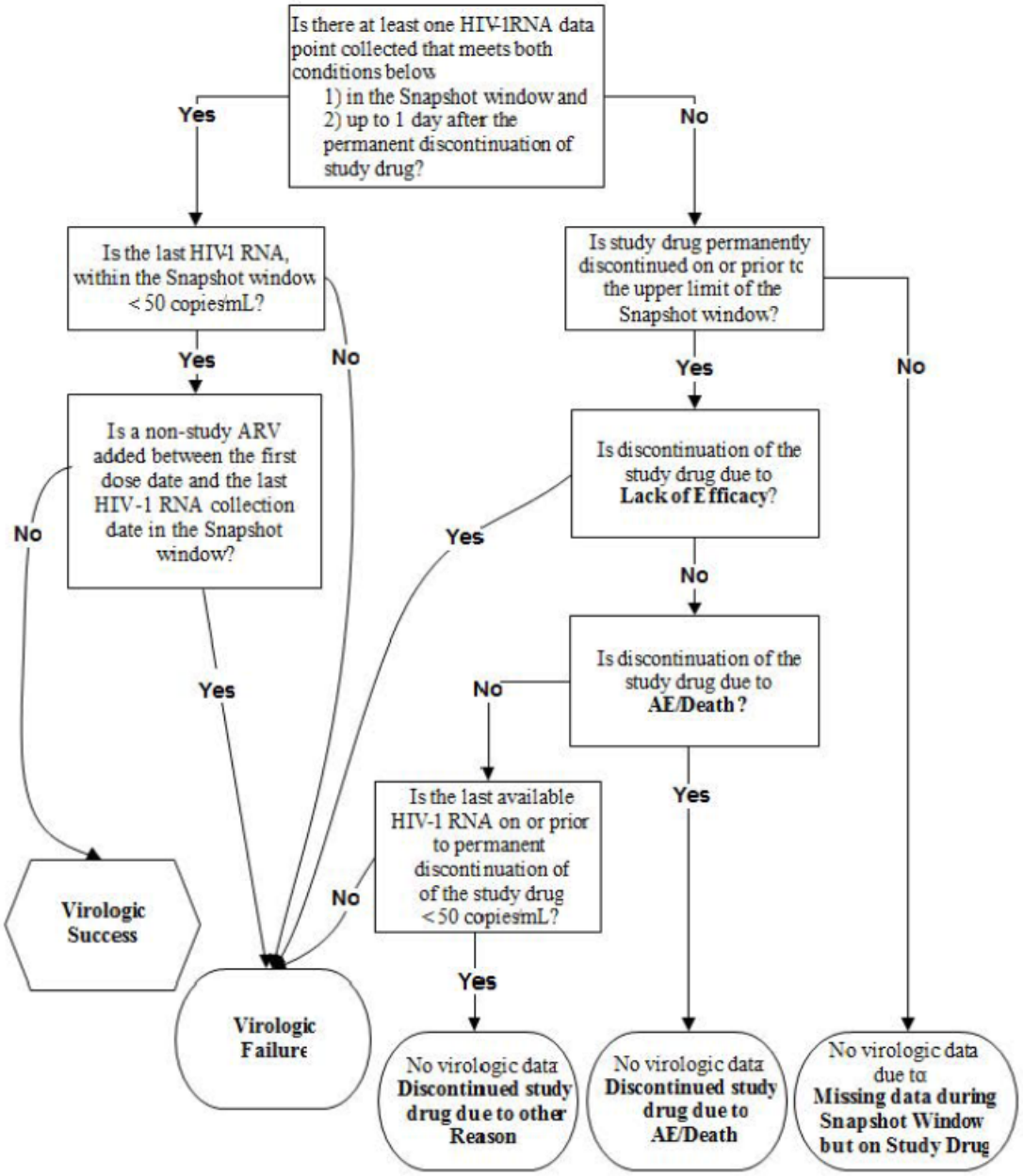
The primary efficacy endpoint in this trial was achievement of plasma HIV-1 RNA <50 copies/mL at Week 24. This analysis used the following "snapshot" algorithm that categorized subjects as follows, and is shown in more detail in the flowchart below.

- Virologic success: Subjects who have the last available HIV-1 RNA < 50 copies/ML in the Week 24 analysis window while on randomized treatment.
- Virologic failure:
    - Discontinuation of study drug prior to or in the Week 24 analysis window due to lack of efficacy. "Lack of efficacy" was here defined with a check box on the study drug completion page of the electronic case report form.
    - Discontinuation of study drug prior to or in the Week 24 analysis window due to reasons other than an adverse event, death or lack of efficacy with the last available HIV-1 RNA on treatment being ≥50 copies/mL.
    - Addition of non-study antiretroviral therapy between the first dose date and the last HIV-1 RNA collection date in the Week 24 analysis window.
- No virologic data in the Week 24 analysis window because of:
    - Discontinuation of study drug due to an adverse event or death
    - Discontinuation of study drug prior to or in the Week 24 analysis window due to reasons other than an adverse event, death, or lack of efficacy (e.g., withdrew consent, loss to follow-up) and the last available HIV-1 RNA on treatment was < 50 copies/mL.
    - Missing data during the Week 24 analysis window but the subject was on study medication.

The following secondary efficacy endpoints were used in the trial:

- HIV-1 RNA < 50 copies/mL at Week 48, as defined by a snapshot analysis algorithm analysis analogous to that used for the Week 24 primary endpoint.
- Change from baseline in CD4+ cell count at Week 24 and Week 48.
- Change from baseline in $\log_{10}$ HIV-1 RNA copies/mL at Week 24 and Week 48.

Figure 1: Flowchart of snapshot analysis algorithm.



Source: GS-US-299-0102 Statistical Analysis Plan, Appendix 4. The Snapshot window was defined as Day 140 to 195 (inclusive).

3.2.2 Statistical methodologies for GS-US-299-0102

This Phase 2 study was designed as a non-inferiority trial. The margin for the primary efficacy endpoint of virologic success at Week 24 was 12% on the risk difference scale.

The point estimate and confidence interval for the treatment effect on the Week 24 virologic success primary efficacy endpoint was based on the Cochran-Mantel-Haenszel (CMH) method, and was stratified by HIV-1 RNA level (≤100,000 copies/mL or

>100,000 copies/mL) and race (Black or non-Black). These were the same factors used to stratify the randomization. The analysis compared virologic success rates in the two treatment groups, with the denominator including both subjects with virologic failure and with missing virologic data. The secondary endpoint of Week 48 virologic success was handled similarly.

For continuous outcomes such as the secondary efficacy endpoints of change from baseline in CD4 cell count or $\log_{10}$ HIV-1 RNA, the two-sided Wilcoxon rank sum test was used to obtain p-values and subjects with missing observations were excluded from comparisons of mean values.

The statistical analysis plan defined the following analysis populations and described their use of efficacy, secondary analysis, and safety summaries:

- The full analysis set (FAS): All randomized subjects who received at least one dose of study medication. In this trial all randomized subjects were dosed. The FAS was the primary analysis population for efficacy.
- The per-protocol analysis set (PP) was defined separately for Week 24 and Week 48. These analysis populations were comprised of subjects who were randomized, received at least one dose of study drug, and did not commit any major protocol violation or violate key entry criteria. The statistical analysis plan pre-specified that a secondary analysis of the Week 24 virologic success endpoint was to be conducted in the per-protocol analysis set.
- The safety analysis set was defined as subjects who were randomized into the study and received at least one dose of study medication, and subjects were grouped according to the treatment actually received rather than randomized. However, in this trial the safety analysis set coincided with the full analysis set. Safety was analyzed descriptively and safety summaries were based on events recorded up to 30 days after subjects permanently discontinued all study drugs.

In addition, several other analysis sets were defined for a pharmacokinetic substudy and analyses of dual energy x-ray absorptiometry scans.

The study drug adherence rate was computed for each subject by dividing the total number of active pills (i.e., non-placebos) taken within a specified timeframe by the total number of active pills prescribed during that timeframe. The numbers of drugs dispensed and returned were captured on study drug accountability forms.

The statistical analysis plan made the following comments regarding the planned sample size and 2:1 randomization:

> *"A sample size of 100 subjects in the single-tablet regimen (D/C/F/TAF) group was chosen to estimate the response rate of HIV-1 RNA < 50 copies/mL at Week 24 for the regimen to allow for the planning of Phase 3 studies. A total sample size of 150 subjects has 56% power to evaluate non-inferiority with respect to the response rate of HIV-1 RNA < 50 copies/mL at Week 24 if a response rate of 88% for both groups and a non-inferiority margin of 0.12 are assumed.*

The total sample size of 150 subjects provides 43% power to observe a smaller decrease of 1% with a standard deviation of 3.2% in hip bone mineral density in D/C/F/TAF group relative to DRV+COBI+TVD group."

The trial included an independent data monitoring committee (IDMC). The charter specified that the IDMC was to regularly monitor safety of subjects in the trial. In addition, the IDMC was to descriptively analyze efficacy after all subjects had respectively completed the Week 12 visit or prematurely discontinued study drug, after the last subject enrolled had completed their Week 24 visit or prematurely discontinued study drug, and after the last subject enrolled had completed their Week 48 visit or prematurely discontinued study drug. The planned interim analyses did not include any formal stopping boundaries for efficacy or futility. The trial was not stopped early and thus was run to completion.

3.2.3 Patient disposition and baseline characteristics for GS-US-299-0102

The following figures and tables in this section display the disposition and baseline characteristics of randomized subjects in the GS-US-299-0102 Phase 2 trial.

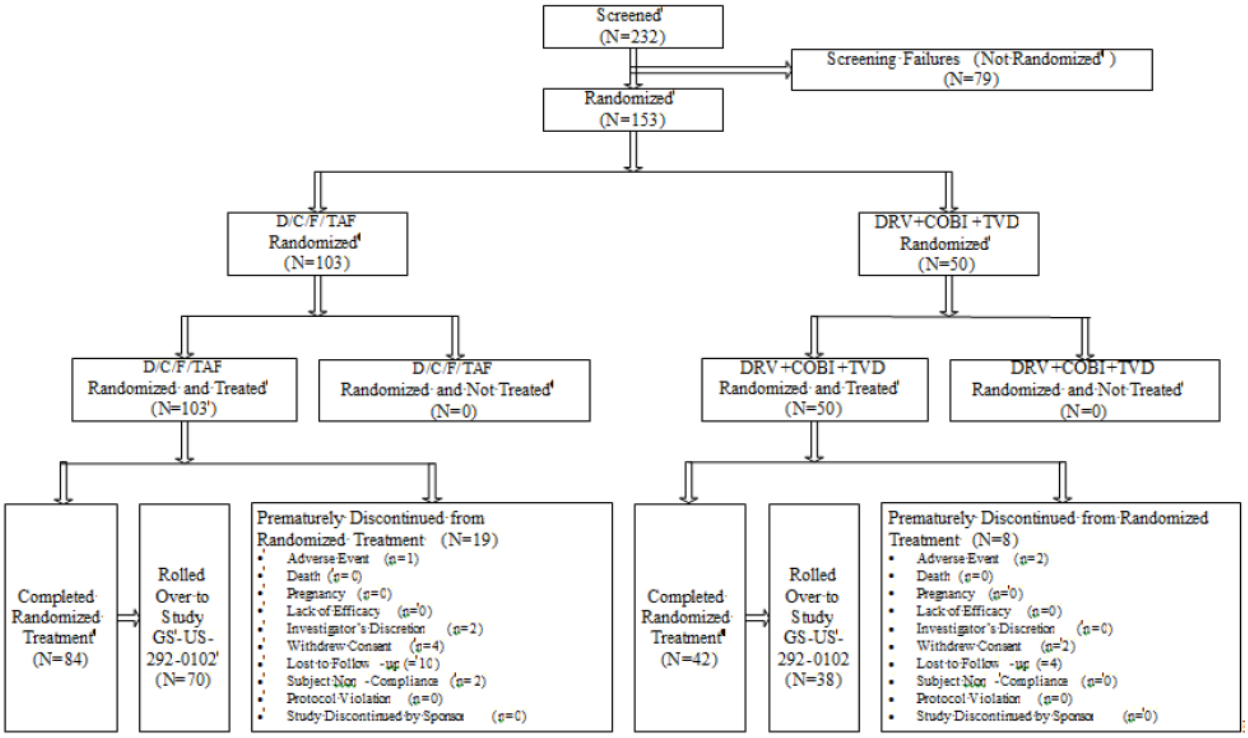
All randomized subjects were treated with study medication, and consequently included in the full analysis set used for the primary efficacy analysis.

The rates of premature discontinuation from randomized treatment were 19/103 (18%) in the D/C/F/TAF group and 8/50 (16%) in the DRV+COBI+TVD group. Thus, a nontrivial fraction of subjects prematurely discontinued therapy, but rates were similar across arms. Section 3.2.5 of this review discusses discontinuations and missing outcomes in greater detail.

The randomized groups appeared similar to this reviewer in terms of demographics. Subjects enrolled in this trial were predominately male, with an average age of 35 years old. The trial enrolled exclusively in the United States, including 3 subjects in Puerto Rico.

Baseline disease characteristics were likewise relatively well-balanced between the randomized D/C/F/TAF and DRV+COBI+TVD groups. There was a statistically non-significant numerical difference in that a greater proportion of subjects in the DRV+COBI+TVD group had baseline HIV-1 RNA ≤100,000 copies/mL, which was somewhat surprising to this reviewer because this category was used as a randomization stratification factor. The majority of subjects in this trial had homosexual sex as an HIV risk factor. Most subjects were asymptomatic at baseline, and only 5/153 (3%) subjects had AIDS.

Figure 2: Disposition of study subjects in GS-US-299-0102



Source: GS-US-299-0102 Clinical Study Report, Figure 8-1.

Table 6: Demographics of study subjects in GS-US-299-0102, full analysis set

Characteristic	D/C/F/TAF (N = 103)	DRV+COBI+TVD (N = 50)	Total (N = 153)
Age (years)			
N	103	50	153
Mean (SD)	35 (11.3)	37 (10.9)	35 (11.2)
Median	31	36	33
Q1, Q3	25, 42	28, 44	26, 43
Min, Max	20, 68	18, 57	18, 68
Sex (n, %)			
Male	95 (92.2%)	47 (94.0%)	142 (92.8%)
Female	8 (7.8%)	3 (6.0%)	11 (7.2%)
Race (n, %)			
White	62 (60.2%)	30 (60.0%)	92 (60.1%)
Black or African American	36 (35.0%)	17 (34.0%)	53 (34.6%)
Asian	2 (1.9%)	1 (2.0%)	3 (2.0%)
Native Hawaiian or Other Pacific Islander	1 (1.0%)	1 (2.0%)	2 (1.3%)
Other	2 (1.9%)	1 (2.0%)	3 (2.0%)
Ethnicity (n, %)			
Hispanic or Latino	23 (22.3%)	9 (18.0%)	32 (20.9%)
Not Hispanic or Latino	80 (77.7%)	41 (82.0%)	121 (79.1%)
Baseline Body Mass index (kg/m^2)			
N	103	50	153
Mean (SD)	26.3 (4.97)	26.1 (4.53)	26.2 (4.81)
Median	25.1	24.7	24.9
Q1, Q3	22.4, 29.6	22.7, 29.0	22.7, 29.2
Min, Max	18.2, 42.7	17.6, 37.9	17.6, 42.7

Source: GS-US-299-0102 Clinical Study Report, Table 8-4.

Table 7: Baseline characteristics of subjects in GS-US-299-0102, full analysis set

	D/C/F/TAF (N = 103)	DRV+COBI+TVD (N = 50)	Total (N = 153)
HIV-1 RNA (log10 copies/mL)			
N	103	50	153
Mean (SD)	4.70 (0.516)	4.65 (0.514)	4.68 (0.515)
Median	4.67	4.58	4.66
Q1, Q3	4.43, 4.93	4.28, 4.91	4.37, 4.91
Min, Max	3.27, 6.12	3.59, 6.29	3.27, 6.29
HIV-1 RNA Category (copies/mL)			
<= 100,000	80 (77.7%)	43 (86.0%)	123 (80.4%)
> 100,000 to <= 400,000	17 (16.5%)	5 (10.0%)	22 (14.4%)
> 400,000	6 (5.8%)	2 (4.0%)	8 (5.2%)
CD4 Cell Count (/uL)			
N	103	50	153
Mean (SD)	395 (169.3)	464 (261.6)	417 (205.7)
Median	368	433	384
Q1, Q3	270, 515	320, 606	283, 532
Min, Max	7, 909	49, 1463	7, 1463
CD4 Cell Count Category (/uL)			
< 50	1 (1.0%)	1 (2.0%)	2 (1.3%)
>=50 and <200	10 (9.7%)	9 (18.0%)	19 (12.4%)
>=200 and <350	37 (35.9%)	8 (16.0%)	45 (29.4%)
>=350 and <500	27 (26.2%)	12 (24.0%)	39 (25.5%)
>= 500	28 (27.2%)	20 (40.0%)	48 (31.4%)
CD4 Percentage (%)			
N	103	50	153
Mean (SD)	22.9 (8.14)	25.3 (9.95)	23.7 (8.81)
Median	22.1	25.3	23.6
Q1, Q3	17.4, 29.1	18.5, 31.1	17.6, 29.6
Min, Max	1.0, 42.8	6.9, 49.7	1.0, 49.7
HIV Risk Factors			
Heterosexual Sex	19 (18.4%)	8 (16.0%)	27 (17.6%)
Homosexual Sex	86 (83.5%)	43 (86.0%)	129 (84.3%)
IV Drug Use	0	2 (4.0%)	2 (1.3%)
Unknown	3 (2.9%)	0	3 (2.0%)
Other	2 (1.9%)	2 (4.0%)	4 (2.6%)
HIV Disease Status			
Asymptomatic	93 (90.3%)	44 (88.0%)	137 (89.5%)
Symptomatic HIV Infections	8 (7.8%)	3 (6.0%)	11 (7.2%)
AIDS	2 (1.9%)	3 (6.0%)	5 (3.3%)

Source: Source: GS-US-299-0102 Clinical Study Report, Table 8-5.

3.2.4 Results and conclusions for GS-US-299-0102

The following tables in this section show the rates of virologic success at Week 24 and at Week 48.

For the Week 24 primary efficacy endpoint, the point estimates for success rates in the D/C/F/TAF and the DRV+COBI+TVD were similar (75% versus 74%), and the -11.4% lower bound of the confidence interval for the treatment effect exceeded the pre-specified non-inferiority margin of -12%. Rates of missing data (i.e., no virologic data in the Week 24 window according to the snapshot algorithm) were relatively low in the two groups (5% versus 2%), although re-classification of these subjects could impact whether the non-inferiority margin was exceeded.

For the guidance-recommended Week 48 efficacy endpoint the point estimate for the treatment effect showed a numerical trend in favor the DRV+COBI+TVD group, in which the virologic success rate was 6.2% higher than in the D/C/F/TAF group. The confidence interval for the treatment effect was fairly wide (-19.9% to 7.4%), and did not rule out the guidance-recommended 12% non-inferiority margin. The results did not show statistical inferiority of D/C/F/TAF (two-sided $p = 0.35$).

Table 8: Applicant's analysis of Week 24 virologic outcome, full analysis set

	D/C/F/TAF (N=103)	DRV+COBI +TVD (N=50)	D/C/F/TAF vs. DRV+COBI+TVD	
			p-value[a]	Difference in Percentages (95% CI)[b]
Virologic Success at Week 24[c]				
HIV-1 RNA < 50 copies/mL	77 (74.8%)	37 (74.0%)	0.64	3.3% (-11.4% to 18.1%)
Virologic Failure at Week 24[c]	21 (20.4%)	12 (24.0%)		
HIV-1 RNA ≥ 50 copies/mL	14 (13.6%)	11 (22.0%)		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL[d]	7 (6.8%)	1 (2.0%)		
Added New ARV	0	0		
No Virologic Data in Week 24 Window[c]	5 (4.9%)	1 (2.0%)		
Discontinued Study Drug Due to AE/Death	1 (1.0%)	0		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL	4 (3.9%)	1 (2.0%)		

a P-value for the superiority test comparing the percentages of virologic success was from the CMH test stratified by baseline HIV-1 RNA and race strata.
b Difference in percentages of virologic success and its 95% CI were calculated based on baseline HIV-1 RNA stratum-adjusted MH proportion.
c Week 24 window was between Day 140 and 195 (inclusive).
d Discontinuation due to other reasons included subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, subject noncompliance, protocol violation, pregnancy, and study discontinued by sponsor.

Source: GS-US-299-0102 Clinical Study Report, Table 9-1.

Table 9: Applicant's analysis of Week 48 virologic outcome, full analysis set

	D/C/F/TAF (N=103)	DRV+COBI +TVD (N=50)	D/C/F/TAF vs. DRV+COBI+TVD	
			p-value[a]	Difference in Percentages (95% CI)[b]
Virologic Success at Week 48[c]				
HIV-1 RNA < 50 copies/mL	79 (76.7%)	42 (84.0%)	0.35	-6.2% (-19.9% to 7.4%)
Virologic Failure at Week 48[c]	16 (15.5%)	6 (12.0%)		
HIV-1 RNA ≥ 50 copies/mL	7 (6.8%)	4 (8.0%)		
Discontinued Study Drug Due to Lack of Efficacy	0	0		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL[d]	9 (8.7%)	2 (4.0%)		
Added New ARV	0	0		
No Virologic Data in Week 48 Window[c]	8 (7.8%)	2 (4.0%)		
Discontinued Study Drug Due to AE/Death	1 (1.0%)	1 (2.0%)		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL	7 (6.8%)	1 (2.0%)		

a P-value for the superiority test comparing the percentages of virologic success was from the CMH test stratified by baseline HIV-1 RNA and race strata.
b Difference in percentages of virologic success and its 95% CI were calculated based on baseline HIV-1 RNA stratum-adjusted MH proportion.
c Week 48 window was between Day 308 and 337 (inclusive).
d Discontinuation due to other reasons included subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, subject noncompliance, protocol violation, pregnancy, and study discontinued by sponsor.

Source: GS-US-299-0102 Clinical Study Report, Table 9-2.

The overall results for this Phase 2 trial were considered inconclusive by this reviewer, in that they did not provide substantial evidence of efficacy, but did not provide a statistically persuasive basis for concern.

The reasons the trial did not provide substantial evidence of efficacy for the D/C/F/TAF regimen were that (i) this was a single Phase 2 trial without replicated clinical trial evidence for the same regimen; (ii) the regimen did not meet the 12% non-inferiority margin for the guidance-recommended Week 48 endpoint, and numerical trends favored the control group. Regarding the first point, the statistical analysis plan specified that the sample size "was chosen to estimate the response rate of HIV-1 RNA < 50 copies/mL at Week 24 for the regimen *to allow for the planning of Phase 3 studies* [emphasis added]."

The reasons this trial did not raise statistical concerns about reduced efficacy of D/C/F/TAF were that (i) the regimen met the pre-specified non-inferiority margin for the Week 24 primary endpoint with no difference in point estimates for virologic success rates between the randomized comparison groups; (ii) the Week 48 results did not approach statistical inferiority.

3.2.5 Cross-study comparisons of GS-US-299-0102, GS-US-292-0104/0111

In a mid-cycle communication for this NDA the Division sent the following italicized comments to the sponsor. These comments expressed concern about the efficacy of D/C/F/TAF, based on cross-study comparisons.

> *In Study 299-0102, virologic success for treatment naïve subjects was approximately 75% for both study arms of which one consisted of cobicistat boosted darunavir, emtricitabine and TAF at the 10mg dosage. In comparison, when elvitegravir is substituted for darunavir and all other elements are identical, the virologic success rate for a similar population is 93% for E/C/F/TAF. This suggests reduced efficacy possibly due to lower TAF exposure when F/TAF is combined with darunavir/cobicistat. In our view, the finding of reduced efficacy observed in Study 299-0102 is very concerning.*

The following table displays virologic success rates across the relevant trials.

Table 10: Applicant's comparison of virologic outcome at Week 48 in GS-US-299-0102 and GS-US-292-0104/0111, full analysis sets

	GS-US-299-0102		GS-US-292-0104 and GS-US-292-0111	
	D/C/F/TAF (N = 103)	DRV+COBI+TVD (N = 50)	E/C/F/TAF (N = 866)	STB (N = 867)
Virologic Success at Week 48[c]				
HIV-1 RNA < 50 copies/mL	79 (76.7%)	42 (84.0%)	800 (92.4%)	784 (90.4%)
Virologic Failure at Week 48[c]	16 (15.5%)	6 (12.0%)	31 (3.6%)	35 (4.0%)
HIV-1 RNA ≥ 50 copies/mL	7 (6.8%)	4 (8.0%)	20 (2.3%)	23 (2.7%)
Discontinued Study Drug Due to Lack of Efficacy	0	0	2 (0.2%)	3 (0.3%)
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL[d]	9 (8.7%)	2 (4.0%)	8 (0.9%)	8 (0.9%)
Added New ARV	0	0	1 (0.1%)	1 (0.1%)
No Virologic Data in Week 48 Window[c]	8 (7.8%)	2 (4.0%)	35 (4.0%)	48 (5.5%)
Discontinued Study Drug Due to AE/Death	1 (1.0%)	1 (2.0%)	8 (0.9%)	14 (1.6%)
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL	7 (6.8%)	1 (2.0%)	21 (2.4%)	31 (3.6%)
Missing Data During Window but on Study Drug	0	0	6 (0.7%)	3 (0.3%)

a P-value for the superiority test comparing the percentages of virologic success was from the CMH test stratified by baseline HIV-1 RNA and race strata.
b Difference in percentages of virologic success and its 95% CI were calculated based on baseline HIV-1 RNA stratum-adjusted MH proportion.
c Week 48 window was between Day 308 and 337 (inclusive).
d Discontinuation due to other reasons included subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, subject noncompliance, protocol violation, pregnancy, and study discontinued by sponsor.

Source: Applicant's Response to FDA Mid-Cycle Meeting Comments, Module 1.11.3.

Rates of virologic success were lower in GS-US-299-0102 than in the pooled trials GS-US-292-0104 and GS-US-292-0111. The latter trials were the Phase 3 studies comparing E/C/F/TAF to STB reviewed under NDA 207561. As noted in the above italicized comments, the E/C/F/TAF regimen was similar to the D/C/F/TAF regimen under consideration in this review, but with the integrase strand transfer inhibitor elvitegravir used in place of the protease inhibitor darunavir. The comparator STB regimen was the combination of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate.

The overall designs of GS-US-292-0104 and GS-US-292-0111 were similar to the Phase 2 trial of D/C/F/TAF already considered in this review in terms of inclusion and exclusion criteria, study procedures, endpoint definitions, and statistical analyses. All three trials were conducted between the years 2012 and 2014, and were randomized, double-blind, multicenter studies of treatment-naïve adults with HIV-1 infection. Please refer to the statistical and clinical reviews of NDA 207561 by Thomas Hammerstrom, PhD, and William Tauber, MD, for additional details concerning these Phase 3 trials.

In a response to this mid-cycle communication, the Applicant provided several possible explanations for the decreased efficacy seen with D/C/F/TAF in the above cross-study comparisons. The following subsections consider the Applicant's explanations and then summarize this reviewer's conclusions.

3.2.5.1 Discontinuations

The first explanation given by the Applicant for lower results under D/C/F/TAF than E/C/F/TAF related to the rates of discontinuation across the studies, and handling of these discontinuations in the snapshot algorithm used for determining virologic success. The italicized text below is taken from the Applicant's response.

> *"Gilead considers that the numerically lower virologic response rate at Week 48 with D/C/F/TAF (Study GS-US-299-0102) as compared to E/C/F/TAF (Studies GS-US-292-0104 and GS-US-292-0111) (76.6% [79/103] vs 92.4% [800/866], respectively) is due to the high rate of study drug discontinuation in the D/C/F/TAF group."*

This reviewer does not consider study drug discontinuations sufficient to explain the efficacy differences. At each timepoint (e.g., Week 24 or Week 48) a certain number of subjects in each trial were known to have either HIV-1 RNA <50 copies/mL or HIV-1 RNA ≥50 copies/mL. Remaining subjects with unknown HIV-1 RNA levels were handled algorithmically in endpoint definitions depending on reasons for study drug discontinuation, missing data, and viral loads at the time of discontinuations. The most favorable cross-study comparison for D/C/F/TAF would be to consider subjects with unknown outcomes to be successes in the D/C/F/TAF group but failures in the E/C/F/TAF group. As shown in the table below, when this "best/worst analysis" is done for Week 24 virologic success rates there is still a difference disfavoring D/C/F/TAF that is too large to be explained by chance alone. Therefore, discontinuations in GS-US-299-0102 could not fully explain the lower rates of virologic success in this trial.

Table 11: Reviewer's best/worst analysis of cross-study comparisons

Week 24	GS-US-299-0102 D/C/F/TAF	GS-US-292-0104/0111 E/C/F/TAF	Difference (95% CI) [p-value]
HIV-1 RNA <50 copies/mL	77/103 (75%)	810/866 (94%)	
HIV-1 RNA ≥50 copies/mL	14/103 (14%)	29/866 (3%)	
Virologic success (best/worst analysis)	89/103 (86%)	810/866 (94%)	-7% (-15% to -1%) $p < 0.02$

Sources: Study GS-US-292-0104 Interim Week 48 Clinical Study Report, Table 17.1; Study GS-US-292-0111 Interim Week 48 Clinical Study Report, Table 17.1; Study GS-US-299-0102 Clinical Study Report, Table 9-1.

3.2.5.2 Adherence

In its response to the mid-cycle communication, the Applicant also claimed that lower study drug adherence in GS-US-299-0102 may have contributed to the lower virologic success rates seen in both arms of this study, and that this could be related to either patient selection or an artifact of the high pill burden required to maintain blinding.

> *The virologic response rates in studies of boosted PI in treatment naïve patients, including GS-US-299-0102 as noted by the Agency, were generally lower than in recent studies of integrase strand transfer inhibitors (INSTIs) (e.g. GS-US-292-0104 and GS-US-292-0111). The reason for this may be that subjects who participate in studies of boosted PI are different from those who do in studies of INSTIs. For example, given the high genetic barrier for boosted PIs, investigators may preferentially enroll subjects at risk for suboptimal adherence into studies of boosted PI over INSTI (i.e. channeling bias). In fact, the adherence to study drug was lower in Study GS-US-299-0102 than in Studies GS-US-292-0104/GS-US-292-0111. The low adherence in Study GS-US-299-0102 may be related to the high pill burden, which included placebo given the double-blind design; subjects in the study had to take 5 tablets (including 2 DRV 400 mg tablets), as compared to 2 tablets in Studies GS-US-292-0104/GS-US-292-0111.*

This reviewer is unclear how patients at risk for suboptimal adherence could have been disproportionately enrolled in Study GS-US-299-0102 when all subjects were treatment naïve, without a history of being adherent or non-adherent. This reviewer defers to the Medical Officer to evaluate whether this claim from the Applicant is plausible.

Measurement of adherence was previously described in this reviewer's overview of the study design for GS-US-299-0102, and was based on dividing the number of active pills taken over a specified timeframe (as captured on a study drug accountability form) by the number of active pills prescribed. The following table compares adherence rates through Week 48 across the trials of interest. In spite of the fact that only two pills per day were required to maintain blinding in the trials of E/C/F/TAF while five pills per day were required to maintain blinding in the trial of D/C/F/TAF, adherence rates appeared roughly

similar. For instance, the number of subjects achieving ≥95% adherence did not differ between GS-US-299-0102 and pooled GS-US-292-0104 and GS-US-292-0111 by an amount meeting nominal statistical significance.

Table 12: Adherence through Week 48. Adherence was calculable for subjects who returned at least 1 bottle and was based on dividing the pill count of active drugs taken (i.e., non-placebos) by the number of prescribed active drugs.

Adherence	Study GS-US-299-0102		Studies GS-US-292-0104/0111	
	D/C/F/TAF (N = 103)	DRV+COBI+TVD (N = 50)	E/C/F/TAF (N = 866)	STB (N = 867)
Not calculable	2 (2%)	0 (0%)	4 (<1%)	6 (<1%)
<80%	4 (4%)	0 (0%)	18 (2%)	12 (1%)
≥80 to <90%	10 (10%)	5 (10%)	40 (5%)	50 (6%)
≥90 to <95%	12 (12%)	6 (12%)	101 (12%)	103 (12%)
≥95%	75 (73%)	39 (78%)	703 (82%)	696 (80%)

Sources: Study GS-US-292-0104 Interim Week 48 Clinical Study Report, Table 8-6; Study GS-US-292-0111 Interim Week 48 Clinical Study Report, Table 8-6; Study GS-US-299-0102 Clinical Study Report, Table 8-6.

3.2.5.3 Patient Factors

In any cross-study comparison, there is a danger that results could be driven by underlying differences in the patients studied rather than the interventions applied. Although GS-US-299-0102, GS-US-292-0104, and GS-US-292-0111 had similar designs, unbiased estimation of causal effects between D/C/F/TAF and E/C/F/TAF could not be guaranteed by randomization. As can be computed from the table below, subjects in GS-US-299-0102 were significantly more likely to be male, Black, have the risk factor of homosexual sex, or be enrolled ex-US than subjects in GS-US-292-0104 and GS-US-292-0111.

Table 13: Comparison of subject baseline characteristics in Study GS-US-299-0102 and Studies GS-US-292-0104/0111

Characteristic	Study GS-US-299-0102		Studies GS-US-292-0104/0111	
	D/C/F/TAF (N = 103)	DRV+COBI+TVD (N = 50)	E/C/F/TAF (N = 866)	STB (N = 867)
Male	95 (92%)	47 (94%)	733 (85%)	740 (85%)
Black	36 (35%)	17 (34%)	223 (26%)	213 (25%)
HIV-1 RNA >100,000 copies/mL	23 (22%)	7 (14%)	196 (23%)	195 (23%)
CD4 cell count <200 cells/μL	11 (11%)	10 (20%)	112 (13%)	117 (13%)
Homosexual sex	86 (83%)	43 (86%)	652 (75%)	645 (74%)
Symptomatic HIV infection or AIDS	10 (10%)	6 (12%)	83 (10%)	61 (7%)
Enrolled ex-US	1 (1%)	2 (4%)	334 (39%)	335 (39%)

Sources: Adapted from the clinical study reports for the respective trials.

Furthermore, selection effects may have caused subjects in the two sets of trials to differ with respect to other unknown factors that are not encapsulated by the above table.

3.2.5.4 Results from additional studies

The Applicant stated in its response to the mid-cycle communication that results in the reviewed Phase 2 trial were consistent with previous studies of darunavir regimens:

> "*In Study GS-US-299-0102, the virologic response rates in both treatment groups (D/C/F/TAF 76.6% vs DRV+COBI+FTC+TDF 84.0%) are consistent with those in many studies of boosted [protease inhibitor] regimen in treatment naïve patients. In studies of boosted [darunavir] in treatment naïve patients, the virologic response rate has never exceeded 90%*."

The rationale for the Applicant's statement is that the relatively high response rates seen for E/C/F/TAF may have been due to idiosyncratic features of the Phase 3 trials GS-US-292-0104 and GS-US-292-0111, and not due to D/C/F/TAF having lower efficacy than E/C/F/TAF that is mediated through lower TAF exposure. This reviewer did not attempt to meta-analyze the literature on darunavir regimens for treatment-naïve HIV-1 infection. Because GS-US-299-0102, GS-US-292-0104, and GS-US-292-0111 were conducted by the same sponsor in the same timeframe with similar designs, and the only difference between the D/C/F/TAF and E/C/F/TAF regimens in these trials was the substitution of darunavir for elvitegravir, these trials most specifically addressed the concern of interest expressed by the Division in its mid-cycle communication.

3.2.5.5 Exposure levels

The Applicant responded as follows to the Division's mid-cycle comments regarding TAF exposures:

> "*Gilead considers that the plasma TAF exposures and intracellular TFV-DP exposures in the D/C/F/TAF study were efficacious, as they were comparable to those in the E/C/F/TAF studies, in which high virologic response rates were achieved or maintained."*
>
> *"TAF exposures (AUC and C_{max}), stratified by virologic success and failure in Study GS-US-299-0102, demonstrate that virologic failure was not due to lower TAF exposure."*

This reviewer defers analysis of these issues to the clinical pharmacology review team.

3.2.5.6 Conclusions from cross-study comparisons

In assessing the non-randomized comparison between D/C/F/TAF and E/C/F/TAF cited by the Division in its mid-cycle communication, this reviewer considered whether the commonly cited Pocock criteria (Pocock SJ. The combination of randomized and

historical controls in clinical trials. *J Chron Dis* 1976;29:175-188) were applicable. This reviewer deemed the Pocock criteria appropriate for the assessment of cross-study comparisons for this application. Pocock's conditions for the validity of non-randomized comparisons are italicized below.

The acceptability of a historical control group requires that it meets the following conditions:

1. *Such a group must have received a precisely defined standard treatment which must be the same as the treatment for the randomized controls.*
2. *The group must have been part of a recent clinical study which contained the same requirements for patient eligibility.*
3. *The methods of treatment evaluation must be the same.*
4. *The distributions of important patient characteristics in the group should be comparable with those in the new trial.*
5. *The previous study must have been performed in the same organization with largely the same clinical investigators.*
6. *There must be no other indications leading one to expect differing results between the randomized and historical controls. For instance, more rapid accrual on the new study might lead one to suspect less enthusiastic participation of investigators in the previous study so that the process of patient selection may have been different.*

Only if all these conditions are met can one safely use the historical controls as part of a randomized trial. Otherwise, the risk of a substantial bias occurring in treatment comparisons cannot be ignored.

This reviewer considered criteria 1, 2, 3, 5, and 6 to be roughly satisfied, because the relevant trials had similar inclusion criteria, procedures, and endpoint definitions and were conducted by the same sponsor within the 2012-2014 timeframe. The largest unknown was with respect to criterion 4, meaning whether baseline patient factors were comparable between those receiving D/C/F/TAF and those receiving E/C/F/TAF in different trials. From Section 3.2.5.3, differences in baseline characteristics were larger than would be expected in a randomized comparison, but were qualitatively similar except for region of enrollment. It is unknown whether subtle selection effects may have driven the observed cross-study difference in virologic success rates.

Based on analyses in Sections 3.2.5.1-2 this reviewer concluded that the Applicant's cited rationales regarding treatment discontinuations and adherence rates were not sufficient to explain the observed differences in success rates between D/C/F/TAF and E/C/F/TAF.

In summary, the cross-study comparison between Week 48 virologic success rates under D/C/F/TAF in the trial GS-US-299-0102 and E/C/F/TAF in the trials GS-US-292-0104 and GS-US-292-0111 led the Division to express concern in a mid-cycle communication that reduced efficacy is possible when TAF is used in a darunavir regimen. The Applicant's proposed explanations were insufficient to ameliorate this concern, and many of the Pocock conditions for cross-study comparisons are satisfied. However, due to the inherent limitations of non-randomized comparisons, only a randomized trial comparing

D/C/F/TAF to E/C/F/TAF in treatment-naïve adults with HIV-1 infection could definitively confirm or refute the signal for reduced efficacy.

3.3 Evaluation of Safety

Review of safety for this application is primarily deferred to the Medical Officer William Tauber, MD. The safety of TAF was previously evaluated in the Phase 3 trials of E/C/F/TAF that were reviewed under NDA 207561.

The table below displays treatment emergent adverse events and serious adverse events in the GS-US-299-0102 trial of D/C/F/TAF and DRV+COBI+TVD that is the subject of this review. Recall that the safety analysis set was identical to the full analysis set used for efficacy analysis, as all randomized subjects received at least one dose of the assigned regimen. The Applicant's clinical study report provided the following summary of safety:

> *One subject (1.0%) in the D/C/F/TAF group had a serious AE (SAE) (hypersensitivity) that was considered by the investigator to be related to study drug; no subjects in the DRV+COBI+TVD group had a treatment-related SAE. Two subjects (1.9%) had 3 AEs resulting in discontinuation of study drug in the D/C/F/TAF group (hypersensitivity and rash; substance abuse), and 2 subjects (4.0%) had 2 AEs resulting in discontinuation of study drug in the DRV+COBI+TVD group (diarrhea; renal tubular disorder). No subject died. No pregnancies were reported. The AEs by [preferred term] reported for at least 10% of subjects in either treatment group were as follows:*
>
> - *D/C/F/TAF group – diarrhea (21.4%, 22 subjects); upper respiratory tract infection (15.5%, 16 subjects); fatigue (13.6%, 14 subjects); nausea (12.6%, 13 subjects); and rash (11.7%, 12 subjects)*
> - *DRV+COBI+TVD group – diarrhea (26.0%, 13 subjects); fatigue (18.0%, 9 subjects); upper respiratory tract infection (14.0%, 7 subjects); flatulence (12.0%, 6 subjects); and nausea, pain in extremity, vitamin D deficiency, and vomiting (each in 10.0%, 5 subjects)*

In its clinical study report, the Applicant was motivated by the need for F/TAF based on the perceived suboptimal bone and renal safety profile of tenofovir disoproxil fumarate, which was used in the comparator regimen in the reviewed Phase 2 trial. For instance, in its clinical study report the Applicant states that tenofovir disoproxil fumarate *"has been associated with nephrotoxicity, requires dose adjustment when creatinine clearance falls below 50 mL/min, and has been shown to result in a greater decline in bone mineral density (BMD) relative to some other [nonnucleoside reverse transcriptase inhibitors]."* Regarding bone safety, there were no fracture events in either treatment group of the trial. With respect to renal safety, one subject in the DRV+COBI+TVD group had a serious adverse event of renal tubular disorder that resulted in discontinuation of study drug, but was not judged by the investigator to be drug-related.

Table 14: Summary of adverse events in GS-US-299-0102, safety analysis set

Subjects Experiencing Any	D/C/F/TAF (N = 103)	DRV+COBI+TVD (N = 50)
Treatment-Emergent AE	95 (92.2%)	47 (94.0%)
Any Grade 2, 3, or 4 Treatment-Emergent AE	57 (55.3%)	24 (48.0%)
Any Grade 3 or 4 Treatment-Emergent AE	7 (6.8%)	4 (8.0%)
Any Treatment-Emergent Study Drug–Related AE	43 (41.7%)	19 (38.0%)
Any Grade 2, 3, or 4 Treatment-Emergent Study Drug–Related AE	10 (9.7%)	3 (6.0%)
Any Grade 3 or 4 Treatment-Emergent Study Drug–Related AE	1 (1.0%)	1 (2.0%)
Any Treatment-Emergent SAE	5 (4.9%)	2 (4.0%)
Any Treatment-Emergent Study Drug–Related SAE	1 (1.0%)	0
Any Treatment-Emergent AE Leading to Premature Study Drug Discontinuation	2 (1.9%)	2 (4.0%)
Treatment-Emergent Death	0	0

Source: Study GS-US-299-0102 Clinical Study Report, Table 11-2.

Ocular safety was also previously raised as a potential issue for TAF before review of the Phase 2 trial in this application. For instance, in the clinical review of E/C/F/TAF under NDA 207561 the Medical Officer wrote the following:

> *Ocular safety was a concern during the conduct of these trials [of E/C/F/TAF versus STB]. During the preclinical development of E/C/F/TAF posterior uveitis was detected in the dog toxicology studies at the highest doses at the 3 and 9 month time period. Because of this finding, the Applicant instituted increased vigilance for eye disorders including the institution of a substudy and investigator instruction and incorporation of specific language into the protocols and informed consents. This increased vigilance did not identify an increased incidence of any form of uveitis. None the less, there did appear to be some evidence of increased inflammation of E/C/F/TAF use compared with that of [STB] with numerically higher levels of conjunctivitis, visual blurring, and photophobia. Continued heightened vigilance is recommended.*

Results in the reviewed Phase 2 trial added to the existing concern regarding ocular safety of F/TAF. Although there were no uveitis adverse events in either arm of the trial, the numerical trend was toward higher rates of eye disorders in the D/C/F/TAF group than the DRV+COBI+TVD group, as summarized by the Applicant in the following table.

Table 15: Eye disorder adverse events in GS-US-299-0102, safety analysis set

Adverse Events by System Organ Class and Preferred Term[a,b,c,d]	D/C/F/TAF (N = 103)	DRV+COBI+TVD (N = 50)
Eye disorders	6 (5.8%)	0
Eye irritation	2 (1.9%)	0
Lacrimation increased	1 (1.0%)	0
Eye pruritus	1 (1.0%)	0
Ocular hyperaemia	1 (1.0%)	0
Photophobia	1 (1.0%)	0

Source: Study GS-US-299-0102 Clinical Study Report, Table 11-8.

As noted above, this reviewer defers to the Medical Officer for a more complete evaluation of adverse events in this application and the impact of these events on the benefit-to-risk profile of regimens containing F/TAF.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The table below displays results for the Week 48 virologic success endpoint, as computed by the previously described snapshot algorithm, in demographic subgroups for the Phase 2 trial GS-US-299-0102 that randomized subjects to D/C/F/TAF or DRV+COBI+TVD. Despite the execution of multiple comparisons, no estimated treatment effect reached nominal statistical significance within any subgroup. Due to the small overall sample size of this trial, even a descriptive analysis was not possible or potentially informative for many subgroups due to the lack of subjects (e.g., females, ex-US subjects). No findings from these subgroup analyses changed the interpretation of the overall trial results.

Table 16: Rates of HIV-1 RNA <50 copies/mL at Week 48 by gender, race, age, and geographic region in the full analysis set of Study GS-US-299-0102

Characteristic	D/C/F/TAF	DRV+COBI+TVD	Difference (95% CI)
Gender			
Male	75/95 (79%)	39/47 (83%)	-4.0% (-17% to 11%)
Female	4/8 (50%)	3/3 (100%)	NC
Race			
White	54/62 (87%)	27/30 (90%)	-2.9% (-16% to 14%)
Black	21/36 (58%)	12/17 (71%)	-12.3% (-36% to 16%)
Other	4/5 (80%)	3/3 (100%)	NC
Age (years)			
<40	53/70 (76%)	25/29 (86%)	-10.5% (-25% to 8%)
≥40	26/33 (79%)	17/21 (81%)	-2.2% (-23% to 22%)
Geographic region			
United States	78/102 (77%)	40/48 (83%)	-6.9% (-20% to 8%)
Puerto Rico	1/1 (100%)	2/2 (100%)	NC

Sources: Table 13 of GS-US-299-0102 Clinical Study Report, and reviewer's analysis of adeffout.xpt dataset. NC = not calculated due to small sample sizes.

4.2 Other Special/Subgroup Populations

This reviewer also analyzed Week 48 virologic success rates, as computed by the previously described snapshot algorithm, in baseline subgroups defined by HIV-1 RNA level, CD4 cell count, the risk factor of homosexual sex, and type of HIV-1 infection. The subgroup-defining cutoffs for viral load and CD4 cell count were as chosen by the Applicant for emphasis in its clinical study report or statistical analysis plan. As with the demographic subgroups, results for these analyses were limited by small sample sizes for some subsets (e.g., subjects with CD4 cell count <200 cells/μL, subjects without the

homosexual sex risk factor, or subjects with symptomatic infection or AIDS). None of the estimated treatment effects within subgroups reached the level of nominal statistical significance, and this reviewer did not consider any results from these analyses to impact the overall interpretation of the trial.

Table 17: Rates of HIV-1 RNA <50 copies/mL at Week 48 in additional baseline subgroups of the full analysis in Study GS-US-299-0102

Characteristic	D/C/F/TAF	DRV+COBI+TVD	Difference (95% CI)
HIV-1 RNA level			
<100,000 copies/mL	63/80 (79%)	37/43 (86%)	-7.3% (-20% to 8%)
≥100,000 copies/mL	16/23 (70%)	5/7 (71%)	NC
CD4 cell count			
<200 cells/μL	8/11 (73%)	7/10 (70%)	NC
≥200 cells/μL	71/92 (77%)	35/40 (88%)	-10.3% (-23% to 5%)
Homosexual sex			
No	10/17 (59%)	6/7 (86%)	NC
Yes	69/86 (80%)	36/43 (84%)	-3.5% (-16% to 12%)
HIV infection			
Asymptomatic	72/93 (77%)	37/44 (84%)	-6.7% (-20% to 9%)
Symptomatic	5/8 (63%)	2/3 (67%)	NC
AIDS	2/2 (100%)	3/3 (100%)	NC

Sources: Table 13 of GS-US-299-0102 Clinical Study Report, and reviewer's analysis of adeffout.xpt and adsl.xpt datasets. NC = not calculated due to small sample sizes.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues , Collective Evidence, Conclusions, and Recommendations

This reviewer's summary of statistical conclusions and recommendations is as follows:

- This statistical review focused on the evidence for safety and efficacy of D/C/F/TAF provided by the Phase 2 trial GS-US-299-0102, and the potential signal for decreased efficacy of D/C/F/TAF relative to E/C/F/TAF based on cross-study comparisons.
- The reviewed Phase 2 trial was not an adequate and well-controlled study providing standalone substantial evidence for safety and efficacy. Although D/C/F/TAF met the pre-specified non-inferiority margin of 12% for the primary efficacy endpoint of Week 24 virologic success, and the design was generally consistent with the current FDA guidance document with respect to inclusion/exclusion criteria and study procedures, D/C/F/TAF did not meet the guidance-recommended margin of 12% for the guidance-recommended endpoint of Week 48 virologic success. Further, this was the single clinical trial of the D/C/F/TAF regimen, and was sized only to allow planning for Phase 3 studies.
- However, this reviewed Phase 2 trial did not provide a statistically persuasive cause for alarm regarding decreased virologic success of D/C/F/TAF relative to the DRV+COBI+TVD comparator. Although the point estimate for the Week 48 treatment effect was negative, results did not approach statistical inferiority.

- Cross-study comparisons, identified prior to this reviewer's involvement, suggested reduced efficacy for D/C/F/TAF relative to E/C/F/TAF. These findings could not be fully explained by rates of discontinuations, poor adherence, or observed differences in patient characteristics, as suggested by the Applicant. In addition, the relevant trials were conducted by the same sponsor over the same timeframe and had similar designs on factors other than the interventions being compared. Nevertheless, the degree to which selection effects influenced results, rather than efficacy differences, cannot be statistically determined based on information provided in this application. Only a randomized comparison between D/C/F/TAF and E/C/F/TAF would reliably answer this question.
- As noted in the introduction, several statistical issues were considered beyond the scope of this review, including the appropriateness of the guidance-recommended snapshot algorithm for defining virologic success and the guidance-recommended 12% non-inferiority margin in the presence of background therapy.
- This reviewer defers to the other respective review disciplines regarding whether bioequivalence findings provide sufficient evidence of safety and efficacy for this application.

5.2 Labeling Recommendations

From a statistical perspective, the Applicant has not provided substantial evidence that F/TAF is safe and effective when used in combination with darunavir and cobicistat for antiretroviral therapy in treatment-naïve adults with HIV-1 infection, which would require an adequate and well-controlled Phase 3 trial.

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/s/

DANIEL B RUBIN
12/18/2015

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