

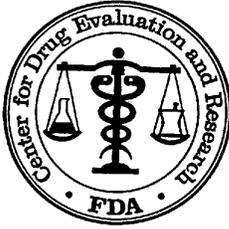
**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203094Orig1s000

203094Orig2s000

STATISTICAL REVIEW(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

STATISTICAL TEAM LEADER MEMO—CLINICAL STUDIES

NDA: 203-094 / N000

Name of Drug: Tybost® (cobicistat) 150 mg tablets

Applicant: Gilead Sciences

Indication (Draft): TYBOST is a CYP3A inhibitor indicated to increase systemic exposure of atazanavir in the treatment of HIV-1 infection in adults [*See Dosage and Administration (2)*]. This indication is based on Week 48 clinical trial data [*See Clinical Studies (14)*] and supported by pharmacokinetic data [*See Clinical Pharmacology (12.2)*].

Documents Reviewed: Primary review by Yanming Yin, Ph.D. concurred by secondary reviewer Fraser Smith, Ph.D.

Cross-Discipline Team Leader Review by Kimberly Struble, Pharm. D.

Project Manager: Abiola Olagundoye, Pharm. D., RPh.

Clinical Reviewer: Peter Miele, M.D., Medical Reviewer

Date Received: June 28, 2012

From: Greg Soon, Ph.D.

Concurred By: Daphne Lin, Ph.D.

Date Finalized: April 25, 2013

1 INTRODUCTION

The purpose of this memo is to provide the statistical team leader's perspective on the main efficacy results, particularly to clarify the interpretation of the non-inferiority (NI) claim. The cross-discipline team leader's memo by Kimberly Struble, PharmD (CDTL memo), expressed some difficulties in the understanding of the statistical review by Yanming Yin, Ph.D. (Secondary statistical reviewer, Fraser Smith, Ph.D.). Please refer to these documents for details on their opinions.

2 BACKGROUND

This new drug application (NDA) seeks approval of cobicistat (COBI) as a pharmacokinetic (PK) enhancer to increase the systemic exposure of the HIV-1 protease inhibitors (PIs) atazanavir (ATV) and darunavir (DRV) once daily regimens in adults.

The statistical review evaluated the 48-week data from a Phase III trial GS-US-216-0114 and 96-week data from a Phase II trial GS-US-216-0105. Both studies were in treatment naïve subjects. The main results at Week 48 are summarized below, based on subjects who were randomized and received at least one dose of the study medication:

Study	ATV/co (300/150mg) +FTC+TDF	ATV/r(300/100mg) +FTC+TDF	Diff	95% CI
GS-US-216-0114 ¹	85.2% (293/344)	87.4% (304/348)	-2.2%	(-7.4%, 3.0%)
GS-US-216-0114 GS-US-216-0105 ²	84.8% (334/394)	87.3% (329/377)	-2.5%*	(-7.5%, 2.4%)

¹: See Section 3.2.4.1 of the Statistical Review by Dr. Yin.

²: See Section 3.2.5.1 of the Statistical Review by Dr. Yin.

*: In addition to the stratification by baseline viral load stratum, this is also stratified by studies to account for imbalances in treatment assignment. However the results do not change.

In the statistical review, Dr. Yin stated "After reviewing the efficacy results of Atazanavir (NDA 21567), the reviewer concluded that the 12% margin used in study GS-US-216-0114 was too large. The sponsor should have used a much smaller margin (0-2.5%)." Based on this assessment, Dr. Yin concluded "Therefore, the applicant failed to demonstrate that Cobicistat (COBI) 150 mg once daily in combination with atazanavir 300 mg once daily and emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg (Truvada) was non-inferior to Ritonavir 100 mg in combination with atazanavir 300 mg and emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg (Truvada) based on the primary efficacy result of study GS-US-216-0114." However, the CDTL memo acknowledged Dr. Yin's position and stated that "I do not agree with this assessment and further discussion about the margin can be found below." Further, it acknowledged that "I do not fully understand the statistical comment that ATV 300 mg should be compared to ATV/RTV 300/100 mg in order to help justify the non-inferiority margin."

The goal of this memo is to provide further explanation of and clarification on the assessment of these trials and to provide my perspective on how these considerations should

be weighed together with other evidence.

3 MY INTERPRETATION

In order to approve COBI as a PK enhancer, it would be necessary to (1) show directly through PK studies that COBI increases systemic exposure of ATV and DRV, and (2) support by clinical data that its use is beneficial to the patients. The PK requirement is reviewed by the PK reviewer and is not covered here. The statistical review is concerned with the second question of clinical benefit of COBI.

The difference in opinions between the CDTL memo and the statistical review came from the different interpretation of the requirements for demonstrating clinical benefits. See the Appendix in the Section 5 below for some possible definitions. The CDTL memo stated that “These trials were conducted to obtain actual use data for this regimen” (page 4) and “As stated previously a clinical trial was not needed for the efficacy evaluation of COBI” (Page 7). Further, it elaborated “Technically an efficacy trial is not needed for approval; however, a comparative trial was conducted and the outcome was used to support the basis of approval for ATV/COBI along with trial 110” (page 9). This appears to require, at most, the “Regimen NI” or “Boosted ATV NI” as defined in the Appendix. This is in contrast with the statistical review where NI margin was targeted to establish COBI’s contribution in the regimen, i.e., to show “PK Booster NI.” In my view, this means that the CDTL memo considers that the NI margin should be a clinical NI margin, and if a statistical margin is needed it would be based on the contribution from ATV/r combination instead of ritonavir alone. The statistical reviewer, on the other hand, would like to make sure that COBI is contributing to efficacy and therefore focused on the statistical margin for COBI alone.

In the CDTL memo, the 12% margin was also justified as a statistical margin, based on the large contribution of PI over placebo. However, this statistical margin can only be used to show the contribution of ATV/COBI, not COBI by itself. There is no doubt that ATV/COBI contributes significantly in the regimen but this contribution could have been driven solely by unboosted ATV and not by the PK enhancement from COBI.

The major difficulty in the evaluation of COBI’s contribution from these two trials is the lack of strong evidence of ritonavir’s contribution in the treatment naïve population from historical trials. This is why in the Dr. Yin’s review a margin at best of 2.5% was suggested, based on Study 089.

Questions were raised in the CDTL memo on the use of the comparison of “ATV/r 300mg/100mg” vs “ATV 400mg” in the Study 089 for the determination of the NI margin for ritonavir (Page 9). It is true that ATV/r 300mg/100mg could be similar in exposure compared to ATV 400mg and therefore there may be no additional benefit expected from the PK enhancement of ritonavir. However, in Dr. Yin’s review the goal was to establish indirectly the contribution of ritonavir against ATV 300mg, not ATV 400mg. Dr. Yin bridged the ATV400mg with ATV300mg through Studies 007, 008 and 121 where different doses (ranging from 200mg to 600mg) of unboosted ATV showed similar responses. Because 300mg dose is between 200mg and 600mg doses studied, one would reasonably infer that ATV300mg unboosted dose would perform similarly to these ATV doses that

were studied, including the ATV400mg that was used in Study 089. See the tables on Pages 46-47 of the Dr. Yin's review for the details. Note these are relatively small studies and comparisons are made cross trials and it is difficult to ascertain the ritonavir contribution (or lack of it).

This reviewer agrees that PK studies should provide the main evidence for the approval of this PK enhancer and demonstration of "clinical benefits" should be supportive. This is because unboosted ATV400mg is the approved dose, and ATV/COBI 300mg/150mg is "expected to have comparable ATV exposures" (CDTL memo Page 9). This reviewer considers that the trials have demonstrated that the COBI boosted ATV regimen is NI to the ritonavir boosted ATV regimen, and ATV/co is contributing to the overall efficacy. This is supportive evidence for clinical benefits for COBI, in the sense that COBI is not adversely affecting the regimen benefits when compared to the ritonavir boosted regimen. This does not establish that COBI is absolutely needed in this regimen to achieve a similar response up to Week 48 due to difficulties in isolating the ritonavir contribution when used as a PK enhancer for ATV using the historical data, even though one would reasonably expect that the increased exposure through the PK enhancer will lead to better efficacy. There are some signals on this potential advantage as mentioned in the CDTL memo: "Twice as many patients in the ATV 400 mg experienced virologic failure (> 50 copies/mL) compared to patients in the ATV/RTV group. This result was primarily driven by patients with virologic rebound (13% ATV/RTV vs 24% ATV)." And "ATV/RTV decreased the virologic failure rate and lessened the development of ATV-associated resistance and NRTI resistance and this was the main basis for concluding ATV/RTV is an acceptable alternative treatment regimen for antiretroviral treatment-naïve subjects." However these signals have not yet been translated into an advantage on the primary endpoint, and the better efficacy could require longer follow-up to be apparent in the treatment naïve population.

4 CONCLUSION

The disagreements between the CDTL memo and the statistical review are due to the different interpretations of the requirements on the demonstration of the clinical benefits. These differences directly translated into different definitions and calculations of the NI margin. The trials submitted are sufficient to demonstrate regimen non-inferiority, but isolating the contribution of COBI alone is difficult from the statistical perspective.

5 APPENDIX: CLINICAL BENEFITS

"Clinical benefits" referred in this review could have different layers of meanings. Listed below are some potential definitions and interpretations.

1. "**Regimen NI**": *COBI, through increased systemic exposure of the ATV, together with FTC and TDF, provide similar overall response to ritonavir boosted ATV+FTC+TDF.*

In this regard, we focus on the whole regimen without seeking to understand the role of each individual drug or PK enhancer, answering a clinical question of "Can a ritonavir boosted regimen be replaced by a cobicistat boosted regimen?" This is

typically assessed by the NI comparison with only a clinical NI margin M2. M2 represents the potential loss of efficacy that we can tolerate with the replacement of an old regimen by a new regimen, due to possible benefits in other areas such as safety and convenience. The M2 is typically set between 10~12% based on FDA's guidance for HIV drug development, consistent with the sponsor's choice of 12%. To this end both assessments in Section 2 met this goal. Considering that "COBI does not appear to have any apparent advantages over RTV" (See CDTL Memo by Kimberly Struble, PharmD), 12% margin could be too large. FDA communicated to the sponsor during the protocol review that 12% is acceptable for sample size calculation, but the final margin will be a review issue. This is because the clinical margin has to depend on the safety, convenience and resistance which will be known only after review.

What this assessment does not answer is the question on the contribution of the PK enhancer COBI through the increased ATV concentration. In other words, we could not rule out the possibility that ATV (300mg) +FTC+TDF would perform the same as ATV/co (300/150mg) +FTC+TDF, i.e., the high response rates could have solely been driven by the part of the regimen without COBI. This point will be elaborated further in 3 below.

2. **"Boosted ATV NI"**: *ATV/COBI is NI to ATV/r. This means that ATV/COBI is proving to be contributing in the regimen, in addition to the regimen NI described in 1 above.*

It is well known that PIs could contribute significantly when combined with 2 NRTIs in treatment naïve patients, and an NI margin of 12% is sufficient for this purpose.

Again, this does not prove that COBI is absolutely necessary in order for this regimen to achieve the high response rates observed.

3. **"PK Booster NI"**: *This means that the added benefit of COBI, through boosting ATV, is "not much worse" than the added benefit of ritonavir. In other words, if we remove COBI from the ATV/co (300/150mg) +FTC+TDF, then we expect a decrease in the overall response rate, and therefore COBI is necessary in the regimen to maintain a comparable response rate to the ritonavir boosted ATV regimen.*

In order to make this determination, it is necessary to know that (1) ritonavir does have the added benefit in ATV/r (300/100mg) +FTC+TDF and (2) ATV/co (300/150mg) +FTC+TDF is NI to ATV/r (300/100mg) +FTC+TDF using a margin based on (1). This is how the NI is being evaluated in the statistical review by Dr. Yin (Secondary reviewer Dr. Smith).

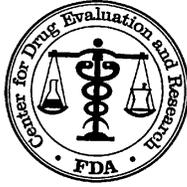
The difficulty here is that we do not have solid evidence that ritonavir has added benefit from the historical trials in this population, so we do not have assay sensitivity to establish a credible NI margin with high confidence.

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/s/

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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/BLA #: NDA 203094 Original

Supplement #:

Drug Name: Cobicistat 150-mg tablet

Indication(s): HIV-1 infected, antiretroviral treatment-Naïve adults

Applicant: Gilead

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Review Priority: Standard

Biometrics Division: DBIV

Statistical Reviewer: Yanming Yin, Ph. D.

Concurring Reviewers: Fraser Smith, Ph. D.

Medical Division: DAVP

Clinical Team: Kimberly Struble, Pharm. D.; Medical Team Leader
Peter Miele, M.D.; Medical Reviewer

Project Manager: Abiola Olagundoye, Pharm. D., RPh.

Keywords:

HIV-1 infection, treatment-naïve, Cobicistat(COBI), Atazanavir(ATV), Truvada(TVD)

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1 EXECUTIVE SUMMARY

On June 26, 2012, Gilead submitted the NDA to seek the agency's approval of **Cobicistat (COBI)** 150 mg tablets for use once daily as a pharmacokinetic enhancer of the HIV-1 protease inhibitors atazanavir (ATV) and darunavir (DRV) in adults.

The statistical reviewer evaluated the efficacy results from study **GS-US-216-0114**, a pivotal Phase III, randomized, double-blind, multicenter, active-controlled study to treat HIV-1 infected, antiretroviral treatment-naive adult subjects. The additional data from the 96 week interim analysis of phase II study **GS-US-216-0105** was also evaluated.

In the primary efficacy analysis snapshot approach was applied for study GS-US-216-0114. At week 48 the virologic success rate was 85.2% (293/344) in the ATV/co+TVD arm and 87.4% (304/348) in the ATV/r+TVD arm based on the ITT analysis set. The stratum adjusted difference (ATV/co+TVD vs. ATV/r+TVD) was -2.2% with 95% confidence interval (CI) of (-7.4%, 3.0%).

Twelve randomized patients were excluded from the ITT analysis set in phase II study (**GS-US-216-0105**) and Phase III data (**GS-US-216-0114**) because those patients did not receive study medication. Sensitivity analysis was performed by the statistical reviewer based on the randomized population set by integrating the phase II study (**GS-US-216-0105**) and Phase III study (**GS-US-216-0114**) data. In this analysis virologic success rate at Week 48 was 82.5% (334/405) in the ATV/co+TVD arm and 87.0% (329/378) in the ATV/r+TVD arm. The adjusted difference of the virologic success rates was -4.6% with 95% CI of (-9.7%, 0.5%). The upper boundary of the 95% CI (0.5%) was very close to 0. This indicated that ATV/co+TVD regime was close to inferior to ATV/r+TVD regime based on analysis performed on randomized analysis set of the integrated data.

In the trial design of study **GS-US-216-0114**, 12% was pre-specified by Gilead as the non-inferiority margin in the protocol. At the end of phase II meeting, FDA indicated to the sponsor that the 12% non-inferiority margin was acceptable for planning purposes but would be assessed further during the review. The applicant did not provide justification for the 12% margin in the protocol or in the clinical study report but claimed that ATV/co was non-inferior to ATV/r because the lower bound of the 95% confidence interval of -7.4% for the adjusted difference of virologic success rates exceeded -12%. After reviewing the efficacy results of Atazanavir (NDA 21567), the reviewer concluded that the 12% margin used in study **GS-US-216-0114** was too large. The sponsor should have used a much smaller margin (0-2.5%).

Therefore, the applicant **failed to demonstrate** that Cobicistat (COBI) 150 mg once daily in combination with atazanavir 300 mg once daily and emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg (Truvada) was **non-inferior** to Ritonavir 100 mg in combination with atazanavir 300 mg and emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg (Truvada) based on the primary efficacy result of study GS-US-216-0114. This trial was useful for

providing pharmacokinetic data and information about the safety of Cobicistat but was not adequately designed to make credible statistical comparisons between ATV/co and ATV/r arms.

2 INTRODUCTION

2.1 Overview

GS-9350 (chemical name 1,3-Thiazol-5-ylmethyl (2*R*,5*R*)-(5- {[(2*S*)-2-[(methyl { [2-(propan-2-yl)-1,3-thiazol-4-yl] methyl} carbamoyl)amino]] -4-(morpholin-4-yl)butanamido} -1,6-diphenylhexan-2-yl)carbamate) is a new chemical entity that is a structural analogue of RTV. Cobicistat was developed as a pharmacoenhancer (“booster”) to increase the systemic levels of coadministered agents metabolized by CYP3A enzymes, including elvitegravir (EVG) and the PIs atazanavir (ATV) and darunavir (DRV). The sponsor claims that Cobicistat has no anti-HIV-1 activity, therefore it may have fewer adverse metabolic effects than RTV, and can be coformulated as a tablet with other antiretroviral agents requiring boosting. In addition, COBI is more selective than RTV with respect to inhibition and induction of other enzymes and transporters in vitro, indicating that COBI may have less potential for clinically significant drug interactions via these pathways. Thus, the COBI “booster” is anticipated by sponsor to be a desirable alternative to RTV for antiretroviral treatment-naïve patients with HIV-1 infection. The proposed indication for the COBI tablet is for use once daily as a pharmacokinetic (PK) enhancer of the HIV-1 protease inhibitors atazanavir and darunavir in adults.

Additionally, COBI is a component in the 4-drug fixed-dose combination tablet (the QUAD STR) which is comprised of elvitegravir (EVG), COBI, and the current standard-of-care dual nucleoside/nucleotide reverse transcriptase inhibitor (NRTI/NtRTI) backbone FTC/TDF (Truvada [TVD]) under NDA203100. This NDA was submitted to FDA on 27 October 2011, with an indication as a complete regimen for the treatment of HIV-1 infection in adults who are antiretroviral treatment-naïve or who have no known resistance mutations to the individual components and it was approved on August 27, 2012.

The sponsor wishes to establish the safety and efficacy of COBI tablets through one randomized, controlled Phase 2 (GS-US-216-0105) study and one Phase 3 (GS-US-216-0114) study employing COBI as a booster of ATV in treatment-naïve adults with HIV-1 infection.

Study GS-US-216-0105 is an ongoing Phase 2, randomized, double-blind, multicenter, multiple-dose, active-controlled study evaluating the safety and efficacy of COBI-boosted ATV versus RTV-boosted ATV when each is coadministered with TVD. The study is ongoing in an open-label extension phase; data through Week 96 was summarized in the CSR. Study GS-US-216-0114 is an ongoing Phase 3, randomized, double-blind, multicenter, multiple-dose, active-controlled study evaluating the safety and efficacy of COBI-boosted ATV versus RTV-boosted ATV when each is coadministered with TVD. The double-blind phase of the study is ongoing; interim 48-week data was submitted for this NDA.

Table 1: List of all studies included in analysis

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm (efficacy analysis Tested/control)	Study Population
GS-US-216-0114	Phase 3	48 weeks	30 days	344/348	HIV-1 infected, antiretroviral treatment-naïve adults
GS-US-216-0105	Phase 2	48 weeks	30days	50/29	HIV-1 infected, antiretroviral treatment-naïve adults

2.2 Data Sources

Application package is located at:

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Both SDTM and ADAM datasets were submitted. Some of the SAS programs were also submitted.

The SDTM datasets of study 114 are under the directory of:

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The ADAM datasets of study 114 are under the directory of:

\\CDSESUB1\EVSPROD\NDA203094\0000\m5\datasets\gs-us-216-0114\analysis\adam

The SDTM datasets of study 105 are under the directory of:

\\CDSESUB1\EVSPROD\NDA203094\0000\m5\datasets\gs-us-216-0105\tabulations\sdm

The ADAM datasets of study 105 are under the directory of:

\\CDSESUB1\EVSPROD\NDA203094\0000\m5\datasets\gs-us-216-0105\analysis\adam

Per Agency's request Gilead resubmitted their analysis datasets to facilitate the review. The resubmitted datasets were under the directory:

\\CDSESUB1\EVSPROD\NDA203094\0005

However, the statistical reviewer's analysis was based on the original submitted datasets since there was no change to the raw datasets.

The statistical reviewer's requested the information of other HIV drugs that subjects took in the study; the sponsor submitted the information under the directory:

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The applicant submitted the data with good quality. The reviewer was able to reproduce the primary analysis from the SDTM datasets. The reviewer also was able to verify the randomized treatment code using the IVRS dataset for study GS-US-216-0114. For Study GS-US-216-0105, there were 7 patients (table 2) had different site numbers between the DM dataset and IVRS dataset. This difference was due to sites/investigators changes and it was confirmed by the applicant. In order to be consistent with applicant's analysis, reviewer used the patient id in the SDTM datasets instead of the IVRS dataset. Statistical analysis plans were submitted.

Table 2: US-216-0105 Patients with different site numbers in the IVRS dataset

Subject ID	Randomized ARM
GS-US-216-0105-0356-5552	ATV/co+TVD
GS-US-216-0105-0356-5553	ATV/r+TVD
GS-US-216-0105-0433-5565	ATV/co+TVD
GS-US-216-0105-0433-5583	ATV/r+TVD
GS-US-216-0105-3943-5537	ATV/r+TVD
GS-US-216-0105-3943-5539	ATV/co+TVD
GS-US-216-0105-3943-5581	ATV/r+TVD

Source: Statistical Reviewer's analysis.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

3.2.1.1 Study GS-US-216-0105

Study GS-US-216-00105 was a Phase 2, Randomized, Double-Blinded Study of the Safety and Efficacy of COBI-boosted Atazanavir (ATV/COBI) Compared to Ritonavir-boosted Atazanavir (ATV/r) in Combination with Emtricitabine/Tenofovir Disoproxil Fumarate (FTC/TDF) in HIV-1 Infected, Antiretroviral Treatment-Naive Adults.

The primary objective of this study was:

- To evaluate the efficacy of a regimen containing COBI-boosted ATV (ATV/co)+ emtricitabine/tenofovir disoproxil fumarate (Truvada[®] [TVD]) versus RTV-boosted ATV (ATV/r) +TVD in HIV-1 infected, ARV treatment-naïve adult subjects as determined by the achievement of HIV-1 ribonucleic acid (RNA) <50 copies/mL at Week 24

The secondary objectives of this study were:

- To evaluate the efficacy of a regimen containing ATV/co+TVD versus ATV/r+TVD in HIV-1 infected, ARV treatment-naïve adult subjects as determined by the achievement of HIV-1 RNA <50 copies/mL at Week 48
- To evaluate the safety and tolerability of the 2 treatment regimens through 48 weeks of treatment

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

Treatment Group 1: COBI 150 mg once daily+RTV placebo once daily+ATV 300 mg once daily+TVD (single-tablet FTC/TDF 200/300 mg) once daily

Treatment Group 2: RTV 100 mg once daily+COBI placebo once daily+ATV 300 mg once daily+TVD (single-tablet FTC/TDF 200/300 mg) once daily

Randomization was stratified by HIV-1 RNA level ($\leq 100,000$ copies/mL or $>100,000$ copies/mL) at screening.

The primary efficacy endpoint was the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 24 and the secondary efficacy endpoints include:

- The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48.
- The change from baseline in log₁₀ HIV-1 RNA and in CD4+ cell count at Weeks 24 and 48.

3.2.1.2 Study GS-US-216-0114

Study GS-US-216-0114 was a randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of a regimen containing GS-9350-boosted atazanavir (ATV/GS-9350) versus ritonavir-boosted atazanavir (ATV/r) each administered with emtricitabine/tenofovir disoproxil fumarate (Truvada[®], FTC/TDF) in HIV-1 infected, antiretroviral treatment-naïve adult subjects.

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

Treatment Arm 1: GS-9350 150 mg + atazanavir 300 mg + emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg + Placebo to match ritonavir 100 mg QD (n = 350)

Treatment Arm 2: Ritonavir 100 mg + atazanavir 300 mg + emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg + Placebo to match GS-9350 150 mg QD (n = 350)

Randomization was stratified by HIV-1 RNA level ($\leq 100,000$ copies/mL or $> 100,000$ copies/mL) at screening.

After Week 96, subjects would continue to take their blinded study drug and attend visits every 12 weeks until treatment assignments have been unblinded, at which point all subjects will return for an Unblinding Visit and would be given the option to participate in an open-label rollover study to receive GS-9350-boosted ATV+FTC/TDF until GS-9350 becomes commercially available, or until Gilead Sciences elects to terminate the development of GS-9350.

The primary objective of this study was:

- To evaluate the efficacy of a regimen containing GS-9350-boosted atazanavir versus ritonavir-boosted atazanavir, each administered with emtricitabine/tenofovir disoproxil fumarate, in HIV-1 infected, antiretroviral treatment-naïve adult subjects as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 48

The secondary objective of this study was:

- To evaluate the efficacy, safety and tolerability of the two treatment regimens through 96 weeks of treatment

The primary efficacy endpoint was the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as defined by the FDA snapshot analysis.

The secondary efficacy endpoints included:

- The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 96 as defined by the FDA snapshot analysis.
- The change from baseline in CD4+ cell count at Weeks 48 and 96

The submission was based on the 48 weeks interim data analysis.

3.2.2 Statistical Methodologies

The primary efficacy endpoint was the percentage of subjects who achieve HIV-1 RNA < 50 copies/mL at Week 48 as defined by the snapshot analysis algorithm. The baseline HIV-1 RNA stratum ($\leq 100,000$ copies/mL or $> 100,000$ copies/mL) weighted difference in the response rate ($P_1 - P_2$) and its 95.2% CI were calculated based on stratum-adjusted Mantel-Haenszel (MH) proportion. For the phase III study (GS-US-216-0114) non-inferiority was assessed. The non-inferiority margin was pre-specified by Gilead to be 12%. However, this non-inferiority margin was not statistically justified in the protocol and clinical study report. At the end of phase II meeting, FDA indicated to the sponsor that the 12% non-inferiority margin was acceptable for planning purposes but would be assessed further during the review.

ITT population was used to summarize the efficacy endpoints. The **intent-to-treat (ITT)** analysis set included all subjects who (1) were randomized into the study and (2) have received at least one dose of study drug.

The reviewer also performed the primary efficacy analysis based on **randomized analysis set** which included all subjects who were randomized.

In calculating the HIV PCR the following rules in the statistical analysis plan were followed by both the Applicant and the Reviewer:

The Ultra 1.5 Cobas result was used first if available. If it was not available or HIV PCR was greater than 100,000 copies/mL, the Standard 1.5 Cobas result was used. If the Ultra 1.5 Cobas result was not present or greater than 750000 copies/mL, the Standard 1.5 Cobas-Dilution result

was used. If a HIV-1 RNA test value was reported as greater than 100,000 or greater than 750,000 and no reflex results available, then a numeric value of 100,001 or 750,001 was used for summary purpose; If HIV RNA Ultra 1.5 Cobas value less than 50 HIV RNA Detected, or less than 50 No HIV RNA Detected, the value 49 copies/mL for all calculation was used.

For efficacy data: HIV-1 RNA, CD4 cell count and CD4 percentage, the latest record in the window was selected. For the analysis of the Week 48 virologic outcome, the analysis window was from study Day 309 to Day 378 (inclusive). Only on treatment HIV-1 RNA data (prior to or on the date of last dose of study drug) were used in the analysis.

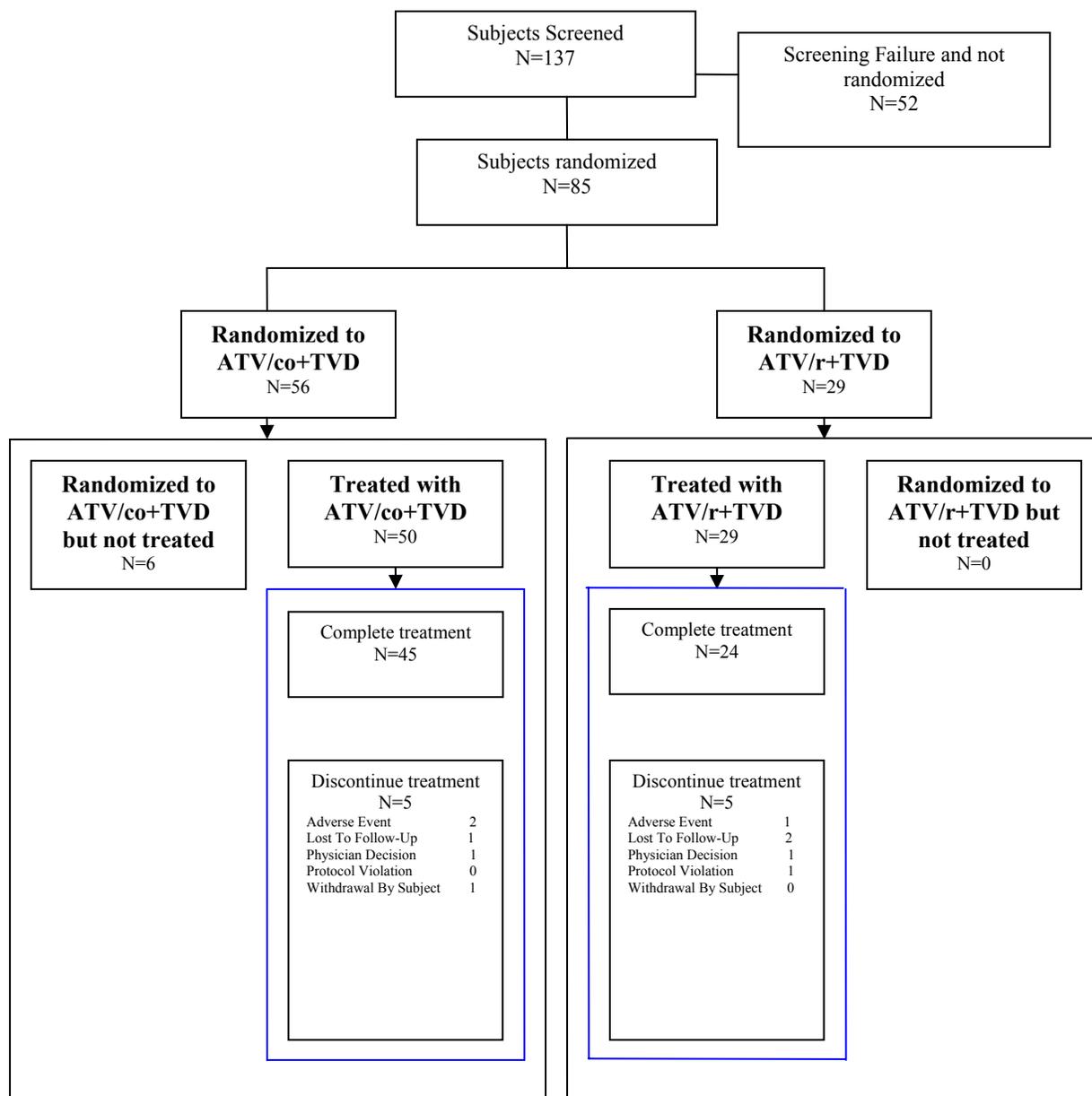
3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Study GS-US-216-0105

3.2.3.1.1 Patient Disposition

Figure 1 and Table 3 displayed the patient dispositions for study GS-US-216-0105. There were 137 patients screened. Eight-five of them were randomized. Fifty-six patients were randomized to ATV/co+TVD and 29 patients were randomized to ATV/r+TVD. However 6 patients that were randomized to ATV/co+TVD were not treated at all and those 6 patients were excluded from the ITT analysis set. The reasons of discontinuing the study for those 6 patients were listed in Table 4 below. In the ATV/co+TVD arm, 45 (90%) patients finished the 48 weeks treatment. While in the ATV/r+TVD arm 24(83%) patients finished the treatment. Ten Patients (5 in each arm) discontinued treatment due to AE, lost to Follow-up, physician decision and withdrew consent.

Figure 1: GS-US-216-0105: Summary of subject disposition and completion of treatment



Source: Statistical Reviewer's analysis.

Table 3: GS-US-216-0105: Subject treatment completion status (ITT Population)

Treatment Disposition	ATV/co+TVD N=50	ATV/r+TVD N=29	TOTAL N=79
Completed	45 (90.0%)	24 (82.8%)	69 (87.3%)
Discontinued	5 (10.0%)	5 (17.2%)	10 (12.7%)
Adverse Event	2 (4.0%)	1 (3.4%)	3 (3.8%)
Lost To Follow-Up	1 (2.0%)	2 (6.9%)	3 (3.8%)
Physician Decision	1 (2.0%)	1 (3.4%)	2 (2.5%)
Protocol Violation	0	1 (3.4%)	1 (1.3%)
Withdrawal By Subject	1 (2.0%)	0	1 (1.3%)

Source: Statistical Reviewer’s analysis.

Table 4: GS-US-216-0105 Reasons of study discontinuation for randomized but not treated patients

Subject ID	Randomized ARM	Reason of study discontinuation
GS-US-216-0105-0566-5574	ATV/co+TVD	WITHDRAWAL BY SUBJECT
GS-US-216-0105-0744-5542	ATV/co+TVD	PROTOCOL VIOLATION
GS-US-216-0105-1598-5569	ATV/co+TVD	WITHDRAWAL BY SUBJECT
GS-US-216-0105-1598-5580	ATV/co+TVD	PROTOCOL VIOLATION
GS-US-216-0105-1965-5516	ATV/co+TVD	PROTOCOL VIOLATION
GS-US-216-0105-1965-5517	ATV/co+TVD	PROTOCOL VIOLATION

Source: Statistical Reviewer’s analysis.

3.2.3.1.2 Demographic and Baseline Characteristics

Table 5 and Table 6 summarized the demographic and baseline characteristics. The demographic and baseline characteristics were similar between two treatment arms. Majority of the patients were Male (91.1%) with median age of 35 years. Around 60% of the patients were white. At the baseline, 70.9% of the patients had HIV-1 RNA \leq 100,000 copies/mL. The average CD4 cell count (/uL) was 357. Around 80% of the patients were homosexual and majority of the patients (83.5%) had asymptomatic HIV-1 infection.

**Table 5: GS-US-216-0105: Demographics and Baseline Characteristics
(Safety Analysis Set)**

Characteristic^{a,b}	ATV/co+TVD (N=50)	ATV/r+TVD (N=29)	Total (N=79)
Age (years)^c			
N	50	29	79
Mean (SD)	37 (9.6)	34 (10.1)	36 (9.8)
Median	37	34	35
Q1, Q3	31, 43	27, 43	28, 43
Min, Max	19, 57	19, 55	19, 57
Sex			
Male	47 (94.0%)	25 (86.2%)	72 (91.1%)
Female	3 (6.0%)	4 (13.8%)	7 (8.9%)
Race			
Asian	0	2 (6.9%)	2 (2.5%)
Black	18 (36.0%)	9 (31.0%)	27 (34.2%)
White	31 (62.0%)	16 (55.2%)	47 (59.5%)
Other	1 (2.0%)	2 (6.9%)	3 (3.8%)
Ethnicity			
Hispanic/Latino	7 (14.0%)	5 (17.2%)	12 (15.2%)
Non-Hispanic/Latino	43 (86.0%)	24 (82.8%)	67 (84.8%)
Weight (kg)			
N	50	29	79
Mean (SD)	78.6 (14.34)	73.7 (12.20)	76.8 (13.72)
Median	75.3	72.1	73.9
Q1, Q3	65.9, 90.2	63.0, 81.6	65.3, 88.0
Min, Max	51.7, 117.9	55.3, 109.9	51.7, 117.9
Height (cm)			
N	50	29	79
Mean (SD)	175.5 (7.86)	174.3 (8.49)	175.0 (8.06)
Median	175.3	175.3	175.3
Q1, Q3	170.2, 180.3	167.6, 180.3	170.2, 180.3
Min, Max	154.9, 195.6	154.9, 188.0	154.9, 195.6
Body Mass Index (kg/m²)			
N	50	29	79
Mean (SD)	25.5 (4.07)	24.5 (5.44)	25.1 (4.61)
Median	25.4	23.6	24.5
Q1, Q3	22.7, 27.8	21.0, 25.8	21.9, 27.0
Min, Max	17.3, 35.3	18.5, 45.8	17.3, 45.8

Source: Source: Table 8-4 of the GS-US-216-0105 study report.

**Table 6: GS-US-216-0105: Baseline Disease Characteristics
(Safety Analysis Set)**

Disease Characteristic^a	ATV/co+TVD (N=50)	ATV/r+TVD (N=29)	Total (N=79)
HIV-1 RNA (log₁₀ copies/mL)			
N	50	29	79
Mean (SD)	4.56 (0.657)	4.69 (0.530)	4.61 (0.614)
Median	4.51	4.61	4.58
Min, Max	2.98, 6.02	3.48, 5.73	2.98, 6.02
HIV-1 RNA Category (copies/mL)			
<= 100,000 copies/mL	38 (76.0%)	18 (62.1%)	56 (70.9%)
> 100,000 copies/mL	12 (24.0%)	11 (37.9%)	23 (29.1%)
CD4 Cell Count (uL)			
N	50	29	79
Mean (SD)	365 (201.3)	343 (178.1)	357 (192.2)
Median	341	367	345
Min, Max	32, 1022	49, 743	32, 1022
CD4 Cell Count (uL) Category			
<= 50	1 (2.0%)	1 (3.4%)	2 (2.5%)
51 - <= 200	9 (18.0%)	6 (20.7%)	15 (19.0%)
201 - <= 350	16 (32.0%)	7 (24.1%)	23 (29.1%)
351 - <= 500	17 (34.0%)	11 (37.9%)	28 (35.4%)
> 500	7 (14.0%)	4 (13.8%)	11 (13.9%)
CD4 Percentage (%)			
N	50	29	79
Mean (SD)	22.1 (8.96)	22.0 (9.25)	22.0 (9.01)
Median	22.2	23.4	22.3
Min, Max	4.6, 43.1	7.1, 40.6	4.6, 43.1
HIV Risk Factors^c			
Heterosexual Sex	10 (20.0%)	5 (17.2%)	15 (19.0%)
Homosexual Sex	39 (78.0%)	24 (82.8%)	63 (79.7%)
IV Drug Use	1 (2.0%)	0	1 (1.3%)
Transfusion	0	0	0
Vertical Transmission	0	0	0
Unknown	1 (2.0%)	0	1 (1.3%)
Other	0	0	0
HIV Disease Status			
Asymptomatic	41 (82.0%)	25 (86.2%)	66 (83.5%)
Symptomatic HIV Infections	1 (2.0%)	1 (3.4%)	2 (2.5%)
AIDS	8 (16.0%)	3 (10.3%)	11 (13.9%)

Source: Source: Table 8-5 of the GS-US-216-0105 study report.

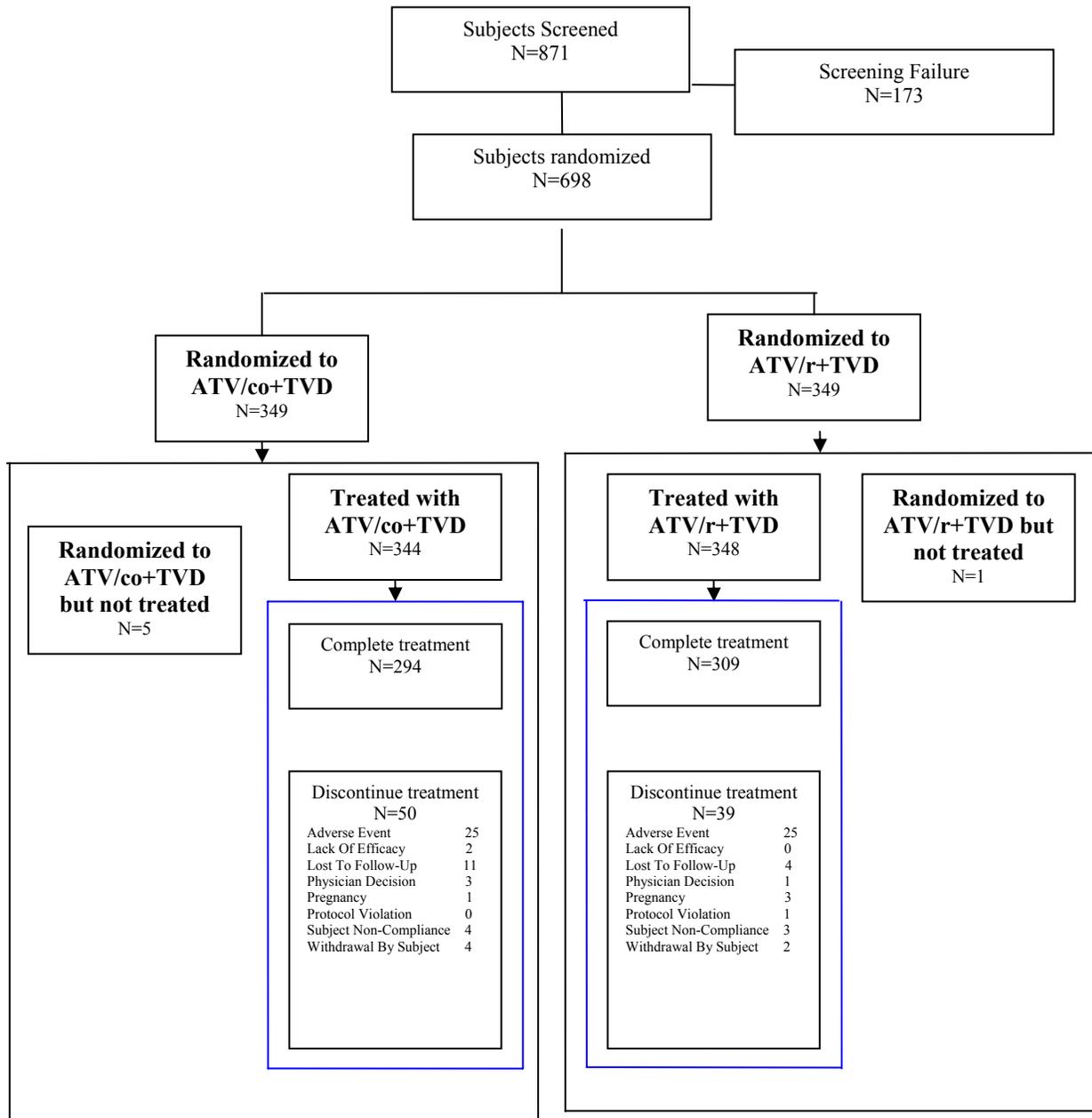
3.2.3.2 Study GS-US-216-0114

3.2.3.2.1 Patient Disposition

Figure 2, Table 7 and Table 8 summarized patient disposition of study GS-US-216-0114. There were 871 patients screened (according to the DM dataset) and 698 patients were randomized. However six randomized patients did not receive study medication. Table 9 summarized the reasons of study discontinuation for those six patients. Therefore there were 692 randomized and treated patients (ITT and safety analysis sets). Of the 344 treated patients that were randomized to ATV/co +TVD, 14.5% (150/344) of them discontinued treatment prematurely. The common reasons for treatment discontinuation were: Adverse Event (7.3%), lost to follow-up (3.2%). In the ATV/r +TVD arm, 348 patients were randomized and treated. Thirty-nine (11.2%) patients discontinued treatment prematurely. The primary reason of treatment discontinuation was Adverse Event (7.2%).

Up to the week 48 cutoff analyses there were still 91.3% (637/698) of the patients in the study. Thirty-nine (11.2%) patients in the ATV/co+TVD arm discontinued from the study and 22 (6.3%) of the patients discontinued study in the ATV/r+TVD arm. Six patients who never received study medication were included into those 61 patients who discontinued from the study.

Figure 2: GS-US-216-0114: Summary of subject disposition and completion of treatment



Source: Statistical Reviewer’s analysis.

Table 7: Subject treatment completion status (All treated patients)

	ATV/co+TVD N=344	ATV/r+TVD N=348	TOTAL N=692
Treatment Disposition			
Still On Treatment By The Week 48 Cutoff	294 (85.5%)	309 (88.8%)	603 (87.1%)
Discontinued	50 (14.5%)	39 (11.2%)	89 (12.9%)
Adverse Event	25 (7.3%)	25 (7.2%)	50 (7.2%)
Lack Of Efficacy	2 (0.6%)	0	2 (0.3%)
Lost To Follow-Up	11 (3.2%)	4 (1.2%)	15 (2.2%)
Physician Decision	3 (0.9%)	1 (0.3%)	4 (0.6%)
Pregnancy	1 (0.3%)	3 (0.9%)	4 (0.6%)
Protocol Violation	0	1 (0.3%)	1 (0.1%)
Subject Non-Compliance	4 (1.2%)	3 (0.7%)	7 (1.0%)
Withdrawal By Subject	4 (1.2%)	2 (0.6%)	6 (0.9%)

Source: Statistical Reviewer's analysis.

Table 8: Subject study completion status (All randomized patients)

	ATV/co+TVD N=349	ATV/r+TVD N=349	TOTAL N=698
Treatment Disposition			
Still in study by the Week 48 cutoff	310 (88.8%)	327 (93.7%)	637 (91.3%)
Discontinued	39 (11.2%)	22 (6.3%)	61 (8.7%)
Adverse Event	13 (3.7%)	9 (2.6%)	22 (3.2%)
Lack Of Efficacy	1 (0.3%)	0	1 (0.1%)
Lost To Follow-Up	13 (3.7%)	4 (1.2%)	17 (2.4%)
Physician Decision	2 (0.6%)	1 (0.3%)	3 (0.4%)
Pregnancy	0	2 (0.6%)	2 (0.3%)
Protocol Violation	1 (0.3%)	1 (0.3%)	2 (0.3%)
Subject Non-Compliance	2 (0.6%)	2 (0.6%)	4 (0.6%)
Withdrawal By Subject	7 (2.0%)	3 (0.9%)	10 (1.4%)

Source: Statistical Reviewer's analysis.

Table 9: GS-US-216-0114 Reasons of study discontinuation for randomized but not treated patients

Subject ID	Randomized ARM	Reason of study discontinuation
GS-US-216-0114-2843-8417	ATV/co+TVD	WITHDRAWAL BY SUBJECT
GS-US-216-0114-3957-8405	ATV/co+TVD	PROTOCOL VIOLATION
GS-US-216-0114-4169-8480	ATV/co+TVD	WITHDRAWAL BY SUBJECT
GS-US-216-0114-4301-8595	ATV/co+TVD	WITHDRAWAL BY SUBJECT
GS-US-216-0114-5123-8518	ATV/r+TVD	PROTOCOL VIOLATION
GS-US-216-0114-5127-8409	ATV/co+TVD	WITHDRAWAL BY SUBJECT

Source: Statistical Reviewer's analysis.

3.2.3.2.2 Demographic and Baseline Characteristics

Table 10 and Table 11 summarized the demographics and baseline disease characteristics. Overall the demographic and baseline characteristics were similar between two treatment arms. Majority of the patients were Male (82.9%) with median age of 36 years. Around 60% of the patients were white. At baseline, 60.3% of the patients had HIV-1 RNA \leq 100,000 copies/mL. The average CD4 cell count (/uL) was 352 at baseline. Around 66% of the patients were homosexual and majority of the patients (83.4%) had asymptomatic HIV-1 infection. The mean of baseline GFR (Cockcroft-Gault) was 117.2 mL/min.

Table 10: GS-US-216-0114: Demographics and Baseline Characteristics (Safety Analysis Set)

Characteristic ^a	ATV/co+TVD (N=344)	ATV/r+TVD (N=348)	Total (N=692)
Age (years)			
N	344	348	692
Mean (SD)	37 (9.8)	38 (9.6)	37 (9.7)
Median	36	37	36
Q1, Q3	29, 44	30, 44	30, 44
Min, Max	19, 62	19, 70	19, 70
Sex			
Male	287 (83.4%)	287 (82.5%)	574 (82.9%)
Female	57 (16.6%)	61 (17.5%)	118 (17.1%)
Race			
American Indian or Alaska Native	1 (0.3%)	2 (0.6%)	3 (0.4%)
Asian	44 (12.8%)	37 (10.6%)	81 (11.7%)
Black or African Heritage	65 (18.9%)	63 (18.1%)	128 (18.5%)
Native Hawaiian or Pacific Islander	1 (0.3%)	1 (0.3%)	2 (0.3%)
White	198 (57.6%)	215 (61.8%)	413 (59.7%)
Not Permitted ^c	2 (0.6%)	3 (0.9%)	5 (0.7%)
Other	33 (9.6%)	27 (7.8%)	60 (8.7%)
Ethnicity			
Hispanic/Latino	98 (28.5%)	92 (26.4%)	190 (27.5%)
Non-Hispanic/Latino	244 (70.9%)	253 (72.7%)	497 (71.8%)
Not Permitted ^c	2 (0.6%)	3 (0.9%)	5 (0.7%)
Baseline Weight (kg)			
N	344	348	692
Mean (SD)	74.6 (14.87)	75.4 (16.36)	75.0 (15.63)
Median	73.3	73.8	73.5
Q1, Q3	64.0, 82.7	64.9, 84.4	64.4, 83.4
Min, Max	45.0, 151.5	36.7, 147.4	36.7, 151.5
Baseline Height (cm)			
N	344	348	692
Mean (SD)	172.2 (9.59)	173.3 (10.47)	172.7 (10.05)
Median	173.0	174.0	174.0
Q1, Q3	166.0, 178.3	167.5, 180.3	167.0, 180.0
Min, Max	146.0, 193.0	138.0, 204.0	138.0, 204.0
Baseline Body Mass Index (kg/m²)			
N	344	348	692
Mean (SD)	25.2 (4.54)	25.0 (4.70)	25.1 (4.62)
Median	24.5	24.5	24.5
Q1, Q3	22.3, 27.4	21.8, 27.3	22.0, 27.3
Min, Max	16.8, 49.3	16.9, 46.8	16.8, 49.3

a The denominator for percentages is based on the number of subjects in the safety analysis set.

b For categorical data, p-value was from the CMH test (general association statistic was used for nominal data). For continuous data, p-value was from the 2-sided Wilcoxon rank sum test.

c Not Permitted = Regulators do not allow collection of race or ethnicity information.

Source: Table 8-4 of the GS-US-216-0114 study report.

**Table 11: GS-US-216-0114: Baseline Disease Characteristics
(Safety Analysis Set)**

Disease Characteristic ^a	ATV/co+TVD (N=344)	ATV/r+TVD (N=348)	Total (N=692)
HIV-1 RNA (log10 copies/mL)			
N	344	348	692
Mean (SD)	4.81 (0.585)	4.84 (0.594)	4.83 (0.589)
Median	4.78	4.84	4.81
Q1, Q3	4.36, 5.20	4.43, 5.27	4.41, 5.24
Min, Max	3.22, 6.43	3.21, 6.44	3.21, 6.44
HIV-1 RNA Category (copies/mL)			
≤ 100,000	212 (61.6%)	205 (58.9%)	417 (60.3%)
> 100,000	132 (38.4%)	143 (41.1%)	275 (39.7%)
CD4 Cell Count (/uL)			
N	344	348	692
Mean (SD)	353 (170.5)	351 (175.5)	352 (172.9)
Median	348	341	343
Q1, Q3	240, 452	250, 442	242, 448
Min, Max	1, 1075	10, 1455	1, 1455
CD4 Cell Count Category (/uL)			
≤ 50	11 (3.2%)	12 (3.4%)	23 (3.3%)
51 to ≤ 200	49 (14.2%)	45 (12.9%)	94 (13.6%)
201 to ≤ 350	114 (33.1%)	126 (36.2%)	240 (34.7%)
351 to ≤ 500	123 (35.8%)	117 (33.6%)	240 (34.7%)
> 500	47 (13.7%)	48 (13.8%)	95 (13.7%)
CD4 Percentage (%)			
N	344	348	692
Mean (SD)	20.4 (8.72)	20.8 (8.42)	20.6 (8.57)
Median	20.2	20.4	20.4
Q1, Q3	13.7, 26.0	15.6, 26.3	14.6, 26.2
Min, Max	0.4, 49.3	0.6, 46.5	0.4, 49.3

**Table 11: GS-US-216-0114: Baseline Disease Characteristics
(Safety Analysis Set)**

Disease Characteristic ^a	ATV/co+TVD (N=344)	ATV/r+TVD (N=348)	Total (N=692)
HIV Risk Factors^b			
Heterosexual Sex	112 (32.6%)	123 (35.3%)	235 (34.0%)
Homosexual Sex	226 (65.7%)	227 (65.2%)	453 (65.5%)
IV Drug Use	7 (2.0%)	8 (2.3%)	15 (2.2%)
Transfusion	0	0	0
Vertical Transmission	0	0	0
Other	5 (1.5%)	6 (1.7%)	11 (1.6%)
Unknown	9 (2.6%)	5 (1.4%)	14 (2.0%)
HIV Disease Status			
Asymptomatic	285 (82.8%)	292 (83.9%)	577 (83.4%)
Symptomatic HIV Infection	31 (9.0%)	32 (9.2%)	63 (9.1%)
AIDS	28 (8.1%)	24 (6.9%)	52 (7.5%)
HBV Surface Antigen Status			
Positive	16 (4.7%)	9 (2.6%)	25 (3.6%)
Negative	328 (95.3%)	339 (97.4%)	667 (96.4%)
HCV Antibody Status			
Positive	21 (6.1%)	16 (4.6%)	37 (5.3%)
Negative	323 (93.9%)	331 (95.1%)	654 (94.5%)
Indeterminate	0	1 (0.3%)	1 (0.1%)
Estimated Glomerular Filtration Rate by Cockcroft-Gault (CG) Formula (mL/min)			
N	344	348	692
Mean (SD)	116.1 (28.59)	118.3 (31.48)	117.2 (30.08)
Median	111.5	115.5	112.3
Q1, Q3	98.2, 128.5	96.2, 133.8	97.2, 131.6
Min, Max	68.3, 273.8	54.2, 260.5	54.2, 273.8
Estimated Glomerular Filtration Rate by Modification of Diet in Renal Disease (MDRD) Formula (mL/min/1.73 m²)			
N	344	348	692
Mean (SD)	101.7 (17.08)	103.0 (20.22)	102.4 (18.73)
Median	100.4	100.2	100.2
Q1, Q3	89.5, 111.9	89.0, 114.4	89.3, 112.6
Min, Max	61.8, 150.6	57.5, 215.9	57.5, 215.9
Estimated Glomerular Filtration Rate by Cystatin C Clearance, Adjusted for Age, Sex, and Race Formula (mL/min/1.73 m²)			
N	339	335	674
Mean (SD)	101.2 (22.23)	100.4 (19.94)	100.8 (21.11)
Median	100.6	99.4	99.8
Q1, Q3	87.0, 114.4	88.3, 113.5	87.5, 113.8
Min, Max	43.1, 232.8	47.2, 154.6	43.1, 232.8

a The denominator for percentages is based on the number of subjects in the safety analysis set.

b For categorical data, p-value was from the CMH test (general association statistic was used for nominal data and row mean scores differ statistic was used for ordinal data). For continuous data, p-value was from the 2-sided Wilcoxon rank sum test.

c A subject may fit more than 1 HIV risk factor category; therefore, percentages may add to more than 100.

Source: Table 8-5 of the GS-US-216-0114 study report.

3.2.4 Results and Conclusions

3.2.4.1 The Applicant's Results and Conclusion

Study GS-US-216-0105

Table 12 below summarized the applicant's analysis of the primary efficacy results of study GS-US-216-0105 based on the snapshot analysis. At week 48 the virologic success rate was 82.0% (41/50) in the ATV/co+TVD arm and 86.2% (25/29) in the ATV/r+TVD arm. The stratum adjusted difference (ATV/co+TVD vs. ATV/r+TVD) was -5.4% with 95% confidence interval (CI) of (-23.8%, 13.1%) after adjusting for the baseline HIV-1 RNA stratum ($\leq 100,000$ copies/mL or $> 100,000$ copies/mL).

Table 12: GS-US-216-0105: Virologic Outcomes at Weeks 24 and 48 using Snapshot Analysis and HIV-1 RNA < 50 copies/mL (ITT Analysis Set)

Time Point HIV-1 RNA Category	ATV/co+TVD (N=50)	ATV/r+TVD (N=29)	ATV/co+TVD vs ATV/r+TVD	
			p-value ^a	Difference in Percentages (95% CI) ^b
Snapshot Analysis				
Virologic Success at Week 48				
HIV-1 RNA < 50 copies/mL	41 (82.0%)	25 (86.2%)	0.55	-5.4% (-23.8% to 13.1%)
Virologic Failure at Week 48				
HIV-1 RNA ≥ 50 copies/mL	4 (8.0%)	1 (3.4%)		
Discontinued Study Drug Due to Lack of Efficacy				
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL ^c	1 (2.0%)	2 (6.9%)		
No Virologic Data in Week 48 Window ^e				
Discontinued Study Drug Due to AE/Death	2 (4.0%)	1 (3.4%)		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL ^c	2 (4.0%)	0		
Missing Data during Window but on Study Drug	0	0		

a p-value was from the CMH test stratified by baseline HIV-1 RNA category ($\leq 100,000$ or $> 100,000$ copies/mL).

b Difference in percentages of virologic success and its 95% CI were calculated based on baseline HIV-1 RNA stratum-adjusted MH proportion.

c Discontinuation due to other reasons includes subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, subject non-compliance, and protocol violation.

d Week 24 window is between Day 141 and 196 (inclusive)

e Week 48 window is between Day 309 and 378 (inclusive)

Source: Table 9-3, Week 96 interim clinical study report of GS-US-216-0105.

Study GS-US-216-0114

The applicant's analysis of the primary efficacy results of study GS-US-216-0114 based on the snapshot analysis was summarized in Table 13 below. At week 48 the virologic success rate was 85.2% (293/344) in the ATV/co+TVD arm and 87.4% (304/348) in the ATV/r+TVD arm. The stratum adjusted difference (ATV/co+TVD vs. ATV/r+TVD) was -2.2% with 95% confidence interval (CI) of (-7.4%, 3.0%). The applicant claimed that non-inferiority was demonstrated based on the 12% non-inferiority margin.

Table 13: GS-US-216-0114: Virologic Outcome at Week 48 (HIV-1 RNA Cutoff at 50 copies/mL, Snapshot Analysis, ITT Analysis Set)

Time Point HIV-1 RNA Category			ATV/co+TVD vs. ATV/r+TVD	
	ATV/co+TVD (N=344)	ATV/r+TVD (N=348)	p-value ^a	Difference in Percentages (95.2% CI) ^b
Virologic Success at Week 48				
HIV-1 RNA < 50 copies/mL	293 (85.2%)	304 (87.4%)	0.40	-2.2% (-7.4% to 3.0%)
Virologic Failure at Week 48				
HIV-1 RNA ≥ 50 copies/mL	20 (5.8%)	14 (4.0%)		
Discontinued Study Drug Due to Lack of Efficacy	6 (1.7%)	7 (2.0%)		
Discontinued Study Drug Due to Other Reasons ^c and Last Available HIV-1 RNA ≥ 50 copies/mL	1 (0.3%)	0		
No Virologic Data in Week 48 Window ^d				
Discontinued Study Drug Due to AE/Death	13 (3.8%)	7 (2.0%)		
Discontinued Study Drug Due to Other Reasons ^c and Last Available HIV-1 RNA < 50 copies/mL	9 (2.6%)	7 (2.0%)		
Missing Data during Window but on Study Drug	31 (9.0%)	30 (8.6%)		
	22 (6.4%)	23 (6.6%)		
	0	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 stratum.

b Difference in percentages of virologic success and its 95.2% CI were calculated based on baseline HIV-1 RNA stratum-adjusted MH proportion.

c Discontinuation due to other reasons includes subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, subject noncompliance, protocol violation, and pregnancy.

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

Programming Details: .../version1/prog/t-snapshot.sas v9.2 Output file: t-snapshot-48.out 01DEC2011:19:54

Source: Source: Table 9-1, Week 48 interim clinical study report of GS-US-216-0114.

3.2.4.2 Reviewer's Results

3.2.4.2.1 Non-inferiority Margin Justification

In the trial design of study GS-US-216-0114, the non-inferiority margin was pre-specified by Gilead as 12%. However no statistical justification was provided in the protocol or the clinical study report. The added effect of Ritonavir was investigated by the reviewer using the Atazanavir (NDA 21567) submission data.

In NDA 21567, study 89 was the only study that had a head to head comparison between the boosted and unboosted atazanavir in the HIV naïve population. In this study, Atazanavir/ritonavir at 300/100mg qd was compared to Atazanavir 400mg qd when each combined with lamivudine(3TC) at 300mg qd+stavudine XR(d4T XR) at 100mg qd. At week 48, the virologic success rate (HIV RNA <50 copies/ml) was 70% (73/105) in the Atazanavir 400mg arm and 75% (71/95) in the Atazanavir 300mg/ritonavir100mg arm. The difference was 5% with 95% confidence interval of (-7%, 18%). Ideally, in order to evaluate the contribution of ritonavir, Atazanavir 300mg should be used to compared to Atazanavir 300mg/ritonavir100mg.

However the results of study 007, study 008 and study 121 indicated that the virologic success rates difference between Atazanavir 300mg and Atazanavir 400mg could be quite small (see appendix for results). If we could assume the virologic success rates of Atazanavir 300mg and Atazanavir 400mg were the same, and not taking into account the variability of the point estimates, then the non-inferiority margin of study GS-US-216-0114 should be no more than half of the estimated difference in trial 89 of NDA21567 which was 2.5% instead of the 12% specified in the GS-US-216-0114 protocol. If we take the variability of the point estimates into account, since the lower bound of the 95% confidence interval was <0, then there is no margin.

3.2.4.2.2 Primary Efficacy Analysis

Study GS-US-216-0105

In protocol amendment 1 (29 July 2009), the HIV-1 RNA assay method was changed to the COBAS Amplicor HIV-1 Monitor Test (version 1.5) from the COBAS AmpliPrep/COBAS Taqman HIV-1 Test (Version 2.0). Back-testing using the Amplicor HIV-1 RNA assay was performed for all visits except screening. Therefore only Amplicor HIV-1 RNA assay results were used in this analysis.

The reviewer applied the same snapshot approach to summarize the percentage of subjects with virologic success at Week 48 (HIV-1 RNA <50 copies/mL) based on the ITT analysis set and was able to repeat the result in Table 12.

However six patients that were randomized to ATV/co +TVD arm were excluded from the ITT analysis set since they were not treated with the study medication while there was no patient in the ATV/r + TVD arm that was randomized but not treated. A sensitivity analysis was performed by the reviewer based on the randomized analysis set with those 6 patients were included. The result was summarized in Table 14. In the ATV/co+TVD arm, 73.2% (41/56) of the subjects achieved virologic success (HIV-1 RNA <50 copies/mL) compared with the 82.0% (41/50) based on the ITT analysis set, while in the ATV/r+TVD arm 86.2% (25/29) of the patients were able to achieve virologic success. The weighted difference was -13.8% with 95% CI of (-32.7%, 5.0%) after adjusting for the baseline HIV-1 RNA stratum ($\leq 100,000$ copies/mL or $> 100,000$ copies/mL).

**Table 14: GS-US-216-0105: Virologic Outcome at Week 48 (HIV-1 RNA <50 copies/mL)
(Randomized Analysis Set)**

Virologic Response	ATV/co+TVD N=56	ATV/r+TVD N=29	Difference of Success Rates ATV/co+TVD vs. ATV/r+TVD (95% CI)*
Virologic Success	41 (73.2%)	25 (86.2%)	-13.8% (-32.7%, 5.0%)
Virologic Failure	5 (8.9%)	3 (10.3%)	
HIV RNA >=50 copies/mL	4 (7.1%)	1 (3.4%)	
Discontinued Due To Lack Of Efficacy	0	0	
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA >= 50 copies/mL	1 (1.8%)	2 (6.9%)	
No Virologic Data at 48 weeks Window	10 (17.8%)	1 (3.4%)	
Adverse Event	2 (3.6%)	1 (3.4%)	
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL	8 (14.3%)	0	

* The weighted difference was calculated by adjusting the baseline HIV-1 RNA stratum (\leq 100,000 copies/mL or $>$ 100,000 copies/mL). For those subjects without baseline HIV-1 RNA, screening HIV-RNA was used.
Source: Statistical reviewer's analysis.

Study GS-US-216-0114

The reviewer applied the same snapshot approach to summarize the percentage of subjects with virologic success at Week 48 (HIV-1 RNA <50 copies/mL) based on the ITT analysis set and was able to repeat the result in Table 13.

In study GS-US-216-0114 there were also six patients that were randomized but not treated (5 in the ATV/co +TVD arm and 1 in the ATV/r + TVD arm). Those 6 patients were excluded from the ITT analysis set. A sensitivity analysis was performed by the reviewer based on the randomized analysis set. The result was summarized in Table 15. In the ATV/co+TVD arm, 84.0% (293/349) of the patients achieved virologic success (HIV-1 RNA <50 copies/mL) while in the ATV/r+TVD arm 87.1% (304/349) of the patients were able to achieve virologic success. The weighted difference was -3.2% with 95% CI of (-8.5%, 2.1%) after adjusting for the baseline HIV-1 RNA stratum (\leq 100,000 copies/mL or $>$ 100,000 copies/mL).

**Table 15: US-216-0114: Virologic Outcome at Week 48 (HIV-1 RNA <50 copies/mL)
(Randomized Analysis Set)**

Virologic Response	ATV/co+TVD N=349	ATV/r+TVD N=349	Difference of Success Rates ATV/co+TVD vs. ATV/r+TVD (95.2% CI)
Virologic Success	293 (84.0%)	304 (87.1%)	-3.2% (-8.5%, 2.1%)*
Virologic Failure	20 (5.7%)	14 (4.0%)	
HIV RNA >=50 copies/mL	6 (1.72%)	7 (2.0%)	
Discontinued Due To Lack Of Efficacy	1 (0.3%)	0	
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA >= 50 copies/mL	13 (3.7%)	7 (2.0%)	
No Virologic Data at 48 weeks Window	36 (10.3%)	31 (8.9%)	
Adverse Event	22 (6.3%)	23 (6.6%)	
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL	14 (4.0%)	8 (2.3%)	

* The weighted difference was calculated by adjusting the baseline HIV-1 RNA stratum ($\leq 100,000$ copies/mL or $> 100,000$ copies/mL) and its 95.2% CI were calculated. For those subjects without baseline HIV-1 RNA, screening HIV-RNA was used.

Source: Statistical Reviewer's analysis.

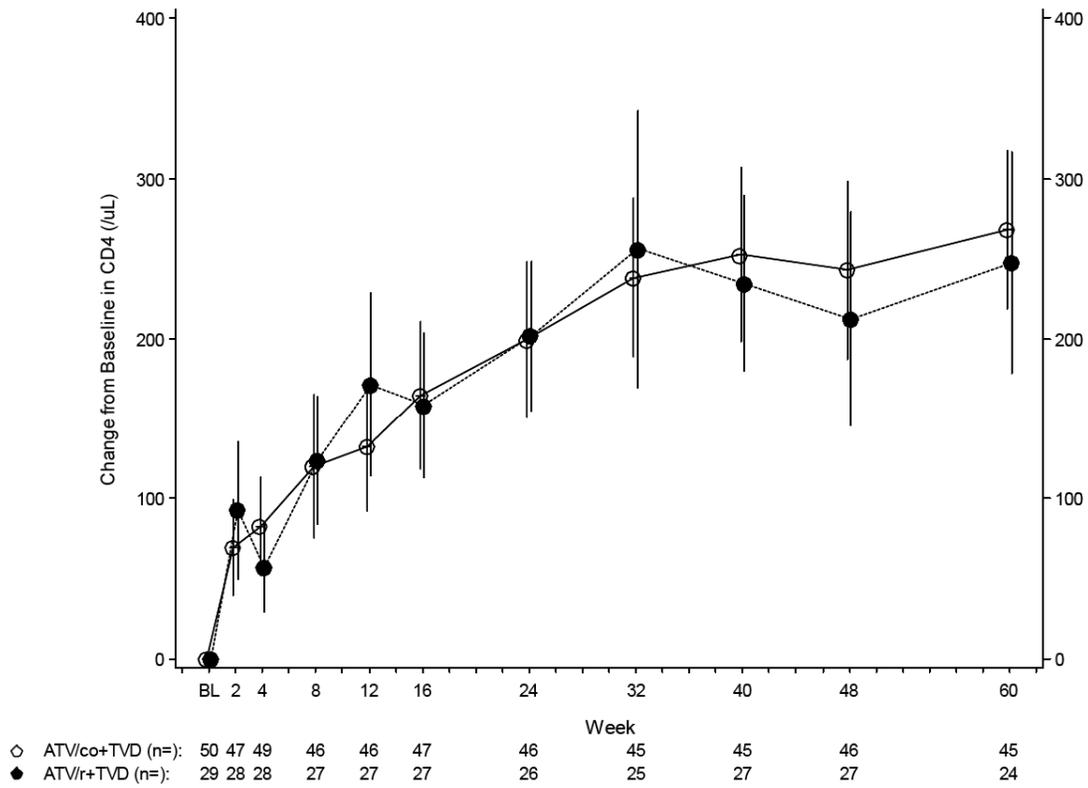
3.2.4.2.3 Analysis of Selected Secondary Efficacy Endpoints

CD4 Cell Count

The change from baseline in CD4 cell count was summarized for study GS-US-216-0105 and GS-US-216-014 in Figure 3 and Figure 4 below. The change from baseline in CD4 count was similar between two arms across baseline to week 60. Only patients with available data were summarized in those two figures.

Table 16 summarized the CD4 cell count using the missing=baseline approach for week 48. Missing CD4 cell count at week 48 was imputed as the baseline CD4 cell count here.

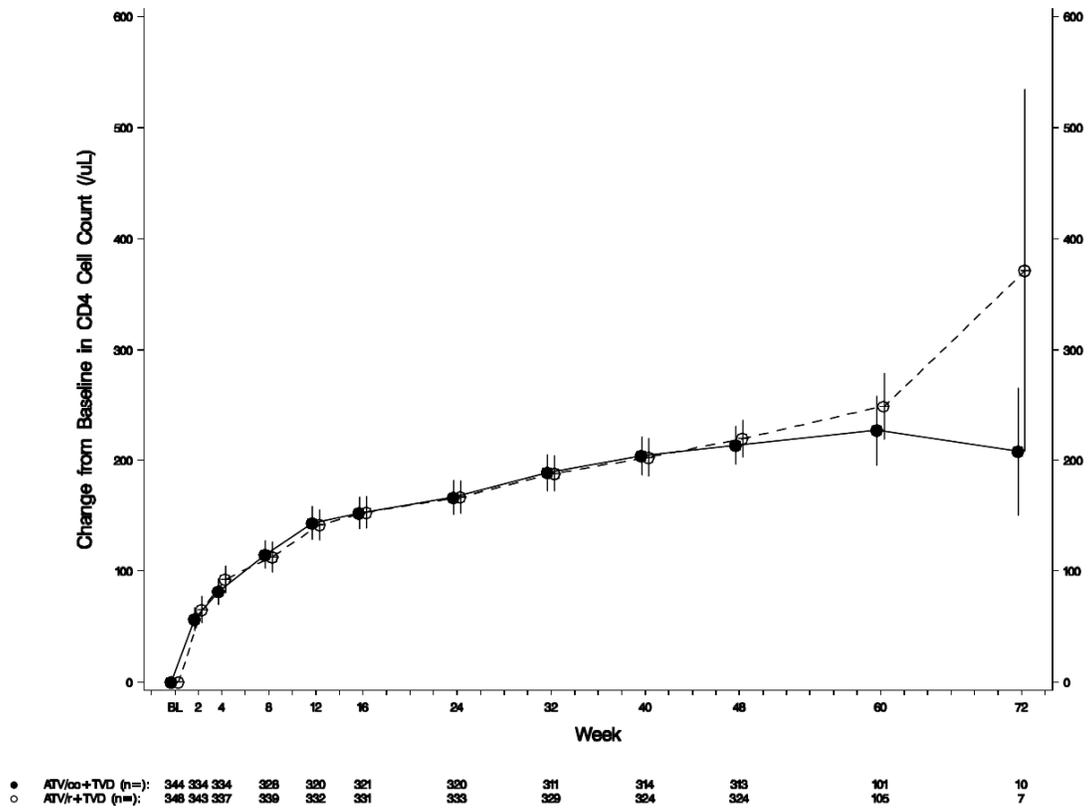
**Figure 3: GS-US-216-0105: Mean and 95% CIs of Change from Baseline in CD4 Cell Count (cells/ μ L)
(Randomized Phase; ITT Analysis Set)**



BL=Baseline.

Source: Figure 9-3 of the GS-US-216-0105 study report.

Figure 4: GS-US-216-0114: Mean and 95% CIs of Change from Baseline in CD4 Cell Count (cells/ μ L) (ITT Analysis Set)



Source: Figure 9-4 of the GS-US-216-0114 study report.

Table 16: US-216-0114: The CD4 Count (cells/ μ L) at Baseline, Week48 and Week 48 Change from Baseline (Missing=Baseline)

Virologic Response	ATV/co+TVD	ATV/r+TVD
CD4 at Baseline(cells/ μ L)		
N	344	348
Mean(std)	353.3 (170.5)	351.3 (175.5)
Median	348	340
Range	(1.0 , 1075.0)	(10.0, 1455.0)
CD4 at Week 48(cells/ μ L)		
N	344	348
Mean(std)	547.3 (226.5)	555.4 (223.0)
Median	512.5	537.0
Range	(2.0, 1364.0)	(17.0, 1319.0)
<50	2 (0.6%)	1 (0.3%)
50-<200	12 (3.5%)	13 (3.7%)
200+	330 (95.9%)	334 (96.0%)
CD4 Change from Baseline at Week 48(cells/ μ L)		
N	344	348
Mean(std)	194.0 (156.5)	204.1 (155.4)
Median	180.5	189.0
Range	(-225.0, 888.0)	(-548.0, 763.0)

Source: Statistical Reviewer's analysis.

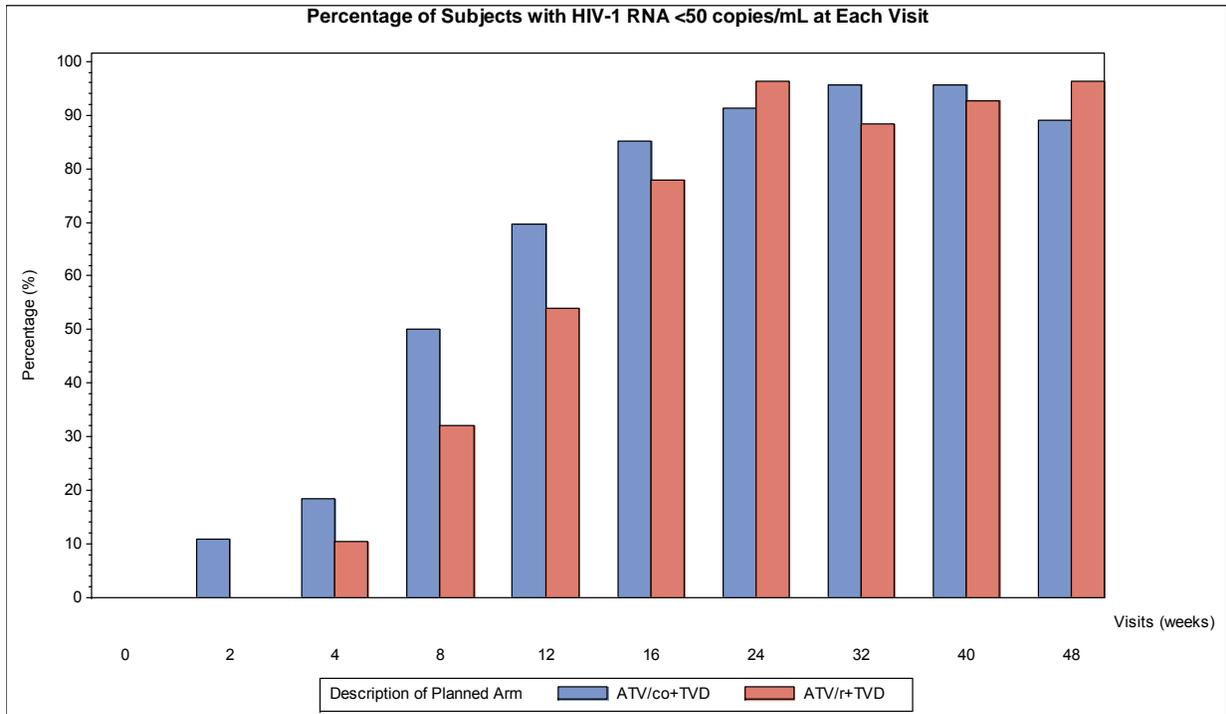
Percentage Of Subjects With HIV-1 RNA <50 Copies/ml At Each Visit

In Figure 5 and Figure 6 below, the percentage of subjects with HIV-RNA <50 copies/mL were summarized at each visit. Only patients with available data were summarized at each visit in these two figures.

In study GS-US-216-0114, the percentage of patients with HIV-RNA <50 copies/mL was 97.1% in the ATV/co+TVD arm and 96.0% in the ATV/r+TVD arm at week 48. The difference between two arms was similar across the visits. The largest difference was 5.5% which occurred at week 12.

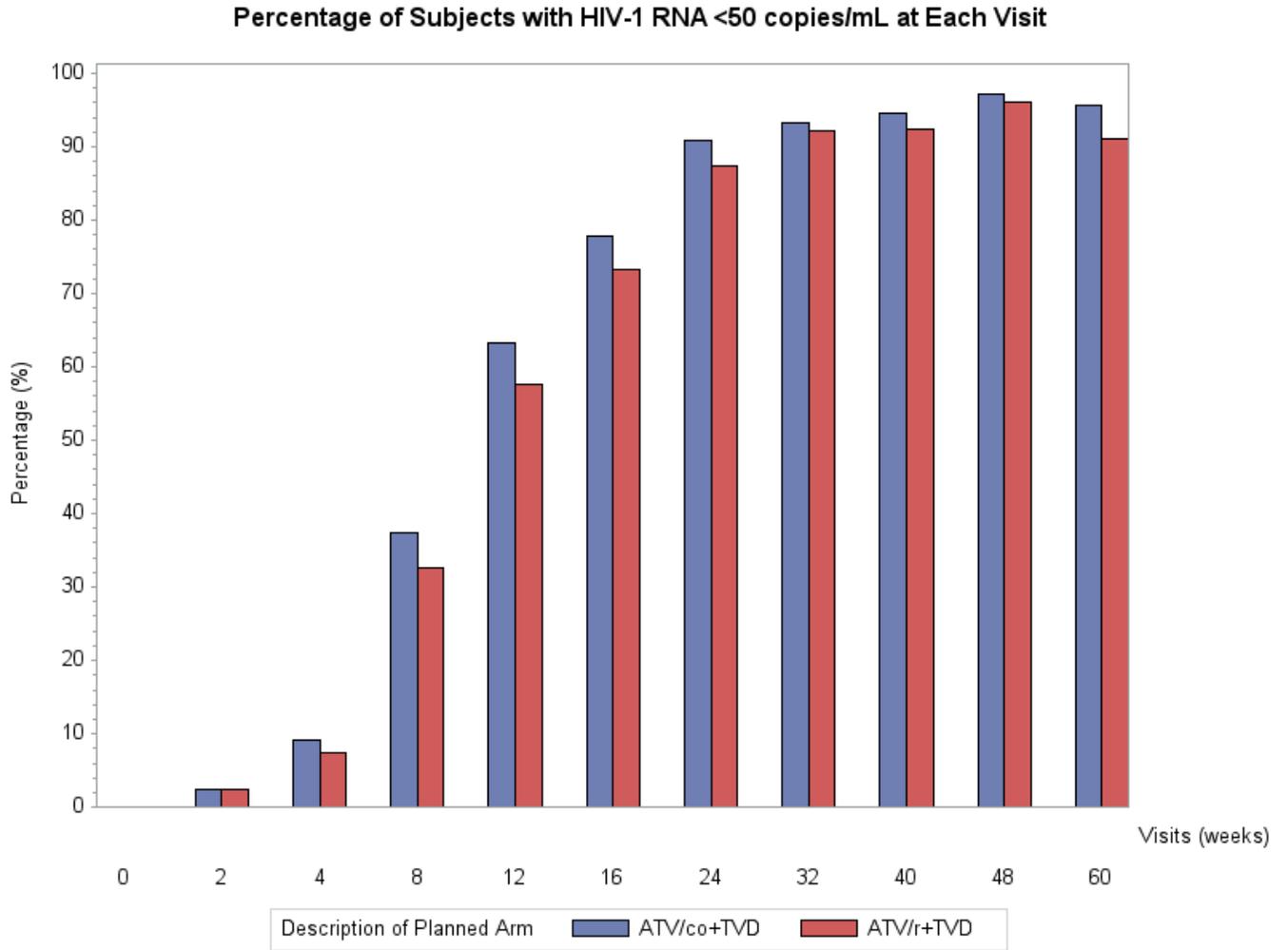
Figure 7 applied the approach of missing=failure for study GS-US-216-0114 by the sponsor. The result was similar to the result in Figure 6.

Figure 5: GS-US-216-0105: Percentage of Subjects with HIV-1 RNA <50 copies/mL at Each Visit



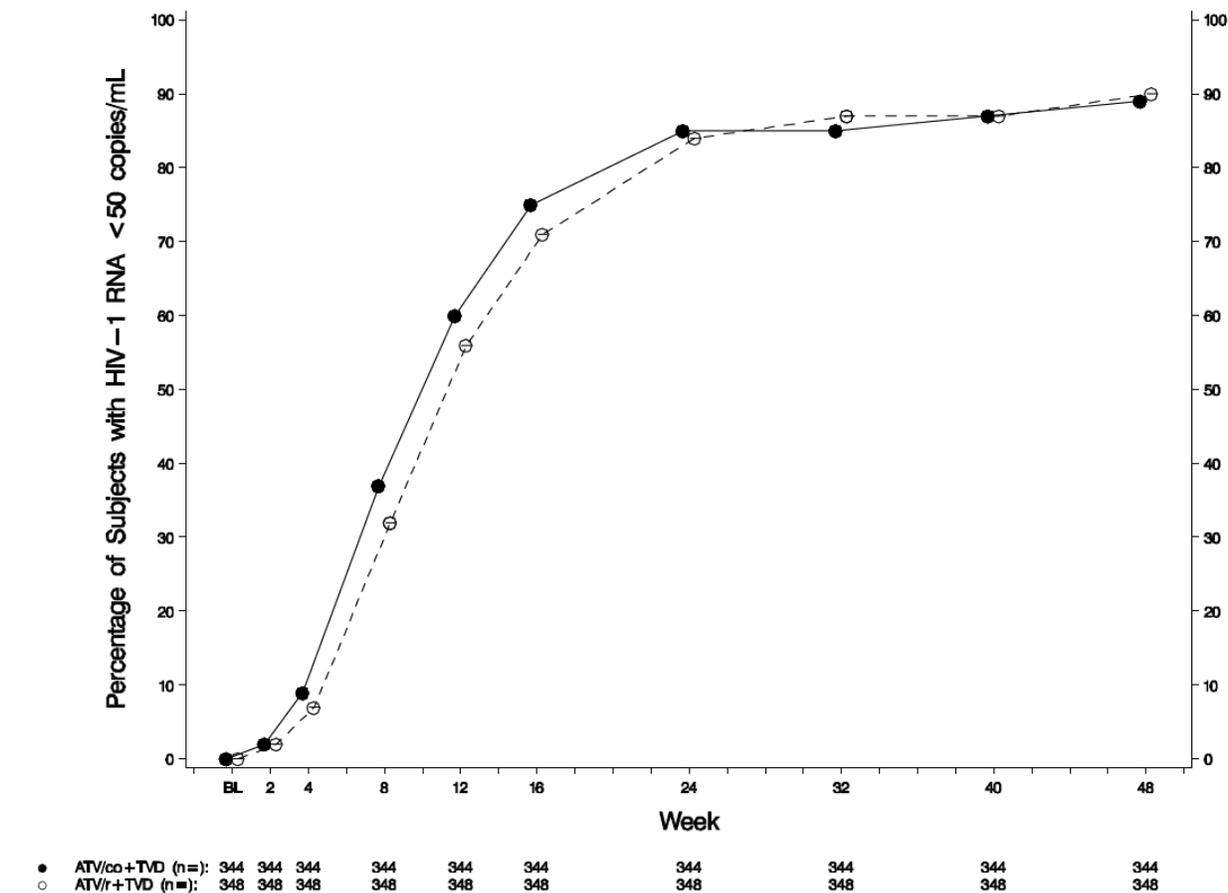
Source: Statistical Reviewer's analysis.

Figure 6: GS-US-216-0114: Percentage of Subjects with HIV-1 RNA <50 copies/mL at Each Visit



Source: Statistical Reviewer's analysis.

Figure 7: GS-US-216-0114: Percentage of Subjects with HIV-1 RNA <50 copies/mL at Each Visit(Missing=Failure)



Source: Figure 9-2 of the GS-US-216-0114 study report.

3.2.5 Combination of GS-US-216-0105 and GS-US-216-0114

3.2.5.1 Primary Efficacy Analysis

Due to the similarity of the trial design of study GS-US-216-0105 and GS-US-216-0114, integrated analyses were performed by combining those two trials. Table 17 summarized the primary efficacy analysis result based on ITT analysis set. The virologic success rate at Week 48 was 84.8% (334/394) in the ATV/co+TVD arm and 87.3% (329/377) in the ATV/r+TVD arm. The difference of the virologic success rates between those two arms (ATV/co+TVD vs. ATV/r+TVD) was -2.5% with 95% CI of (-7.5%, 2.5%) adjusted for baseline HIV-1 RNA. Gilead claimed that ATV/co was non-inferior to ATV/r because the lower bound of the 95% confidence interval of -7.5% for the adjusted difference of virologic success rates exceeded -12%.

However twelve randomized patients were excluded from the ITT analysis set because those patients didn't receive the randomized study medication. The reviewer repeated the primary

efficacy analysis based on the randomized analysis set. The result was shown in Table 18. In this analysis the virologic success rate at Week 48 was 82.5% (334/405) in the ATV/co+TVD arm and 87.0% (329/378) in the ATV/r+TVD arm. The adjusted difference of the virologic success rates was -4.6% with 95% CI of (-9.7%, 0.5%). The upper boundary of the 95% CI was 0.5% which was very close to 0. This indicated that the integrated analysis based on randomized population set showed that ATV/co+TVD regime is close to inferior to ATV/r+TVD regime.

Table 17: GS-US-216-0105 and 0114: Virologic Outcome at Week 48 (HIV-1 RNA <50 copies/mL) (ITT Analysis Set)

Virologic Response	ATV/co+TVD N=394	ATV/r+TVD N=377	Difference of Success Rates ATV/co+TVD vs. ATV/r+TVD (95.2% CI)
Virologic Success	334(84.8%)	329(87.3%)	-2.5%(-7.5%, 2.4%)*
Virologic Failure	25(6.3%)	17(4.5%)	
HIV RNA >=50 copies/mL	10(2.5%)	8(2.1%)	
Discontinued Due To Lack Of Efficacy	1(0.3%)	0	
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA >= 50 copies/mL	14(3.6%)	9(2.4%)	
No Virologic Data at 48 weeks Window	35(8.9%)	31(8.2%)	
Adverse Event	24(6.1%)	24(6.4%)	
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL	11(2.8%)	7(1.9%)	

*The baseline HIV-1 RNA stratum ($\leq 100,000$ copies/mL or $> 100,000$ copies/mL) weighted difference in the response rate (P1 – P2) and its 95.2% CI were calculated based on stratum-adjusted Mantel-Haenszel (MH) proportion.

Source: Statistical Reviewer’s analysis.

Table 18: GS-US-216-0105 and 0114: Virologic Outcome at Week 48 (HIV-1 RNA <50 copies/mL) (Randomized Analysis Set)

Virologic Response	ATV/co+TVD N=405	ATV/r+TVD N=378	Difference of Success Rates ATV/co+TVD vs. ATV/r+TVD (95.2% CI)
Virologic Success	334(82.5%)	329(87.0%)	-4.6%(-9.7%, 0.5%)*
Virologic Failure	25(6.2%)	17(4.4%)	
HIV RNA >=50 copies/mL	10(2.5%)	8(2.1%)	
Discontinued Due To Lack Of Efficacy	1(0.3%)	0	
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA >= 50 copies/mL	14(3.5%)	9(2.4%)	
No Virologic Data at 48 weeks Window	46(11.4%)	32(8.5%)	
Adverse Event	24(5.9%)	24(6.4%)	
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL	22(5.4%)	8(2.1%)	

*The baseline HIV-1 RNA stratum (\leq 100,000 copies/mL or $>$ 100,000 copies/mL) weighted difference in the response rate (P1 – P2) and its 95.2% CI were calculated based on stratum-adjusted Mantel-Haenszel (MH) proportion. For those subjects without baseline HIV-1 RNA, screening HIV-RNA was used.
Source: Statistical Reviewer’s analysis.

3.2.5.2 Baseline Predictors for Virologic Success

To investigate the relationship between virologic success (HIV-1 RNA <50 Copies/mL) and baseline variables, logistic regression model was fit for the integrated data. The covariates that were tested were:

- Age (years)
- African American
- Sex
- Baseline HIV-1 RNA (copies/mL)
- Baseline CD4 cell count (/μL)
- Arm
- Study

Each variable was fit first. Significant ones (with p-value ≤ 0.05) were put together into the model. Non-significant ones were dropped from the model until all the variables left in the model were significant. Two-way interactions between those significant variables were also tested. In the final model (Table 19), age and African American were significant. According to the model older people tend to have better chance of achieving virologic success. Non-African American patients also might have higher probability of achieving virologic success compared with African American patients.

Table 19: GS-US-216-0105 and 0114: Logistic Regression Model for Virologic Success (HIV-1 RNA <50 Copies/mL) At Week48 (ITT Analysis Set)

Parameter	Parameter Estimate (standard Error)	Odds Ratio	95% Confidence Limits of the odds ratio		P-value
Age	0.037 (0.012)				0.0012
Race Group (Non-African American Vs. African American)	0.343 (0.116)	1.99	1.26	3.13	0.0032

Source: Statistical Reviewer's analysis.

3.3 Evaluation of Safety

For detailed safety evaluation, please refer to the clinical review written by Dr. Peter Miele. Changes from baseline in total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides are presented in below tables. In tables 20 and 21, data in study 114 was summarized. Integrated data of study 105 and 114 were summarized in tables 22 and 23. Patients who took Statins (ATORVASTATIN, ATORVASTATIN CALCIUM, PRAVASTATIN, PRAVASTATIN SODIUM, ROSUVASTATIN, ROSUVASTATIN CALCIUM, SIMVASTATIN) were excluded from tables 21 and 23. The difference of including and excluding statin users was minor.

Table 20: US-216-0114: Lipid Values, Mean Change from Baseline (Safety Analysis Set)

	ATV/co+TVD		ATV/r+TVD	
	Baseline	Week 48	Baseline	Week 48
	mg/dL	Change from baseline ^a	mg/dL	Change from baseline ^a
Total Cholesterol (fasted)	164 [N=278]	+5 [N=278]	167 [N=287]	+9 [N=287]
HDL-cholesterol (fasted)	43 [N=277]	+4 [N=277]	42 [N=287]	+3 [N=287]
LDL-cholesterol (fasted)	103 [N=278]	+6 [N=278]	104 [N=288]	+8 [N=288]
Triglycerides (fasted)	130 [N=278]	+19 [N=278]	134 [N=287]	+32 [N=287]

1. Only patients with both baseline and Week 48 results were summarized.

Source: Statistical Reviewer's analysis.

Table 21: US-216-0114: Lipid Values, Mean Change from Baseline (Safety Analysis Set Excluding Statin Users)

	ATV/co+TVD		ATV/r+TVD	
	Baseline	Week 48	Baseline	Week 48
	mg/dL	Change from baseline ^a	mg/dL	Change from baseline ^a
Total Cholesterol (fasted)	164 [N=267]	+4 [N=267]	166 [N=275]	+8 [N=275]
HDL-cholesterol (fasted)	43 [N=266]	+4 [N=266]	43 [N=275]	+3 [N=275]
LDL-cholesterol (fasted)	103 [N=267]	+5 [N=267]	104 [N=276]	+8 [N=276]
Triglycerides (fasted)	128 [N=267]	+18 [N=267]	131 [N=275]	+31 [N=275]

1. Only patients with both baseline and Week 48 results were summarized.

Source: Statistical Reviewer's analysis.

Table 22: GS-US-216-0105 and 0114: Lipid Values, Mean Change from Baseline (Safety Analysis Set)

	ATV/co+TVD		ATV/r+TVD	
	Baseline	Week 48	Baseline	Week 48
	mg/dL	Change from baseline ^a	mg/dL	Change from baseline ^a
Total Cholesterol (fasted)	165 [N=319]	+5 [N=319]	166 [N=311]	+9 [N=311]
HDL-cholesterol (fasted)	44 [N=318]	+3 [N=318]	43 [N=311]	+3 [N=311]
LDL-cholesterol (fasted)	102 [N=319]	+6 [N=319]	103 [N=312]	+8 [N=312]
Triglycerides (fasted)	130 [N=319]	+16 [N=319]	133 [N=311]	+30 [N=311]

1. Only patients with both baseline and Week 48 results were summarized.

Source: Statistical Reviewer's analysis.

Table 23 : GS-US-216-0105 and 0114: Lipid Values, Mean Change from Baseline (Safety Analysis Set Excluding Statin Users)

	ATV/co+TVD		ATV/r+TVD	
	Baseline	Week 48	Baseline	Week 48
	mg/dL	Change from baseline ^a	mg/dL	Change from baseline ^a
Total Cholesterol (fasted)	164 [N=307]	+4 [N=307]	165 [N=299]	+8 [N=299]
HDL-cholesterol (fasted)	44 [N=306]	+3 [N=306]	43 [N=299]	+3 [N=299]
LDL-cholesterol (fasted)	102 [N=307]	+5 [N=307]	103 [N=300]	+7 [N=300]
Triglycerides (fasted)	128 [N=307]	+15 [N=307]	131 [N=299]	+29 [N=299]

1. Only patients with both baseline and Week 48 results were summarized.

Source: Statistical Reviewer's analysis.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and other factors

Table 24 below summarized the virologic success by subgroups for each individual study and the integrated studies. The subgroup analysis results were very consistent with the logistic regression results in section 3.2.5.2: older patients, non-African American patients had higher virologic success rates. Based on the integrated data, for patients <40 years old the virologic success rate was 80.0% (192/240) in the ATV/co + TVD arm and 86.3% (195/226) in the ATV/r + TVD arm, while in the patients ≥40 years old group, the virologic success rate was 92.2% (142/154) in the ATV/co + TVD arm and 88.7% (134/151) in the ATV/r + TVD arm.

African Americans had relatively lower virologic success rates compared with non-African American patients. In the African American population the virologic success rate was 74.7% (62/83) in the ATV/co + TVD arm and 81.9% (59/72) in the ATV/r + TVD arm, while in the non-African American population, the virologic success rate was 87.5% (272/311) in the ATV/co + TVD arm and 88.5% (270/305) in the ATV/r + TVD arm.

Table 24: Treatment Difference in Virologic Success at Week 48 (HIV-1 RNA < 50 copies/mL, Snapshot Analysis) by Subgroup (ITT Analysis Set)

		ATV/co+TVD (N=394)	ATV/r+TVD (N=377)
Overall	Study		
	216-0105	41/50 (82.0%)	25/29 (86.2%)
	216-0114	293/344 (85.2%)	304/348 (87.4%)
	Pooled	334/394 (84.8%)	329/377 (87.3%)
Age(years)			
< 40	216-0105	23/31 (74.2%)	19/21 (90.5%)
	216-0114	169/209 (80.9%)	176/205 (85.9%)
	Pooled	192/240 (80.0%)	195/226 (86.3%)
≥ 40	216-0105	18/19 (94.7%)	6/8 (75.0%)
	216-0114	124/135 (91.9%)	128/143 (89.5%)
	Pooled	142/154 (92.2%)	134/151 (88.7%)
Sex			
Male	216-0105	39/47 (83.0%)	22/25 (88.0%)
	216-0114	244/287 (85.0%)	256/287 (89.2%)
	Pooled	283/334 (84.7%)	278/312 (89.1%)
Female	216-0105	2/3 (66.7%)	3/4 (75.0%)
	216-0114	49/57 (86.0%)	48/61 (78.7%)
	Pooled	51/60 (85.0%)	51/65 (78.5%)
Race			
African American	216-0105	14/18(77.8%)	7/9(77.8%)
	216-0114	48/65(73.9%)	52/63(82.5%)
	Pooled	62/83(74.7%)	59/72(81.9%)
Non-African American	216-0105	27/32(84.4%)	18/20(90.0%)
	216-0114	245/279(87.8%)	252/285(88.4%)
	Pooled	272/311(87.5%)	270/305(88.5%)
Baseline HIV-1 RNA Level (copies/mL)			
≤ 100,000	216-0105	33/38 (86.8%)	15/18 (83.3%)
	216-0114	179/212 (84.4%)	181/205 (88.3%)
	Pooled	212/250 (84.8%)	196/223 (87.9%)
> 100,000	216-0105	8/12 (66.7%)	10/11 (90.9%)
	216-0114	114/132 (86.4%)	123/143 (86.0%)
	Pooled	122/144 (84.7%)	133/154 (86.4%)
Baseline CD4 Cell Count (μL)			
≤ 200	216-0105	6/10(60.0%)	7/7(100.0%)
	216-0114	53/60(88.3%)	50/57(87.7%)
	Pooled	59/70(84.3%)	57/64(89.1%)
> 200	216-0105	35/40(87.5%)	18/22(81.8%)
	216-0114	240/284(84.5%)	254/291(87.3%)
	Pooled	275/324(84.9%)	272/313(86.9%)

Source: Statistical Reviewer's analysis.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There were two major statistical issues in this application:

- Twelve randomized patients were excluded from the ITT analysis set in phase II study (**GS-US-216-0105**) and Phase III trial (**GS-US-216-0114**) because those patients did not receive study medication. Sensitivity analyses were performed by the statistical reviewer based on the randomized population set by integrating the phase II study (**GS-US-216-0105**) and Phase III study (**GS-US-216-0114**) data. In this analysis virologic success rate at Week 48 was 82.5% (334/405) in the ATV/co+TVD arm and 87.0% (329/378) in the ATV/r+TVD arm. The adjusted difference of the virologic success rates was -4.6% with 95% CI of (-9.7%, 0.5%). The upper boundary of the 95% CI (0.5%) was very close to 0. This indicated that ATV/co+TVD regime is close to inferior to ATV/r+TVD regime based on analysis performed on randomized analysis set of the integrated data.
- In the trial design of study **GS-US-216-0114**, 12% was specified as the non-inferiority margin. At the end of phase II meeting, FDA indicated to the sponsor that the 12% non-inferiority margin was acceptable for planning purposes but would be assessed further during the review. After reviewing the efficacy results of Atazanavir (NDA 21567), the reviewer concluded that the 12% margin used in study **GS-US-216-0114** was too large. The applicant should have used a much smaller margin (0-2.5%). Taking variability of the point estimates into account from atazanavir study 089 (NDA 21-567) that had a head to head comparison between ATV/r and unboosted atazanavir, there was no margin.

5.2 Collective Evidence

In the primary efficacy analysis the snapshot approach was applied for study GS-US-216-0114. At week 48 the virologic success rate was 85.2% (293/344) in the ATV/co+TVD arm and 87.4% (304/348) in the ATV/r+TVD arm based on the ITT analysis set. The stratum adjusted difference (ATV/co+TVD vs. ATV/r+TVD) was -2.2% with 95% confidence interval (CI) of (-7.4%, 3.0%). The applicant did not provide justification for the 12% margin but claimed that ATV/co was non-inferior to ATV/r because the lower bound of the 95% confidence interval of -7.4% exceeded -12%.

5.3 Conclusions and Recommendations

The applicant **failed to demonstrate** that Cobicistat (COBI) 150 mg once daily in combination with atazanavir 300 mg once daily and emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg (Truvada) was **non-inferior** to Ritonavir 100 mg in combination with atazanavir 300 mg and emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg (Truvada) based on the primary efficacy result of study GS-US-216-0114. This trial was useful for providing pharmacokinetic

data and information about the safety of Cobicistat but was not adequately designed to make credible statistical comparisons between ATV/co and ATV/r arms.

5.4 Labeling Recommendations (as applicable)

The applicant summarized the primary efficacy analysis in Table 10 of the Clinical Studies section of the label (b) (4)



The applicant summarized the Lipid values in Table 4 of the **adverse reactions** section of the label (shown below). (b) (4)

(b) (4) It was recommended by the agency to replace this table by Table 23 in this review document.

APPENDICES

Some of the Atazanavir trial results in treatment-naïve patients from NDA 21567 were previously reviewed by FDA and are summarized below. These results indicate that the 12% NI margin proposed by Gilead was too large.

Trial 89

- Only head to head comparison trial of boosted and unboosted ATV
- To compare ATV/r at 300/100 mg qd to ATV at 400 mg qd when each combined with lamivudine (3TC) at 300 mg qd+stavudine XR(d4T XR) at 100 mg qd
- Patients were treatment naïve, with HIV RNA ≥ 2000 copy/mL at screening

Table 25: Efficacy result of trial 89

	ATV400 N=105	ATV300/r N=95	Difference (ATV/r vs. ATV) % (95% CI)
HIV RNA <400 c/ml at week 48 % (n/N)	85% (89/105)	86% (82/95)	-1.5% (-11.1, 8.2)
HIV RNA <50 c/ml at week 48 % (n/N)	70% (73/105)	75% (71/95)	5% (-7%, 18%)

Trial 007

- Evaluation of the Safety and Antiviral Efficacy of ATV Alone and in Combination with d4T and ddI as Compared to a Reference Combination Regimen
- Patients were antiretroviral naïve HIV-1 infected adults with HIV RNA ≥ 2000 copies/mL
- Arms:
 - Treatment Regimen I: Atazanavir 200 mg QD + ddI QD + d4T BID
 - Treatment Regimen II: Atazanavir 400 mg QD + ddI QD + d4T BID
 - Treatment Regimen III: Atazanavir 500 mg QD + ddI QD + d4T BID
 - Regimen IV: NFV 750 mg TID + ddI QD + d4T BIDqd+EFV 600mg qd

Table 26: Efficacy result of trial 007

	ATV200 N=83	ATV400 N=78	ATV500 N=79	NFV750 N=82
HIV RNA < 400 c/ml at week 48 % (n/N)	61% (51/83)	59% (46/78)	61% (48/79)	60% (49/82)
HIV RNA < 50 c/ml at week 48 % (n/N)	30% (25/83)	33% (26/78)	35% (28/79)	28% (23/82)

Trial 008

- Evaluation of the Safety and Antiviral Efficacy of ATV, in Combination with d4T and 3TC as Compared to a Reference Combination Regimen
- Patients were antiretroviral naïve HIV-1 infected adults with HIV RNA ≥ 2000 copies/mL
- Arms:
 - Treatment Regimen I: Atazanavir 400 mg QD + 3TC BID + d4T BID
 - Treatment Regimen II: Atazanavir 600 mg QD + 3TC BID + d4T BID
 - Treatment Regimen III: NFV 1,250 mg BID + 3TC BID + d4T BID

Table 27: Efficacy result of trial 008

	ATV400 N=181	ATV600 N=195	NFV1250 N=91
HIV RNA <400 c/ml at week 48 % (n/N)	65% (118/181)	62% (120/195)	59% (54/91)
HIV RNA <50 c/ml at week 48 % (n/N)	31% (57/181)	36% (70/195)	38% (35/91)

Trial 121

- To demonstrate the safety and efficacy of 2 ATV regimens
- Patients were antiretroviral naïve HIV-1 infected adults
- Arms:
 - ATV300 mg qd+RTV100mg qd+EFV 600mg qd
 - ATV400 mg qd+RTV100mg qd+EFV 600mg qd

Table 28: Efficacy result of trial 121

	ATV300 N=32	ATV400 N=33
HIV RNA <400 c/ml at week 48 % (n/N)	75% (24/32)	67% (22/33)
HIV RNA <50 c/ml at week 48 % (n/N)	63% (20/32)	61% (20/33)

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/s/

YANMING YIN
03/19/2013

FRASER B SMITH
03/19/2013

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 203094

Applicant: Gilead

Stamp Date: 6/26/2012

Drug Name: Cobicistat

NDA/BLA Type: NDA

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)			X	Text of ISS and ISE are covered in SCS and SCE. ISS and ISE outputs were submitted in module 5.3.5.3. Complete study reports are available.
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			Subgroup analyses were performed for primary efficacy endpoint.
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? _____ **Yes**__

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

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the	X			

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

protocols/statistical analysis plans.				
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	X			Interim analyses were pre-specified in the protocol. DSMB minutes are available for week 12 and week 24 open sessions.
Appropriate references for novel statistical methodology (if present) are included.			NA	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

Brief summary of controlled clinical trials

The following table contains information on the relevant trials contained in the submission.

Study number	Design	Treatment arms/Sample size	Primary endpoint/Analysis	Sponsor's findings
GS-US-216-0114	A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of GS-9350-boosted Atazanavir Versus Ritonavir-boosted Atazanavir Each Administered with Emtricitabine/Tenofovir Disoproxil Fumarate in HIV-1 Infected, Antiretroviral	Treatment Arm 1: GS-9350 150 mg + atazanavir 300 mg + emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg + Placebo to match ritonavir 100	The primary efficacy endpoint is the proportion of subjects that achieve HIV-1 RNA < 50 copies/mL at Week 48 as defined by the snapshot analysis. The primary analysis will consist of a non inferiority test of GS-9350 versus ritonavir, with respect to the	According to the sponsor: <ul style="list-style-type: none"> • ATV/co+TVD was noninferior to ATV/r+TVD in HIV-1 infected, antiretroviral treatment-naive subjects with the difference of -2.2% and 95.2% CI of (-7.4%, 3%). The efficacy results of the ATV/co+TVD regimen were robust and confirmed by multiple sensitivity and subgroup analyses. • No subject developed resistance to PIs, and resistance

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

	<p>Treatment-Naïve Adults</p>	<p>mg QD (n = 344) Treatment Arm 2: Ritonavir 100 mg + atazanavir 300 mg + emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg + Placebo to match GS-9350 150 mg QD (n = 348)</p>	<p>proportion of subjects with HIV-1 RNA less than 50 copies/mL at Week 48 as defined by the snapshot analysis. It will be concluded that the GS 9350 arm is not inferior to the ritonavir arm if the lower bound of the two-sided 95% confidence interval of the difference (GS-9350 arm – ritonavir arm) in the response rate (HIV-1 RNA < 50 copies/mL as defined by the snapshot analysis) is greater than -12%; i.e., a margin of 12% is applied to non-inferiority assessment. The 95% confidence interval will be constructed using normal approximation method stratified by baseline HIV-1 RNA level (\leq 100,000 copies/mL or > 100,000 copies/mL).</p>	<p>to NRTIs occurred in only 2 subjects in the ATV/co+TVD group.</p> <ul style="list-style-type: none"> • The plasma exposures of ATV were comparable when boosted by COBI or RTV. • Both ATV/co+TVD and ATV/r+TVD were generally safe and well tolerated. • The renal and hepatic safety profiles of the ATV/co+TVD and ATV/r+TVD treatment groups were comparable. • As expected, small increases in serum creatinine were observed in both treatment groups. • Renal AEs leading to study drug discontinuation were generally balanced between treatment groups, reversible, and without clinical sequelae. • Although a larger percentage of subjects in ATV/co+TVD group had Grade 3 or 4 elevations of total bilirubin, the rate of discontinuations due to bilirubin-related AEs was low and comparable between treatment groups.
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STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Yanming Yin

7/26/2012

Reviewing Statistician

Date

Fraser Smith

7/26/2012

Supervisor/Team Leader

Date

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/s/

YANMING YIN
08/08/2012

FRASER B SMITH
08/08/2012