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 Serial Number:** | 208,215 / S-0012 | |
| **Drug Name:** | DESCOVY (Emtricitabine/Tenofovir Alafenamide; F/TAF or DVY) | |
| **Indication(s):** | Pre-exposure prophylaxis (PrEP) of human immunodeficiency virus type 1 (HIV-1) infection | |
| **Applicant:** | Gilead Science, Inc. | |
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| **Review Priority** | Priority | |
| **Biometrics Division:** | Division of Biometrics IV | |
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**Keywords:** DESCOVY, DVY, F/TAF, Pre-exposure prophylaxis (PrEP), HIV-1 Infection, Men and transgender women who had sex with men (MSM/TGW).

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# 1. EXECUTIVE SUMMARY

Descovy (DVY or F/TAF) is a fixed-dosed combination tablet containing emtricitabine (FTC) 200 mg and tenofovir alafenamide (TAF) 25 mg, and both are HIV nucleoside analog reverse transcriptase inhibitors (NRTIs). Descovy was approved in 2016 as a part of a complete regimen for treatment of chronic HIV-1 infection in adults and pediatric patients weighing at least 35 kg. In this submission, the Applicant seeks to extend the indication of Descovy for pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection from sexual acquisition in adults and adolescents weighing at least 35 kg.

For HIV-1 PrEP, FDA approved the fixed-dose combination of FTC 200 mg and tenofovir disoproxil fumarate (TDF) 300 mg (Truvada®, F/TDF, or TVD) to reduce the risk of sexually-acquired HIV-1 infection in at-risk adults, in 2012. The PrEP indication for Truvada was expanded to include at-risk adolescents weighing at least 35 kg in 2018.

Tenofovir disoproxil fumarate (TDF) is a prodrug hydrolyzed to tenofovir (TFV) which circulates in plasma. The TAF prodrug is also hydrolyzed to TFV in plasma but this occurs much more slowly than TDF in plasma. Because one prodrug of TFV has already been approved for this indication and F/TAF has already approved for HIV-1 treatment, one phase 3 trial was considered as sufficient to support this sNDA submission.

The Applicant submitted one phase 3 trial, GS-US-412-2055 (DISCOVER), to support the evaluation of Descovy for PrEP of HIV-1 infection in at-risk adults and adolescents. The DISCOVER trial is an ongoing multinational, randomized, double-blind trial to compare the safety and efficacy of F/TAF versus F/TDF in HIV-1 negative adult men and transgender women who have sex with men (MSM/TGW) and are at high risk of HIV-1 infection. The trial is being conducted in 94 sites across 11 countries in North America and the European Union in cities known to be historic urban epicenters of the HIV epidemic and with high prevalence of people living with HIV, as well as in cities where new HIV cases are increasing, and where HIV-associated sexual risk behavior is high. The primary efficacy endpoint was the rate of HIV-1 infection in MSM/TGW who were administered daily F/TAF or F/TDF with a minimum follow-up of 48 weeks and at least 50% of subjects have 96 weeks of follow-up after randomization. This was a non-inferiority (NI) design and the NI margin of 1.62 was determined from three historical trials with 50% preservation of F/TDF benefit over placebo.

A total 5399 subjects were randomized using 1:1 ratio to either F/TAF or F/TDF arm. The primary efficacy analysis was based on the full-analysis set (FAS), which included 5335 subjects who were randomized, dosed, not HIV-1 positive on Study Day 1, and had at least one post-baseline HIV laboratory assessment. Twenty-two (0.4%) of 5335 subjects in the FAS were infected with HIV-1 during the trial,  of which, 7 were in the F/TAF arm and 15 were in the F/TDF arm. The HIV-1 infection rates were 0.160 per 100 person-years (PY) and 0.342 per 100 person-years in F/TAF arm and F/TDF arm respectively. The upper bound of the 95.003% confidence interval (CI) of the rate ratio of F/TAF vs. F/TDF was 1.149, which was lower than the pre-specified NI margin of 1.62. Therefore, the trial demonstrated that F/TAF was non-inferior to F/TDF in reducing the risk of acquiring HIV-1 infection in the MSM/TGW population.

The Applicant sought a broad indication to include cisgender women and adolescent. Thus, the Applicant also submitted two extrapolation reports, one for cis-gender women and one for adolescents, to support Descovy for PrEP in women and adolescents. An advisory committee (AC) meeting was hold on August 7, 2019 to discuss these. Please see other discipline's reviews for details and the impact on the final indication.

**Key statistical issue:** The NI margin.

The NI margin used in this trial was determined from three historical trials with F/TDF vs. placebo for PrEP in MSM population (Table 1 below).

**Table 1:** Efficacy Information from Truvada as PrEP in MSMs

| Clinical Trial | Sample Size Placebo (PY Follow-Up) | Sample Size F/TDF (PY Follow-Up) | HIV Infections (Incidence per 100 PY [95% CI]) | | Rate Ratios in HIV Infection Rates, per 100 PY [95% CI] | Enrolment |
|---|---|---|---|---|---|---|
| | | | PBO | F/TDF | | |
| iPrEX (URAI subgroup) at screening | 753 (1054) | 732 (1055) | 56 (5.3) [4.0, 6.8] | 23 (2.2) [1.4, 3.2] | 2.4 [1.5, 3.9] | July 10, 2007 - Dec 17, 2009 |
| PROUD | 255 (222) | 268 (243) | 20 (9.0) [5.6, 13.4] | 3 (1.2) [0.3, 3.5] | 7.3 [2.2, 24.2] | Nov 29, 2012 – Apr 30, 2014 |
| IPERGAY | 201 (212) | 199 (220) | 14 (6.6) [3.9, 10.6] | 2 (0.9) [0.2, 3.2] | 7.3 [1.7, 31.6] | Feb 22, 2012 – Oct 23, 2014 |
| Pool | 1209 (1488) | 1199 (1518) | 90 (6.0) [4.9, 7.5] {6.96}* | 28 (1.9) [1.3, 2.6] {1.44}* | 5.1* [2.64, 9.70]* | |

Source: iPrEX from {Grant 2010}; IPERGAY from {Molina 2015}; PROUD from {McCormack 2015}

* The pooled incidence rate for placebo and F/TDF, based on equal weighting of three studies, are within {} which are used for estimating the rate ratio and its 95% CI.

Source: Table 1-1 in statistical analysis plan (SAP) for this study.

Based on these three historical trials, the Applicant estimated the weighted pooled HIV-1 incidence rate for F/TDF to be 1.44 per 100 PY, and the rate ratio compared to placebo was 5.1 per 100 PY and the lower bound of the 95% CI was 2.64. The NI margin of 1.62 was determined based on the square-root of 2.64, 50% preservation of the F/TDF effect over placebo. Consequently, a sample size of 2500 in each arm (1:1 randomization) provides at least 82% power to show F/TAF is non-inferior to F/TDF with respect to the HIV-1 infection rate.

The infection rate in F/TDF arm in the current trial was 0.342 per 100 PY, which is approximately 4-folder lower than expected infection rate of 1.44 per 100 PY based on the

historical data. This raises question(s) about the validity of the constancy assumption of the control effect over placebo and the possible need to adjust the NI margin.

One possible explanation for the lower infection rate in the F/TDF arm in the current trial compared to that observed in the historical trials is the higher adherence rate of F/TDF in the current trial. According to the study report, the median self-reported adherence was greater than 95% at all visits by computer-assisted self-interview (CASI) questionnaire and mean of pill-count adherence was 93% in both treatment arms. In the dried blood spot (DBS) substudy, most subjects in both arms had tenofovir diphosphate (TFV-DP) levels in red blood cells consistent with high adherence (≥ 4 days of dosing per week).

Additionally, we do not have any direct information about the infection rate of the non-existent or putative placebo arm. If we assume a proportional change for placebo to that observed in the control arm, the unknown placebo incidence rate may have also reduced by 4-fold from the historical rate corresponding to F/TDF. This scenario may also require an assumption that the sexual partner's risk to infect was unchanged during the trial. Note that the interpretability of findings could be impacted if the unknown placebo incidence rate is much lower than the proportional change in the current trial. The Applicant did summarize the 2016 CDC infection data in non-study PrEP-eligible MSM at risk of HIV-1 in 25 US metropolitan statistical areas (MSAs), which are overlapping with GS-US-412-2055 sites. The infection rate was 4.02 per 100 PY with 95% CI of [3.56, 3.66].

Based on the above explanations, if we believe that the infection rate in the placebo arm is less than the 4-fold decrease from historical rate, there is no need to adjust the current NI margin as the primary analysis used a rate ratio metric. From the perspective of the reviewer, the rate ratio metric is more stable for any reduction in the event rate of the active control arm compared to rate difference approach.

A sensitivity analysis was performed to evaluate the impact on the findings if the non-inferiority margin was re-adjusted to account for the lower observed HIV-1 incidence rate in the F/TDF arm. The re-adjusted non-inferiority margin was 1.13, which was the quadratic-root of the original NI margin, and the upper bound of the 95.003% CI of the rate ratio of F/TAF versus F/TDF (1.149) falls slightly outside the margin. This is one potential way to adjust the NI margin if there are other concerns on the validity of the historical evidence of treatment effect, although it is conservative.

Overall, the reviewer concludes that the original NI margin of 1.62 is applicable in this case and the trial demonstrated that F/TAF was non-inferior to F/TDF in reducing the risk of acquiring HIV-1 infection in the MSM/TGW population.

# 2. INTRODUCTION

## 2.1 Overview

### 2.1.1 The Study Reviewed

The description of the study is listed in Table 2. Study GS-US-412-2055 (DISCOVER) was conducted in 94 sites across 11 countries, Austria, Canada, Denmark, France, Germany, Ireland, Italy, Netherlands, Spain, United Kingdom, and United States. The detailed design characteristics of the phase 3 study are described in section 3.2.1.

**Table 2** Phase 3 trial design details included in this review

| Study | Phase and Design | Objectives/Primary Endpoint | Treatment Period | # of Subjects per Arm | Study Population |
|---|---|---|---|---|---|
| GS-US-412-2055 | A phase 3, double-blind, randomized, active-controlled study to evaluate the safety and efficacy of F/TAF QD for PrEP in men/TGW who have sex with men and are at-risk of HIV-1 infection. | The primary efficacy endpoint was the rate of HIV-1 infection in MSM/TGW who were administered daily F/TAF or F/TDF with a minimum follow-up of 48 weeks and at least 50% of subjects had 96 weeks of follow-up after randomization. | The total duration is 96 weeks. | F/TAF QD (n=2694)<br><br>F/TDF QD (n=2693) | MSM /TGW |

## 2.2 Data Sources

NDA 208,215 / S12 contains the efficacy and safety results for subjects in Study GS-US-412-2055. This reviewer conducted primary efficacy analyses to verify the Applicant's results.

1. Reviewed protocols, statistical analysis plans, efficacy results and conclusions in the following submitted documents entitled "Statistics Section":
    - Module 1- labeling materials
    - Module 2- 2.5 Clinical Overview and 2.7.3 Summary of Clinical Efficacy
    - Module 5- Clinical Study Reports (CSRs) of the Phase 3 Study GS-US-412-2055

2. Converted SAS transportable files '*.xpt' in \analysis\adam\datasets subfolder as analysis datasets, some of the raw datasets in \tabulations\sdtm subfolder into SAS data files for verification based on the definitions in 'define.xml', 'acrf.pdf', and SAP in the clinical study report (CSR). These files are under CDER Electronic Document Room (EDR) directory of

   \\CDSESUB1\evsprod\NDA208215\0098\m5\datasets\gs-us-412-2055

# 3. STATISTICAL EVALUATION

Study GS-US-412-2055 will be reviewed and reported in the following sections. All tables and figures were prepared by the statistical reviewer unless otherwise stated.

## 3.1 Data and Analysis Quality

Overall, the reviewer reproduced primary efficacy analysis findings based on dataset, ADEFF.

The reviewer guides, SAPs and the SAS programs submitted were useful and assisted in an efficient review.

## 3.2 Evaluation of Efficacy

### 3.2.1 Study Design of GS-US-412-2055 (DISCOVER) and Endpoints

Note that the summary in Section 3.2.1 is either directly taken from the sponsor's NDA or previous IND submissions, or paraphrased, unless otherwise specified.

**Title:** A Phase 3, Randomized, Double-blind Study to Evaluate the Safety and Efficacy of Emtricitabine and Tenofovir Alafenamide (F/TAF) Fixed-Dose Combination Once Daily for Pre-Exposure Prophylaxis in Men and Transgender Women Who Have Sex with Men and Are at Risk of HIV-1 Infection.

A total of 5000 subjects were planned to be enrolled to receive blinded study drug for 96 weeks, although there were 5399 subjects enrolled in total. Subjects were randomized in a 1:1 ratio to either receive F/TAF or F/TDF (Figure 1). With the assumption of a noninferiority margin of 1.62 and a HIV-1 infection rate of 1.44 per 100 person-years (PY) for both arms (please see "Key statistical issue: The NI margin" section-1 for details), a sample size of 2500 subjects in each arm was expected to provide at least 82% power to show noninferiority of F/TAF to F/TDF.

After randomization, subjects were seen in follow-up visits at Weeks 4, 12, and every 12 weeks thereafter. At each study visit, subjects had the following procedures: HIV tests performed via central laboratory or local laboratory; drug dispensation and adherence and risk reduction counseling; and other assessments.

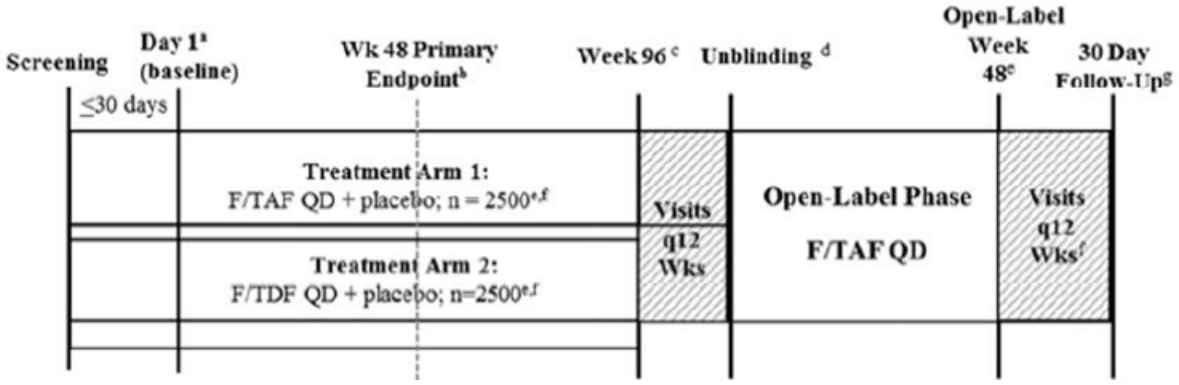


**Figure 1**: Study Diagram of GS-US-412-2055
(Source: Protocol)

**Treatment Arms:**

- Treatment Group 1: FDC of emtricitabine 200 mg / tenofovir alafenamide 25 mg(F/TAF) + Placebo-to-match FDC of emtricitabine 200 mg / tenofovir disoproxil fumarate 300 mg (F/TDF), administered orally once daily (n=2500)
- Treatment Group 2: FDC of emtricitabine 200 mg / tenofovir disoproxil fumarate 300 mg (F/TDF) + Placebo-to-match FDC of emtricitabine 200 mg / tenofovir alafenamide 25 mg (F/TAF), administered orally once daily (n=2500)

Two sub-studies were conducted based on tenofovir diphosphate (TFV-DP) concentrations in red blood cells from dried blood spot (DBS) samples, an indicator of long-term adherence:

1) a cohort sub-study of approximately 10% of subjects randomly pre-selected to estimate overall rate of adherence, and
2) a case-control sub-study consisting of all subjects who became HIV-infected during the trial matched to 5 randomly selected control subjects (matched by treatment, time, location, and risk behavior) to assess the association between adherence and efficacy.

**Statistical Hypothesis for the Primary Efficacy Endpoint:**

- **Null hypothesis:** The HIV infection rate ratio of F/TAF over F/TDF is at least 1.62 or higher.
- **Alternative hypothesis:** The HIV infection rate ratio of F/TAF over F/TDF is less than 1.62.

**Primary Endpoint:** The rate of HIV-1 infection in MSM/TGW who were administered daily F/TAF or F/TDF with a minimum follow-up of 48 weeks and at least 50% of subjects have 96 weeks of follow-up after randomization.

The primary analysis was conducted after all subjects had a minimum follow-up of 48 weeks and at least 50% of the subjects had 96 weeks of follow-up after randomization or prematurely discontinued from the study. The analysis assessed the noninferiority of treatment with F/TAF relative to treatment with F/TDF based on HIV infection rate ratio estimation from a Poisson

regression model. Noninferiority was assessed using a 95% CI constructed using a generalized model associated with a Poisson distribution and logarithmic link with the treatment group being the main effect and a noninferiority margin of 1.62.

An external multidisciplinary Independent Data Monitoring Committee (IDMC) reviewed the progress of the study and performed interim reviews of the safety data to protect subject welfare and preserve study integrity. There were three interim analysis performed for the IDMCs after 50% of subjects reached Weeks 24, 48 and 72, respectively, an alpha of 0.00001 was spent. Therefore, the significance level for the 2-sided test in the primary analysis was 0.04997 (corresponding to 95.003% CI).

No formal interim efficacy analysis, which may have led to early termination for efficacy or futility, was planned.

**Duration of at risk of HIV infection** was defined as the time between Day 1 (first dose date) and the end date (end date – Day 1 date +1), where end date was defined as the last at-risk of HIV infection date:

- For subjects who had been diagnosed as infected with HIV: the date of HIV infection diagnosis

- For subjects who had not been infected with HIV: the date of the last post-baseline HIV laboratory test (either local HIV or (b) (4) HIV laboratory tests, including the 30-day follow-up visit)

In the person-year (PY) calculation, a year is 365.25 days.

**HIV-1 infection** was defined by one or more of the following criteria of contributing HIV tests performed via central lab or local lab:

1) Serologic evidence of seroconversion (reactive screening HIV Antigen/Antibody or Antibody test, confirmed by reactive HIV-1/HIV-2 differentiation assay), or

2) Virologic evidence of HIV-1 infection (positive qualitative HIV-1 RNA test or any detectable quantitative HIV-1 RNA test), or

3) Evidence of acute HIV-1 infection (reactive p24 Antigen or positive qualitative or quantitative RNA, in the absence of reactive HIV-1 Antibody results)

**The date of HIV infection diagnosis** was assessed by a retrospective look, starting from the date of the first positive virologic evidence, through the preceding test results from other contributing HIV tests (including both (b) (4) and local tests). The look back stops at the first date with negative assessments on all available HIV tests prior to the date of first positive virologic evidence. The date of HIV-1 diagnosis is set at the earliest positive result in the retrospective look process from either an on-site rapid test, a test sent to the central (b) (4)

laboratory, or any other provided local test performed outside of the study that documents the presence of HIV infection.

In the SAP, the Applicant specified **six safety endpoints** with a fallback procedure in the sequential order given below with pre-specified 2-sided alpha levels:

a) Hip bone mineral density (BMD) (alpha spent =0.02)
b) Spine BMD (alpha spent =0.01)
c) Urine beta-2-microglobulin to creatinine ratio (alpha spent =0.02)
d) Urine retinol binding protein (RBP) to creatinine ration (alpha spent =0.00)
e) Distribution of urine protein (UP) and urine protein-to-creatinine ratio (UPCR) categories (alpha spent = 0.00)
f) Serum creatinine (alpha spent = 0.00)

**Comments:** This review will not cover these safety endpoints. Please see clinical review for more details regarding any clinical relevance of these analysis results.

**Populations for Analyses:**

- **Safety analysis set (Safety):** included all subjects who were randomized and have received at least 1 dose of study drug.

  Safety analysis set was the primary analysis set for safety analyses. Subjects were grouped according to the treatment received.

- **Full analysis set (FAS):** included all subjects who

  1) were randomized into the study,
  2) had received at least 1 dose of study drug,
  3) were not HIV positive on Day 1 which defined as subjects with either:
     a) negative (b) (4) antibody test results at first post baseline assessment or
     b) negative local lab Day 1 rapid test, and
  4) had at least one post-baseline HIV laboratory assessment (from either local or central laboratory). Negative (b) (4) antibody test results are defined as either:
     a) a negative HIV Screening antibody test result or
     b) a positive Screening antibody test plus a negative discrimination antibody test result.

  Subjects were grouped according to the treatment to which they were randomized. The FAS was the primary analysis set for the efficacy analyses.

- **Per Protocol analysis set (PP):** consisted of all subjects in the FAS excluding those with any of the major protocol violations, such as pre-existing HIV infection, vaccinated for HIV, or subjects who meet exclusion criterion, etc. Subjects was grouped according to

the treatment they received. The PP analysis set was used for an on-study drug PrEP treatment (on-treatment) HIV infection sensitivity analyses of the primary endpoint.

**Analysis Windows:**

- **Study Day 1** is defined as the day when the first dose of study drug (i.e., F/TAF or Placebo-to-match F/TAF, F/TDF or Placebo -to-match F/TDF) was taken, as recorded on the Study Drug Administration eCRF form.

- **Study Days** are calculated relative to Study Day 1. For events that occurred on or after the Study Day 1 date, the number of study days is calculated as (visit date minus Study Day 1 date plus 1). For events that occurred prior to Study Day 1, the number of study days is calculated as (visit date minus Study Day 1 date).

- **Last Study Date** is the latest of the study drug start dates and end dates, the clinic visit dates, and the laboratory visit dates, including the 30-day follow-up visit date, for subjects who prematurely discontinued study or who completed study according to the Study Completion eCRF.

- **Last At-Risk of HIV Infection Date** is

    1) the date of HIV infection diagnosis as defined above for subjects who have been diagnosed as infected with HIV or

    2) the date of the last post-baseline HIV laboratory test (either local rapid or (b) (4) HIV laboratory tests, including the 30-day follow-up visit date) for subjects who have not been infected with HIV.

- **Duration of at risk of HIV infection** is defined as the time between Day 1 (first dose date) and the end date (end date – Day 1 date +1), where end date is defined as the last at-risk of HIV infection date. A year is 365.25 days.

Subject visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, observations will be assigned to analysis windows. The analysis windows are listed in Table 3 below.

**Table 3** Analysis Windows for HIV, Hematology, Chemistry, Urinalysis, Renal Biomarkers, eGFRCG, Vital Signs, Weight, CASI Follow-Up Questionnaire, and DBS

| Visit ID | Nominal Day | Lower Limit | Upper Limit |
|---|---|---|---|
| Baseline | 1 | (none) | 1 |
| Week 4 | 28 | 2 | 56 |
| Week 12 | 84 | 57 | 126 |
| Week 24 | 168 | 127 | 210 |
| Week 36 | 252 | 211 | 294 |
| Week 48 | 336 | 295 | 378 |
| Week 60 | 420 | 379 | 462 |
| Week 72 | 504 | 463 | 546 |
| Week 84 | 588 | 547 | 630 |
| Week 96 | 672 | 631 | 714 |
| Week K<br>(K is every 12 weeks after previous visit) | K*7 | (K-6)*7+1 | (K+6)*7 |

HIV laboratory tests include both (b) (4) central laboratory tests (HIV antibody screening tests, HIV Antibody Supplemental tests, qualitative and quantitative tests) and local laboratory tests (rapid HIV-1 Ag/Ab test or other local laboratory tests collected from eCRFs).
CASI follow-up questionnaire collected at post-baseline visits only, no baseline analysis window will be applied.
Source: Table 3-1 in the SAP

From now on, DVY and TVD are used instead of F/TAF and F/TDF in order to be consistent with the CSR.

### 3.2.2 Patient Disposition, Demographic and Baseline Characteristics

#### 3.2.2.1 Disposition

The statistical reviewer reproduced the Applicant's disposition results in safety population for the study.

Screening for the trial began in September 2016 and full enrollment was completed in June 2017. Of 5857 subjects from 94 study sites in North America and the European Union (EU) screened, 364 failed screening, of which 49 were HIV positive at screening. As a result, a total of 5399 subjects were randomized, and only 5387 subjects received study drug (2694 in DVY arm and 2693 in TVD arm). These 5387 subjects consist of safety analysis set**.**

Of note, in the ADSL dataset submitted for the trial, there were 5895 records, with 5890 subjects with SCRNFL='Y' instead of 5857 subjects as stated in the clinical study report (CSR), 5400 subjects with RANDFL='Y' instead of 5399 subjects as stated in the CSR (2700 subjects randomized in the TVD arm instead of 2699 as stated in the CSR). According to the Applicant, the discrepancies were due to the limited number of individuals who did not meet enrollment criteria and were re-screened by the investigator. For the screened population, all screening records were captured in the ADSL dataset. Therefore, if a subject was screened twice, two

separate records were created in the ADSL dataset. In contrast, the CSR only presented the "unique" number of screened subjects based on date of birth, race, ethnicity, sex, country, and initials among subjects with screening visits.

The difference between 5890 subjects with SCRNFL='Y' in the ADSL dataset and 5857 subjects in the CSR is 33. Thirty-one subjects were screen failures at the first screening visit, but met enrollment criteria and were randomized at the second screening visit. One subject (b) (6) (b) (6) was screened and failed twice. The remaining one subject was screened and randomized twice by mistake, which led to the one subject difference in the randomized population TVD arm (2700 subjects in the ADSL dataset vs. 2699 subjects in the CSR):

- Subject ID (b) (6) – randomized in error
- Subject ID – confirmed by the clinical site to be the correct Subject ID continuing in the study

**Comments:** The number of subjects in the safety and FAS analysis sets match with the CSR.

Among 5387 subjects in the safety analysis set (DVY 2694, TVD 2693), 83.6% (4505 subjects; DVY 83.2%, 2242 subjects; TVD 84.0%, 2263 subjects) were continuing study drug, and 85.8% (4623 subjects) were continuing in the study off study drug at the time of the primary analysis data cut date (Table 4 below). Overall, 16.4% (882 subjects) of the randomized and treated subjects prematurely discontinued study drug prior to the primary analysis data cut date. The proportions of subjects continuing study drug were evenly distributed across the 2 treatment arms. Only 0.4% (22 subjects) prematurely discontinued study drug due to HIV-1 infection.

**Table 4:** Subjects Disposition for study GS-US-412-2055 (Safety)

| | DVY | TVD | Total |
|---|---|---|---|
| Total | 2694 | 2693 | 5387 |
| Continuing study Drug | | | |
| Y | 2242( 83.2%) | 2263( 84.0%) | 4505( 83.6%) |
| N | 452( 16.8%) | 430( 16.0%) | 882( 16.4%) |
| Reasons of prematurely stopped Study Drug | | | |
| Death | 1( 0.2%) | 2( 0.5%) | 3( 0.3%) |
| HIV-1 Infection | 4( 0.9%) | 9( 2.1%) | 13( 1.5%) |
| Adverse Event | 36( 8.0%) | 49( 11.4%) | 85( 9.6%) |
| Lost to Follow-Up | 201( 44.5%) | 170( 39.5%) | 371( 42.1%) |
| Investigator's Discretion | 5( 1.1%) | 10( 2.3%) | 15( 1.7%) |
| Non-Compliance with Study Drug | 8( 1.8%) | 12( 2.8%) | 20( 2.3%) |
| Protocol Violation | 4( 0.9%) | 3( 0.7%) | 7( 0.8%) |
| Subject Decision | 193( 42.7%) | 175( 40.7%) | 368( 41.7%) |
| Reasons of prematurely stopped Study Drug of HIV-1 infected subjects | | | |
| n | 7 | 15 | 22 |
| HIV-1 Infection | 4( 57.1%) | 9( 60.0%) | 13( 59.1%) |
| Adverse Event | 1( 14.3%) | 2( 13.3%) | 3( 13.6%) |

| | | | |
|---|---|---|---|
| Non-Compliance with Study Drug | ( %) | 2( 13.3%) | 2( 9.1%) |
| Subject Decision | 2( 28.6%) | 2( 13.3%) | 4( 18.2%) |

Among 5387 subjects in the safety analysis set, 52 subjects (DVY 24, TVD 28) did not have any post-baseline HIV laboratory assessment and were excluded from the full analysis set (FAS). As a result, FAS consists of 5335 subjects (DVY 2670, TVD 2665) for the primary efficacy analyses.

#### 3.2.2.2 Demographic and Baseline Characteristics

Demographics and baseline characteristics were generally similar between the 2 treatment arms (**Table 13** in Appendix). The median age of subjects was 34 years (range, 18-76); 84% were White, 9% Black/Mixed Black, 4% Asian, and 24% Hispanic/Latino. Only 1% (74 subjects) were TGW and 99% of subjects were MSM. The highest educational level attained by 57% of the population was 4 years of college or higher. Seventy-one percent of subjects (71%) were employed full-time. Sixty percent of subjects (60%) were in the U.S.

At baseline, 905 subjects (17%) reported receiving TRUVADA for PrEP. Sixty-one percent of subjects (61%) reported that they did not use a condom frequently to manage the risk of getting HIV, and 74% of subjects did not ask their partner to use a condom for anal sex to manage the risk of getting HIV. Fifty-six percent of subjects (56.0%) were circumcised. Fifty-nine percent of subjects (59%) reported via the CASI questionnaire having 3 or more unprotected receptive anal sex intercourse (URAI) partners in the 90 days prior to screening. Forty-four percent of subjects (44%) reported having 3 or more unprotected insertive anal intercourse (UIAI) partners in the 90 days prior to screening.

### 3.2.3 Statistical Methodologies

Ulm (1990) method used to calculate the exact 95% CI for individual rate (a single Poisson parameter). For rate ratio, the Applicant used a generalized model associated with a Poisson distribution and logarithmic link with the treatment group being the main effect to construct its 95.003% CI. The reviewer used PROC Poisson in StatXact PROC to verify the CIs.

### 3.2.4 Results and Conclusions

#### 3.2.4.1 Summary of Applicant's Results

In the FAS, there were a total 22 subjects infected during the study, 7 in DVY arm and 15 in TVD arm. The rate ratio for the HIV incidence rate (DVY vs TVD) was 0.468 (95.003% CI: 0.191, 1.149) (**Table 5**). DVY was demonstrated to be noninferior to TVD, as the upper bound of the 2-sided 95.003% CI of the rate ratio (1.149) was less than 1.62.

**Comments:** Of note, the Applicant did present rate difference analysis results as the secondary analysis in the table. This analysis was deemed by this reviewer to not be appropriate for this case.

**Table 5:** Applicant's HIV-1 Infection Rates Results for Study GS-US-412-2055 (FAS)

**Table 18. GS-US-420-2055: HIV Incidence Rates While at Risk of HIV Infection (Rate Ratio and Rate Difference Methods) (Full Analysis Set)**

| | DVY (N = 2670) | TVD (N = 2665) | DVY vs. TVD (95.003% CI) |
|---|---|---|---|
| Person-years of Follow-Up | 4369.7 | 4386.2 | — |
| Number of HIV Infection Events | 7 | 15 | — |
| HIV Infection Rate per 100 Person-years | 0.160 | 0.342 | — |
| 95% Exact CI | 0.064, 0.330 | 0.191, 0.564 | — |
| Rate Ratio (Primary Analysis)[a] | 0.468 | | 0.191, 1.149 |
| Rate Difference[b] | −0.182 | | −0.424, 0.045 |

a Noninferiority margin 1.62
b Noninferiority margin 1.2 per 100 PY
HIV infection based on serologic evidence (excluding HIV vaccinated participants), virologic evidence, and/or evidence of acute infection.
Person-years is the summation of all participants' total number of years (year=365.25 days) of follow-up in study between the first dose date and either 1) date of HIV diagnosis for participants with HIV or 2) date of last post-baseline HIV laboratory test (incl. 30-day follow-up visit and either local or (b) (4) labs) for participants not infected with HIV.
95.003% CI of HIV infection rate ratio from a generalized model with a Poisson distribution and logarithmic link with treatment as main effect.
Hybrid 95.003% exact CI for HIV infection rate difference of F/TAF - F/TDF based on the single Poisson rate parameter approach (Li 2011, Ulm 1990).
95% exact CI was based on the single Poisson rate parameter method (Ulm 1990).

Source: study GS-US-412-2055 CSR, Table 18.

**The Applicant did a sensitivity analysis** as 5 out of 22 infected subjects did not have post-baseline HIV-1 laboratory assessment before infection were detected. These 5 subjects (1 in DVY and 4 in TVD) were called suspected baseline infection. If these 5 subjects were excluded from the primary efficacy analysis:

- DVY: 6 subjects; 0.138 infections per 100 PY of follow-up (95% exact CI: 0.050, 0. 299)
- TVD: 11 subjects; 0.252 infections per 100 PY of follow-up (95% exact CI: 0.126, 0.450)

DVY was demonstrated to be noninferior to TVD, as the upper bound of the 2-sided 95.003% CI of the rate ratio (0.547 [95.003% CI: 0.202, **1.479**]) was less than 1.62.

**The forest plot of selected subgroup analysis** of HIV incidence rate ratio is shown in Figure 2 below. Only subgroups of age < 25 years and Ex-US had incidence rate ratios larger than 1 in terms of the point estimate, however, the 95% CIs still covered 1. Analyses comparing HIV infection rates between the DVY and TVD groups within prespecified subgroups showed that DVY and TVD were similar for use as PrEP in all prespecified subgroups, as the 2-sided 95% exact CIs for the HIV-1 infection rates overlapped between the 2 treatment arms.

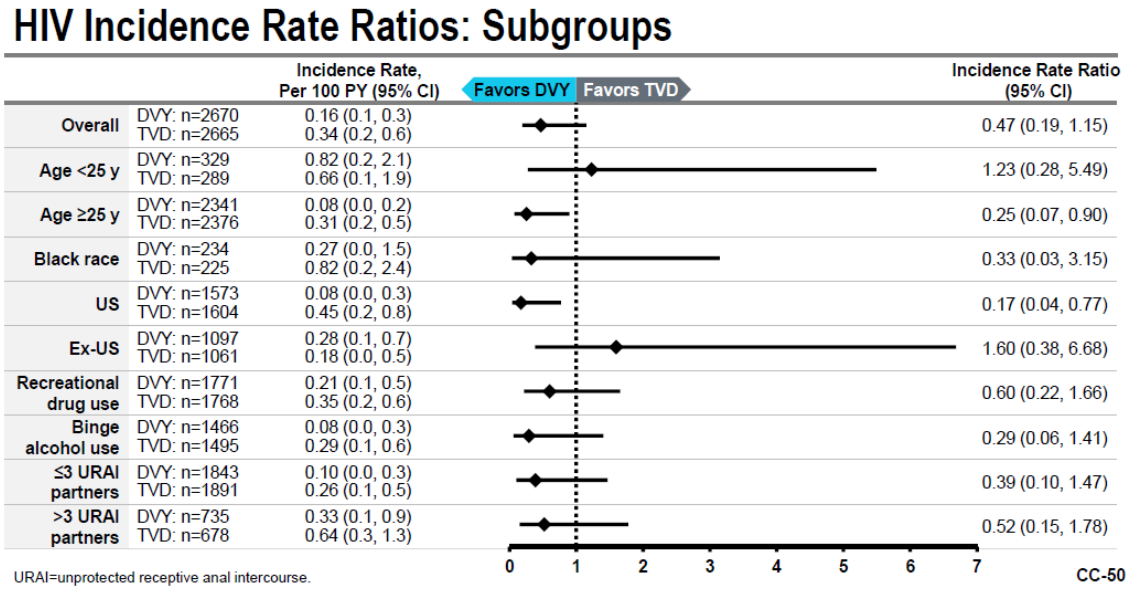


**Figure 2**: Forest Plot of Subgroup Analyses of HIV Incidence Rate Ratio of GS-US-412-2055 (Source: AC slides from the Applicant)

The Applicant summarized epidemiology data and showed that use of DVY or TVD for PrEP was more effective for preventing HIV-1 infection than not using PrEP, as the upper limits of the 95% exact CIs for the HIV-1 incidence rates in subjects using DVY or TVD for PrEP in this study were below the lower limit of the 95% CI for the HIV-1 infection rate in MSM not using PrEP across 25 US MSAs overlapping with Study GS-US-412-2055 sites, which was 4.02 per 100 PY with 95% CI of [3.56, 3.66].

**Comments:** Of note, the reviewer cannot verify these epidemiology data results.

### 3.2.4.2 Study Primary Efficacy Results

- **Primary Efficacy Analysis Results**

The reviewer replicated the Applicant's primary efficacy endpoint results (Table 6). DVY was demonstrated to be noninferior to TVD, as the upper bound of the 2-sided 95.003% CI of the rate ratio (1.149) was less than 1.62.

**Table 6:** Primary Efficacy Analysis HIV-1 Infection Rates for Study GS-US-412-2055 (FAS)

| | | **DVY (N=2670)** | **TVD (N=2665)** | **Ratio of DVY / TVD (95.003% CI)** |
|---|---|---|---|---|
| Person-years of Follow-Up | | 4369.7 | 4386.2 | |
| Number of HIV-1 Infected Events | | 7 | 15 | |
| HIV-1 Infection Rate per 100 PYs | | **0.160** | **0.342** | |
| Sponsor used | 95% Exact CI[a] | (0.064, 0.330) | (0.191, 0.564) | |
| | Rate Ratio | **0.468** | | (0.191, **1.149**)[b] |
| 95% exact CI of a Poisson Rate[c] | | (0.06, 0.33) | (0.19, 0.56) | |

a: Ulm (1990) method used to calculate the exact 95% CI for individual rate (a single Poisson parameter).
b: 95.003% CI was constructed using a generalized model associated with a Poisson distribution and logarithmic link with the treatment group being the main effect.
c: Using PROC Poisson in StatXact PROC.

There were 5 out of 22 infected subjects who did not have a post-baseline HIV-1 laboratory assessment before infection was detected. These 5 subjects (1 in DVY and 4 in TVD) were labeled as suspected baseline infection. Four subjects were infected within approximately 4 weeks of treatment and one subject was on treatment for about 12 weeks (**Table 7**).

The rate ratio changed from 0.468 to 0.547 and its 95.003% CI was [0.202, **1.481**] (**Table 8**), which is the same as the Applicant's results in the CSR, but the overall conclusion remained the same.

**Table 7:** Study Drug Duration of 5 Subjects Who were Suspected to Have Baseline Infection for Study GS-US-412-2055 (FAS)

| Usubjid* | Treatment Received | Follow-up in years | Number of Days Infection Detected |
|---|---|---|---|
| (b) (6) | TVD | 0.0794 | 29 |
| | TVD | 0.2327 | 85 |
| | TVD | 0.0794 | 29 |
| | DVY | 0.0794 | 29 |
| | TVD | 0.0986 | 36 |

*: unique subject ID.

**Table 8:** Sensitivity Analysis HIV-1 Infection Rates Excluding 5 Subjects Who were Suspected to Have Baseline Infection for Study GS-US-412-2055 (FAS)

| | | **DVY (N=2669)** | **TVD (N=2661)** | **Ratio of DVY / TVD (95.003% CI)** |
|---|---|---|---|---|
| Person-years of Follow-Up | | 4369.6 | 4385.7 | |
| Number of HIV-1 Infected Events | | 6 | 11 | |
| HIV-1 Infection Rate per 100 PY | | **0.137** | **0.251** | |
| Sponsor used | 95% Exact CI[a] | (0.050, 0.299) | (0.125, 0.449) | |
| | Rate Ratio | **0.547** | | (0.202, **1.481**)[b] |
| 95% exact CI of a Poisson Rate[c] | | (0.05, 0.30) | (0.13, 0.45) | |

a: Ulm (1990) method used to calculate the exact 95% CI for individual rate (a single Poisson parameter).
b: 95.003% CI was constructed using a generalized model associated with a Poisson distribution and logarithmic link with the treatment group being the main effect.
c: Using PROC Poisson in StatXact PROC.

- **Other Sensitivity Efficacy Analysis Results**

First, there were 52 subjects who were in the safety analysis set and excluded from the FAS because they did not have any post-baseline HIV-1 laboratory assessment. The treatment duration for these 52 subjects are listed in **Table 9**. If subjects with at least 14 days of treatment were not excluded from the FAS, a total of 15 subjects (9 in DVY and 6 in TVD) will be added back to FAS for efficacy analysis. If assuming all these 15 subjects were infected as the worst scenario, the analysis results are listed in **Table 10** below. The rate ratio changed from 0.468 to 0.765 and its 95.003% CI was [0.399, **1.466**]. The conclusion remained unchanged.

**Table 9**: Study Drug Duration of 52 Subjects Who were Excluded from FAS

| Arm | Treatment Duration (in days) | | | | | Total |
|---|---|---|---|---|---|---|
| | 1 | 2 – 6 | 7 - 13 | 14 – 20 | 21- 35 | |
| DVY | 10 | 3 | 2 | 3 | 6 | 24 |
| TVD | 16 | 2 | 4 | 4 | 2 | 28 |
| total | 26 | 5 | 6 | 7 | 8 | 52 |

**Table 10:** Sensitivity Analysis HIV-1 Infection Rates including 15 Subjects Who were Excluded from FAS for Study GS-US-412-2055

| | | **DVY (N=2669)** | **TVD (N=2661)** | **Ratio of DVY / TVD (95.003% CI)** |
|---|---|---|---|---|
| Person-years of Follow-Up | | 4370.4 | 4386.7 | |
| Number of HIV-1 Infected Events | | 16 | 21 | |
| HIV-1 Infection Rate per 100 Person-years | | **0.366** | **0.479** | |
| Sponsor used | 95% Exact CI[a] | (0.209, 0.595) | (0.296, 0.732) | |
| | Rate Ratio | **0.765** | | (0.399, **1.466**)[b] |
| 95% exact CI of a Poisson Rate[c] | | (0.21, 0.59) | (0.30, 0.73) | |

a: Ulm (1990) method used to calculate the exact 95% CI for individual rate (a single Poisson parameter).
b: 95.003% CI was constructed using a generalized model associated with a Poisson distribution and logarithmic link with the treatment group being the main effect.
c: Using PROC Poisson in StatXact PROC.

Second, the reviewer explored the number of infected subjects in the DVY arm that would be needed to fail to demonstrate NI if the number of infection events in the TVD arm remained consistent at 15. As shown in **Table 11** below, when there were 12 infected subjects in the DVY arm, the rate ratio changed from 0.468 to 0.803 and its 95.003% CI was [0.376, **1.716**]. DVY would fail to demonstrate that DVY was noninferior to TVD, as the upper bound of the 2-sided 95.003% CI of the rate ratio (1.716) was greater than 1.62.

**Table 11:** Sensitivity Analysis HIV-1 Infection Rates with Different Number of Subjects Infected in DVY Arm for Study GS-US-412-2055 (FAS)

| Case | DVY | | | TVD | | | **Ratio of DVY / TVD (95.003% CI)** |
|---|---|---|---|---|---|---|---|
| | PY | Infected | Infection rate (95% CI) | PY | Infected | Infection rate (95% CI) | |
| 1 | 4369.7 | 7 | 0.160 (0.064, 0.330) | 4386.2 | 15 | 0.342 (0.191, 0.564) | 0.468 (0.191, 1.149) |
| 2 | | 8 | 0.183 (0.079, 0.361) | | | | 0.535 (0.227, **1.263**) |
| 3 | | 9 | 0.206 (0.094, 0.391) | | | | 0.602 (0.264, 1.376) |
| 4 | | 10 | 0.229 (0.110, 0.421) | | | | 0.669 (0.301, 1.490) |
| 5 | | **11** | 0.252 (0.126, 0.450) | | | | 0.736 (0.338, **1.603**) |
| 6 | | **12** | 0.275 (0.142, 0.480) | | | | 0.803 (0.376, **1.716**) |
| 7 | | 13 | 0.300 (0.158, 0.509) | | | | 0.870 (0.414, **1.828**) |

- **Adherence Rate by Pill Count**

There are two assumptions used in the calculation of adherence rate by pill count:

- If return is missing, assume return=0;
- Last dispense w/o returned data, assume all pills taken as scheduled;

The adherence rate=(pill count dispensed – pill count returned)/total pill count supposed to take.

The median of overall adherence rate was 97.9% (**Table 12**). The median of adherence rate among infected subjects (94.5%) was slightly lower than that among uninfected subjects (97.9%). This difference was mainly due to the difference in adherence rates between infected vs. uninfected subjects within TVD arm.

**Table 12:** Study Drug Adherence Rate by Pill Count (Safety)

| | Infected | Uninfected | Total |
|---|---|---|---|
| N | 22 | 5313 | 5335 |
| Adherence Rate (Pill Count) -- Overall | | | |
| Mean (SE) | 85.77 (4.244) | 93.62 (0.179) | 93.59 (0.179) |
| **Median** | **94.51** | **97.90** | 97.89 |
| Range | (32.05, 100.0) | ( 0.17, 100.0) | ( 0.17, 100.0) |
| STD | 19.90 | 13.02 | 13.06 |
| Adherence Rate Category (Pill Count) -- Overall | | | |
| < 30% | ( %) | 78( 1.5%) | 78( 1.5%) |
| >=30 to <60% | 3( 13.6%) | 71( 1.3%) | 74( 1.4%) |
| >=60 to <80% | 3( 13.6%) | 220( 4.1%) | 223( 4.2%) |
| >=80 to <90% | 2( 9.1%) | 493( 9.3%) | 495( 9.3%) |
| >=90 to <95% | 4( 18.2%) | 822( 15.5%) | 826( 15.5%) |
| >= 95% | 10( 45.5%) | 3629( 68.3%) | 3639( 68.2%) |
| | Infected | Uninfected | Total |
| **DVY only (N)** | **7** | **2663** | **2670** |
| Adherence Rate (Pill Count) -- DVY only | | | |
| Mean (SE) | 87.96 (9.385) | 93.39 (0.259) | 93.38 (0.260) |
| Median | **97.56** | **97.89** | 97.88 |
| Range | (32.05, 100.0) | ( 0.67, 100.0) | ( 0.67, 100.0) |
| STD | 24.83 | 13.37 | 13.41 |
| Adherence Rate Category (Pill Count) -- DVY only | | | |
| < 30% | ( %) | 42( 1.6%) | 42( 1.6%) |
| >=30 to <60% | 1( 14.3%) | 39( 1.5%) | 40( 1.5%) |
| >=60 to <80% | ( %) | 116( 4.4%) | 116( 4.3%) |
| >=80 to <90% | ( %) | 262( 9.8%) | 262( 9.8%) |
| >=90 to <95% | 2( 28.6%) | 399( 15.0%) | 401( 15.0%) |
| >= 95% | 4( 57.1%) | 1805( 67.8%) | 1809( 67.8%) |
| **TVD only (N)** | **15** | **2650** | **2665** |
| Adherence Rate (Pill Count) -- TVD only | | | |

| | | | |
|---|---|---|---|
| Mean (SE) | 84.74 (4.666) | 93.85 (0.246) | 93.80 (0.246) |
| Median | **93.70** | **97.92** | 97.91 |
| Range | (43.82, 100.0) | ( 0.17, 100.0) | ( 0.17, 100.0) |
| STD | 18.07 | 12.65 | 12.70 |
| Adherence Rate Category (Pill Count) -- TVD only | | | |
| < 30% | ( %) | 36( 1.4%) | 36( 1.4%) |
| >=30 to <60% | 2( 13.3%) | 32( 1.2%) | 34( 1.3%) |
| >=60 to <80% | 3( 20.0%) | 104( 3.9%) | 107( 4.0%) |
| >=80 to <90% | 2( 13.3%) | 231( 8.7%) | 233( 8.7%) |
| >=90 to <95% | 2( 13.3%) | 423( 16.0%) | 425( 15.9%) |
| >= 95% | 6( 40.0%) | 1824( 68.8%) | 1830( 68.7%) |

**Comments:** The reviewer did not conduct independent analysis of TFV-DP level in red blood cells.

According to the CSR, most subjects in both groups had TFV-DP levels in red blood cells consistent with high adherence (≥ 4 days of dosing per week) in the DBS substudy. Other objective adherence measure, such as TFV and FTC levels in plasma and TFV-DP and FTC-TP levels measured in PBMCs at Week 4, confirmed the high adherence results from the DBS substudy. The estimated high adherence rates likely explain the low numbers of HIV seroconversions observed in this trial.

### 3.3 Evaluation of Safety

See the clinical review for the evaluation of safety.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Note that subgroup analyses need to be interpreted with caution because they were post-hoc (with the exception of gender, race, age and geographic region), with no multiple comparison adjustments small sample sizes within subgroups, and small number of subjects who were infected.

### 4.1 Gender, Race, Age, and Geographic Region

The subgroup analysis for these covariates were conducted, and none had significant impact on the infection rate as the 2-sided 95% CI for the HIV-1 infection rates in DVY and TVD arms overlapped (**Table 14** in appendix).

### 4.2 Other Special/Subgroup Populations

The subgroup analysis for other baseline covariates were conducted, and none had significant impact on the infection rate as the 2-sided 95% CI for the HIV-1 infection rates in DVY and TVD arms overlapped (**Table 14** in appendix).

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

Among 5335 subjects in the FAS, 22 subjects (0.4%) were infected with HIV-1 during the trial, and of which, 7 were in the DVY arm and 15 were in the TVD arm. The HIV-1 infection rates were 0.160 per 100 PY and 0.342 per 100 PY in DVY arm and TVD arm respectively. The upper bound of 95.003% CI of ratio of DVY vs. TVD was 1.149, which is lower than pre-specified NI margin of 1.62. Therefore, the trial demonstrated that DVY was non-inferior to TVD in reducing the risk of acquiring HIV-1 infection in the MSM/TGW population.

Sensitivity analyses, by excluding the 5 suspected baseline infected subjects and including 15 additional subjects (9 in DVY and 6 in TVD) who were excluded from FAS due to lack of post-baseline HIV laboratory assessment, also demonstrated that DVY was non-inferior to TVD in reducing the risk of acquiring HIV-1 infection in the MSM/TGW population.

The Applicant summarized the 2016 CDC infection data in non-study PrEP-eligible MSM at risk of HIV-1 in 25 US metropolitan statistical areas (MSAs), which are overlapping with GS-US-412-2055 sites, as supportive. The infection rate was 4.02 per 100 PY with 95% CI of [**3.56**, 3.66]. The upper limits of the 95% exact CIs for the HIV-1 incidence rates in subjects using DVY or TVD for PrEP in this study were below the lower limit of the 95% CI for the HIV-1 infection rate in MSM not using PrEP across 25 US MSAs overlapping with Study GS-US-412-2055 sites.

Overall, the reviewer concluded that the trial demonstrated non-inferiority of DVY to TVD in reducing the risk of acquiring HIV-1 infection in the MSM/TGW population. There was no other statistical issue identified.

### 5.2 Conclusions and Recommendations

The trial demonstrated that DVY was non-inferior to TVD in reducing the risk of acquiring HIV-1 infection in the MSM/TGW population.

The Applicant proposed to extrapolate the treatment effect to cis-gender women for a possible broad indication. However, there are no data to support the indication to cis-gender women based on the data reviewed. Please see the clinical review for more details regarding the discussion on the indication to all adults including cis-gender women and adolescents.

## 5.3 Labeling Recommendations

The final efficacy table for study GS-US-412-2055 in the label is as follows:

**HIV-1 Infection Results in DISCOVER Trial – Full Analysis Set**

| | DESCOVY (N=2,670) | TRUVADA (N=2,665) | Rate Ratio (95% CI) |
|---|---|---|---|
| | 4,370 person-years | 4,386 person-years | |
| HIV-1 infections n (%) | 7 | 15 | |
| Rate of HIV-1 infections per 100 person-years | 0.16 | 0.34 | 0.468 (0.19, 1.15) |

CI = Confidence interval.

There will be limitations of use associated with the indication. Please see the clinical review for details.

## APPENDICES

**Table 13:** Demographics and Baseline Characteristics for Study GS-US-412-2055 (Safety)

| | DVY | TVD | Total |
|---|---|---|---|
| Treated (Safety) | | | |
| N | 2694 | 2693 | 5387 |
| Men Who Have Sex with | | | |
| MSM | 2649( 98.3%) | 2664( 98.9%) | 5313( 98.6%) |
| TGW | 45( 1.7%) | 29( 1.1%) | 74( 1.4%) |
| Race | | | |
| AMERICAN INDIAN OR ALASKA NATIVE | 12( 0.4%) | 14( 0.5%) | 26( 0.5%) |
| ASIAN | 113( 4.2%) | 120( 4.5%) | 233( 4.3%) |
| BLACK OR AFRICAN | 222( 8.2%) | 216( 8.0%) | 438( 8.1%) |
| NATIVE HAWAIIAN OR PACIFIC ISLANDER | 17( 0.6%) | 23( 0.9%) | 40( 0.7%) |
| WHITE | 2264( 84.0%) | 2247( 83.4%) | 4511( 83.7%) |
| OTHER | 63( 2.3%) | 68( 2.5%) | 131( 2.4%) |
| NOT PERMITTED | 3( 0.1%) | 5( 0.2%) | 8( 0.1%) |
| Race Category 1 | | | |
| Black | 240( 8.9%) | 234( 8.7%) | 474( 8.8%) |
| Non-Black | 2451( 91.1%) | 2454( 91.3%) | 4905( 91.2%) |
| Ethnicity | | | |
| HISPANIC OR LATINO | 635( 23.6%) | 683( 25.4%) | 1318( 24.5%) |
| NOT HISPANIC OR LATINO | 2058( 76.4%) | 2008( 74.6%) | 4066( 75.5%) |
| NOT PERMITTED | 1( 0.0%) | 2( 0.1%) | 3( 0.1%) |
| Age (Year) | | | |
| Mean (SE) | 35.97 (0.204) | 36.42 (0.207) | 36.19 (0.145) |
| Median | 34.00 | 34.00 | 34.00 |
| Range | (18.00, 76.00) | (18.00, 72.00) | (18.00, 76.00) |
| STD | 10.56 | 10.73 | 10.65 |
| Age Category 1 (25yrs) | | | |
| < 25 | 336( 12.5%) | 293( 10.9%) | 629( 11.7%) |
| >= 25 | 2358( 87.5%) | 2400( 89.1%) | 4758( 88.3%) |
| Age Category 2 (25, 50, 65yrs) | | | |
| < 25 | 336( 12.5%) | 293( 10.9%) | 629( 11.7%) |
| >=25 to <50 | 2028( 75.3%) | 2014( 74.8%) | 4042( 75.0%) |
| >=50 to <65 | 297( 11.0%) | 350( 13.0%) | 647( 12.0%) |
| >=65 | 33( 1.2%) | 36( 1.3%) | 69( 1.3%) |
| Baseline Weight (kg) | | | |
| Mean (SE) | 83.48 (0.338) | 82.75 (0.323) | 83.12 (0.234) |
| Median | 80.70 | 80.00 | 80.30 |
| Range | (45.80, 188.3) | (45.20, 179.7) | (45.20, 188.3) |
| STD | 17.56 | 16.77 | 17.17 |

| | | | |
|---|---|---|---|
| Baseline Height (cm) | | | |
| Mean (SE) | 178.0 (0.144) | 177.7 (0.144) | 177.8 (0.102) |
| Median | 178.0 | 177.8 | 177.8 |
| Range | (139.7, 203.2) | (142.2, 203.2) | (139.7, 203.2) |
| STD | 7.498 | 7.498 | 7.499 |
| Baseline BMI (kg/m^2) | | | |
| Mean (SE) | 26.31 (0.097) | 26.20 (0.096) | 26.26 (0.068) |
| Median | 25.28 | 25.31 | 25.31 |
| Range | (15.95, 53.09) | (16.58, 61.83) | (15.95, 61.83) |
| STD | 5.013 | 4.982 | 4.997 |
| Baseline BMI Category 1 (kg/m^2) | | | |
| <=25 | 1260( 46.8%) | 1260( 46.8%) | 2520( 46.8%) |
| 25<=, <30 | 952( 35.3%) | 987( 36.7%) | 1939( 36.0%) |
| >=30 | 481( 17.9%) | 446( 16.6%) | 927( 17.2%) |
| missing | 1( 0.0%) | ( %) | 1( 0.0%) |
| Baseline HBV Infection Status | | | |
| N | 2686(100.0%) | 2683(100.0%) | 5369(100.0%) |
| Baseline HCV Infection Status | | | |
| N | 1916(100.0%) | 1892(100.0%) | 3808(100.0%) |
| Any prior Truvada for PrEP | | | |
| N | 2066( 76.7%) | 2074( 77.0%) | 4140( 76.9%) |
| Y | 628( 23.3%) | 619( 23.0%) | 1247( 23.1%) |
| Took Truvada for PrEP at Baseline | | | |
| N | 2229( 82.7%) | 2253( 83.7%) | 4482( 83.2%) |
| Y | 465( 17.3%) | 440( 16.3%) | 905( 16.8%) |
| Sexuality | | | |
| Bisexual | 171( 6.4%) | 214( 8.0%) | 385( 7.2%) |
| Gay/Homosexual | 2461( 91.8%) | 2434( 90.9%) | 4895( 91.4%) |
| Straight/Heterosexual | 25( 0.9%) | 16( 0.6%) | 41( 0.8%) |
| Other | 23( 0.9%) | 13( 0.5%) | 36( 0.7%) |
| Highest Education Level | | | |
| Less than high school | 52( 1.9%) | 41( 1.5%) | 93( 1.7%) |
| High school/GED | 285( 10.6%) | 257( 9.6%) | 542( 10.1%) |
| Some college | 479( 17.9%) | 487( 18.2%) | 966( 18.0%) |
| 2-year college/AA | 291( 10.9%) | 325( 12.1%) | 616( 11.5%) |
| 4-year college | 892( 33.3%) | 880( 32.9%) | 1772( 33.1%) |
| Master's degree | 445( 16.6%) | 430( 16.1%) | 875( 16.3%) |
| Doctoral degree | 82( 3.1%) | 96( 3.6%) | 178( 3.3%) |
| Professional degree | 124( 4.6%) | 129( 4.8%) | 253( 4.7%) |
| Other | 30( 1.1%) | 32( 1.2%) | 62( 1.2%) |
| Work Situation | | | |
| Full-time employment | 1884( 70.3%) | 1903( 71.1%) | 3787( 70.7%) |
| Part-time employment | 297( 11.1%) | 280( 10.5%) | 577( 10.8%) |
| Part/full time student/education/training | 193( 7.2%) | 198( 7.4%) | 391( 7.3%) |

| | | | |
|---|---|---|---|
| Retired | 51( 1.9%) | 48( 1.8%) | 99( 1.8%) |
| Unemployed | 207( 7.7%) | 210( 7.8%) | 417( 7.8%) |
| Other | 48( 1.8%) | 38( 1.4%) | 86( 1.6%) |
| Baseline Hip BMD (g/cm2) | | | |
| Mean (SE) | 1.03 (0.011) | 1.02 (0.010) | 1.02 (0.007) |
| Median | 1.01 | 1.01 | 1.01 |
| Range | ( 0.65, 1.66) | ( 0.70, 1.40) | ( 0.65, 1.66) |
| STD | 0.154 | 0.132 | 0.144 |
| Baseline Spine BMD (g/cm2) | | | |
| Mean (SE_ | 1.13 (0.012) | 1.13 (0.010) | 1.13 (0.008) |
| Median | 1.13 | 1.13 | 1.13 |
| Range | ( 0.76, 1.70) | ( 0.78, 1.50) | ( 0.76, 1.70) |
| STD | 0.161 | 0.138 | 0.150 |
| Baseline eGFR (mL/min) | | | |
| Mean (SE) | 127.9 (0.661) | 126.4 (0.661) | 127.2 (0.467) |
| Median | 122.9 | 121.2 | 121.8 |
| Range | (60.10, 345.3) | (61.50, 391.4) | (60.10, 391.4) |
| STD | 34.30 | 34.30 | 34.30 |
| Baseline Serum Creatinine (mg/dL) | | | |
| Mean (SE) | 0.96 (0.003) | 0.96 (0.003) | 0.96 (0.002) |
| Median | 0.94 | 0.94 | 0.94 |
| Range | ( 0.58, 1.71) | ( 0.52, 1.95) | ( 0.52, 1.95) |
| STD | 0.146 | 0.148 | 0.147 |
| Medical History - Rectal Gonorrhea | | | |
| N | 2420( 89.8%) | 2431( 90.3%) | 4851( 90.1%) |
| Y | 274( 10.2%) | 262( 9.7%) | 536( 9.9%) |
| Baseline Rectal Gonorrhea | | | |
| Positive | 123( 4.6%) | 113( 4.2%) | 236( 4.4%) |
| Indeterminate | 9( 0.3%) | 4( 0.1%) | 13( 0.2%) |
| Negative | 2536( 95.1%) | 2552( 95.6%) | 5088( 95.3%) |
| Baseline Urine Gonorrhea | | | |
| Detected | 17( 0.6%) | 12( 0.5%) | 29( 0.6%) |
| Not Detected | 2601( 99.4%) | 2600( 99.5%) | 5201( 99.4%) |
| Baseline Oral Gonorrhea | | | |
| Positive | 103( 4.5%) | 130( 5.7%) | 233( 5.1%) |
| Indeterminate | 5( 0.2%) | 1( 0.0%) | 6( 0.1%) |
| Negative | 2160( 95.2%) | 2140( 94.2%) | 4300( 94.7%) |
| Medical History - Rectal Chlamydia | | | |
| N | 2352( 87.3%) | 2360( 87.6%) | 4712( 87.5%) |
| Y | 342( 12.7%) | 333( 12.4%) | 675( 12.5%) |
| Baseline Rectal Chlamydia | | | |
| Positive | 199( 7.5%) | 189( 7.1%) | 388( 7.3%) |
| Indeterminate | 8( 0.3%) | 3( 0.1%) | 11( 0.2%) |
| Negative | 2462( 92.2%) | 2478( 92.8%) | 4940( 92.5%) |
| Baseline Urine Chlamydia | | | |

| | | | |
|---|---|---|---|
| Detected | 61( 2.3%) | 54( 2.1%) | 115( 2.2%) |
| Not Detected | 2557( 97.7%) | 2558( 97.9%) | 5115( 97.8%) |
| **Baseline Oral Chlamydia** | | | |
| Positive | 47( 2.1%) | 43( 1.9%) | 90( 2.0%) |
| Indeterminate | 1( 0.0%) | ( %) | 1( 0.0%) |
| Negative | 2215( 97.9%) | 2225( 98.1%) | 4440( 98.0%) |
| **Medical History - Syphilis** | | | |
| N | 2463( 91.5%) | 2430( 90.2%) | 4893( 90.8%) |
| Y | 230( 8.5%) | 263( 9.8%) | 493( 9.2%) |
| **Baseline Syphilis Diagnosis** | | | |
| N | 2687( 99.7%) | 2689( 99.9%) | 5376( 99.8%) |
| Y | 7( 0.3%) | 4( 0.1%) | 11( 0.2%) |
| **RAI Partners in 90 Days Prior to Screening** | | | |
| Mean (SE) | 6.13 (0.175) | 6.01 (0.186) | 6.07 (0.128) |
| Median | 3.00 | 3.00 | 3.00 |
| Range | ( 0.00, 99.00) | ( 0.00, 99.00) | ( 0.00, 99.00) |
| STD | 8.915 | 9.473 | 9.197 |
| **URAI Partners in 90 Days Prior to Screening** | | | |
| Mean (SE) | 3.59 (0.116) | 3.45 (0.121) | 3.52 (0.084) |
| Median | 2.00 | 2.00 | 2.00 |
| Range | ( 0.00, 70.00) | ( 0.00, 99.00) | ( 0.00, 99.00) |
| STD | 5.937 | 6.186 | 6.062 |
| **URAI Partners in 90 Days Prior to Screening - Group1** | | | |
| <=2 URAI | 1508( 58.0%) | 1577( 60.7%) | 3085( 59.3%) |
| > 2 URAI | 1094( 42.0%) | 1020( 39.3%) | 2114( 40.7%) |
| **IAI Partners in 90 Days Prior to Screening** | | | |
| Mean (SE) | 6.89 (0.191) | 6.85 (0.211) | 6.87 (0.142) |
| Median | 4.00 | 3.00 | 4.00 |
| Range | ( 0.00, 99.00) | ( 0.00, 99.00) | ( 0.00, 99.00) |
| STD | 9.757 | 10.73 | 10.25 |
| **UIAI Partners in 90 Days Prior to Screening** | | | |
| Mean (SE) | 4.24 (0.132) | 4.13 (0.143) | 4.18 (0.097) |
| Median | 2.00 | 2.00 | 2.00 |
| Range | ( 0.00, 70.00) | ( 0.00, 99.00) | ( 0.00, 99.00) |
| STD | 6.759 | 7.277 | 7.022 |
| **IRAI Partners in 90 Days Prior to Screening - Group1** | | | |
| <=2 IRAI | 1440( 55.3%) | 1476( 56.8%) | 2916( 56.1%) |
| > 2 IRAI | 1162( 44.7%) | 1121( 43.2%) | 2283( 43.9%) |
| **Use Condoms to Manage HIV risk at Screening** | | | |
| N | 1660( 61.9%) | 1628( 60.8%) | 3288( 61.4%) |
| Y | 1020( 38.1%) | 1049( 39.2%) | 2069( 38.6%) |
| **Ask Partners to Use Condoms to Manage HIV risk at Screening** | | | |
| N | 1991( 74.3%) | 1981( 74.0%) | 3972( 74.1%) |
| Y | 689( 25.7%) | 696( 26.0%) | 1385( 25.9%) |

| | | | |
|---|---|---|---|
| Recreational Drug Usage 3 months prior to screening | | | |
| N | 895( 33.4%) | 891( 33.3%) | 1786( 33.3%) |
| Y | 1785( 66.6%) | 1786( 66.7%) | 3571( 66.7%) |
| Circumcised (Y/N) | | | |
| Y | 1485( 55.4%) | 1513( 56.5%) | 2998( 56.0%) |
| N | 1185( 44.2%) | 1160( 43.3%) | 2345( 43.8%) |
| N/A (Post-Operative) | 10( 0.4%) | 4( 0.1%) | 14( 0.3%) |
| Alcohol Usage at Screening | | | |
| Never | 254( 9.6%) | 213( 7.9%) | 467( 8.8%) |
| Monthly or less | 439( 16.5%) | 470( 17.5%) | 909( 17.0%) |
| 2 to 4 times a month | 897( 33.8%) | 942( 35.1%) | 1839( 34.5%) |
| 2 to 3 times a week | 792( 29.8%) | 792( 29.6%) | 1584( 29.7%) |
| 4 or more times a week | 275( 10.4%) | 263( 9.8%) | 538( 10.1%) |
| Country | | | |
| AUT | 35( 1.3%) | 42( 1.6%) | 77( 1.4%) |
| CAN | 191( 7.1%) | 162( 6.0%) | 353( 6.6%) |
| DEU | 187( 6.9%) | 183( 6.8%) | 370( 6.9%) |
| DNK | 98( 3.6%) | 104( 3.9%) | 202( 3.7%) |
| ESP | 219( 8.1%) | 195( 7.2%) | 414( 7.7%) |
| FRA | 18( 0.7%) | 14( 0.5%) | 32( 0.6%) |
| GBR | 247( 9.2%) | 265( 9.8%) | 512( 9.5%) |
| IRL | 40( 1.5%) | 38( 1.4%) | 78( 1.4%) |
| ITA | 37( 1.4%) | 21( 0.8%) | 58( 1.1%) |
| NLD | 31( 1.2%) | 40( 1.5%) | 71( 1.3%) |
| USA | 1591( 59.1%) | 1629( 60.5%) | 3220( 59.8%) |
| Region 1 | | | |
| Canada | 191( 7.1%) | 162( 6.0%) | 353( 6.6%) |
| European Union | 912( 33.9%) | 902( 33.5%) | 1814( 33.7%) |
| US-Midwest | 103( 3.8%) | 97( 3.6%) | 200( 3.7%) |
| US-Northeast | 78( 2.9%) | 64( 2.4%) | 142( 2.6%) |
| US-South | 591( 21.9%) | 664( 24.7%) | 1255( 23.3%) |
| US-West | 819( 30.4%) | 804( 29.9%) | 1623( 30.1%) |
| Region 2 | | | |
| Ex-US | 1103( 40.9%) | 1064( 39.5%) | 2167( 40.2%) |
| **US** | **1591( 59.1%)** | **1629( 60.5%)** | **3220( 59.8%)** |
| Region 3 | | | |
| European Union | 912( 33.9%) | 902( 33.5%) | 1814( 33.7%) |
| US/Canada | 1782( 66.1%) | 1791( 66.5%) | 3573( 66.3%) |

**Table 14:** The Summary Subgroup Analyses of HIV-1 Infection Rate for Study GS-US-412-2055 (FAS)

| | DVY | | | TVD | | |
|---|---|---|---|---|---|---|
| Factors | N (PY) | Infected | Infection rate (95% CI) | N (PY) | Infected | Infection rate (95% CI) |
| Overall | 2670 (4369.7) | 7 | 0.160 (0.064, 0.330) | 2665 (4386.2) | 15 | 0.342 (0.191, 0.564) |
| Age (years) | | | | | | |
| <25 | 329 (489.8) | 4 | 0.817 (0.223, 2.091) | 289 (451.5) | 3 | 0.664 (0.137, 1.942) |
| ≥25 | 2341 (3879.9) | 3 | 0.077 (0.016, 0.226) | 2376 (3934.7) | 12 | 0.305 (0.158, 0.533) |
| Race | | | | | | |
| Any Black (Black/Mixed Black) | 234 (371.3) | 1 | 0.269 (0.007, 1.501) | 225 (364.8) | 3 | 0.822 (0.170, 2.404) |
| Nonblack | 2433 (3996.6) | 6 | 0.150 (0.055, 0.327) | 2435 (4012.7) | 12 | 0.299 (0.155, 0.522) |
| Region - 01 | | | | | | |
| US | 1573 (2598.4) | 2 | 0.077 (0.009, 0.278) | 1604 (2688.4) | 12 | 0.446 (0.231, 0.278) |
| Ex-US | 1097 (1771.4) | 5 | 0.282 (0.092, 0.659) | 1061 (1697.8) | 3 | 0.177 (0.036, 0.516) |
| Region - 02 | | | | | | |
| North America (US/Canada) | 1762 (2917.1) | 3 | 0.103 (0.021, 0.301) | 1766 (2953.6) | 14 | 0.474 (0.259, 0.795) |
| European Union | 908 (1452.6) | 4 | 0.275 (0.075, 0.705) | 899 (1432.6) | **1** | **0.070 (0.002, 0.389)** |
| Highest Level of Education at Screening (CASI) | | | | | | |
| <4 Year College | 1123 (1788.8) | 5 | 0.280 (0.091, 0.652) | 1121 (1803.5) | 9 | 0.490 (0.228, 0.947) |
| ≥4 Year College | 1533 (2557.0) | 2 | **0.078 (0.009, 0.283)** | 1528 (2560.0) | 6 | 0.234 (0.086, 0.510) |
| Baseline F/TDF used for PrEP | | | | | | |
| Yes | 459 (770.9) | 0 | 0 (*, 0.479) | 438 (727.7) | 1 | 0.137 (0.003, 0.766) |
| No | 2211 (3598.9) | 7 | 0.195 (0.078, 0.401) | 2227 (3658.4) | 14 | 0.383 (0.209, 0.642) |
| Recreational Drug Use in the Last 3 Months Prior to Screening (CASI) | | | | | | |
| Yes | 1771 (2875.3) | 6 | 0.209 (0.077, 0.454) | 1768 (2884.5) | 10 | 0.347 (0.166, 0.638) |
| No | 885 (1470.5) | 1 | **0.068 (0.002, 0.379)** | 881 (1479.1) | 5 | 0.338 (0.110, 0.789) |
| Have Six or More Drinks on One Occasion (AUDIT) | | | | | | |
| No | 1167 (1911.1) | 5 | 0.262 (0.085, 0.611) | 1157 (1191.8) | 8 | 0.419 (0.181, 0.825) |
| Yes | 1466 (2398.5)) | 2 | 0.083 (0.010, 0.301) | 1495 (2452.9) | 7 | 0.285 (0.115, 0.588) |
| Any History of Rectal Gonorrhea, Rectal Chlamydia, or Syphilis in the Past 24 Weeks | | | | | | |
| Yes | 709 (1151.9) | 3 | 0.260 (0.054, 0.761) | 706 (1150.7) | 11 | 0.956 (0.477, 0.761) |
| No | 1961 (3217.8) | 4 | 0.124 (0.034, 0.318) | 1959 (3235.5) | 4 | 0.124 (0.034, 0.317) |
| Any History of Rectal Gonorrhea in the Past 24 Weeks | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Yes | 272 (430.8) | 2 | **0.464 (0.056, 1.677)** | 261 (417.3) | 3 | 0.719 (0.148, 2.101) |
| No | 2398 (3939.0) | 5 | 0.127 (0.041, 0.296) | 2404 (3968.8) | 12 | 0.302 (0.156, 0.528) |
| Any History of Rectal Chlamydia in the Past 24 Weeks | | | | | | |
| Yes | 342 (562.1) | 3 | **0.534 (0.110, 1.560)** | 333 (536.1) | 6 | **1.119 (0.411, 2.436)** |
| No | 2328 (3807.6) | 4 | 0.105 (0.029, 0.269) | 2335 (3850.0) | 9 | 0.234 (0.107, 0.444) |
| Any History of Syphilis in the Past 24 Weeks | | | | | | |
| Yes | 227 (378.9) | 0 | **0 (*, 0.974)** | 261 (430.9) | 5 | **1.160 (0.377, 2.708)** |
| No | 2442 (3989.7) | 7 | 0.176 (0.071, 0.362) | 2404 (3955.2) | 10 | 0.253 (0.121, 0.465) |
| Use Condoms to Manage HIV Risk at Screening | | | | | | |
| Yes | 1012 (1658.0) | 3 | 0.181 (0.037, 0.529) | 1040 (1710.3) | 2 | 0.117 (0.014, 0.422) |
| No | 1644 (2687.8) | 4 | 0.149 (0.041, 0.381) | 1609 (2653.2) | 13 | 0.490 (0.261, 0.838) |
| Ask Partners Use Condoms to Manage HIV Risk at Screening | | | | | | |
| Yes | 684 (1120.7) | 1 | 0.089 (0.002, 0.497) | 690 (1156.5) | 4 | 0.346 (0.094, 0.886) |
| No | 1972 (3225.1) | 6 | 0.186 (0.068, 0.405) | 1959 (3207.1) | 11 | 0.343 (0.171, 0.614) |
| Ethnicity | | | | | | |
| Hispanic | 628 (1021.0) | 3 | 0.294 (0.061, 0.859) | 673 (1101.7) | 3 | 0.272 (0.056, 0.796) |
| Non-Hispanic | 2041 (3348.6) | 4 | 0.119 (0.033, 0.306) | 1990 (3280.9) | 12 | 0.366 (0.189, 0.639) |
| Circumcised at Screening (CASI) | | | | | | |
| Yes | 1470 (2429.5) | 2 | 0.082 (0.010, 0.297) | 1496 (2505.0) | 10 | 0.392 (0.191, 0.734) |
| No | 1176 (1900.8) | 5 | 0.263 (0.085, 0.614) | 1149 (1852.6) | 5 | 0.270 (0.088, 0.630) |
| RAI Partners in the Last 90 Days Prior to Screening (CASI) | | | | | | |
| ≤3 RAI Partners | 1347 (2208.4) | 2 | 0.091 (0.011, 0.327) | 1388 (2297.9) | 2 | 0.087 (0.011, 0.314) |
| >3 RAI Partners | 1231 (2011.3) | 5 | 0.249 (0.081, 0.580) | 1181 (1931.9) | 13 | 0.673 (0.358, 1.151) |
| URAI Partners in the Last 90 Days Prior to Screening (CASI) | | | | | | |
| ≤3 URAI Partners | 1843 (3018.0) | 3 | 0.099 (0.020, 0.290) | 1891 (3134.5) | 8 | 0.255 (0.110, 0.503) |
| >3 URAI Partners | 735 (1201.7) | 4 | 0.333 (0.091, 0.852) | 678 (1095.3) | 7 | 0.639 (0.257, 1.317) |
| IAI Partners in the Last 90 Days Prior to Screening (CASI) | | | | | | |
| ≤3 IAI Partners | 1279 (2085.9) | 4 | 0.192 (0.052, 0.491) | 1282 (2118.5) | 9 | 0.425 (0.194, 0.806) |
| >3 IAI Partners | 1299 (2133.9) | 3 | 0.141 (0.029, 0.411) | 1287 (2111.3) | 6 | 0.284 (0.104, 0.619) |
| UIAI Partners in the Last 90 Days Prior to Screening (CASI) | | | | | | |
| ≤3 UIAI Partners | 1747 (2848.3) | 4 | 0.140 (0.038, 0.360) | 1765 (2902.7) | 9 | 0.310 (0.142, 0.589) |
| >3 UIAI Partners | 831 | 3 | 0.219 | 804 | 6 | 0.452 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | (1371.4) | | (0.045, 0.639) | (1327.1) | | (0.166, 0.984) |
| Baseline Rectal Gonorrhea Local Lab | | | | | | |
| Positive | 121 (193.4) | 0 | 0 (*, 1.907) | 112 (181.9) | 2 | 1.099 (0.133, 0.971) |
| Negative | 2514 (4118.4) | 6 | 0.146 (0.053, 0.317) | 2525 (4154.7) | 13 | 0.313 (0.167, 0.535) |
| Baseline Urine Gonorrhea (b) (4) Lab | | | | | | |
| Detected | 17 (27.4) | 0 | 0 (*, 13.471) | 12 (12.7) | 1 | 6.38 (0.162, 35.58) |
| Not Detected | 2579 (4221.5) | 7 | 0.166 (0.067, 0.342) | 2572 (4240.9) | 14 | 0.330 (0.180, 0.342) |
| Baseline Oral Gonorrhea Local Lab | | | | | | |
| Positive | 101 (156.6) | 0 | 0 (*, 2.356) | 128 (209.4) | 3 | 1.432 (0.295, 4.186) |
| Negative | 2141 (3457.5) | 5 | 0.145 (0.047, 0.337) | 2116 (3433.3) | 8 | 0.233 (0.101, 0.459) |
| Baseline Rectal Chlamydia Local Lab | | | | | | |
| Positive | 197 (323.1) | 0 | 0 (*, 1.142) | 188 (309.6) | 4 | 1.292 (0.352, 3.309) |
| Negative | 2440 (3992.9) | 6 | 0.150 (0.055, 0.327) | 2451 (4031.2) | 11 | 0.273 (0.136, 0.488) |
| Baseline Urine Chlamydia (b) (4) Lab | | | | | | |
| Detected | 59 (91.4) | 2 | 2.189 (0.265, 7.907) | 54 (92.2) | 0 | 0 (*, 4.001) |
| Not Detected | 2537 (4157.5) | 5 | 0.120 (0.039, 0.281) | 2530 (4164.4) | 15 | 0.360 (0.202, 0.281) |
| Baseline Oral Chlamydia Local Lab | | | | | | |
| Positive | 47 (74.6) | 0 | | 42 (66.9) | 0 | |
| Negative | 2194 (3537.2) | 5 | 0.141 (0.046, 0.330) | 2200 (3571.2) | 11 | 0.308 (0.154, 0.551) |
| Baseline Syphilis Diagnosis | | | | | | |
| Yes | 7 (10.8) | 0 | | 4 (6.5) | 0 | |
| No | 2663 (4358.9) | 7 | 0.161 (0.065, 0.331) | 2661 (4379.7) | 15 | 0.343 (0.192, 0.565) |

**(some of them may not added up to 2670 and 2665 due to missing information or undetermined category)**

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