CLINICAL PHARMACOLOGY REVIEW

NDA (Supplement #)	208215 (S-12)
Type of Submission and Proposal	Efficacy supplement to expand indication to pre-exposure prophylaxis of HIV-1 infection (PrEP) in adults and adolescents with body weight at least 35 kg
Submission Date	04/05/2019
Drug	DESCOVY [emtricitabine (FTC, F)/tenofovir alafenamide (TAF)]
Applicant	Gilead
Dosage regimen	One tablet (a fixed dose combination of FTC 200 mg/TAF 25 mg) once daily without regard to food
Clinical Pharmacology Reviewer	Jenny Zheng, Ph.D
Clinical Pharmacology Team Leader	Su-Young Choi, Pharm.D, Ph.D

EXECUTIVE SUMMARY

Descovy (F/TAF) is a fixed-dose combination tablet containing emtricitabine (FTC, F) 200 mg and tenofovir alafenamide (TAF) 25 mg. Descovy is an oral once-daily medication that was approved for use in chronic HIV treatment in combination with other antiretroviral agents. In this supplement, the Applicant seeks approval of Descovy for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in at-risk adults and adolescents weighing at least 35 kg. Currently, Truvada, a fixed-dose combination of FTC 200 mg and tenofovir disoproxil fumarate (TDF) 300 mg, is the only medication approved for PrEP.

To support the proposed indication, the applicant submitted the efficacy and safety results from a Phase 3 clinical trial, Study GS-US-412-2055 (DISCOVER), entitled "*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 (MSM) and Transgender Women (TGW) Who Have Sex with Men and Are At Risk of HIV-1 Infection"* (NCT02842086). DISCOVER is a noninferiority trial evaluating the incidence of HIV-1 infection per 100 patient years (PY) in subjects who were administered Descovy as compared to that in subjects who were administered Truvada. The multidiscipline review team has determined that the efficacy and safety data from the DISCOVER trial demonstrated that Descovy is non-inferior to Truvada in efficacy and safety for PrEP in MSM and TGW.

No clinical trials were conducted for the PrEP indication in cisgender women or adolescents. The applicant proposed a pharmacokinetic (PK) extrapolation approach to bridge the efficacy data from the DISCOVER trial as well as efficacy data from Truvada to cisgender women or adolescents based on systemic and/or mucosal PK data. To this end, the Applicant provided data from an external PK study, entitled "*Exploratory Pharmacokinetic and Pharmacodynamic Study of Oral F/TAF for the Prevention of HIV Acquisition"* (b) (4) CONRAD Protocol A15-137) and summary of available PK data of Truvada and Descovy in men and women.

An Advisory Committee Meeting was held on August 7, 2019. Sixteen (16) of 18 committee members voted for the approval of a PrEP indication in MSM and TGW, although some members expressed reservations for the approval for TGW due to the limited number of TGW subjects that were included in

the DISCOVER trial. In addition, 10 of 18 committee members were against expanding the PrEP indication to cisgender women due to the lack of efficacy data in this population. The majority of the committee members who voted "Yes" indicated that their reasoning was that another PrEP agent should be available to cisgender women. They also recommended conducting efficacy trials in cisgender women following approval. Based on the review of the submitted data and the advisory committee's recommendation, the clinical pharmacology review team has determined that the available data are inadequate to support the PrEP indication for Descovy in cisgender women.

The clinical pharmacology review team has also concluded that extrapolation of efficacy and safety results from the DISCOVER trial in MSM/TGW adults to male adolescents is acceptable.

RECOMMENDATIONS

The Office of Clinical Pharmacology has reviewed the application and determined that the efficacy supplement is approvable for adults and adolescent MSM/TGW. However, OCP has concluded that the available PK data are not adequate to support expansion of the PrEP indication to cisgender women.

PHASE 4 TRIAL COMMITMENTS

There are no clinical pharmacology related Phase 4 trial commitments.

LABELING

We recommend the following general labeling recommendations to be included in the final USPI (Clinical Pharmacology relevant sections only). In addition, several changes have been recommended to the applicant to be consistent with current labeling practices and for PLLR conversion.

Section 1 Indication and Usage

- Add PrEP indication. In this section, the Agency
    - recommends adding the limitation to exclude the PrEP indication for receptive vaginal sex and indicate that the safety and efficacy have not been evaluated in individuals at risk of HIV-1 infection from receptive vaginal sex (e.g., cisgender women)
    - agrees with the applicant to add the indication for adolescents weighing at least 35 kg, similar to the Truvada label

Section 2 Dosage and Administration

- Add the dosage for PrEP, which is the same as the treatment indication for Descovy

Section 8 Specific Population - Pediatrics

- Add the information indicating the efficacy and safety for pediatric patients at least 35 kg is supported by the adult PrEP trial and previous safety and PK data from adults and pediatrics
- Add the recommendation and rationale for more frequent visits for at risk adolescents under pediatrics
- Add "Safety and effectiveness of DESCOVY for HIV-1 PrEP in pediatric patients less than 35 kg have not been established" under pediatrics

Section 12.3 Pharmacokinetics

- Add "HIV status has no effect on the pharmacokinetics of FTC or TAF in adults"
- Replace "no dosage adjustment is recommended" with "there are no clinically meaningful differences" for race or gender

QUESTION-BASED REVIEW

Background

The Applicant is seeking an HIV PrEP indication for Descovy for use in at-risk adults and adolescents weighing at least 35 kg. To support the indication, the Applicant conducted a Phase 3 clinical trial in MSM/TGW, Study GS-US-412-2055 (DISCOVER), entitled "*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"* (NCT02842086). The HIV infection rate per 100 person-years was 0.160 for Descovy and 0.342 for Truvada, and the multidiscipline review team has concluded that the trial demonstrated non-inferiority of Descovy to Truvada in MSM/TGW. However, the Applicant did not conduct an efficacy trial in cisgender women or adolescents. Therefore, the key clinical pharmacology review question is whether the available clinical pharmacology information can support the expansion of the indication to cisgender women and adolescents.

Substantial clinical pharmacology related information used to support the applicant's claim, effectiveness in cisgender women, is from the clinical pharmacology information of Truvada, the only approved product for HIV PrEP. TRUVADA is a fixed-dose combination tablet containing emtricitabine (FTC) 200 mg and tenofovir disoproxil fumarate (TDF) 300 mg. Both TAF (in Descovy) and TDF (in Truvada) are prodrugs and form the active metabolite TFV-DP intracellularly. While the intracellular active metabolite TFV-DP is the same for both drugs, TAF and TDF exhibit distinct PK properties; the administration of TAF 25 mg results in 4- to 7-fold higher intracellular levels of TFV-DP in peripheral blood mononuclear cells (PBMCs) and approximately 90% lower plasma concentrations of TFV compared with TDF 300 mg. Both Truvada and Descovy contain 200 mg of FTC and plasma concentrations of FTC are comparable following administration of each drug. This review will focus on comparison of TAF and TDF component of Descovy and Truvada, respectively, and its implication for extrapolating efficacy of Descovy for HIV PrEP to cisgender women. It should be noted that the exact contribution of FTC to PrEP efficacy, and whether this contribution differs depending on the route of HIV exposure (e.g., rectal vs. vaginal), is largely unknown.

Review Question 1. Can HIV PrEP indication be expanded to cisgender women?

The Applicant proposed two approaches to extrapolate efficacy to support a PrEP indication for F/TAF in cisgender women as follows.

1. To extrapolate efficacy from MSM/TGW receiving F/TAF in the DISCOVER trial by demonstrating comparable plasma TAF concentrations and PBMC TFV-DP concentrations between MSM/TGW and cisgender women.

In this approach, the applicant argues that the efficacy in MSM/TGW observed in the DISCOVER trial can be extrapolated to cisgender women as plasma TAF and TFV-DP in PBMC are comparable between MSM/TGW and cisgender women. However, the unique aspect of sexually acquired HIV infection and pharmacological prevention is that the route of infection is different between cisgender women (mostly receptive vaginal intercourse) and MSM/TGW (mostly receptive or insertive anal intercourse). Currently, the relevant site of drug action to prevent HIV-1 infection, or the relative contribution of tissue versus PBMC drug concentrations to PrEP efficacy, have not been established. However, previous clinical studies using Truvada have indicated that 1) mucosal (rectal vs. vaginal) concentrations of TFV-DP can be significantly different despite similar systemic concentrations and 2) the importance of mucosal tissue concentrations cannot be ignored at this time as topical microbicides demonstrated some level of efficacy despite significantly low TFV-DP concentrations in PBMC. Therefore, although there is no clinically relevant difference in the PK of TAF in plasma and TFV-DP in PBMC between men and women, the clinical pharmacology review team concluded that this approach alone is not acceptable to support the indication in cisgender women due to the potential importance of mucosal tissue concentrations for HIV PrEP efficacy.

2. To extrapolate efficacy from Truvada to Descovy

Truvada is currently approved in adults and adolescents of both sexes, including cisgender women. The efficacy of Truvada in cisgender women was supported by the Partners PrEP trial (NCT00557245) in heterosexual HIV discordant couples. In this approach, efficacy would be extrapolated by demonstrating comparable or higher TFV-DP concentrations in PBMCs and cervicovaginal mucosal tissues following the administration of Descovy as compared with Truvada. Since it has already been demonstrated that TFV-DP concentrations in PBMCs are 4-7-fold higher following the administration of Descovy compared with Truvada, the extrapolation would need to demonstrate comparable or higher exposures of TFV-DP in cervicovaginal tissues following the administration of Descovy compared to Truvada. This is under the assumption that drug concentrations in tissue homogenates are reflective of those in target cells such as local CD4+ cells. To this end, the Applicant provided data from an external PK study, entitled "*Exploratory Pharmacokinetic and Pharmacodynamic Study of Oral F/TAF for the Prevention of HIV Acquisition"* (cross-referenced to (b) (4) CONRAD Protocol A15-137). In this study, the pharmacokinetics of TAF, TFV, FTC and their intracellular metabolites (TFV-DP and FTC-TP) in PBMCs and PrEP-relevant mucosal tissues and fluids were determined following administration of single and multiple doses (once daily for 14 days) of Descovy or Truvada in HIV-negative, healthy adult female volunteers.

Following single-dose administration of F/TAF or F/TDF, 83% of TFV-DP concentrations in vaginal tissue samples were below the limit of quantitation (BLQ) at 4 hours post-dose. Therefore, it is not feasible to compare TFV-DP concentrations in vaginal tissue samples following single dose administration.

TFV-DP concentrations were higher in vaginal tissues at 4 hours post-dose following 14 days of F/TAF administration as compared with F/TDF; following the administration of F/TAF, median TFV-DP concentrations in vaginal tissues were 3-fold above the lower limit of quantitation (LLOQ) at 4 hours after the last dose. In contrast, 62% (5/8) of vaginal tissue samples were BLQ at this same time point following 14-day administration of F/TDF (Table). It is not feasible therefore to determine the magnitude of difference in vaginal tissue TFV-DP concentrations between the treatment groups due to the limited number of quantifiable samples in the F/TDF arm. In both treatment groups, TFV-DP concentrations were mostly (70-80%) BLQ at 24 hours and 48 hours post-dose following 14 days of administration of F/TAF or F/TDF. Results for cervical tissue samples were largely consistent with those for vaginal tissues.

Table 1: Mucosal Tissue TFV-DP Concentrations Following 14-Day Administration of F/TAF 200/25 mg or F/TDF 200/300 mg (CONRAD Protocol A15-137)

		Vaginal tissue		Cervical tissue		Rectal tissue	
		F/TAF	F/TDF	F/TAF	F/TDF	F/TAF	F/TDF
4 hours	% BLQ*	0% (0/8)	62% (5/8)	25% (2/8)	88% (7/8)	31% (9/29)	3% (1/30)
	Median TFV-DP† (pmol/g)	151	N/A	126	N/A	150	2521
24 hours	% BLQ*	80% (12/15)	69% (11/16)	10/15 (67%)	81% (13/16)	Not Collected	
	Median TFV-DP† (pmol/g)	N/A	N/A	N/A	N/A		
48 hours	% BLQ*	80% (12/15)	79% (11/14)	93% (14/15)	100% (14/14)		
	Median TFV-DP† (pmol/g)	N/A	N/A	N/A	N/A		

* Percentage of samples below the lower limit of quantitation (BLQ) = number of samples BLQ/ total number of samples
† Median values of all subjects including those with a value of BLQ
N/A = cannot be determined as the median concentration value was below the lower limit of quantitation.
Source: FDA analysis of data from Clinical Study Report Table 15 and Appendix 16.2.5 (individual subject concentration data) from CONRAD A15-137 trial

While TFV-DP concentrations were higher in vaginal tissues at 4 hours post-dose following 14 days of F/TAF administration as compared with F/TDF, it is unclear whether this translates to comparable or higher TFV-DP concentrations beyond 4 hours following 14 days of administration, due to potential (but undetermined) differences in tissue PK between F/TAF and F/TDF. For instance, F/TDF may have a delayed Cmax compared to F/TAF and achieve higher TFV-DP concentrations in mucosal tissues between 4 hours and 24 hours post-dose.

Although the Applicant initially submitted CONRAD A15-137 trial results to support the indication in cisgender women, the applicant did not use the results of CONRAD A15-137 trial to support their claim during the AC meeting. Instead, the Applicant primarily relied on the published clinical EC_{90} value, 40 fmol/million cells of TFV-DP (Anderson et al. 2012) and claimed that Descovy should be effective in cisgender women as EC_{90} value can be quickly achieved (within 2-3 hours) following the administration of Descovy in cisgender women. However, this EC_{90} value was obtained from a previous PrEP trial evaluating Truvada in MSM/TGW. Therefore, it is not clear if this EC_{90} value is relevant for all tenofovir-based PrEP efficacy in all populations given the potential role of mucosal tissues for PrEP. Specifically, 40 fmol/million cells in MSM receiving Truvada is associated with significantly higher rectal tissue concentrations of TFV-DP (> 100 fmol/mg) while 40 mol/million cells in cisgender women receiving DESCOVY is associated with very low (mostly undetectable) levels of TFV-DP in vaginal tissue homogenates.

In summary, the submitted data do not support the expansion of the indication to cisgender women.

Review Question 2: Can HIV PrEP indication be expanded to MSM and TGW adolescents?

The efficacy and safety of Descovy for PrEP have not been evaluated in pediatric subjects, including adolescents. The multidiscipline review team has agreed that extrapolation of efficacy data from the adult PrEP trials to support the indication of PrEP in adolescents is scientifically valid. The biologic

mechanism through which HIV is transmitted and the effects of a drug on that process are expected to be similar between MSM/TGW adults and adolescents. However, no TAF PK data are available following the administration of Descovy in HIV uninfected adolescents. Therefore, the Applicant proposed a two-step approach: 1) demonstrating comparable plasma TAF exposures between HIV infected adults and HIV infected adolescents weighing at least 35 kg following the administration of TAF-containing regimens (e.g., Genvoya) and 2) demonstrating that there is no clinically relevant impact of HIV infection on the PK of TAF.

Based on available TAF PK data in HIV infected adolescents, HIV infected adults, and HIV uninfected adults, the clinical pharmacology review team has concluded that plasma TAF exposures are expected to be comparable between HIV uninfected adults and HIV uninfected adolescents weighing at least 35 kg. Refer to Appendix 4 for the detailed comparison. The use of FTC in adolescents weighing at least 35 kg is supported by the same approach, and it was previously reviewed for the approval of Truvada in adolescent patients. Therefore, the extension of the PrEP indication to adolescents weighing at least 35 kg is acceptable from a clinical pharmacology perspective.

APPENDIX:

Appendix 1: Plasma and Mucosal Tissue Concentrations of TAF and TFV-DP following the administration of F/TAF and F/TDF

Study Title: Exploratory Pharmacokinetic and Pharmacodynamic Study of Oral F/TAF for the Prevention of HIV Acquisition (CONRAD A15-137, (b) (4) SDN006, 04/02/2019)

Primary Objectives:

- PK: Characterize the PK of oral F/TAF and F/TDF in plasma, PBMCs, cervicovaginal (CV) and rectal fluid, and CV and rectal tissue of healthy premenopausal women
- PD (not discussed in this review due to its exploratory nature):
  - Characterize the anti-HIV activity of F/TAF and F/TDF in CV and rectal fluid
  - Characterize HIV infectivity in CV and rectal tissue at baseline and after treatment with F/TAF and F/TDF

Study Design: This was an external Phase I, open label, parallel PK/pharmacodynamic (PD) study to examine the CV, rectal, PBMC and plasma PK and PD of single and multiple doses of F/TAF and F/TDF conducted by Conrad. There were two phases of this study; the Single Dose Phase followed by the Multiple Dose Phase.

- Single dose
  - F/TAF (200/25 mg) (n = 12)
  - F/TDF (200/300 mg) (n = 12)
- Multiple dose (once daily for 14 days)
  - F/TAF (200/10 mg) (n =24)
  - F/TAF (200/25 mg) (n = 24)
  - F/TDF (200/300 mg) (n = 24)

Although no prior or concomitant medications were restricted, it is not expected that concomitant medications affected the systemic PK of F/TAF or F/TDF. Concomitant medications were reported for 62.5% and 68.0% of participants in the Single and Multiple Dose Phases, respectively, and were similar between treatment groups (58.3% to 66.7% in Single Dose Phase treatment groups; 65.4% to 72.0% in the Multiple Dose Phase treatment groups). In the Multiple Dose Phase, the most frequently reported classes of concomitant medications were anilides (44.0%), vitamins (13.3%), progestogens and estrogens, fixed combinations (10.7%), and selective serotonin reuptake inhibitors (SSRIs) and progestogens and estrogens, sequential preparations (6.7% each).

Samples were collected from plasma, PBMC, rectal and cervicovaginal fluid, and tissue biopsies as shown in the following table:

Table 1: Pharmacokinetic Sampling time

Specimen type (analyte)	**Single Dose Phase**[1] FTC: 200 mg TAF: 25 mg	**Multiple Dose Phase** FTC: 200 mg TAF: 10 or 25 mg		
	Visits 3S – 6S	Visit 2Mb	Visits 3M – 5M	Visits 5M – 8M
	Single dose	First dose (day 1)	Pre-dose troughs	Final dose (Day 14) decay
Plasma[2] (TAF, TFV, FTC)	0.5, 1, 2, 4, 8, 24, 48, and 72h after dose	0.5, 1, 2, 4, and 8h after first MD dose	Days 2, 7 and 14	0.5, 1, 2, 4, 8, 24, 48, and 72h after dose (all participants)
PBMCs (TFV-DP, FTC-TP, dATP, dCTP)	1, 2, 4, 8, 24, 48, and 72h after dose	1, 2, 4, and 8h after first MD dose	Days 2, 7 and 14	1, 2, 4, 8, 24, 48, and 72h after dose (all participants)
CV Tissue[3] (TAF, TFV, FTC, TFV-DP, FTC-TP, dATP, dCTP)	4h after dose			4, 24, and 48h after dose (per site assignment)
CV Fluid (TAF, TFV, FTC)	4h after dose	1, 2, 4, and 8h after first MD dose	Days 2, 7 and 14	4, 8, 24, 48, and 72h after dose (all participants)[5]
Rectal Fluid (TAF, TFV, FTC)				
Rectal Tissue[4] (TAF, TFV, FTC, TFV-DP, FTC-TP, dATP, dCTP)				4h after dose

CV=cervicovaginal; dATP=deoxyadenosine triphosphate; dCTP=deoxycytidine triphosphate; (b) (4) (b) (4) FTC=emtricitabine; FTC-TP=emtricitabine-triphosphate; MD=multiple dose; (b) (4) PBMCs=peripheral blood mononuclear cells; PD=pharmacodynamic; PK=pharmacokinetics; TAF=tenofovir alafenamide; TFV=tenofovir; TFV-DP=tenofovir-diphosphate.

[1] The Single Dose Phase, and PD assessments in CV tissue in the Multiple Dose phase, were only performed at (b) (4).

[2] At Visits 2S (b) (4), 2Ma (b) (4), and 2Mb (b) (4), a baseline plasma sample for possible PK assessment was collected.

[3] (b) (4) collected CV tissue samples for PK at 4 hours, (b) (4) at 24 hours, and (b) (4) at 48 hours.

[4] Rectal tissue was only collected at (b) (4).

[5] CV fluid was not collected at the 8 hour time point at (b) (4).

Source: Clinical study report

Reviewer's comments

1. Since TFV-DP is the active metabolite and is the most relevant moiety for the purpose of efficacy extrapolation from Truvada to Descovy in cisgender women, the review focuses on the results of TFV-DP concentrations in tissue and PBMC.

2. Tissue samples were collected at different clinical sites at different time points (e.g., all 4 hour post dose samples were collected at (b) (4) while all 24 hour post dose samples were collected at (b) (4)). Each subject contributed cervicovaginal tissue samples at only one given timepoint. Therefore, tissue PK parameters (e.g., AUC or Cmax) for an individual subject or correlations between samples collected at different time points cannot be determined

Bioanalysis and OSIS Inspection

Tissue concentrations were analyzed using LC-MS/MS methods using extracts from tissue homogenates. Assuming a tissue density of 1 g/mL, final sample concentrations and the lower limit of quantitation (LLOQ of 0.3 ng/mL) were converted to fmol/g for TFV-DP. PBMC concentrations were analyzed using LC-MS/MS methods. Final TFV-DP concentrations and lower limit of quantitation (LLOQ of 0.200 ng/mL) results were converted to fmol/million cells in PBMC.

Clinical sites and analytical site inspections were conducted by The Office of Study Integrity and Surveillance (OSIS). OSIS inspections concluded that no objectionable conditions were observed, and no Form FDA 483 was issued. However, OSIS has concluded that the data from tissue, peripheral blood mononuclear cells (PBMC), cervicovaginal fluid (CVF), and rectal fluid (RF)samples are acceptable as supportive data, but not pivotal data supporting a regulatory decision, because of the following findings

1) Determination of the recovery of TFV, TFV-dp, FTC, and FTC-tp from tissue was not feasible during the homogenization;
2) Long term and short-term storage stability for TFV, TFV-dp, FTC, and FTC-tp in tissue were not available;
3) For the analysis of TFV-dp, FTC-tp, dATP, and dCTP in PBMC samples, the site did not report the acceptance criteria of accuracy correctly for standards and QCs;
4) For the analysis of TFV-dp and FTC-tp in PBMC samples, performance of analytical runs was not monitored using QCs prepared in the same matrix as subject samples;
5) The site could not obtain blank matrix of cervicovaginal fluid and rectal fluid, thus has no data demonstrating parallelism between the cervicovaginal fluid/rectal fluid and saliva, which was used as a surrogate matrix;
6) Cervicovaginal fluid and rectal fluid samples were collected using MeroCels sponge; however, the recovery of TAF, TFV, and FTC from MeroCel sponge during the extraction process is unknown;
7) Stability data for TAF, TFV, and FTC in CVF or RF are not available.

Please see OSIS reviews conducted by Dr. Zhang (7/23/2019), Dr. Cai and Dr. Gupta (7/23/2019), for details.

PK Results

Mucosal Tissue TFV-DP Concentrations:

Following single dose administration of Descovy or Truvada, 83% of vaginal tissue samples were below the lower limit of quantitation (BLQ) at 4 hours. Following 14-day administration of Descovy, median TFV-DP concentrations in vaginal tissues were 3-fold above the lower limit of quantitation (LLOQ) at 4 hours after the last dose. In contrast, 62% (5/8) of vaginal tissue samples were BLQ at this same time point following 14-day administration of Truvada. In both treatment groups, TFV-DP concentrations were mostly (70-80%) BLQ at 24 hours and 48 hours post-dose following 14 days of administration. Results for cervical tissue samples were largely consistent with those for vaginal tissues.

It is unclear if the results at 4 hours translates to comparable or higher TFV-DP concentrations beyond 4 hours following 14-day administration of Descovy. In rectal tissue, more than 10-fold of TFV-DP concentrations were observed following F/TDF administration as compared to F/TAF.

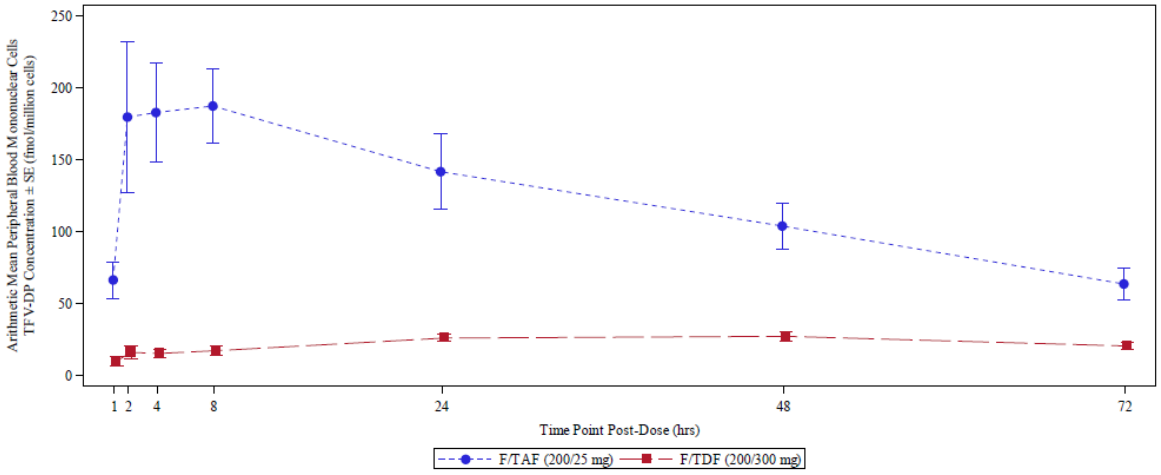
Table 2: Mucosal Tissue TFV-DP Concentrations Following 14 days of administration of F/TAF 200/25 mg and F/TDF 200/300 mg

		Vaginal tissue		Cervical tissue		Rectal tissue	
		F/TAF	F/TDF	F/TAF	F/TDF	F/TAF	F/TDF
4 hours	% BLQ*	0% (0/8)	62% (5/8)	25% (2/8)	88% (7/8)	31% (9/29)	3% (1/30)
	Median TFV-DP† (fmol/mg)	151	N/A	126	N/A	150	2,521
24 hours	% BLQ*	80% (12/15)	69% (11/16)	67% (10/15)	81% (13/16)	Not Collected	
	Median TFV-DP† (fmol/mg)	N/A	N/A	N/A	N/A		
48 hours	% BLQ*	80% (12/15)	79% (11/14)	93% (14/15)	100% (14/14)		
	Median TFV-DP† (fmol/mg)	N/A	N/A	N/A	N/A		

PBMC TFV-DP Concentrations:

Median TFV-DP concentrations were 6- to 8-fold higher in PBMC following single or multiple doses of F/TAF 200/25 mg compared to F/TDF 200/300 mg. There were about a 5-fold accumulation of TFV-DP following 14-days of administration of both F/TAF and F/TDF. Tmax was highly variable, particularity for F/TDF, because of a flat concentration-time profile. Therefore, it is hard to determine if F/TAF and F/TDF reaches Cmax at the same time.

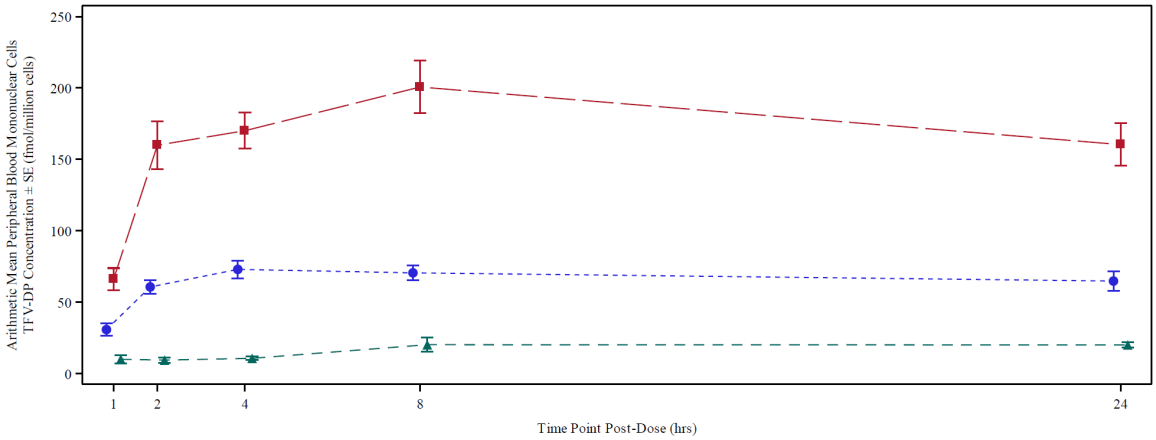
Figure 1: PBMC Mean TFV-DP Concentrations over Time – Single dose Phase



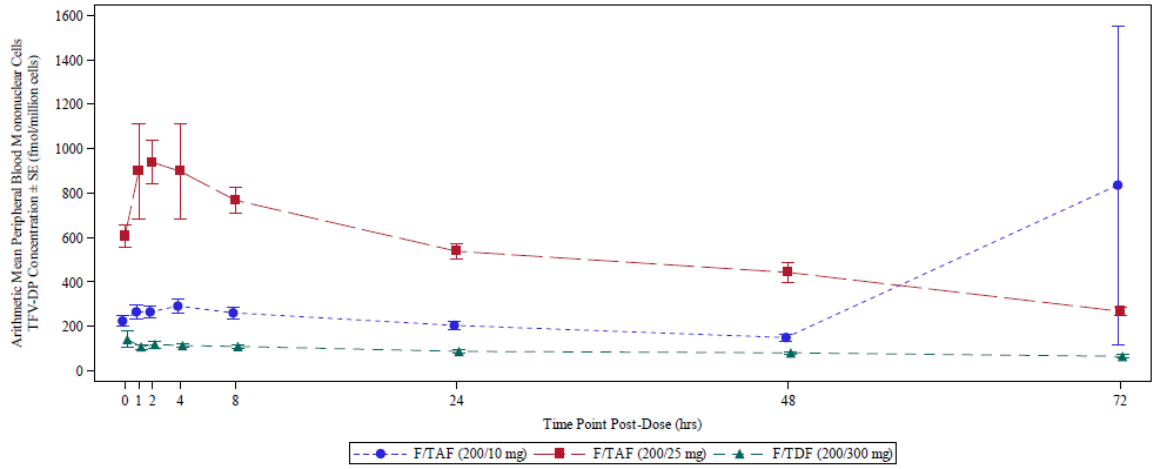
Note: Concentrations below LLOQ were imputed as 0.5 * LLOQ.
Source: Study Report

Figure 2: PBMC Mean TFV-DP Concentrations over Time – Multiple dose Phase

Day 1



Day 14



Note: Mean analyte concentrations with F/TAF (200/10 mg) at 72 hours following 14 days of administration were artificially elevated due to an outlier (low) PBMC cell count in one participant (b) (6)).
Note: Concentrations below LLOQ were imputed as 0.5 * LLOQ.
Source: Study Report

Table 3: PBMC Median TFV-DP PK Parameters

Median TFV-DP PK Parameters in PBMC	Multiple Dose Phase Median (Range)			Single Dose Phase Median (Range)	
	After 14 Daily Doses of F /TAF 200/25 mg (N=24)	After 14 Daily Doses of F/TDF 200/300 mg (N=25)	After 1 Dose of F/TAF 200/25 mg (N=24)	After Single Dose of F/TAF 200/25 mg (N= 12)	After Single Dose of F/TDF 200/300 mg (N= 12)
AUC_{0-24h} (h•fmol/million cells)	15,214.8 (8700.0, 42,688.6)	2497.5 (561.7, 3993.1)	3781.1 (2058.4, 8287.5)	3503.9 (1564.9, 10009.4)	429.9 (180.4, 842.0)
Cmax (fmol/million cells)	1020.9 (439.5, 5725.8)	139.2 (26.2, 999.9)	195.2 (116.8, 440.3)	184.1 (79.9, 740.7)	33.3 (12.5, 59.7)
Tmax (h)	4 (1, 72)	2 (1, 48)	8 (2, 24)	4 (2, 8)	24 (2, 72)
C_{24h} (fmol/million cells)	523.2 (272.9, 931.3)	86.7 (25.0, 141.5)	Not determined	Not determined	Not determined

TAF and TFV concentrations in plasma were consistent with those previously observed in healthy subjects. TAF was undetectable in vaginal and rectal fluid. TFV AUC_{0-24h} was about 9- to 10-fold higher for F/TDF than F/TAF in rectal fluid and cervicovaginal fluid. Plasma and tissue concentrations of FTC and FTC-TP following the administration of Descovy or Truvada are consistent with previously reported results and there were no differences between F/TDF and F/TAF.

Conclusion:

- The tissue concentration results from this study are not sufficient to support the PrEP indication because most of the cervicovaginal tissue samples were unquantifiable.

Appendix 2: PK Summary of DISCOVER trial

DISCOVER trial is a Phase 3, randomized, double-blind study to evaluate the safety and efficacy of F/TAF fixed-dose combination once daily for PrEP in men and transgender women who have sex with men and are at risk of HIV-1 infection. Eligible participants were randomized in a 1:1 ratio to 1 of the following 2 treatment groups:

Treatment Arm 1: Descovy (F/TAF 200/25 mg) FDC + placebo-to-match Truvada (n = 2500)
Treatment Arm 2: Truvada (F/TDF 200/300 mg) FDC + placebo-to-match Descovy (n = 2500)

FTC and TFV in plasma PK samples, and FTC-TP and TFV-DP in PBMC PK samples from F/TAF and F/TDF groups were analyzed and evaluated at Week 4 (trough concentrations) in a subset (planned: ~ 10%) of participants, as well as for all participants diagnosed with HIV infection.

Mean plasma trough concentrations (Ctau) of TFV were 84% lower for F/TAF as compared to F/TDF. Mean plasma FTC Ctau was similar between the 2 groups. In PBMCs, the mean TFV-DP Ctau was 6.3-fold higher in participants with F/TAF versus F/TDF, and mean FTC-TP Ctau was similar between the 2 groups. The results were consistent with the known PK of F/TAF and F/TDF.

Table 4: Summary and Statistical Comparisons of TFV, FTC, TFV-DP and FTC-TP PK Parameters

Mean (%CV) PK Parameter (b) (4)	F/TAF (Test)	F/TDF (Reference)	GLSM Ratio% (90% CI) (Test/ Reference)
TFV (plasma)	N = 164	N = 160	
Ctau (ng/mL)	9.4 (73.9)	62.6 (71.7)	15.74 (14.02,17.68)
FTC (plasma)	N = 160	N = 160	
Ctau (ng/mL)	150.5 (201.0)	141.8 (206.8)	100.06 (85.60,116.95)
TFV-DP (PBMC)	N = 158	N = 151	
Ctau (fmol/million cells)	728.9 (156.8)	157.5 (234.2)	630.60 (514.44,772.99)
FTC-TP (PBMC)	N = 152	N = 145	
Ctau (fmol/million cells)	11016.4 (102.5)	9258.7 (94.8)	109.18 (92.09,129.44)

Appendix 3: Pooled Data to Demonstrate No Clinically Significant Difference between Gender or HIV-1 infection status for TAF

The applicant provided pooled plasma exposures of TAF, and PBMC-associated TFV-DP from female and male volunteers in multiple-dose, Phase 1 studies following administration of Descovy, Genvoya, Biktarvy, or Vemlidy, as well as pooled plasma exposures of TAF, and PBMC-associated TFV-DP from women with HIV-1 in Phase 2 and Phase 3 studies following administration of Genvoya or Biktarvy, to support extrapolation of efficacy data from Study GS-US-412-2055 to cisgender women for PrEP indication.

Table 5: Summary and Statistical Comparison of TAF Plasma Pharmacokinetic Parameters between Women and Men Volunteers

	Mean (%CV) Min, Max		
TAF PK Parameter	**Women (N = 138)**	**Men (N = 161)**	**% GLSM Ratio (90% CI)**
AUC_{tau} (h•ng/mL)[a]	338.5 (34.9) 142.4, 835.6	255.9 (37.4) 101.9, 659.0	135.57 (126.54, 145.23)
C_{max} (ng/mL)	313.3 (65.9) 63.2, 1510.0	237.8 (59.4) 58.2, 814.0	123.81 (112.07, 136.77)

The estimates and 90% CI were from an ANCOVA model adjusted by Study ID.
Data were pooled from the following multiple-dose, Phase 1 PK studies: Studies GS-US-180-4149, GS-US-292-0101, GS-US-292-0103, GS-US-292-0108, GS-US-292-1316, GS-US-311-0101, GS-US-342-1167, GS-US-367-1657, GS-US-380-1761, GS-US-380-1999, and GS-US-380-4017
a N = 133 women; N = 160 men for AUC_{tau}
Source: Applicant's Extrapolation Report for Women

Table 6: Summary of PBMC-Associated TFV-DP Pharmacokinetic Parameters for Women and Men Volunteers

TFV-DP PK Parameter	Mean (%CV) Min, Max	
	Women (N = 42)	Men (N = 13)
AUC_{tau} (h•fmol/million cells)	16,416.8 (90.3) 3311.4, 56,803.7	10,040.8 (46.3) 4732.2, 19,406.1
C_{tau} (fmol/million cells)	353.2 (122.9) 6.7, 1889.7	377.9 (48.4) 187.4, 706.7

Data were pooled from the following multiple-dose, Phase 1 PK studies: Studies GS-US-180-4149 and GS-US-380-4017
Source: Applicant's Extrapolation Report for Women

Table 7: Summary and Statistical Comparison of TAF Plasma Pharmacokinetic Parameters between Female Volunteers and Women with HIV-1

TAF PK Parameter	Mean (%CV) Min, Max		% GLSM Ratio (90% CI)
	Female Volunteers (N = 138)	Women with HIV-1 (N = 169)	
AUC_{tau} (h•ng/mL)[a]	338.5 (34.9) 142.4, 835.6	226.5 (132.1) 51.7, 3337.4	176.33 (161.26,192.81)
C_{max} (ng/mL)	313.3 (65.9) 63.2, 1510.0	158.5 (50.7) 21.1, 569.9	190.94 (173.10,210.63)

The estimates and 90% CI were from an ANOVA model.
Data from female volunteers were pooled from the following multiple-dose, Phase 1 PK studies: GS-US-180-4149, GS-US-292-0101, GS-US-292-0103, GS-US-292-0108, GS-US-292-1316, GS-US-311-0101, GS-US-342-1167, GS-US-367-1657, GS-US-380-1761, GS-US-380-1999, and GS-US-380-4017
Data from women with HIV-1 were pooled from the following Phase 2 and Phase 3 studies: GS-US-292-0102, GS-US-292-0104, GS-US-292-0109, GS-US-292-0111, GS-US-380-1489, and GS-US-380-1490
a N = 133 female volunteers for AUC_{tau}
Source: Applicant's Extrapolation Report for Women

Reviewer's Assessment
While we agree that there is no clinically significantly difference in TAF plasma concentrations or TFV-DP concentrations in PBMC between males and females, we disagree that this information alone is enough to support the extrapolation of efficacy. Refer to the Question-Based Review.

Appendix 4: Pooled Data to Demonstrate No Clinically Significant Difference on TAF Exposures between Adolescents with HIV-1 and Adults with HIV-1 or between Adult Volunteers and Adults with HIV-1 for TAF

Descovy is currently approved in pediatric patients weighing at least 35 kg for HIV treatment based on PK, safety, and efficacy data from patients receiving F/TAF in combination with elvitegravir and cobicistat (Genvoya). In addition, there are PK, safety, and efficacy data from patients receiving F/TAF in combination with bictegravir (Biktarvy).

To support the extension of the PrEP indication to adolescents, the Applicant proposed an extrapolation approach, demonstrating comparable plasma TAF concentrations between HIV uninfected adults and

adolescents weighing at least 35 kg. Since there are no TAF PK data in HIV uninfected adolescents, the Applicant proposed a two-step approach; demonstrating comparable plasma TAF exposures between HIV infected adults and adolescents weighing at least 35 kg and demonstrating that there is no clinically relevant impact of HIV infection on the PK of TAF.

Following the administration of Genvoya, comparable AUC, but approximately 40 % lower Cmax, were observed in HIV infected adolescents as compared to HIV infected adults (Table 8). The difference in Cmax is likely driven by variability rather than a true difference between the two populations. Following the administration of Biktarvy, there was no difference in Cmax of TAF between adult patients and adolescent patients (Biktarvy USPI). In addition, popPK analyses for TAF of Genvoya and Biktarvy indicated that age and weight were not significant covariates.

Table 8: Summary and Statistical Comparison of TAF Plasma PK Parameters in Adolescents with HIV-1 Versus Adults with HIV-1 Treated with Genvoya

	Mean (%CV) Min, Max		
TAF PK Parameter	**Adolescents[a] (N = 46)**	**Adults[b] (N = 539)**	**% GLSM Ratio (90% CI)**
AUC_{tau} (h•ng/mL)	195.3 (48.2) (68.6, 464.9)	206.4 (71.8) (47.2, 1869)	97.09 (85.33, 110.46)
C_{max} (ng/mL)	92.3 (68.2) (14.0, 263.2)	162.2 (51.1) (19.7, 968.2)	50.42 (42.17, 60.29)

a PK parameters for adolescents were population PK parameters from Cohort 1 participants in Study GS-US-292-0106 (QP-2018-1027 TAF TFV HIV Pediatric Pop PK).
b PK parameters for adult population were population PK parameters from Studies GS-US-292-0104 and GS-US-292-0111 {GENVOYA® 2019}.
The estimates and 90% CI were from an ANOVA model.
Source: Applicant's Extrapolation Report for Adolescents

The Applicant compared Cmax and AUC of TAF between HIV uninfected adults (adult volunteers) and HIV adult patients (Table 9). While Cmax and AUC of TAF are approximately 60% higher in HIV uninfected adults and HIV infected adults this is not considered clinically relevant for safety.

Table 9: Summary and Statistical Comparisons of TAF Plasma PK Parameters in Adult Volunteers Versus Adults with HIV-1 Treated with Descovy, Genvoya, Biktarvy, and Vemlidy

	Mean (%CV) Min, Max		
TAF PK Parameter	**Adult Volunteers (N = 299)**	**Adults with HIV-1 (N = 1362)**	**% GLSM Ratio (90% CI)**
AUC_{tau} (h•ng/mL)	293.4 (38.9)[a] (101.9, 835.6)	185.8 (85.5) (24.5, 3337.4)	157.90 (150.40, 165.78)
C_{max} (ng/mL)	272.6 (65.3) (58.2, 1510.0)	146.7 (50.2) (19.5, 1281.9)	165.83 (157.85, 174.21)

a N = 293
The estimates and 90% CI were from an ANCOVA model.
Source: Applicant's Extrapolation Report for Adolescents
Adult volunteers: TAF PK parameters were pooled from Phase 1 studies of Descovy, Genvoya, Biktarvy, and Vemlidy
Adults with HIV-1: TAF PK parameters were determined using data from Phase 2 and Phase 3 studies of Genvoya and Biktarvy

Reviewer's Assessment

Overall, the proposed approach and the submitted data support extension of the indication to adolescent patients. The use of FTC in adolescents weighing at least 35 kg is supported by the same approach, and it was previously reviewed for the approval of Truvada in adolescent patients.

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/s/

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