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Descovy for PrEP® (FTC/TAF) Pharmacokinetic Data from DISCOVER

This document is in response to your request for information regarding Descovy for PrEP® (emtricitabine/tenofovir alafenamide [FTC/TAF] for HIV-1 pre-exposure prophylaxis) and pharmacokinetic (PK) data from the DISCOVER trial.

Some data may be outside of the US FDA-approved Prescribing Information. In providing this data, Gilead Sciences, Inc. is not making any representation as to its clinical relevance or to the use of any Gilead product(s). For information about the approved conditions of use of any Gilead drug product, please consult the FDA approved prescribing information.

The full indication, important safety information, and boxed warnings are available at: www.gilead.com/-/media/files/pdfs/medicines/hiv/descovy/descovy_pi.

Summary

Clinical Data

DISCOVER is a phase 3 study of daily FTC/TAF vs FTC/TDF for HIV-1 PrEP in adult MSM and TGW (N=5387).[1,2]

In PBMC cells, TFV-DP levels >EC_{90} were achieved faster and were expected to remain at >EC_{90} for a longer duration with FTC/TAF than with FTC/TDF.[3]

Please note, the clinical relevance of the PK data presented and the correlation with HIV protection are unknown.

Product Labeling[4]

Pharmacokinetics

The PK properties of the components of FTC/TAF are provided below (Table 1).

Table 1. PK Properties of the Components of FTC/TAF[4]

	FTC	TAF
Absorption		
T_{max}	3 hours	1 hours
Effect of high-fat meal (relative to fasting)[a]	AUC ratio: 0.91 (90% CI: 0.89–0.93) C_{max} ratio: 0.74 (90% CI: 0.69–0.78)	AUC ratio: 1.75 (90% CI: 1.64–1.88) C_{max} ratio: 0.85 (90% CI: 0.75–0.95)
Distribution		
% bound to human plasma proteins	<4	~80
Source of protein binding data	*In vitro*	*Ex vivo*
Blood-to-plasma ratio	0.6	1.0
Metabolism		
Metabolism	Not significantly metabolized	Cathepsin A[b] (PBMCs) CES1 (hepatocytes) CYP3A (minimal)
Elimination		
Major route of elimination	Glomerular filtration and active tubular secretion	Metabolism (>80% of oral dose)
$t_{½}$[c]	10 hours	0.51 hours
% of dose excreted in urine[d]	70	<1
% of dose excreted in feces[d]	13.7	31.7

Abbreviations: CES1=carboxylesterase 1; t½=median terminal plasma half-life
[a]Values refer to geometric mean ratio [high-fat meal / fasting] in PK parameters. High-calorie/high-fat meal = ~800 kcal, 50% fat.
[b]In vivo, TAF is hydrolyzed within cells to form TFV (major metabolite), which is phosphorylated to the active metabolite, TFV-DP. In vitro studies have shown that TAF is metabolized to TFV by cathepsin A in PBMCs and macrophages; and by CES1 in hepatocytes. Upon coadministration with the moderate CYP3A inducer probe efavirenz, TAF exposure was unaffected.
[c]$t_{1/2}$ values refer to median terminal plasma half-life. Note that the pharmacologically active metabolite, TFV-DP, has a half-life of 150–180 hours within PBMCs.
[d]Dosing in mass balance studies: FTC (single dose administration of [^{14}C] FTC after multiple dosing of FTC for 10 days); TAF (single dose administration of [^{14}C] TAF).

Clinical Data

DISCOVER: Once-Daily FTC/TAF vs FTC/TDF for HIV-1 PrEP in MSM and TGW

Study design and demographics

DISCOVER is a phase 3, randomized, double-blind, active-controlled, multinational study in 5387 HIV-negative adult MSM and TGW that is evaluating the safety and efficacy of FTC/TAF (n=2694) vs FTC/TDF (n=2693), both of which are fixed-dose combination products administered once daily for HIV-1 PrEP. Key inclusion criteria included age ≥18 years, HIV- and HBV-negative, eGFR ≥60 mL/min, and at high risk of sexual acquisition of HIV (defined as ≥2 episodes of condomless anal intercourse with ≥2 unique male partners with HIV or unknown HIV status within the previous 12 weeks, or a documented history of

syphilis, rectal gonorrhea, or rectal chlamydia in the previous 24 weeks). Prior use of FTC/TDF for HIV-1 PrEP was allowed.[1,2]

Eligible participants were randomly assigned 1:1 to receive either FTC/TAF 200/25 mg or FTC/TDF 200/300 mg with a corresponding placebo once daily. Follow-up visits occurred at baseline and every 12 weeks; visits included comprehensive screenings for STIs, HIV screening, assessment of adverse events, renal function, sexual behavior, and adherence measured by pill counts, questionnaires, plasma TFV levels, and DBS TFV-DP levels. The primary measured outcome was the incidence of HIV-1 per 100 PY after all participants had ≥48 weeks of follow-up and ≥50% of participants had 96 weeks of follow-up, with a pre-specified non-inferiority margin of 1.62 representing the upper bound of the 95% CI for the measured incidence rate ratio of FTC/TAF over FTC/TDF. All participants were unblinded after 96 weeks, and participants in both arms were offered the opportunity to continue on or switch to ongoing, open-label, once-daily FTC/TAF for an additional 48 weeks.[2]

Participant baseline characteristics were similar between the FTC/TAF and FTC/TDF arms, including risk factors for HIV acquisition (Table 2).[2]

Table 2. Select Baseline Demographics[2]

Key Demographics	FTC/TAF (n=2694)	FTC/TDF (n=2693)
Baseline demographics		
Median age, years (IQR)	34 (28–43)	34 (28–44)
Race		
White, n (%)	2264 (84)	2247 (84)
Black,[a] n (%)	240 (9)	234 (9)
Asian, n (%)	113 (4)	120 (4)
Hispanic or Latinx ethnicity, n (%)	635 (24)	683 (25)
Proportion TGW, n (%)	45 (2)	29 (1)
Taking FTC/TDF for HIV-1 PrEP at baseline, %	17	16

[a]Includes mixed Black race.

PK results

To examine the numerical differences in HIV between the FTC/TAF and FTC/TDF arms of the DISCOVER study, a sub-analysis of HIV risk behavior, STI incidence, adherence, and PK data was conducted. At each 12-week follow-up visit in the DISCOVER study, all participants had their HIV risk behavior assessed by self-interviews, STI testing, and adherence by pill counts and self-reports. Adherence was further measured in a randomized subset of participants via intracellular TFV-DP concentrations in PBMCs at Week 4 (n=324) and in DBS every 12 weeks (n=536). TFV-DP concentrations in PBMCs were compared with PK data from historical phase 1 studies to estimate the onset and duration of HIV protection between the two arms.[3]

There were no significant differences in the number of condomless receptive anal sex partners; incidence of rectal gonorrhea and chlamydia; or adherence as measured by pill counts, self-reports, or DBS TFV-DP levels between the two arms. At Week 4, participants in the FTC/TAF arm (n=158) had 6.3-fold higher steady-state TFV-DP levels in PBMCs than participants in the FTC/TDF arm (n=151) when measured 20 to 28 hours post dose. Despite similar adherence, 98% of participants with available data in the FTC/TAF arm vs 68% in the FTC/TDF arm had PBMC TFV-DP levels above the EC_{90}. Median PBMC TFV-DP levels exceeded EC_{90} within 1 to 2 hours after a single dose of FTC/TAF vs 3 days with once-daily doses needed for FTC/TDF. Study investigators expect median PBMC TFV-DP levels to

remain above EC_{90} longer with FTC/TAF (16 days) vs FTC/TDF (10 days) after the last dose (Table 3).[3]

Table 3. Key HIV-1 Prevention Clinical Pharmacology Parameters: TFV-DP with FTC/TAF vs FTC/TDF[3]

	Drug (Active Moiety)	
	TAF 25 mg (TFV-DP)	TDF 300 mg (TFV-DP)
PBMC TFV-DP C_T, median, fmol/10^6 cells	404	61
TFV-DP EC_{90} in PBMCs, fmol/10^6 cells	40	40
Participants with PBMC TFV-DP C_T >EC_{90},[a] %	98	68
Time to median PBMC TFV-DP >EC_{90}[a]	1–2 hours after a single dose	3 days of once-daily doses
Duration of PBMC TFV-DP >EC_{90}[a]	16 days	10 days

Abbreviation: C_T=drug concentration at trough 20 to 28 hours post dose.
[a]EC_{90} has not been shown to correlate with efficacy.

Please note, the clinical relevance of this PK data and the exact correlation with HIV protection are unknown.

Among TGW who received high-dose estrogens or progestins concomitantly with FTC/TAF (n=17) and FTC/TDF (n=10), trough TFV-DP and FTC-TP concentrations in PBMCs were similar to those in MSM when measured 20 to 28 hours post dose at Week 4.[5] Trough TFV-DP concentrations in PBMCs were higher in TGW who received FTC/TAF than in those who received FTC/TDF.[5,6]

References

1. Ogbuagu O, Ruane PJ, Podzamczer D, et al. Long-term safety and efficacy of emtricitabine and tenofovir alafenamide vs emtricitabine and tenofovir disoproxil fumarate for HIV-1 pre-exposure prophylaxis: week 96 results from a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet HIV.* 2021;8:e397-e407.
2. Mayer KH, Molina JM, Thompson MA, et al. Emtricitabine and tenofovir alafenamide vs emtricitabine and tenofovir disoproxil fumarate for HIV pre-exposure prophylaxis (DISCOVER): primary results from a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. *Lancet.* 2020;396(10246):239-254.
3. Spinner CD, Brunetta J, Shalit P, et al. DISCOVER STUDY for HIV Pre-Exposure Prophylaxis: F/TAF has a more Rapid Onset and Longer Sustained Duration of HIV Protection Compared with F/TDF [Presentation]. Paper presented at: IAS 2019; 21-24 July, 2019; Mexico City, Mexico.
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5. Cespedes MS, Majeed SR, Prins M, et al. DISCOVER: No Effect of Hormones on F/TAF or F/TDF PK, Efficacy, and Safety in Transwomen [Poster 4018]. Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI); 08-11 March, 2020; Boston, MA.
6. Cespedes MS, Das M, Yager J, et al. Gender Affirming Hormones Do Not Affect the Exposure and Efficacy of F/TDF or F/TAF for HIV Preexposure Prophylaxis: A Subgroup Analysis from the DISCOVER Trial. *Transgender Health.* 2022;00:1-7.

Abbreviations

AUC=area under the curve
C_{max}=maximum observed concentration of drug
DBS=dried blood spots
EC_{90}=90% of maximum effective concentration
FTC=emtricitabine
IQR=interquartile range

MSM=men who have sex with men
PBMC=peripheral blood mononuclear cells
PK=pharmacokinetic(s)
PrEP=pre-exposure prophylaxis
PY=patient years
STI=sexually transmitted infection
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
TFV=tenofovir
TFV-DP=tenofovir diphosphate
TGW=transgender women
T_{max}=time that drug is at maximum concentration

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Descovy US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/hiv/descovy/descovy_pi.pdf.

Follow Up

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