Descovy for PrEP® (FTC/TAF) Renal Safety Profile

This document is in response to your request for information regarding the renal safety profile of Descovy® (emtricitabine/tenofovir alafenamide [FTC/TAF] for HIV-1 pre-exposure prophylaxis [PrEP]).

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

Product Labeling[1]

FTC/TAF is not recommended in individuals with severe renal impairment (estimated CrCl of 15 to <30 mL/min) or end-stage renal disease (estimated CrCl <15 mL/min) who are not receiving chronic hemodialysis.

Clinical Data on the Renal Safety Profile of FTC/TAF

- The renal safety profile of TAF-containing regimens has been well-established, with >41,000 PY experience in clinical trials and >3.7 million PY experience with post-approval use worldwide.[2,3]
- In clinical trials of TAF-containing regimens for HIV treatment, PrEP, and HBV treatment, there have been zero cases of PRT.[2,3]

DISCOVER is a phase 3 study comparing the efficacy and safety of once-daily FTC/TAF and FTC/TDF for HIV-1 PrEP among adult cisgender MSM and TGW.[4]

- From baseline to Week 96, the effects of study drugs on renal biomarkers (urine RBP:Cr and β2M:Cr) and $eGFR_{CG}$ significantly favored FTC/TAF (all $P<0.0001$) in the overall study population and in the subgroups of participants aged ≥50 years and those with a baseline $eGFR_{CG}$ of 60 to <90 mL/min ($P<0.001$).[4,5]
- Through Week 96, 2 participants in the FTC/TAF arm and 7 participants in the FTC/TDF arm discontinued study drug due to renal AEs.[5]
- Through Week 96, participants with baseline use of FTC/TDF for PrEP and randomized to the FTC/TAF arm had significant improvements in $eGFR_{CG}$, urine RBP:Cr, and B2M:Cr compared with those who remained on FTC/TDF(P<0.001).[6]
- In an analysis that assessed the long-term safety of participants who were randomly assigned to receive FTC/TAF and continued on FTC/TAF in the OL phase for a total follow-up duration of ≥144 weeks, renal biomarkers remained stable or improved from baseline to Week 144.[7]
- The long-term clinical significance of these renal laboratory changes on adverse reaction frequencies between FTC/TAF and FTC/TDF is not known.[1]

Clinical Data on the Renal Safety Profile of FTC/TAF

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

Study design and demographics

DISCOVER (NCT02842086) 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 once-daily FTC/TAF (n=2694) vs FTC/TDF (n=2693) for HIV-1 PrEP. Prior use of FTC/TDF for HIV-1 PrEP was allowed.[4,8] 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. The primary outcome was the incidence of HIV-1 per 100 person-years 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.[8]

Participant baseline characteristics were similar between the FTC/TAF and FTC/TDF arms, including risk factors for HIV acquisition (Table 1).[5]

Table 1. DISCOVER: Baseline Demographics and HIV Risk Factors[4,5]

Select Demographics and Risk Factors		FTC/TAF (n=2694)	FTC/TDF (n=2693)
Age, median (IQR), years		34 (28–43)	34 (28–44)
Race or ethnicity, n (%)	White	2264 (84)	2247 (84)
	Hispanic or Latinx	635 (24)	683 (25)
	Black or mixed Black	240 (9)	234 (9)
	Asian	113 (4)	120 (5)
Cisgender MSM, n (%)		2649 (98)	2664 (99)
TGW, n (%)		45 (2)	29 (1)
Medical history, %	Hypertension	282 (11)	298 (11)
	Diabetes mellitus	79 (3)	89 (3)
HIV risk factors, n (%)	Recreational drug use in the past 12 weeks	1785 (67)	1786 (67)
	≥2 events of receptive condomless anal sex in the past 12 weeks	1660 (62)	1628 (60)
	Binge drinking[a]	618 (23)	599 (22)
	Received FTC/TDF for HIV-1 PrEP at baseline	465 (17)	440 (16)
	Syphilis diagnosis in the past 24 weeks	230 (9)	263 (10)

[a]Defined as ≥6 drinks on ≥1 occasion, at least monthly.

Renal safety results

At Week 96, the median change from baseline in $eGFR_{CG}$ was significantly higher in the FTC/TAF arm than in the FTC/TDF arm (P<0.0001). At Week 4 and at all observed timepoints up to Week 96, the FTC/TAF arm had significantly lower levels of RBP:Cr and β2M:Cr than the FTC/TDF arm (each timepoint, P<0.001).[4,5]

In the subgroup of participants aged ≥50 years at baseline, there were significant declines in $eGFR_{CG}$ in the FTC/TDF arm (P<0.001) and numerical increases in the FTC/TAF arm; significant differences in RBP:Cr and β2M:Cr between the FTC/TAF and FTC/TDF arms were also observed (each, P<0.001). In participants with an $eGFR_{CG}$ 60 to <90 mL/min at

baseline, $eGFR_{CG}$, RBP:Cr, and β2M:Cr significantly favored FTC/TAF over FTC/TDF (each, $P<0.001$).[4,5]

There were 9 discontinuations due to renal AEs through Week 96 (FTC/TAF, n=2; FTC/TDF, n=7); investigators reported that all but 1 case (in the FTC/TAF arm) were related to study drug. In the FTC/TDF arm, 3 of the 7 participants who discontinued had other contributing factors (ie, hypertension, nonsteroidal anti-inflammatory drug use, and/or a history of kidney disease). In the FTC/TAF arm, both discontinuations had risk factors (ie, myocardial infarction, contrast neuropathy, hypertension, and focal segmental glomerulosclerosis discovered by renal biopsy).[4,5] There were no reported cases of Fanconi syndrome in the FTC/TAF arm and 1 case in the FTC/TDF arm (Table 2).[4]

Table 2. DISCOVER: Renal Safety for All Participants at Week 96[4]

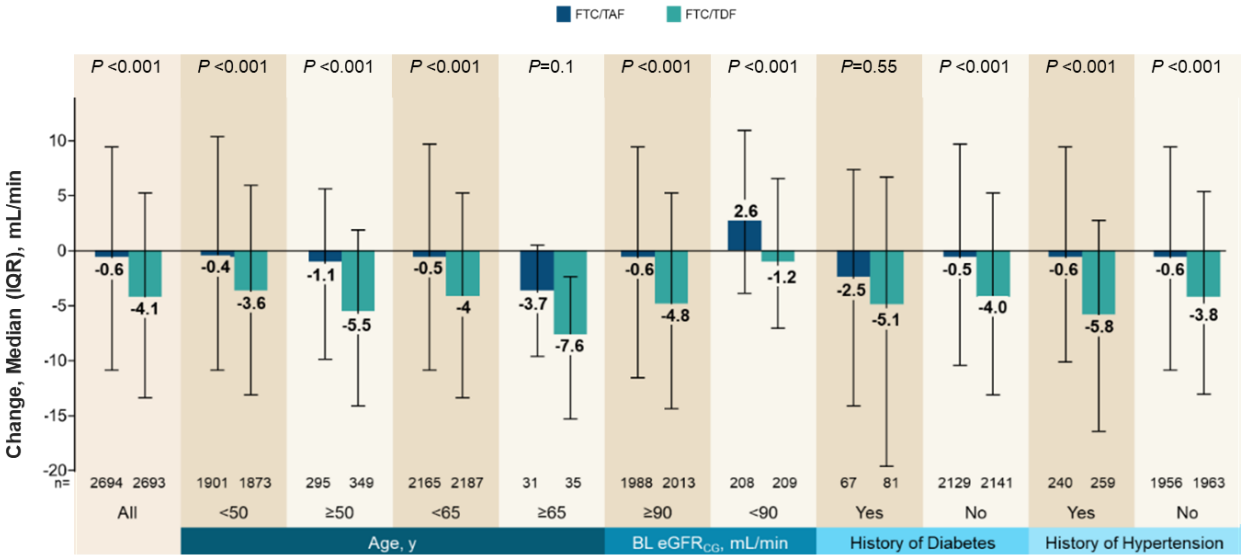
	FTC/TAF (n=2694)	FTC/TDF (n=2693)	*P*-Value
$eGFR_{CG}$ change from baseline,[a] median, mL/min	+3.7	-0.4	<0.0001[d]
RBP:Cr change from baseline,[b] mean, %	+0.2	+21.4	<0.0001[e]
β2M:Cr change from baseline,[c] mean, %	-14.6	+14.2	<0.0001[e]
Participants with treatment emergent UPCR >22.6 mg/mmol, %	1	1.3	0.22
Renal AEs that led to study drug discontinuation, n	2	7	-

[a]FTC/TAF, n=2193; FTC/TDF, n=2217.
[b]FTC/TAF, n=2191; FTC/TDF, n=2216.
[c]FTC/TAF, n=2172; FTC/TDF, n=2200.
[d]*P*-values were from an ANOVA model with baseline FTC/TDF for PrEP and treatment as fixed effects.
[e]*P*-values were from the Van Elteren test stratified by baseline FTC/TDF for HIV-1 PrEP to compare the two arms.

Subanalysis: renal outcomes in participants predisposed to renal dysfunction

In a subanalysis of renal outcomes in participants with demographic or medical characteristics predisposing them to renal dysfunction, numerical improvements or smaller declines in $eGFR_{CG}$ (Figure 1) and renal biomarkers were observed in the FTC/TAF arm than in the FTC/TDF arm. The most pronounced differences in renal biomarkers were observed in subgroups of participants aged ≥50 or 65 years and those with baseline $eGFR_{CG}$ <90 mL/min, a history of diabetes, or a history of hypertension.[9]

Figure 1. DISCOVER: Changes in $eGFR_{CG}$ From Baseline to Week 96 in Participants With Demographic or Medical Predisposition to Renal Dysfunction[9]



Abbreviation: BL=baseline.

Week 144 renal safety results[7]

An analysis assessed the long-term outcomes of participants who were randomly assigned to receive FTC/TAF (n=2694) and continued on FTC/TAF in the OL phase (n=2070) for a total follow-up duration of ≥144 weeks. Markers of renal function were stable or improved from baseline to Week 144 (Table 3).

Table 3. DISCOVER: Renal Safety in Participants Randomly Assigned to FTC/TAF at Week 144[7]

Renal Parameter	FTC/TAF (n=2694)
$eGFR_{CG}$ change from baseline, median (IQR),[a] mL/min	2.2 (-8 to 13)
RBP:Cr change from baseline, median (IQR),[b] %	-1.3 (-28 to 36)
β2M:Cr change from baseline, median (IQR),[c] %	-21 (-51 to 18)
Participants with treatment emergent UPCR >22.6 mg/mmol, n/N (%)	10/1895 (0.5)

[a]n=1930. [b]n=1928. [c]n=1917.

Overall, 7 SAEs (<1%) of acute kidney injury were reported, and 1 SAE (<1%) of nephrotic syndrome was considered related to FTC/TAF treatment.

References

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Abbreviations

AE=adverse event
β2M=beta-2-microglobulin
$eGFR_{CG}$=estimated glomerular filtration rate by Cockcroft-Gault
FTC=emtricitabine
MSM=men who have sex with men
OL=open-label
PrEP=pre-exposure prophylaxis
SAE=serious adverse event
RBP=retinol-binding protein
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
TGW=transgender women
UPCR=urine protein-creatinine ratio

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.

Follow Up

For any additional questions, please contact Gilead Medical Information at:

☎1-866-MEDI-GSI (1-866-633-4474) or www.askgileadmedical.com

Adverse Event Reporting

Please report all adverse events to:

Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or
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FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or www.accessdata.fda.gov/scripts/medwatch

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