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

This document is in response to your request for information regarding the bone safety profile of Descovy® for HIV-1 PrEP (emtricitabine/tenofovir alafenamide [FTC/TAF] for HIV-1 pre-exposure prophylaxis [PrEP]). This response was developed according to principles of evidence-based medicine and contains information from phase 3 clinical trials.

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 indicated in at-risk adults and adolescents weighing ≥35 kg for PrEP to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex. Individuals must have a negative HIV-1 test immediately prior to initiating FTC/TAF for HIV-1 PrEP.

Limitations of Use: The indication does not include the use of FTC/TAF in individuals at risk of HIV-1 from receptive vaginal sex because effectiveness in this population has not been evaluated.

Clinical Data on the Bone Safety Profile of FTC/TAF

DISCOVER is a phase 3, double-blind, multinational study that compared the safety and efficacy of FTC/TAF (n=2694) with FTC/TDF (n=2693) for HIV-1 PrEP among adult, cisgender MSM and TGW. At Week 96, effects on spine and hip BMD significantly favored FTC/TAF (all $P<0.001$).[2]

A BMD substudy was conducted in 383 participants with DXA scans through Week 96.[2]

- Through Week 96, decreases of ≥3% in spine and hip BMD occurred in a lower percentage of participants in the FTC/TAF vs FTC/TDF arm ($P<0.001$).[3]
- Statistically significant differences were found between the FTC/TAF and FTC/TDF mean percent change in hip and spine BMD from baseline in participants ≥25 years and in participants <25 years old.[2]

Participants who switched from FTC/TDF to FTC/TAF on Day 1 of the OL phase had statistically significant increases in hip and spine BMD from the OL baseline to Week 48 of the OL phase, while those who remained on FTC/TAF had stable BMD.[4]

Participants who received FTC/TAF during both the double-blind and OL phases showed increased BMD from baseline to Week 144 at both the hip and spine (median change, 0.54% and 1.02%, respectively).[5]

Clinical Data on the Bone Safety Profile of FTC/TAF

DISCOVER: FTC/TAF vs FTC/TDF 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 evaluated the safety and efficacy of FTC/TAF (n=2694) vs FTC/TDF (n=2693) for HIV-1 PrEP. Eligible participants were aged ≥18 years, were HBV-negative, had eGFR ≥60 mL/min, and were at high risk of sexual acquisition of HIV (defined as ≥2 episodes of condomless anal intercourse with ≥2 unique male partners who had confirmed 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.[2,6]

Eligible participants were randomly assigned in a 1:1 ratio to receive either FTC/TAF 200/25 mg or FTC/TDF 200/300 mg once daily. Study visits occurred at baseline, Week 4, Week 12, and every 12 weeks thereafter. All participants were unblinded after 96 weeks, and participants in both arms were offered the opportunity to continue on or switch to OL, once-daily FTC/TAF for an additional 48 weeks.[5]

In a BMD substudy, DXA scans were conducted in 383 participants to assess bone safety through Week 96. At Week 144, additional BMD analyses were conducted for BMD substudy participants who were randomly assigned to either arm during the double-blind period and then received FTC/TAF in the OL phase.[5]

Participant baseline characteristics were similar between the FTC/TAF and FTC/TDF arms and between the overall and BMD substudy cohorts. In the BMD substudy, the proportions of participants with baseline spine osteopenia and osteoporosis were 24% and 3%, respectively, in the FTC/TAF group and 27% and 2% in the FTC/TDF group. The proportions of participants with baseline hip osteopenia and osteoporosis were 23% and 1%, respectively, in the FTC/TAF group and 25% and 0% in the FTC/TDF group.[6-8]

Bone safety results

Week 48 results[7]

Through Week 48 in the overall population, fracture AEs were reported in the same number of participants in both arms (53 participants each), and most were due to trauma. In the FTC/TAF and FTC/TDF arms, fracture AEs included nontraumatic fractures (1 and 2 participants, respectively), lower extremity fractures (22 and 16 participants), upper extremity fractures (12 and 16 participants), and rib fractures (5 and 7 participants). Of the 3 nontraumatic fractures, 1 was Grade 1 in severity in the FTC/TAF arm, and 1 each was Grade 1 and Grade 2 in severity in the FTC/TDF arm. Initiation of osteoporosis medications occurred at similar frequencies in the FTC/TAF and FTC/TDF arms (calcium or vitamin D only, 2.5% in both arms; other osteoporosis medications, <0.1% in both arms).

Week 96 results

At Week 96 in the overall population, fracture events were reported in 60 participants in both the FTC/TAF and FTC/TDF arms.[2]

In the BMD substudy, the effects on spine and hip BMD significantly favored FTC/TAF.

Participants in the FTC/TAF arm had BMD increases at both the spine and hip, compared with BMD losses observed in the FTC/TDF arm (Table 1).[2] A significantly lower percentage of participants in the FTC/TAF arm had a ≥3% decrease in BMD from baseline at both the spine and hip (Table 1).[3]

Table 1. DISCOVER: BMD Substudy of Bone Safety at Week 96[2,3]

	Spine BMD			Hip BMD		
	FTC/TAF (n=144)	FTC/TDF (n=140)	*P*-Value	FTC/TAF (n=140)	FTC/TDF (n=137)	*P*-Value
BMD change from baseline, mean, %	+1	-1.4	<0.0001	+0.6	-1	<0.0001
Participants with ≥3% increase in BMD from baseline, %	23	7	<0.001	17	6	0.007
Participants with ≥3% decrease in BMD from baseline, %	11	29	<0.001	7	21	<0.001

Mean percent BMD change in the hip was significantly different between the two arms, favoring FTC/TAF among participants aged <25 years, and mean percent BMD change in both the spine and hip favored FTC/TAF among participants aged ≥25 years (Table 2).[3] The mean percent BMD change in hip and spine significantly favored FTC/TAF in participants of non-Black race, Hispanic/Latinx ethnicity, and non-Hispanic/Latinx ethnicity.[9] In the small group of participants (n=20) with baseline FTC/TDF use, no statistically significant changes were seen when comparing hip and spine BMD in participants on FTC/TAF with that of participants on FTC/TDF (Table 2).[10]

Table 2. DISCOVER: Subanalyses of BMD at Week 96[3,9,10],

BMD Cohort		Location	n	Mean Change From Baseline, %		*P*-Value
				FTC/TAF	FTC/TDF	
Ogbuagu Subanalysis[3]	Age <25 years	Hip	24	+1.2	-1.7	0.035
		Spine	25	+1.4	-1.2	0.14
	Age ≥25 years	Hip	253	+0.6	-1	<0.001
		Spine	259	+0.9	-1.4	<0.001
DeJesus Subanalysis[9]	Black	Hip	19	-0.1	-1.6	0.51
		Spine	21	+1.8	-0.8	0.15
	Non-Black	Hip	258	+0.7	-1	<0.001
		Spine	263	+0.9	-1.4	<0.001
	Hispanic/Latinx	Hip	64	+0.8	-1.5	<0.001
		Spine	65	+0.7	-1.6	0.02
	Non-Hispanic/Latinx	Hip	213	+0.6	-0.9	0.001
		Spine	219	+1	-1.3	<0.001
Campbell Subanalysis[10]	Baseline FTC/TDF	Hip	20[a]	+1.8	+1.4	0.75
		Spine	20[b]	+0.9	-1.2	0.13
	No baseline FTC/TDF	Hip	124[c]	+0.4	-1.4	<0.001
		Spine	125	+0.8	-1.5	<0.001

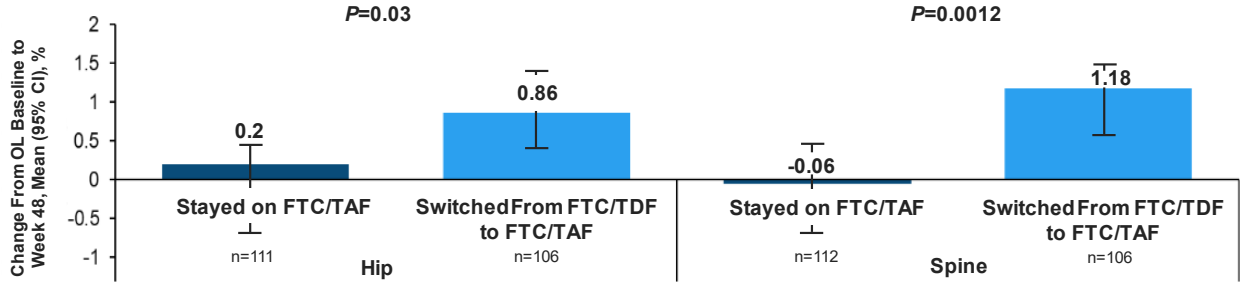
[a]n=20 in baseline FTC/TDF→FTC/TAF group, n=16 in baseline FTC/TDF→FTC/TDF group.
[b]n=20 in baseline FTC/TDF→FTC/TAF group, n=17 in baseline FTC/TDF→FTC/TDF group.
[c]n=124 in no baseline FTC/TDF→FTC/TAF group, n=122 in no baseline FTC/TDF→FTC/TDF group.

Week 144 results

On Day 1 of the OL phase, hip and spine BMDs were not significantly different between study arms. Participants who switched from FTC/TDF to FTC/TAF on Day 1 of the OL phase

had statistically significant increases in hip and spine BMD through Week 48 of the OL phase, and those who remained on FTC/TAF had stable BMD (Figure 1).[4]

Figure 1. DISCOVER: Changes in BMD at Week 48 of the OL Phase[4]



Participants who received FTC/TAF during the double-blind phase and continued to receive it in the OL phase showed increased median BMD from the double-blind baseline to Week 144 in both the hip (+0.54%) and spine (+1.02%).[5]

References

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2. 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. *The lancet. HIV.* 2021;8:e397-e407.
3. Ogbuagu O, Ruane PJ, Podzamczer D, et al. Supplementary appendix 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(7):1-21.
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5. Wohl DA, Spinner CD, Flamm J, et al. HIV-1 infection kinetics, drug resistance, and long-term safety of pre-exposure prophylaxis with emtricitabine plus tenofovir alafenamide (DISCOVER): week 144 open-label extension of a randomised, controlled, phase 3 trial. *Lancet HIV.* 2024;11(8):508-521.
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10. Campbell T, Clarke A, Trottier B, et al. Safety and Efficacy of F/TAF and F/TDF for PrEP in DISCOVER Participants Taking F/TDF for PrEP at Baseline [Poster 995]. Paper presented at: IDWeek Virtual; 21-25 October, 2020.

Abbreviations

AE=adverse event
BMD=bone mineral density
DXA=dual-energy X-ray absorptiometry
FTC=emtricitabine
MSM=men who have sex with men
OL=open-label
PrEP=pre-exposure prophylaxis
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
TGW=transgender women

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

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Please report all adverse events to:

Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or
🖱 www.gilead.com/utility/contact/report-an-adverse-event

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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