GILEAD | Medical Information

Descovy® (FTC/TAF) Use in Severe Renal Impairment or Hemodialysis

This document is in response to your request for information regarding Descovy® (emtricitabine/tenofovir alafenamide [FTC/TAF]) for treatment or PrEP (pre-exposure prophylaxis) in individuals with severe renal impairment (eGFR <30 mL/min), including individuals on hemodialysis.

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 in individuals with ESRD (estimated CrCl <15 mL/min) who are not receiving chronic hemodialysis, as the safety of FTC/TAF has not been established in these populations.

Clinical Data: FTC/TAF Use in Participants With Severe Renal Impairment or Hemodialysis

- Currently, there are no data available regarding the use of the fixed dose combination FTC/TAF in PWH with severe renal impairment, including individuals on hemodialysis. Additionally, no data are available for FTC/TAF when used for PrEP in HIV-negative individuals with impaired renal function, as individuals with eGFR <60 mL/min were excluded from the pivotal DISCOVER study.[2]
- Study 1825, which evaluated FTC/TAF as a component of the STR E/C/F/TAF in virologically suppressed PWH with ESRD (eGFR <15 mL/min) on hemodialysis, demonstrated that exposures of EVG, COBI, and TAF were consistent with historical data in PWH with normal renal function. Exposures of FTC were higher than in individuals with normal renal function, but safety profiles were similar.[3,4]

Product Labeling[1]

Use in Specific Populations

Renal impairment

No dosage adjustment of FTC/TAF is recommended in individuals with estimated CrCl ≥30 mL/min, or in adults with ESRD (estimated CrCl <15 mL/min) who are receiving chronic hemodialysis. On days of hemodialysis, administer the daily dose of FTC/TAF after completion of hemodialysis treatment.

Safety and effectiveness of FTC/TAF coadministered with an HIV-1 PI that is administered with either RTV or COBI have not been established in patients with ESRD.

FTC/TAF is not recommended in individuals with severe renal impairment (estimated CrCl of 15 to <30 mL/min), or in individuals with ESRD (estimated CrCl <15 mL/min) who are not receiving chronic hemodialysis, as the safety of FTC/TAF has not been established in these populations.

Clinical Pharmacology

PK

Specific populations: patients with renal impairment

The PK of FTC + TAF combined with EVG + COBI in participants with HIV-1 and renal impairment ($eGFR_{CG}$ 30–69 mL/min), and in participants with HIV-1 with ESRD ($eGFR_{CG}$ <15 mL/min) receiving chronic hemodialysis were evaluated in subsets of virologically suppressed participants in open-label trials. The PK of TAF were similar among healthy participants, participants with HIV-1 and mild or moderate renal impairment, and participants with HIV-1 and ESRD receiving chronic hemodialysis; increases in FTC and TFV exposures in participants with HIV-1 and renal impairment were not considered clinically relevant.

Clinical Data: FTC/TAF Use in Participants With Severe Renal Impairment or Hemodialysis

Currently, there are no data available regarding the use of the fixed dose combination FTC/TAF in PWH with severe renal impairment, including individuals on hemodialysis. Additionally, no data are available for FTC/TAF when used for PrEP in HIV-negative individuals with impaired renal function, as individuals with eGFR <60 mL/min were excluded from the pivotal DISCOVER study.[2]

Study 1825: E/C/F/TAF in PWH on Chronic Hemodialysis

Study design and demographics[3,4]

Study GS-US-292-1825 was a phase 3b, open-label, multicenter, single-arm study that evaluated the safety, tolerability, PK, and efficacy of E/C/F/TAF STR in virologically suppressed PWH and ESRD (eGFR <15 mL/min) on chronic hemodialysis for ≥6 months. Participants switched their current ARV regimen to E/C/F/TAF once daily and received

treatment for 96 weeks. The primary outcome was the incidence of treatment-emergent, Grade ≥3 AEs up to Week 48. Secondary outcomes included the following: the incidence of treatment-emergent, Grade ≥3 AEs up to Week 96; the proportion of participants with HIV-1 RNA <50 c/mL at Weeks 24, 48, and 96 as defined by the FDA Snapshot algorithm; steady-state plasma PK parameters of EVG, COBI, FTC, TAF, and TFV (TAF metabolite); and HIV Treatment Satisfaction Questionnaire at Week 24 and every 24 weeks thereafter.

Eligible participants were on a stable ARV regimen for ≥6 consecutive months, had plasma HIV-1 RNA <50 c/mL for ≥6 months preceding the screening visit and at screening, had a CD4+ count ≥200 cells/mcL, and had adequate hematologic function (ie, absolute neutrophil count ≥1000/mm^3, platelets ≥50,000/mm^3, and Hgb ≥8.5 g/dL). Participants with a documented history of HIV-1 resistance to EVG, FTC, 3TC, or TFV were excluded. This was the first trial to evaluate the use of a STR in participants undergoing hemodialysis. Baseline demographics and disease characteristics are presented in Table 1.

Table 1. Study 1825: Baseline Demographics and Disease Characteristics[3,4]

Key Demographics and Characteristics		E/C/F/TAF (N=55)
Age, median (range), years		51 (23–64)
Male, n (%)		42 (76)
Race/ethnicity, n (%)	Black	45 (82)
	White	10 (18)
HIV-1 RNA <50 c/mL, n (%)		54 (98)
CD4 count, median (Q1, Q3), cells/mcL		515 (387, 672)
HCV antibody positive, n (%)		12 (22)
CrCl,[a] median (Q1, Q3), mL/min		10.9 (8.8, 13.8)
Duration of hemodialysis, median (Q1, Q3), years		6 (4, 10)
Medical history, n (%)	Hypertension	52 (95)
	Cardiovascular disease	26 (47)
	Hyperlipidemia	23 (42)
	Diabetes	15 (27)
NRTI in regimen before switch,[b,c] n (%)	3TC	36 (65)
	ABC	31 (56)
	TDF	16 (29)
	FTC	4 (7)
Third agent in regimen before switch,[b] n (%)	INSTI	29 (53)
	PI	24 (44)
	NNRTI	15 (27)
	CCR5 antagonist	1 (2)

Abbreviations: CCR5=chemokine receptor type 5; INSTI=integrase strand transfer inhibitor; NNRTI=non-nucleos(t)ide reverse transcriptase inhibitor.
[a]The timing of blood draw was variable.
[b]Some regimens included >1 NRTI or third agent; thus, the total was >100%.
[c]Two participants had ARV therapy prior to switch containing both TDF and ABC.

Safety results through Week 96

At Week 48, Grade ≥3 AEs occurred in 18 participants (33%); none were considered to be related to study drug.[3] At Week 96, Grade ≥3 AEs occurred in 24 participants (44%); none were considered related to study drug. AEs that occurred in ≥10% of participants included nausea (24%), hyperkalemia (22%), cough (16%), pneumonia (15%), anemia (13%), peripheral edema (13%), and pain in extremity (11%). Study drug-related AEs occurred in 7 participants (13%) and included nausea (n=4), diarrhea, asthenia, allergic

pruritus, gastroesophageal reflux disease, myalgia, peripheral neuropathy, and polyuria (each, n=1). Serious AEs occurred in 36 participants (65%). Four AEs led to study drug discontinuation: unrelated generalized edema, related peripheral neuropathy, related allergic pruritus, and unrelated renal transplant (each, n=1). Three deaths were reported due to heart failure and anasarca following endocarditis, cardiac arrest, and sudden cardiac death (each, n=1).[4]

No clinically relevant changes in fasting levels of LDL, HDL, TC:HDL ratio, and serum glucose were observed from baseline to Week 96. Laboratory abnormalities are presented in Table 2. Abnormalities consistent with ESRD included changes in blood urea nitrogen, parathyroid hormone, phosphate, and amylase.[4]

Table 2. Study 1825: Grade 3 or 4 Treatment-Emergent Laboratory Abnormalities in ≥2% of Participants through Week 96[4]

Parameter, n (%)	E/C/F/TAF (N=55)
Any[a]	27 (49)
Amylase increased	11 (20)
Serum glucose (non-fasting, hyperglycemia)	6 (11)
GGT increased	3 (5)
Serum potassium (hyperkalemia)	3 (5)
Corrected calcium (hypocalcemia)	2 (4)
Serum glucose (fasting, hyperglycemia)	1 (2)[b]
TC (fasting, hypercholesterolemia)	1 (2)[b]

Abbreviation: GGT=γ-glutamyl transferase.
[a]Denominator for % is number of participants with ≥1 post-baseline value for test.
[b]Denominator n=46.

Virologic outcomes at Week 96[4]

In the full analysis set at Week 96, 55% of participants (n/N=30/55) had HIV-1 RNA <50 c/mL. A viral load of HIV-1 RNA ≥50 c/mL was reported in 1 participant who had preexisting resistance to FTC (M184V) and EVG (G140S, Q148H), developed treatment-emergent resistance to TAF (K65R) during the study, and discontinued E/C/F/TAF due to lack of efficacy. The participant was resuppressed on DTG + DRV/c. The criteria for resistance testing were not met by any other study participant.

No virologic data were reported in 24 participants (44%); 6 of these participants had HIV-1 RNA <50 c/mL when they discontinued study drug due to AEs or death. Eleven participants discontinued the study for other reasons (ie, lost to follow-up, renal transplant, participant decision), and their last available HIV-1 RNA was <50 c/mL. Seven participants were missing data during the Week 96 window; 6 of these participants were still on study drug and had HIV-1 RNA <50 c/mL at the visit preceding the Week 96 visit, and 1 participant had no further data and was deemed lost to follow-up. By per-protocol analysis, 30/31 participants (97%) had HIV-1 RNA <50 c/mL.

PK results at Week 48[4]

Exposures of EVG, COBI, and TAF (hepatically metabolized) in participants with ESRD were consistent with the ranges of historical data in PWH with normal renal function.

Exposures of the renally eliminated metabolite TFV were higher in participants with ESRD than those seen with TAF in participants with normal renal function (Table 3), but lower than historical data with dose-adjusted TDF in hemodialysis (44,900 h·ng/mL). Exposures of

FTC, which is also renally eliminated, were higher in participants with ESRD than in participants with normal renal function, but safety profiles were similar (Table 3).

Table 3. Study 1825: E/C/F/TAF PK Results of Participants With ESRD vs Participants With Normal Renal Function at Week 48[4]

		n	ESRD, Mean (CV), h·ng/mL	n	Normal Renal Function,[a] Mean (CV), h·ng/mL
EVG	AUC_T	10	14,300 (55)	19	22,800 (35)
COBI	AUC_T	11	10,200 (59)	19	9460 (34)
FTC	AUC_T	11	62,900 (48)	19	11,700 (17)
TAF	AUC_{last}	12	232 (53)	19	228 (47)
TFV	AUC_T	10	8720 (39)	19	326 (15)

Abbreviations: AUC_{last}=area under the concentration-time curve up to last measurable concentration; AUC_T=area under the concentration-time curve over the dosing interval; CV=coefficient of variation.
[a]From intensive PK analysis in a phase 2 trial in PWH.

HIV treatment satisfaction at Week 96[4]

As measured by the HIV Treatment Satisfaction Questionnaire, 86% of participants felt “much more satisfied” with the E/C/F/TAF STR compared with their baseline therapy. Mean adherence at all post-baseline visits through Week 96 was 94% to 97% as measured by a medication adherence questionnaire.

References

1. Enclosed. Gilead Sciences Inc, DESCOVY® (emtricitabine and tenofovir alafenamide) tablets, for oral use. U. S. Prescribing Information. Foster City, CA.
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. Eron Jr JJ, Lelievre JD, Kalayjian R, et al. Safety of Elvitegravir, Cobicistat, Emtricitabine, and Tenofovir Alafenamide in HIV-1-Infected Adults with End-Stage Renal Disease on Chronic Haemodialysis: An Open-Label, Single-Arm, Multicentre, Phase 3b Trial. *The lancet. HIV.* 2019;6:e15-24.
4. Eron Jr JJ, Lelievre JD, Kalayjian R, et al. Longer Term Safety and Efficacy of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide in Virologically Suppressed Adults Living With HIV and End-Stage Renal Disease on Chronic Hemodialysis [Poster 2490]. Paper presented at: IDWeek 2019; 02-06 October, 2019; Washington, DC.

Abbreviations

3TC=lamivudine
ABC=abacavir
AE=adverse event
ARV=antiretroviral
c/mL=copies/mL
CD4=cluster of differentiation 4
CG=Cockcroft-Gault
COBI=cobicistat
DRV/c=darunavir boosted with cobicistat
DTG=dolutegravir
E/C/F/TAF=elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
ESRD=end stage renal disease
EVG=elvitegravir
FTC=emtricitabine
PI=protease inhibitor
PK=pharmacokinetic(s)
PrEP=pre-exposure prophylaxis
PWH=people with HIV
RTV=ritonavir
STR=single tablet regimen
TAF=tenofovir alafenamide
TC=total cholesterol
TDF=tenofovir disoproxil fumarate
TFV=tenofovir

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
🖱 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

Data Privacy

The Medical Information service at Gilead Sciences may collect, store, and use your personal information to provide a response to your medical request. We may share your information with other Gilead Sciences colleagues to ensure that your request is addressed appropriately. If you report an adverse event or concern about the quality of a Gilead or Kite product, we will need to use the information you have given us in order to meet our regulatory requirements in relation to the safety of our medicines.

It may be necessary for us to share your information with Gilead's affiliates, business partners, service providers and regulatory authorities located in countries besides your own. Gilead Sciences has implemented measures to protect the personal information you provide. Please see the Gilead Privacy Statement (www.gilead.com/privacy-statements) for more information about how Gilead handles your personal information and your rights. If you have any further questions about the use of your personal information, please contact privacy@gilead.com.