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Biktarvy® (BIC/FTC/TAF) Hepatic Safety

This document is in response to your request for information regarding Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide [BIC/FTC/TAF]) and its hepatic safety profile from the registrational phase 3 clinical trials.

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

Summary

Product Labeling[1]

Prior to or when initiating BIC/FTC/TAF, test patients for HBV infection.

Severe acute exacerbations of hepatitis B (eg, liver decompensation and liver failure) have been reported in patients who are co-infected with HIV-1 and HBV and have discontinued products containing FTC and/or TDF, and may occur with discontinuation of BIC/FTC/TAF. Patients co-infected with HIV-1 and HBV who discontinue BIC/FTC/TAF should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, anti-hepatitis B therapy may be warranted, especially in patients with advanced liver disease or cirrhosis, since post-treatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure.

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including FTC, a component of BIC/FTC/TAF, and TDF, another prodrug of tenofovir, alone or in combination with other ARVs. Treatment with BIC/FTC/TAF should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Clinical Data on BIC/FTC/TAF and Hepatic Safety

Studies 1489 and 1490 compared outcomes with BIC/FTC/TAF with those of DTG-containing regimens in ARV-naive, adult PWH.[2]

- There were no study drug-related hepatobiliary serious AEs among participants taking BIC/FTC/TAF through Week 144.[2,3]
- Study participants were offered to continue treatment with or switch to treatment with BIC/FTC/TAF during the OLE phase; no study drug-related hepatobiliary serious AEs were reported through Week 240. No treatment discontinuations due to hepatobiliary AEs or abnormal liver function tests occurred.[4]

In clinical studies that compared outcomes of VS participants who switched to BIC/FTC/TAF with those who remained on their baseline regimens (boosted DRV or ATV + 2 NRTIs,

DTG/ABC/3TC, or DTG + ABC/3TC), no study drug-related hepatobiliary serious AEs were reported through Week 48.[5,6]

Clinical Data on BIC/FTC/TAF and Hepatic Safety

GS-US-380-1489 and GS-US-380-1490

Study designs and demographics

Study 1489 was a phase 3, randomized, double-blind, active-controlled, non-inferiority clinical study that compared outcomes in ARV-naive, adult PWH who were treated with BIC/FTC/TAF (n=314) or DTG/ABC/3TC (n=315).[7] Study 1490 was a phase 3, randomized, double-blind, active-controlled, non-inferiority clinical study that compared outcomes in ARV-naive, adult PWH who were treated with BIC/FTC/TAF (n=320) or DTG + FTC/TAF (n=325).[8] Key inclusion criteria for both studies were HIV-1 RNA ≥500 c/mL and no known resistance to FTC, tenofovir, ABC, or 3TC.[2]

Table 1. Studies 1489 and 1490: Baseline Demographics and Disease Characteristics of BIC/FTC/TAF Participants[2]

Key Demographics and Characteristics		BIC/FTC/TAF (n=634)
Age, median (range), years		32 (18–71)
Male, %		89
Race and ethnicity, %	Black or African descent	33
	Hispanic/Latinx	24
HIV-1 RNA, median (IQR), log_{10} c/mL		4.42 (4–4.88)
HIV-1 RNA >100,000 c/mL, %		19
CD4 cell count, median (IQR), cells/mcL		442 (293–590)
CD4 count <200 cells/µL, %		13
$eGFR_{CG}$, median (IQR), mL/min		122 (104–143)
Asymptomatic HIV, %		90

Participants with HIV and HBV at Week 144[3]

Study 1490 permitted participants with HBV, and 14 participants (2%) had HBV at baseline (BIC/FTC/TAF, n=8; DTG + FTC/TAF, n=6). At Week 144, 11 had HBV DNA <29 IU/mL and HIV RNA <50 c/mL by missing=excluded analysis. No hepatic AEs were reported in these participants.

Hepatobiliary AEs through Week 144[3,9]

Through Week 144, no hepatobiliary serious AEs related to BIC/FTC/TAF were reported, and no discontinuations due to hepatic laboratory abnormalities or hepatobiliary AEs occurred. Grade 3 or 4 hepatobiliary laboratory abnormalities are reported in Table 2.

Table 2. Studies 1489 and 1490: Grade 3 or 4 Hepatic Laboratory Abnormalities Through Week 144[9]

Parameter, n (%)	GS-US-380-1489		GS-US-380-1490	
	BIC/FTC/TAF (n=314)	DTG/ABC/3TC (n=315)	BIC/FTC/TAF (n=320)	DTG+FTC/TAF (n=325)
Any Grade 3 or 4 treatment-emergent toxicity	83 (26)	80 (25)	77[a] (25)	74 (23)
Increased AST level	15 (5)	10 (3)	7[b] (2)	9 (3)
Increased ALT level	7 (2)	6 (2)	10[b] (3)	4 (1)
Increased GGT level	5 (2)	5 (2)	-	-

Abbreviation: GGT=γ-glutamyl transferase.
[a]Total n=314. [b]Total n=313.

Hepatobiliary AEs through Week 240 – OLE phase[4]

At Week 144, all participants were offered enrollment in the OLE phase with BIC/FTC/TAF. A total of 252 participants in Study 1489 and 254 participants in Study 1490 from the BIC/FTC/TAF group continued into the OLE phase.

Table 3. Studies 1489 and 1490: Laboratory Abnormalities in BIC/FTC/TAF Participants Through Week 240[4a]

Parameter, %		Study 1489 (n=314)	Study 1490 (n=320)
Any Grade 3 or 4 laboratory abnormality		34	32
Hepatic-related laboratory abnormality in ≥3% of participants	Increased AST level[b]	5	3
	Increased ALT level[b]	3	4

[a]Included only participants who were initially randomly assigned to receive BIC/FTC/TAF.
[b]No cases of drug-related hepatitis were reported.

GS-US-380-1844

Study design and demographics

Study 1844 was a phase 3, randomized, double-blind study that compared the safety and efficacy of switching to BIC/FTC/TAF (n=282) with that of continuing with their baseline regimen of DTG + ABC/3TC or DTG/ABC/3TC (n=281) in VS, adult PWH.[5,10]

Table 4. Study 1844: Baseline Demographics and Disease Characteristics[5]

Key Demographics and Characteristics		BIC/FTC/TAF (n=282)	DTG/ABC/3TC (n=281)
Age, median (range), years		47 (21–71)	45 (20–70)
Male, %		88	90
Race and ethnicity, %	White/Black or African descent	73/21	73/22
	Hispanic/Latinx	16	19
CD4 cell count, median, cells/mcL		732	661
$eGFR_{CG}$, median, mL/min		101	101

Hepatic lab abnormalities through Week 48[11]

Among the 282 participants who received BIC/FTC/TAF, 17% (n=47) experienced Grade 3 or 4 treatment-emergent toxicity, with 2% (n=6) having ALT level elevation. Hepatic AEs or medical histories associated with ALT level elevation included the following: incident HCV

(n=3), acute hepatitis A (n=1), suspected alcohol abuse (n=1), and medical history of non-alcoholic steatohepatitis (n=1). Among the 281 participants in the DTG/ABC/3TC group, 11% (n=32) experienced Grade 3 or 4 treatment-emergent toxicity, and no instances of ALT level increase were observed.

Hepatobiliary AEs through Week 168 – OLE phase[12]

In the OLE phase, the all-BIC/FTC/TAF group consisted of participants who received ≥1 dose of BIC/FTC/TAF; this was defined as the first dose of BIC/FTC/TAF in the OLE for participants who switched at Week 48. Increased ALT level was reported as a Grade 3 or 4 laboratory abnormality by 11 participants (2%).

GS-US-380-1878

Study design and demographics

Study 1878 was a phase 3, prospective, randomized, open-label clinical trial that compared outcomes in VS, adult PWH who switched to BIC/FTC/TAF (n=290) with those who continued with their baseline regimen of boosted DRV or ATV + 2 NRTIs (n=287).[6,13]

Table 5. Study 1878: Baseline Demographics and Disease Characteristics[6,13]

Key Demographics and Characteristics		BIC/FTC/TAF (n=290)	Boosted DRV or ATV + 2 NRTIs (n=287)
Age, median (range), years		48 (20–74)	47 (21–79)
Male, %		84	82
Race and ethnicity, %	White/Black or African descent	65/27	66/25
	Hispanic/Latinx	21	16
CD4 cell count, median, cells/mcL		617	626
Comorbid HBV and HCV, n		8/5	6/5
$eGFR_{CG}$, median, mL/min		107	105

Hepatic lab abnormalities through Week 48[14]

Among the 290 participants who took BIC/FTC/TAF, 16% (n=45) experienced Grade 3 or 4 treatment-emergent toxicity, with 2% (n=6) having ALT level elevations. Among the 287 participants in the boosted DRV or ATV + 2 NRTIs group, 29% (n=83) experienced Grade 3 or 4 treatment-emergent toxicity and only 1% (n=4) had ALT level elevations.

Hepatobiliary AEs through Week 96 – extension phase[15]

Of the 532 participants who completed the 48-week randomized phase, 515 entered the OLE phase. The all-BIC/FTC/TAF group consisted of participants who received ≥1 dose of BIC/FTC/TAF; safety was assessed at the first dose of BIC/FTC/TAF in the OLE for participants who switched at Week 48. Of the 534 participants in the BIC/FTC/TAF group, 2% had each Grade 3 or 4 AST and ALT level elevations.

References

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Abbreviations

3TC=lamivudine
ABC=abacavir
AE=adverse event
ARV=antiretroviral
ATV=atazanavir
BIC=bictegravir
c/mL=copies/mL
CD4=cluster of differentiation 4
DRV=darunavir
DTG=dolutegravir
FTC=emtricitabine
$eGFR_{CG}$=eGFR by Cockcroft-Gault
NRTI=nucleos(t)ide analog reverse transcriptase inhibitor
OLE=open-label extension
PWH=people with HIV
TAF=tenofovir alafenamide
VS=virologically suppressed

Product Label

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

Follow-Up

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

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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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