GILEAD | Medical Information

Biktarvy® (BIC/FTC/TAF) Use in Participants With HIV/HBV Co-Infection

This document is in response to your request for information on the use of Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide [BIC/FTC/TAF]) in participants with HIV and HBV. BIC/FTC/TAF is not indicated for the treatment of HIV/HBV co-infection.

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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]

Patients with HIV-1 should be tested for the presence of chronic HBV infection before or when initiating ARV therapy.

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.

BIC/FTC/TAF in Participants With HIV and HBV in Phase 3 and 4 Clinical Studies

The ALLIANCE study evaluated BIC/FTC/TAF vs DTG + FTC/TDF in participants with HIV and HBV (N=243). At Week 48, BIC/FTC/TAF was noninferior to DTG + FTC/TDF in the achievement of HIV-1 RNA <50 c/mL (95% vs 91%, respectively) and was superior in the achievement of HBV DNA <29 IU/mL (63% vs 43%, respectively). Rates of HIV and HBV suppression remained high through Week 144 among participants who received BIC/FTC/TAF throughout the study and those who switched from DTG + FTC/TDF to open-label BIC/FTC/TAF at Week 96. No treatment-emergent resistance was detected during BIC/FTC/TAF treatment. Safety outcomes were similar between arms during the randomized phase, and most AEs were Grade 1 or 2 in severity through Week 144. One AE of HCC led to discontinuation of BIC/FTC/TAF treatment.[2-4]

In a phase 4 study in adults with HIV and HBV who switched to BIC/FTC/TAF (N=28), 82% of participants had both HIV RNA <50 c/mL and HBV DNA <29 IU/mL at Week 24. Each of the 10 TRAEs were mild in severity, and no AEs led to treatment discontinuation.[5]

In registrational trials of BIC/FTC/TAF in ARV-naïve and virologically suppressed adults, a small number of participants with HIV and HBV (n=16) were included. Most participants (≥85%) achieved or maintained HIV and HBV suppression.[6] BIC/FTC/TAF was well tolerated in the overall participant population, with ≤2% discontinuing due to AEs.[7,8]

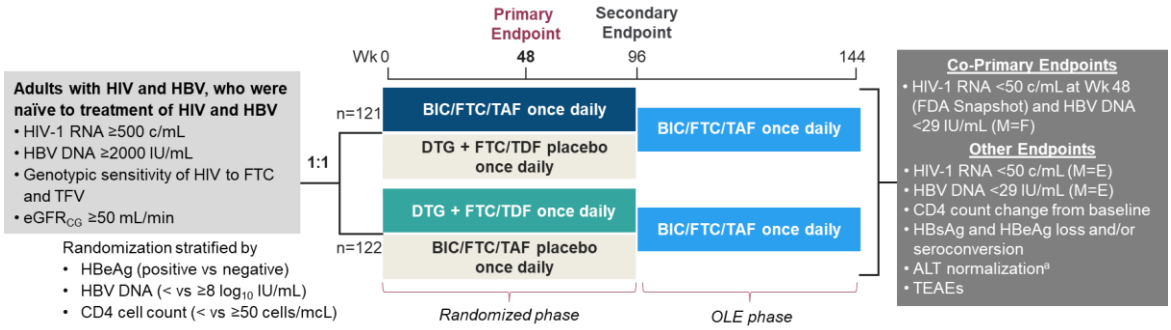
BIC/FTC/TAF in Participants With HIV and HBV in Phase 3 and 4 Studies

ALLIANCE: Phase 3, Randomized, Double-Blind Study

Study design and demographics

ALLIANCE was a phase 3 study that evaluated BIC/FTC/TAF vs DTG + FTC/TDF as initial treatment in adults with HIV and HBV (Figure 1).[2] The co-primary endpoints were the proportions of participants at Week 48 with HIV-1 RNA <50 c/mL (FDA Snapshot algorithm) and HBV DNA <29 IU/mL (M=F analysis). Most of the participants in both arms were male and from Thailand, China, or Malaysia (Table 1). At the end of 96 weeks, participants could enroll in a 48-week OLE, during which all participants received open-label BIC/FTC/TAF. A total of 121 participants who received BIC/FTC/TAF in the randomized phase continued onto the OLE phase; 109 of these participants received BIC/FTC/TAF for ≥144 weeks.[3] A total of 89 participants who received DTG/FTC/TDF in the randomized phase continued onto the OLE.[4]

Figure 1. ALLIANCE: Study Design[2]



Abbreviations: CG=Cockcroft-Gault; TFV=tenofovir.
[a]Participants who had an ALT level <ULN among those who had ALT levels ≥ULN at baseline. ALT ULN was based on AASLD 2018 criteria: females: 25 U/L; males: 35 U/L.

Table 1. ALLIANCE: Baseline Demographics and Disease Characteristics[2]

Key Demographics and Characteristics	BIC/FTC/TAF (n=121)	DTG + FTC/TDF (n=122)
Age, median (IQR), years	31 (27–39)	32 (25–38)
HIV-1 RNA, median (IQR), log_{10} c/mL	4.66 (4.22–5.12)	4.69 (4.26–5.04)
CD4, median (IQR), cells/mcL	245 (127–383)	236 (121–380)
HBV DNA, median (IQR), log_{10} IU/mL	7.96 (6.52–8.38)	8.08 (6.59–8.5)
≥8 log_{10} IU/mL, n (%)	60 (50)	66 (54)
HBV GT, A/B/C/D,[a] n (%)	7 (6)/21 (19)/63 (56)/15 (13)	19 (17)/24 (22)/50 (46)/14 (13)
HBeAg+, n (%)	92 (76)	97 (80)
ALT level >ULN, n (%)	60 (50)	47 (39)

[a]Other GTs (not listed) consisted of GTs of F and mixed. Data were missing for 9 and 13 participants from the BIC/FTC/TAF and DTG + FTC/TDF arms, respectively, during the randomized phase.

Efficacy results

Randomized phase: BIC/FTC/TAF vs DTG + FTC/TDF

At Week 48 (M=F analysis), in the full analysis set (all randomly assigned participants who received ≥1 dose of study drug and had ≥1 on-treatment HIV-1 RNA or HBV DNA assessment after baseline), BIC/FTC/TAF was noninferior to DTG + FTC/TDF in the achievement of HIV-1 RNA <50 c/mL (95% [113/119] and 91% [111/122], respectively; Δ4.1%; *P*=0.21) and was superior in the achievement of HBV DNA <29 IU/mL (63% [75/119] and 43.4% [53/122]; Δ16.6%; *P*=0.0023). At Week 96 (M=F analysis), in the full analysis set, the rates of HIV-1 RNA <50 c/mL were 87% (104/119) with BIC/FTC/TAF and 88% (107/122) with DTG + FTC/TDF (*P*=0.94); the rates of HBV DNA <29 IU/mL were 75% (89/119) and 70% (86/122), respectively (*P*=0.64). The mean change in $\log_{10}$ HBV DNA level in both arms had a similar and gradual decline up to Week 96, with a statistically significant difference (*P*<0.05) in favor of BIC/FTC/TAF compared with DTG + FTC/TDF at Week 12. Treatment adherence was high for both arms through Week 96: BIC/FTC/TAF, 98.5%; DTG + FTC/TDF, 98.3%.[2]

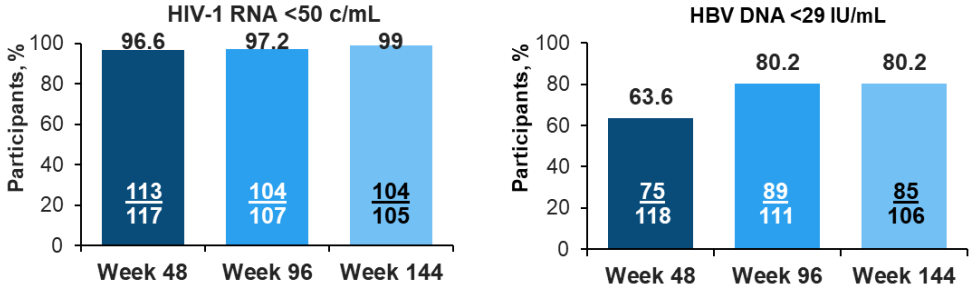
At Week 96, the mean change (SD) in CD4 count from baseline was 261 (161.6) cells/mcL in the BIC/FTC/TAF arm and 229 (174) cells/mcL in the DTG + FTC/TDF arm (*P*=0.19). Participants who received BIC/FTC/TAF had significantly higher rates (*P*<0.05) of HBeAg loss and seroconversion at Week 96 than did participants who received DTG + FTC/TDF. Rates of HBsAg loss and seroconversion were numerically higher in participants who received BIC/FTC/TAF than in those who received DTG + FTC/TDF (*P*=0.066 and *P*=0.44, respectively). A greater proportion of participants who received BIC/FTC/TAF vs DTG + FTC/TDF achieved ALT normalization through Week 96 (*P*<0.05 at Weeks 12, 24, 60, and 72).[2]

A univariate subgroup analysis compared HBV treatment outcomes at Week 96 between BIC/FTC/TAF and DTG + FTC/TDF. In comparison with treatment with DTG + FTC/TDF, treatment with BIC/FTC/TAF was associated with the following: significantly higher rates of HBeAg loss/seroconversion and numerically higher rates of HBsAg loss and ALT normalization across most subgroups analyzed, including Asian participants; study drug adherence ≥95%; age <30 years; baseline HBV DNA <8 $\log_{10}$ IU/mL; baseline HIV-1 RNA ≤100,000 c/mL; HBV GTs B/C; baseline CD4 count ≥200 cells/mcL; abnormal ALT level at baseline or Week 12; HBV DNA <29 IU/mL at Week 48; and no treatment-emergent Grade ≥3 elevations in ALT level by Week 12.[9]

Results through Week 144 in participants who received BIC/FTC/TAF in both study phases[3]

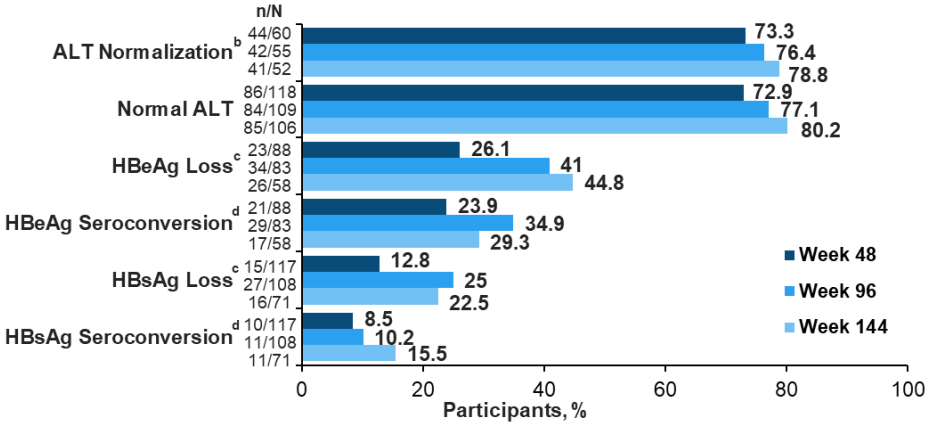
Through Week 144 in the OLE, among participants who continued BIC/FTC/TAF during the randomized phase, rates of HIV-1 RNA and HBV DNA suppression remained high (Figure 2), and rates of ALT normalization and HBeAg and HBsAg loss/seroconversion were maintained (Figure 3).

Figure 2. ALLIANCE: HIV-1 and HBV Suppression With BIC/FTC/TAF Through Week 144 (M=E)[3]



Note: Analysis was performed on the full analysis set (N=119) of participants who received BIC/FTC/TAF in both study phases; the denominators were the number of participants without missing data at each time point.

Figure 3. ALLIANCE: HBV Outcomes With BIC/FTC/TAF Through Week 144 (M=E[a])[3]

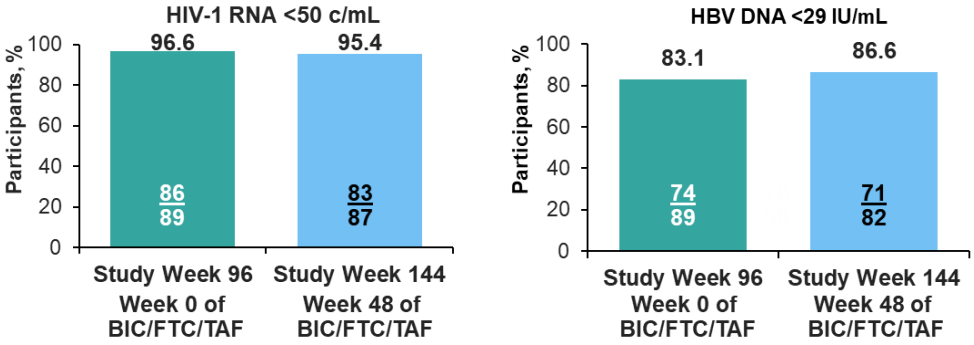


[a]HBeAg and HBsAg loss/seroconversion were assessed in the full analysis set (N=90 for HBeAg; N=119 for HBsAg) of participants who received BIC/FTC/TAF in both study phases. Denominators were the number of participants without missing data at Week 144.
[b]Among participants with ALT level >ULN at baseline, this was defined as a reduction in ALT level to ≤ULN.
[c]Participants who experienced a loss of serum HBeAg/HBsAg and whose baseline HBeAb/HBsAb was negative or missing.
[d]Participants who had a loss of serum HBeAg/HBsAg and whose serum HBeAb/HBsAb changed from negative or missing at baseline to positive at a post-baseline study visit.

OLE phase results through Week 144 in participants who switched to BIC/FTC/TAF[4]

Among the 89 participants who switched from DTG + FTC/TDF to BIC/FTC/TAF at Week 96, rates of HIV-1 RNA and HBV DNA suppression were maintained through Week 144 (48 weeks of BIC/FTC/TAF treatment) in the OLE (Figure 4).

Figure 4. ALLIANCE: HIV-1 and HBV Suppression Through Week 144 in the OLE Among Participants Who Switched to BIC/FTC/TAF at Week 96 (M=E)[4]



Note: Analysis was performed on full analysis set (N=89) of participants who switched to BIC/FTC/TAF from DTG + FTC/TDF; the denominators were the number of participants without missing data at each time point.

Of the 27 participants with abnormal ALT levels at the time of switching to BIC/FTC/TAF (Week 96), approximately half had achieved ALT normalization within 12 weeks of BIC/FTC/TAF treatment (51.9% [14/27]) and this was maintained through 48 weeks of treatment (Week 144: 13/25; 52%). HBV-related outcomes at Week 144 are summarized in Table 2.

Table 2. ALLIANCE: HBV-Related Outcomes at Week 144 in the OLE Among Participants Who Switched to BIC/FTC/TAF at Week 96[4]

Week 144 Outcome, n/N (%)	DTG + FTC/TDF → BIC/FTC/TAF (n=89)
Normal ALT	65/82 (79.3)
HBeAg loss[a]	8/47 (17)
HBeAg seroconversion[b]	6/47 (12.8)
HBsAg loss[a]	3/70 (4.3)
HBsAg seroconversion[b]	0/70 (0)

Note: HBeAg/HBsAg loss/seroconversion analyses were performed in the serologically available full analysis set, which included participants who were HBeAg/HBsAg positive and HBeAb/HBsAb negative or with missing data at baseline (HBeAg, n=52; HBsAg, n=77).

[a]Participants who changed from positive HBeAg/HBsAg at baseline to negative at a post-baseline visit and whose baseline HBeAb/HBsAb was negative or missing.

[b]Participants who had a loss of serum HBeAg/HBsAg and whose serum HBeAb/HBsAb changed from negative or missing at baseline to positive at a post-baseline study visit.

Resistance results

Through Week 96, no HIV-1 treatment-emergent resistance was detected in the BIC/FTC/TAF arm. One participant in the DTG + FTC/TDF arm with known nonadherence developed K70E and M184V/I mutations. No HBV amino acid substitutions associated with TAF or TDF resistance were detected through Week 48.[2]

Resistance analyses using the last-observation-carried-forward method were conducted through Week 144 in participants who met the criteria for post-baseline resistance testing and who did not achieve virological resuppression (HIV-1 RNA <50 c/mL). The criteria for post-baseline resistance testing were as follows: virologic failure (HIV-1 RNA ≥50 c/mL at last on-treatment visit; confirmed HIV-1 RNA ≥50 c/mL after achieving HIV-1 RNA <50 c/mL; or confirmed >1 $\log_{10}$ increase from nadir HIV-1 RNA) plus HIV-1 RNA ≥200 c/mL at confirmation visit or HIV-1 RNA ≥200 c/mL at the end of the randomized phase, end of study, or at the last on-treatment visit. Through Week 144, rates of HIV-1 RNA <50 c/mL were high regardless of the presence of primary RAMs at baseline. At the end of the

randomized phase (Week 96), 7 participants (5.7%) in the DTG + FTC/TDF arm met the criteria for the resistance analysis. Through Week 144, 6 participants (5%) who received BIC/FTC/TAF throughout the study and 1 participant (1.1%) who switched to BIC/FTC/TAF met the criteria for the resistance analysis. No treatment-emergent primary RAMs were detected, and no participant developed resistance to study drugs.[10]

Safety results

Through Week 96, most AEs were Grade 1 or 2 in severity, rates of drug-related AEs were similar between the BIC/FTC/TAF and DTG + FTC/TDF arms (29% and 28%, respectively), and the rate of hepatic AEs was 24% in both arms. The most common (≥5% of participants in either arm) TRAEs in the BIC/FTC/TAF and DTG + FTC/TDF arms were weight increase (8% vs 10%) and ALT increase (2% vs 7%). One AE led to discontinuation in the BIC/FTC/TAF arm (HCC on Day 1115). One SAE (cryptococcal meningitis) was reported as drug related (attributed to immune reconstitution inflammatory syndrome) in the BIC/FTC/TAF arm.[2]

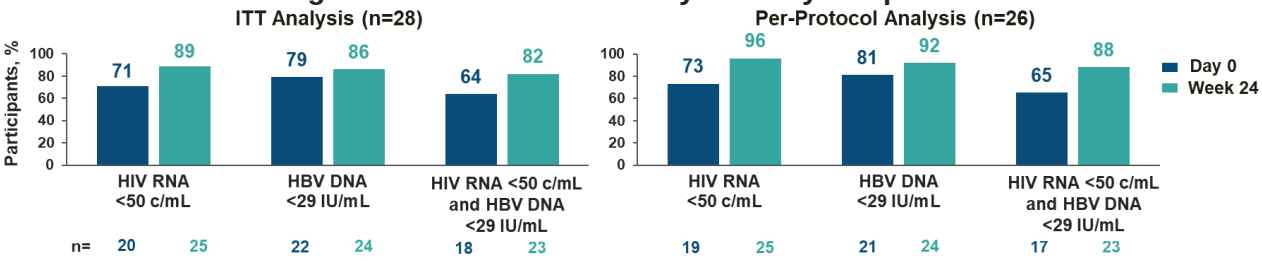
Through Week 144, among participants who received BIC/FTC/TAF in both study phases, most TEAEs were Grade 1 or 2 in severity. The most common drug-related TEAEs were weight increased (7%), and abnormal weight gain, ALT increased, dyslipidemia, and headache (each, 3%). The most common (≥5% of participants) Grade 3/4 laboratory abnormalities included increased ALT and AST levels (>5 × ULN) in 23% and 13% of participants, respectively; increased fasting LDL levels (9%); and increased amylase levels (8%). Seven participants (6%) had confirmed ALT flares (treatment-emergent ALT elevations at ≥2 post-baseline study visits); the flares occurred during the first 3 months in 6 participants. All events were deemed to be not related to treatment, nonserious, and nearly all resolved in <3 months; 1 participant had an ALT flare for 116 days.[3]

Among participants who switched to BIC/FTC/TAF, drug-related TEAEs occurred in 19% of participants during the OLE (through Week 144), with weight gain (9%) and increased LDL cholesterol level (3%) being the most common. Grade 3/4 drug-related AEs occurred in 3 participants (3%) and consisted of abnormal weight gain (n=2) and hyperlipidemia (n=1). Fasting hypercholesterolemia was the only Grade 3/4 laboratory abnormality that occurred in >1 participant (n=3; 3%). No AEs led to discontinuation of BIC/FTC/TAF after participants switched from DTG + FTC/TDF. Small median increases in eGFR (+6.6 mL/min) and total and LDL cholesterol levels (+17 mg/dL and +19 mg/dL, respectively) were observed from OLE baseline (Week 96) to Week 144, and 3 participants (3.4%) initiated lipid-lowering medications. Other metabolic parameters remained stable after participants switched.[4]

BEST-HBV: Phase 4, Open-Label, Single-Arm Study[5]

A phase 4 study evaluated the efficacy and safety of switching to BIC/FTC/TAF in adults with HIV and HBV. The primary endpoints were the proportion of participants who achieved HIV-1 RNA <50 c/mL by FDA Snapshot algorithm and HBV DNA <29 IU/mL by M=F analysis at Week 24. Most participants were male (86%), were Black or African American (89%), and had HIV-1 RNA <50 U/mL (71%) and HBV DNA <29 IU/mL (79%) at baseline.

Figure 3. BEST-HBV: Primary Efficacy Endpoints[5]



Of the 35 AEs reported, 10 were TRAEs (all mild in severity). Nausea was the most common TRAE (n=2; 7%). No participant experienced SAEs, discontinued BIC/FTC/TAF due to AEs, or experienced flares of hepatitis.

Phase 3 Registrational Studies: Studies 1490 and 1878

Two registrational studies (Study 1490 and Study 1878) allowed participants with HIV and HBV to be included. Sixteen participants (<3%) with HIV and HBV were randomly assigned to receive BIC/FTC/TAF in these clinical trials.[6]

Of the 320 ARV-naïve adults randomly assigned to receive BIC/FTC/TAF in Study 1490, 8 had HIV and HBV at screening. At Week 144, 5 of these participants had HBV DNA <29 IU/mL and HIV-1 RNA <50 c/mL. The other 3 participants had missing HBV DNA data at Week 144. No hepatic AEs, Grade 3 or 4 AEs, or treatment interruptions or discontinuations due to AEs were reported in these participants with HIV/HBV co-infection.[7]

Of the 290 virologically suppressed adults randomly assigned to receive BIC/FTC/TAF in Study 1878, 8 had HIV and HBV at screening, and all had HBV DNA <29 IU/mL at baseline. At Week 48, all 8 participants maintained HBV DNA <29 IU/mL and HIV-1 RNA <50 c/mL. The participants were HBsAg+ at baseline and Week 48.[6] Safety outcomes in participants with HIV and HBV were not analyzed separately. In the overall study population, BIC/FTC/TAF was well tolerated, with 1% discontinuing due to AEs and most TRAEs being mild or moderate in severity.[8]

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Abbreviations

AASLD=American Association for the Study of Liver Diseases
AE=adverse event
ARV=antiretroviral
BIC=bictegravir
c/mL=copies/mL
CD4=clusters of differentiation 4
DTG=dolutegravir
FTC=emtricitabine
GT=genotype
HBeAb=hepatitis B envelope antibody
HBeAg=hepatitis B envelope antigen
HBsAb=hepatitis B surface antibody
HBsAg=hepatitis B surface antigen
HCC=hepatocellular carcinoma
M=E=missing equals excluded
M=F=missing equals failure
OLE=open-label extension
RAM=resistance-associated mutation
SAE=serious adverse event
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
TEAE=treatment-emergent adverse event
TRAE=treatment-related adverse event
ULN=upper limit of normal

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

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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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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