GILEAD | Medical Information

Biktarvy® (BIC/FTC/TAF) Bone Safety Profile

This document is in response to your request for information regarding the bone safety profile of Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide [BIC/FTC/TAF]).

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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

Gilead Clinical Data on the Bone Safety Profile of BIC/FTC/TAF

Bone safety data from two phase 3 clinical trials (in ARV-naive participants who initiated BIC/FTC/TAF treatment and VS PWH who switched to BIC/FTC/TAF treatment) showed that changes from baseline in spine and hip BMD were similar between the BIC/FTC/TAF and DTG/ABC/3TC treatment arms.[1-5] In ARV-naive participants randomized to BIC/FTC/TAF, there were small declines in spine and hip BMD from baseline through Week 240.[4]

Non-Gilead Clinical Data on the Bone Safety Profile of BIC/FTC/TAF

In an open-label study, VS PWH switched from a first-line regimen to BIC/FTC/TAF or continued their current regimen (CAR group). The mean percent (SD) change from baseline to Week 48 in lumbar spine BMD was significantly greater in the BIC/FTC/TAF group than in the CAR group: +2.17% (5.23) vs +0.61% (5.44; difference, 1.56%; 95% CI: 0.32–2.79; *P*=0.014).[6]

In a clinical trial that assessed BMD improvement among WLWH, participants who switched to BIC/FTC/TAF from a TDF regimen had an improved mean percent change in BMD at 6 and 12 months.[7]

In a randomized pilot study, VS PWH switched to BIC/FTC/TAF or continued their TDF-based regimen. Bone quality (via BMSi) significantly improved from baseline to Week 24 in the BIC/FTC/TAF group (*P*=0.041).[8]

Gilead Clinical Data on the Bone Safety Profile of BIC/FTC/TAF

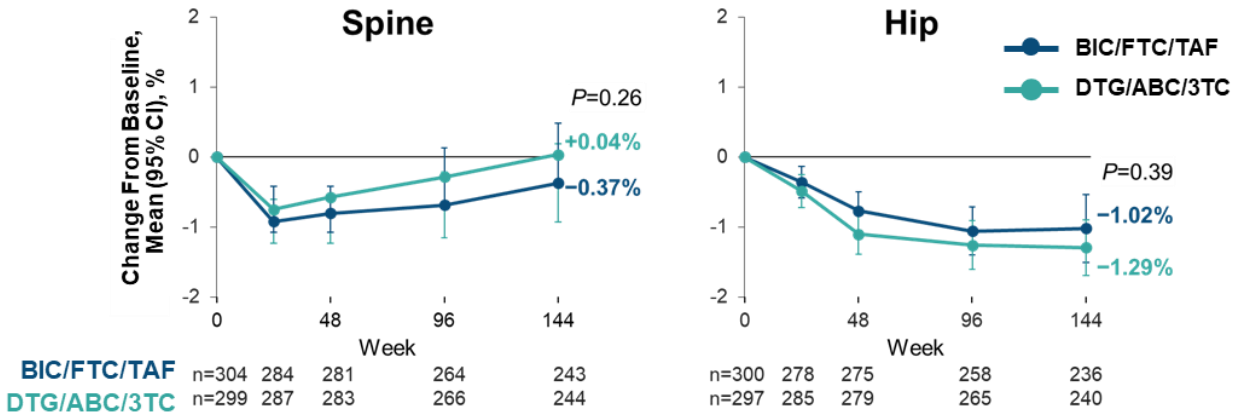
Study GS-US-380-1489

A phase 3, prospective, randomized, double-blind, active-controlled clinical trial compared BIC/FTC/TAF (n=314) to DTG/ABC/3TC (n=315) in ARV-naive PWH. Key inclusion criteria were HIV-1 RNA ≥500 c/mL at screening, $eGFR_{CG}$ ≥50 mL/min, and genotypic sensitivity to

the nucleos(t)ide reverse transcriptase inhibitor components of the study regimen. The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 c/mL at Week 48 by the FDA Snapshot analysis, with a prespecified non-inferiority margin of 12%. Secondary endpoints were efficacy and safety through Week 96 and Week 144, including the mean percent changes from baseline in hip and lumbar spine BMD (via DXA scans).[1]

Changes in hip and lumbar spine BMD from baseline to Week 144 were similar between the BIC/FTC/TAF and DTG/ABC/3TC arms (Figure 1).[5]

Figure 1. Study 1489: Change in Hip and Lumbar Spine BMD Through Week 144[5,9]



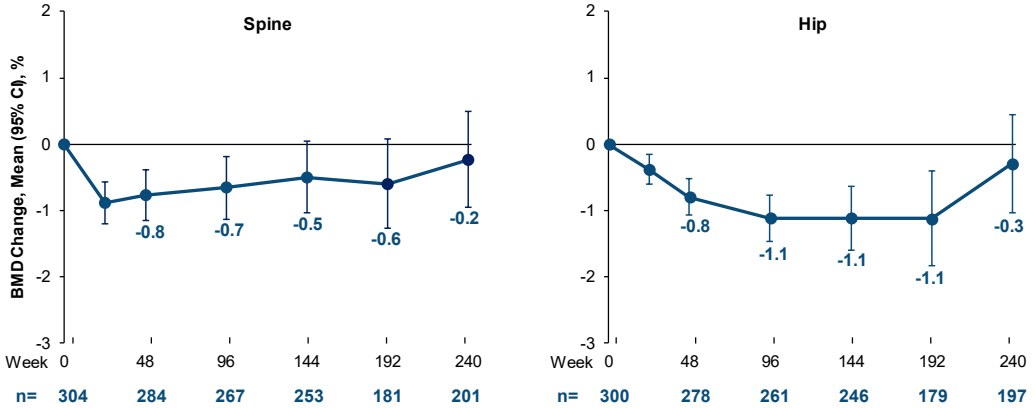
Subanalysis of participants aged ≥50 vs <50 years – bone safety[10]

In a Week 144 subanalysis, changes from baseline in hip and spine BMD were comparable for BIC/FTC/TAF and DTG/ABC/3TC in participants aged ≥50 vs <50 years.

OLE – bone safety[3,4]

At Week 144, all participants were offered enrollment in the OLE phase with BIC/FTC/TAF. In Study 1489, 254 participants who received DTG/ABC/3TC switched to BIC/FTC/TAF, and 252 continued to receive BIC/FTC/TAF in the OLE phase. At Week 240, in participants initially randomized to BIC/FTC/TAF, there were small declines in spine and hip BMD from baseline (Figure 2).

Figure 2. Study 1489: Change in Spine and Hip BMD Through Week 240 With BIC/FTC/TAF[4a]



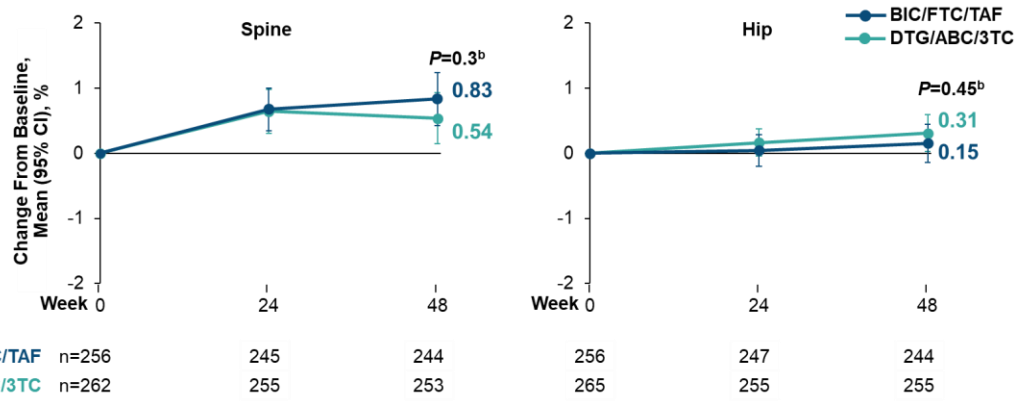
[a]Included only participants initially randomized to receive BIC/FTC/TAF.

Study GS-US-380-1844

A phase 3, randomized, double-blind study evaluated the safety and efficacy of switching to BIC/FTC/TAF (n=282) vs staying on a baseline regimen of DTG + ABC/3TC or DTG/ABC/3TC (n=281) in VS PWH. Key inclusion criteria were HIV-1 RNA <50 c/mL at screening for ≥3 months with no history of treatment failure, $eGFR_{CG}$ ≥50 mL/min, and no documented or suspected resistance to study drugs. The primary endpoint was the proportion of participants with plasma HIV-1 RNA ≥50 c/mL at Week 48 by the FDA Snapshot analysis with a prespecified non-inferiority margin of 4%. Secondary endpoints were the proportion of participants with plasma HIV-1 RNA <50 c/mL by the FDA Snapshot analysis, change from baseline in CD4+ count, and change from baseline in hip and spine BMD, all at Week 48.[2,11]

Changes from baseline in BMD were similar between treatment arms through Week 48 (Figure 3).[2]

Figure 3. Study 1844: Change in Hip and Lumbar Spine BMD Through Week 48[12a]



[a]Based on a data cut date of April 26, 2020.
[b]Analysis of variance model comparing BIC/FTC/TAF with DTG/ABC/3TC at Week 48.

Non-Gilead Clinical Data on the Bone Safety Profile of BIC/FTC/TAF

BIC/FTC/TAF-Elderly Study in African PWH Aged ≥60 Years[6]

A randomized, open-label, active-controlled, non-inferiority, 96-week study in Kenya compared the efficacy and safety of switching from a first-line regimen to BIC/FTC/TAF (n=260) or continuing on the current regimen (CAR group; n=260). Eligible participants were PWH aged ≥60 years who had HIV-1 RNA <50 c/mL for ≥12 weeks, had received an ARV regimen for ≥24 weeks, and had no prior history of virologic failure. The co-primary endpoints at Week 48 were the proportion of participants with HIV-1 RNA ≥50 c/mL via FDA Snapshot (ITT population; non-inferiority margin, 4%) and the mean percent change in lumbar spine BMD from baseline.

Baseline demographics and characteristics in the BIC/FTC/TAF and CAR groups were similar in both groups, with ≥90% currently receiving a TDF based regimen.

The mean percent (SD) change in lumbar spine BMD from baseline to Week 48 was significantly greater in the BIC/FTC/TAF group (n=140) than in the CAR group (n=151): +2.17% (5.23) vs +0.61% (5.44; difference, 1.56%; 95% CI: 0.32–2.79; *P*=0.014).

No treatment-related serious AEs occurred. Study drug discontinuations due to AEs occurred in 1 (0.4%) and 15 (5.8%) participants in the BIC/FTC/TAF and CAR groups, respectively; all of these discontinuations in the CAR group occurred due to worsening kidney function.

Bone Mass Recovery in WLWH[7]

A randomized clinical trial assessed whether switching to BIC/FTC/TAF (n=111) or staying on a TDF ARV regimen (n=110) would lead to bone mass recovery in WLWH who were also receiving DMPA-IM. A third group included WLWH who switched to BIC/FTC/TAF from a TDF ARV regimen and were using a nonhormonal contraception method (n=125). BMD assessments were determined by DXA scans.

In both groups, there was improvement in the mean percent change in BMD at 6 and 12 months after switching to BIC/FTC/TAF. Among the two switch groups, participants receiving nonhormonal contraception had a significantly higher mean percent change in lumbar spine BMD than did participants receiving DMPA-IM (*P*=0.029); differences were not significant at the total hip (*P*=0.516) or femoral neck (*P*=0.615). In both treatment groups, participants receiving nonhormonal contraception had higher BMD Z-scores at baseline and throughout treatment than those receiving DMPA-IM (*P*≤0.021).

Open-Label, Randomized Pilot Study in Spain[8]

An open-label, randomized, single-center pilot study in Spain evaluated the changes in bone quality and BMD in VS PWH who switched from a TDF-based regimen (three-drug regimen including FTC) to BIC/FTC/TAF (n=12) or continued their previous TDF-based regimen (n=12). BMSi (correlated with bone quality using a minimally invasive bone microindentation procedure) and BMD were assessed at baseline and at Week 24. The primary endpoint was the mean percent change in BMSi at Week 24, and secondary endpoints included changes from baseline to Week 24 in spine and hip BMD and bone turnover markers. Most participants were male, with median age at enrollment of 45 years, all with HIV-1 RNA <19 c/mL.

A significant median (IQR) increase in bone quality (BMSi) from baseline to Week 24 was observed for the BIC/FTC/TAF group (81.6 [79–83] to 86 [80–88]; mean change, +5.1%; *P*=0.041); the change in the TDF-based group was not significant (82.35 [76–85] to 82 [73.5–83]; mean change, -0.05%; *P*=0.812). The difference in bone quality at Week 24 between the BIC/FTC/TAF and TDF-based groups was significant (*P*=0.049). No significant changes from baseline or differences between treatment groups in BMD values at Week 24 were observed for the lumbar spine or femoral neck in the BIC/FTC/TAF (median [IQR] Week 24 values, 0.979 [0.863–1.041] and 0.791 [0.668–0.824] g/cm^2, respectively) and TDF-based groups (0.991 [0.811–1.042] and 0.794 [0.689–0.893] g/cm^2, respectively). In both groups, significant decreases at Week 24 in P1NP (bone formation marker) were observed (*P*≤0.032); significant decreases in CTX (bone resorption marker) were only observed in the BIC/FTC/TAF group (*P*=0.028).

References

1. Wohl DA, Yazdanpanah Y, Baumgarten A, et al. Bictegravir Combined with Emtricitabine and Tenofovir Alafenamide Versus Dolutegravir, Abacavir, and Lamivudine for Initial Treatment of HIV-1 Infection: Week 96 Results from a Randomised, Double-Blind, Multicentre, Phase 3, Non-Inferiority Trial. *The Lancet HIV.* 2019;6(6):e355-e363.
2. Molina JM, Ward D, Brar I, et al. Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir plus abacavir and lamivudine in virologically suppressed adults with HIV-1: 48 week results of a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. *The Lancet HIV.* 2018;5(7):e357-365. http://www.ncbi.nlm.nih.gov/pubmed/29925489
3. Workowski K, Orkin C, Sax P, et al. Four-year outcomes of B/F/TAF in treatment-naïve adults [Poster 2268]. Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI) Virtual; 6-10 March, 2021.
4. Wohl DA, Pozniak A, Workowski K, et al. B/F/TAF Five-Year Outcomes in Treatment-Naïve Adults [Poster 494]. Paper presented at: Virtual Conference on Retroviruses and Opportunistic Infections (CROI) 2022; 12-16 February, 2022.
5. Orkin C, DeJesus E, Sax PE, et al. Three-Year Outcomes of the Fixed-Dose Combination Bictegravir, Emtricitabine, and Tenofovir Alafenamide vs Dolutegravir-Containing Regimens for Initial Treatment of HIV-1 Infection: Week 144 Results from Two Randomised, Double-Blind, Multicentre, Phase 3, Non-Inferiority Trials. *The Lancet HIV.* 2020;7:e389–400.
6. Ombajo LA, Penner J, Nkuranga J, et al. A Randomized Trial Switching Adults ≥ 60 Years Old From First-Line ART to B/F/TAF: Week 48 Results [Poster 00643]. Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI); March 3-6, 2024; Denver, CO.
7. Kiweewa F, Beksinska ME, Nabwana M, et al. Recovery of Bone Mass in Women on Depo-Provera and TDF based ART Switched to B/F/TAF [Poster 0685] Paper presented at: CROI; February 19-22, 2023; Washington, USA.
8. Soldado-Folgado J, Rins-Lozano O, Arrieta-Aldea I, et al. Changes in bone quality after switching from a TDF to a TAF based ART: A pilot randomized study. *Front Endocrinol.* 2023;14:1076739.
9. Orkin C, Sax PE, Arribas J, et al. Long-term Efficacy and Safety of Bictegravir/Emtricitabine/Tenofovir Alafenamide in ART-Naïve Adults [Poster PE3/14]. Paper presented at: 17th European AIDS Conference; 06-09 November, 2019; Basel, Switzerland.
10. Mills A, Gupta SK, Brinson C, et al. 144-Week Efficacy and Safety of B/F/TAF in Treatment-Naive Adults Age ≥50 Years [Presentation]. Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI); 08-11 March, 2020; Boston, MA.
11. U.S. National Institutes of Health. Safety and Efficacy of Switching From Dolutegravir and ABC/3TC or ABC/DTG/3TC to B/F/TAF in HIV-1 Infected Adults Who Are Virologically Suppressed. ClinicalTrials.gov Identifier: NCT02603120. Available at: https://www.clinicaltrials.gov/ct2/show/record/NCT02603120.
12. Brar I, Ruane P, Ward D, et al. Long-term Follow-up After a Switch to Bictegravir, Emtricitabine, and Tenofovir Alafenamide From Dolutegravir, Abacavir, and Lamivudine [Poster 1028]. Paper presented at: IDWeek Virtual; 21-25 October, 2020.

Abbreviations

3TC=lamivudine
ABC=abacavir
AE=adverse event
ARV=antiretroviral
BIC=bictegravir
BMD=bone mineral density
BMSi=Bone Material Strength index
c/mL=copies/mL
CAR=continue antiretroviral therapy regimen
CD4=cluster of differentiation 4
CG=Cockcroft-Gault
CTX=collagen type I C-telopeptide
DMPA-IM=intramuscular depot medroxyprogesterone acetate
DTG=dolutegravir
DXA=dual energy X-ray absorptiometry
FTC=emtricitabine
OLE=open-label extension
P1NP=amino propeptide of type I collagen
PWH=people with HIV
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
VS=virologically suppressed
WLWH=women living with HIV

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:

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🖱 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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