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Biktarvy® (BIC/FTC/TAF) Use in Baseline PI Resistance

This document is in response to your request for information regarding Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide [BIC/FTC/TAF]) and its use in patients with baseline protease inhibitor resistance (PI-R).

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/biktarvy/biktarvy_pi.

Summary

Product Labeling[1]

BIC/FTC/TAF is indicated as a complete regimen for the treatment of HIV-1 in adults and pediatric patients weighing ≥14 kg who have no ARV treatment history, or with an ARV treatment history and not virologically suppressed, with no known or suspected substitutions associated with resistance to the INSTI class, FTC, or TFV, or to replace the current ARV regimen in those who are VS (HIV-1 RNA <50 c/mL) on a stable ARV regimen with no known or suspected substitutions associated with resistance to BIC or TFV.

Clinical Data on BIC/FTC/TAF Use in Patients With Baseline PI-R

In a pooled analysis of two phase 3 clinical trials in ARV-naïve participants (Studies 1489 and 1490), 100% of participants (18/18) with preexisting PI-R who received BIC/FTC/TAF were virologically suppressed at Week 144.[2]

In an integrated viral resistance analysis of two phase 3 clinical trials in virologically suppressed participants (Studies 1878 and 1844), 100% of participants (55/55) with baseline PI-R who received BIC/FTC/TAF maintained virologic suppression at Week 48.[3]

In a phase 3, double-blind, active-controlled study (4030), 100% of participants (15/15) with PI-R who received BIC/FTC/TAF maintained HIV-1 RNA <50 c/mL at Week 48 by LOCF.[4]

A phase 3 study (BRAAVE 2020) in virologically suppressed PWH who self-identified as Black, African American, or mixed-race, found that switching to BIC/FTC/TAF was noninferior to continuing a baseline regimen of two NRTIs plus a third agent at Week 24.[5] At Week 72, 100% of participants (61/61) with PI-R had HIV-1 RNA <50 c/mL.[6]

Clinical Data on BIC/FTC/TAF Use in Patients With Baseline PI-R

Pooled Efficacy and Baseline Resistance in ARV-Naïve Participants

Study design and demographics

An integrated viral resistance analysis of two phase 3 BIC/FTC/TAF clinical trials in ARV-naïve participants (Studies 1489 and 1490) was conducted. All participants were screened using HIV-1 genotypic data with PR and RT population sequencing data obtained from the GenoSure MG assay.[7,8] Exclusion criteria included FTC or tenofovir resistance (Studies 1489 and 1490) and ABC or 3TC resistance (Study 1489). Screened participants with mutations that conferred resistance to the NRTIs studied (eg, M184V/I and K65R/E/N) were excluded from study participation as well.[7]

Efficacy results

BIC/FTC/TAF demonstrated noninferior efficacy (HIV-1 RNA <50 c/mL) to DTG/ABC/3TC (Study 1489) and DTG + FTC/TAF (Study 1490) by FDA Snapshot analysis at the Week 48 primary endpoint and the secondary endpoints at Weeks 96 and 144.[9-11] At Week 144, 98% of all participants (598/609) in the BIC/FTC/TAF group had HIV-1 RNA <50 c/mL. Preexisting PI-R using a mutation frequency cut off of ≥15% was discovered in 19 participants taking BIC/FTC/TAF; 100% of participants (18/18) with post-baseline on-treatment data were virologically suppressed at Week 14.[2]

Retrospective next-generation sequencing/deep sequencing techniques were used to analyze low-frequency viral variants in PR, RT, and integrase. Primary PI-R mutations were detected at low frequencies (2–15%) using deep sequencing in an additional 5.8% of ARV-naïve participants (74/1270). Using the LOCF method, high rates of virologic suppression (94–100%) were observed in participants with baseline primary PI-R at Week 96 across all treatment arms.[8]

Safety results at Week 144[11]

A safety analysis was not conducted in the subgroup of participants with PI-R at baseline. The most common any-grade adverse reactions reported in ≥10% of all participants in the BIC/FTC/TAF arms in either study through Week 144 were nausea, diarrhea, URTI, headache, nasopharyngitis, back pain, fatigue, cough, and syphilis. AEs led to study drug discontinuation in no participants in the BIC/FTC/TAF arm in Study 1489 and 6 participants (2%) in the BIC/FTC/TAF arm in Study 1490, compared with 5 discontinuations (2%) in the DTG/ABC/3TC arm and 6 discontinuations (2%) in the DTG + FTC/TAF arm.

Efficacy and Baseline Resistance in Virologically Suppressed Participants With Preexisting PI-R

Resistance analysis: Studies 1878 and 1844

Study design and demographics[3]

An integrated viral resistance analysis of two phase 3 BIC/FTC/TAF clinical trials in virologically suppressed participants (Studies 1878 and 1844) was conducted. Exclusion criteria included documented resistance to study drugs or a history of virological failure. Researchers attempted to perform retrospective analyses of HIV-1 proviral DNA from baseline samples for all participants in the BIC/FTC/TAF group and some participants in the comparator groups.

Efficacy results at Week 48[3]

At Week 48, 98% of all participants (561/570) in the BIC/FTC/TAF group had HIV-1 NA <50 c/mL. Participants in the BIC/FTC/TAF arms with available baseline PI genotypic data (n=543) included 10% with primary PI-R substitutions (M46I/L [n=22]; L90M [n=13]; D30N [n=9]; V82A/L/T [n=7]; I84V [n=5]; I47V, N83D, and N88S [each n=2]; and, V32I, I50V, I54L, Q58E, and L76V [each n=1]). All 55 participants with baseline PI-R who switched to BIC/FTC/TAF maintained virologic suppression at Week 48.

Results from open-label extension phase

In Study 1878, 52/52 participants with baseline PI-R taking BIC/FTC/TAF for a median duration of 103 weeks had HIV-1 RNA <50 c/mL at their last visit.[12] In Study 1844, 53/54 participants with baseline PI-R who received BIC/FTC/TAF for a median duration of 96 weeks had HIV-1 RNA <50 c/mL at their last visit.[13]

Safety results

A safety analysis was not conducted in the subgroup of participants with PI-R at baseline. In Study 1878, the most common all-grade adverse reactions reported in ≥10% of all participants taking ≥1 dose of BIC/FTC/TAF through a median exposure of 101 weeks were headache, nasopharyngitis, URTI, and diarrhea. AEs led to study drug discontinuation in 6 participants (1%) in the pooled BIC/FTC/TAF group.[14] In Study 1844, the most common any-grade adverse reactions reported in ≥10% of all participants taking ≥1 dose of BIC/FTC/TAF through a median exposure of 96 weeks were URTI, nasopharyngitis, and diarrhea. AEs led to study drug discontinuation in 7 participants (1%) in the pooled BIC/FTC/TAF group.[13]

Study 4030

Study design and demographics[15]

A phase 3, randomized, double-blind, multicenter, active-controlled study evaluated the efficacy of BIC/FTC/TAF (n=284) vs DTG + FTC/TAF (n=281) in PWH who were virologically suppressed, including those with known baseline resistance mutations. Known or suspected resistance to NRTIs, PIs, and/or NNRTIs were permitted.

Efficacy results at Week 48

Switching to BIC/FTC/TAF demonstrated noninferior efficacy (HIV-1 RNA ≥50 c/mL) by FDA Snapshot analysis vs staying on DTG + FTC/TAF at the Week 48 primary endpoint.[15] Primary PI-R substitutions were present in 7% of all participants, and HIV-1 RNA <50 c/mL was maintained in 100% of participants in the BIC/FTC/TAF (15/15) and DTG + FTC/TAF (23/23) groups with PI-R at Week 48 by LOCF method.[4]

Safety results at Week 48[15]

A safety analysis was not conducted in the subgroup of participants with PI-R at baseline. The most frequently reported AEs (≥10%) in either group were nasopharyngitis, diarrhea, and URTI. AEs led to study drug discontinuation in 6 participants (2%) in each arm.

BRAAVE 2020 Study

Study design and demographics[16]

A phase 3, randomized, active-controlled study evaluated the safety and efficacy of switching to BIC/FTC/TAF (n=330) or continuing a baseline regimen of two NRTIs plus a third agent (n=165) in PWH who were virologically suppressed, located in the US, and self-identified as Black, African American, or mixed-race, including Black. Exclusion criteria consisted of primary INSTI-R or NRTI-R (K65R/E/N, T69 insertions, or ≥3 TAMs). Resistance to PIs, NNRTIs, and NRTIs (M184V/I, 1–2 TAMs, and other substitutions) were permitted. Baseline resistance was analyzed using historical genotypes and retrospective HIV-1 proviral DNA genotype testing of baseline samples.

Efficacy results through Week 72[6]

Preexisting baseline PI mutations were detected in 13% of participants (n=61); 2% (n=11) were associated with resistance to atazanavir or darunavir. At Week 72, 99% of participants (486/489) in the pooled BIC/FTC/TAF group and 100% of participants (61/61) with PI-R had HIV-1 RNA <50 c/mL.

Safety results[5]

A safety analysis was not conducted in the subgroup of participants with PI-R at baseline. All-grade AEs that occurred in ≥5% of participants receiving BIC/FTC/TAF at any time (n=493) included URTI, syphilis, headache, pain in extremity, arthralgia, hypertension, and nasopharyngitis. AEs led to study drug discontinuation in 12 participants in the pooled BIC/FTC/TAF group.

References

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Abbreviations

3TC=lamivudine
ABC=abacavir
AE=adverse event
ARV=antiretroviral
BIC=bictegravir
DTG=dolutegravir
FTC=emtricitabine
INSTI=integrase strand transfer inhibitor
LOCF=last observation carried forward
NNRTI=non-nucleos(t)ide reverse transcriptase inhibitor
NRTI=nucleos(t)ide reverse transcriptase inhibitor
PI=protease inhibitor
PR=protease
PWH=people with HIV
R=resistance
RT=reverse transcriptase
TAF=tenofovir alafenamide
TAM=thymidine analog mutation
TFV=tenofovir
URTI=upper respiratory tract infection

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

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

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