

# Biktarvy<sup>®</sup> (BIC/FTC/TAF)

## Efficacy and Safety by Baseline CD4

This document is in response to your request for information on the efficacy and general safety profile of Biktarvy<sup>®</sup> (bictegravir/emtricitabine/tenofovir alafenamide [BIC/FTC/TAF]) by baseline (BL) cluster of differentiation 4 (CD4) cell count in antiretroviral (ARV)-naive people with HIV (PWH). This response was developed according to principles of evidence-based medicine and includes data from Gilead-sponsored studies.

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## Summary

### Clinical Data: BIC/FTC/TAF in PWH by BL CD4 Count

Studies 1489 and 1490 compared the efficacy and safety of BIC/FTC/TAF with DTG-containing regimens in ARV-naive PWH.<sup>1,2</sup> In a pooled analysis, BIC/FTC/TAF demonstrated non-inferior efficacy to triple therapy DTG-containing regimens at Week 48, with high virologic response rates regardless of low CD4 count (99%) or both high VL and low CD4 count (97%) at BL.<sup>3</sup> High rates of virologic suppression were maintained at Week 144, and BIC/FTC/TAF remained non-inferior to both DTG-based regimens.<sup>4</sup> In participants who were randomly assigned to BIC/FTC/TAF, high rates of virologic suppression were maintained at Week 240 regardless of BL CD4 cell count.<sup>5</sup>

In the LAPTOP study, which assessed the efficacy and safety of BIC/FTC/TAF (n=220) vs DRV/c/FTC/TAF (n=222) in ARV-naive adults with advanced HIV-1, BIC/FTC/TAF was non-inferior to DRV/c/FTC/TAF in the composite endpoint of virologic failure or clinical events.<sup>6</sup>

### RWD: BIC/FTC/TAF in PWH by BL CD4 Count

In BICSTaR, a large, prospective, observational cohort study, significantly fewer ARV-naive participants with BL CD4 <200 cells/mcL and/or ≥1 AIDS-defining event achieved virologic suppression at 12 months than participants with BL CD4 ≥200 cells/mcL (85.5% vs 96.4%, respectively;  $P=0.006$ ).<sup>7</sup>

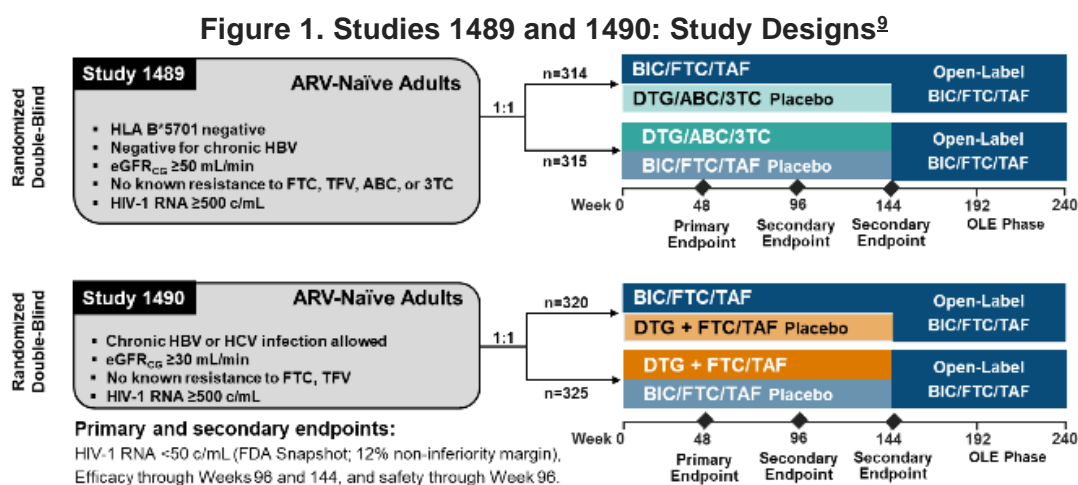
In a study of patients in the OPERA database with a BL CD4 cell count ≤200 cells/mcL, patients treated with BIC/FTC/TAF were more likely to recover to a CD4 cell count >200 cells/mcL and achieve virologic suppression than patients on a boosted regimen.<sup>8</sup>

## Clinical Data: BIC/FTC/TAF in PWH by BL CD4 Count

### Studies 1489 and 1490

#### Study designs and demographics

Studies 1489 and 1490 compared BIC/FTC/TAF to DTG-containing regimens (Figure 1).<sup>1,2</sup> Participants transitioned into the open-label phase after the last participant reached Week 144. A pooled analysis of Studies 1489 and 1490 was also conducted. BL characteristics were similar between treatment arms (Table 1).<sup>4,9</sup>



Abbreviations: eGFR<sub>CG</sub>=eGFR by Cockcroft-Gault; HLA=human leukocyte antigen; OLE=open-label extension; TFV=tenofovir.

**Table 1. Studies 1489 and 1490: BL Demographics and Disease Characteristics<sup>3</sup>**

Key Demographics and Characteristics	BIC/FTC/TAF (n=634)	DTG/ABC/3TC (n=315)	DTG + FTC/TAF (n=325)
Age, median (range), years	32 (18–71)	32 (18–68)	34 (18–77)
Male, %	89	90	89
CD4 count <200 cells/mcL, %	13	10	10

#### Efficacy results through Week 144

BIC/FTC/TAF demonstrated non-inferior efficacy to DTG/ABC/3TC in Study 1489 (92% vs 93%;  $P=0.78$ ) and to DTG + FTC/TAF in Study 1490 (89% vs 93%;  $P=0.12$ ) by FDA Snapshot analysis at the Week 48 primary endpoint.<sup>10,11</sup> Participants who received BIC/FTC/TAF had high response rates regardless of low CD4 count (99%) or both high VL and low CD4 count (97%) at BL.<sup>3</sup> High rates of virologic suppression were maintained at Week 144, and BIC/FTC/TAF remained non-inferior to both DTG-based regimens. Treatment-emergent resistance was not detected in any treatment arm.<sup>4</sup>

#### Safety results through Week 144

AEs are provided in Table 2 below. There were no reports of proximal renal tubulopathy in any arm and no discontinuations due to renal AEs on BIC/FTC/TAF.<sup>4</sup>

**Table 2. Studies 1489 and 1490: Safety Results at Week 144<sup>4,9</sup>**

AEs, %		BIC/FTC/TAF (n=634)	DTG/ABC/3TC (n=315)	DTG + FTC/TAF (n=325)
Serious AE		16	17	12
AEs occurring ≥5% of any arm	Nausea	4	18	5
	Headache	5	5	3
	Diarrhea	5	4	3
AE leading to discontinuation		1	2	2

### Week 240 pooled analysis<sup>5</sup>

A pooled analysis that included all BIC/FTC/TAF-treated participants through Week 240 was conducted. BL demographics and disease characteristics are shown in Table 3.

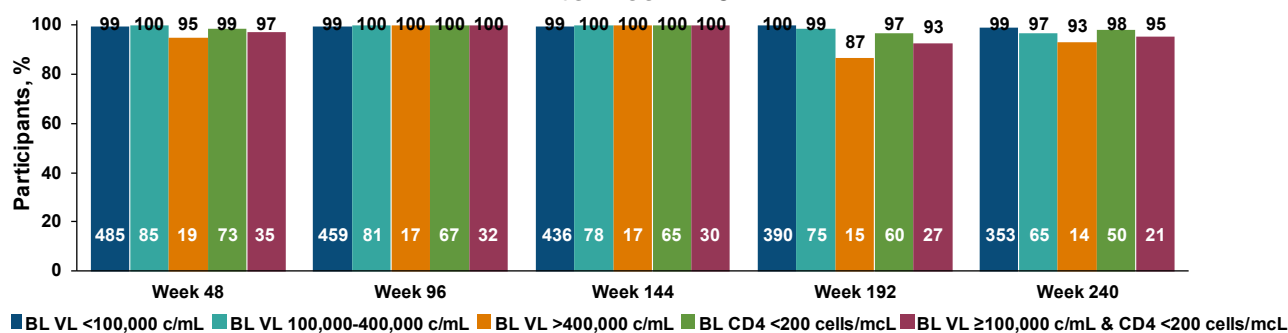
**Table 3. Studies 1489 and 1490 Week 240 Pooled Analysis: BL Demographics of BTC/FTC/TAF-Treated Participants by BL Stratification<sup>5</sup>**

	BL VL <100,000 c/mL (n=515)	BL VL 100,000–400,000 c/mL (n=99)	BL VL >400,000 c/mL (n=20)	BL CD4 ≥200 cells/mcL (n=554)	BL CD4 <200 cells/mcL (n=80)	BL VL ≥100,000 c/mL & CD4 <200 cells/mcL (n=39)
Age, median (range), years	32 (18–71)	33 (18–71)	35 (23–68)	31 (18–71)	36 (22–64)	36 (22–64)
Female at birth, n (%)	64 (12)	5 (5)	0	59 (11)	10 (13)	1 (3)
Body weight, median (Q1, Q3), kg	77.5 (68.2, 89.2)	74.8 (66.7, 84.8)	73.9 (64.9, 83.3)	77.2 (68.2, 88)	71.5 (64.5, 84.7)	71.9 (63.5, 85.3)

Abbreviation: Q=quartile.

High rates of virologic suppression were maintained through Week 240, regardless of BL VL and CD4 count (missing=excluded; Figure 2). No participants developed treatment-emergent resistance to BIC, FTC, or TAF.

**Figure 2. Studies 1489 and 1490 Pooled Analysis: VL by BL Stratification From Week 48 to Week 240<sup>5</sup>**



At Week 240, 77/80 participants with BL CD4 <200 cells/mcL had CD4 ≥200 cells/mcL. Three participants continued to have a CD4 count <200 cells/mcL (183, 180, and 111 cells/mcL) at Week 240, but each attained virologic suppression by Week 4 and remained suppressed through Week 240.

Safety results are provided in Table 4. Five cases of immune reconstitution inflammatory syndrome were reported: 2 occurred among participants who had a CD4 <200 cells/mcL at BL; all occurred within the first 48 weeks, and all resolved with treatment.

**Table 4. Studies 1489 and 1490 Week 240 Pooled Analysis: Safety Results Through Week 240 According to BL Stratification<sup>5</sup>**

AEs, %		BL VL <100,000 c/mL (n=515)	BL VL 100,000–400,000 c/mL (n=99)	BL VL >400,000 c/mL (n=20)	BL CD4 <200 cells/mcL (n=80)	BL VL ≥100,000 c/mL & CD4 <200 cells/mcL (n=39)
Any drug-related AE		28	30	20	25	21
Drug-related AEs that occurred in ≥5% of participants	Nausea	5	4	0	4	3
	Headache	4	7	10	8	10
	Diarrhea	4	7	10	6	8
	Dizziness	2	3	5	0	0
AEs that led to discontinuation of study drug		2	1	0	3	0

At Week 48, participants who had a CD4 count <200 cells/mcL at BL had significantly greater median changes in weight from BL than those who had a CD4 count ≥200 cells/mcL (8.3 kg vs 2.7 kg; *P*<0.001). The median actual weights at Week 240 were comparable across subgroups, despite BL values that were significantly lower in the CD4 <200 cells/mcL subgroup than in the CD4 ≥200 cells/mcL subgroup (71.2 kg vs 77 kg; *P*<0.05).

## LAPTOP: BIC/FTC/TAF vs DRV/c/FTC/TAF in Advanced HIV<sup>6</sup>

### Study design and demographics

A European, multicenter, open-label, randomized, controlled, non-inferiority study was conducted to assess the efficacy and safety of BIC/FTC/TAF (n=220) vs DRV/c/FTC/TAF (n=222) in ARV-naive adults with advanced HIV-1. Eligible participants had a VL >1000 c/mL and AIDS with any CD4 cell count, a severe BI with a CD4 count <200 cells/mcL, a CD4 count <100 cells/mcL with or without symptoms, or a serious OI under treatment at the time of enrollment. The primary outcome was the time to failure, defined as the first occurrence of any composite of virologic failure (either insufficient virologic response [VL reduction <1 log<sub>10</sub> c/mL at Week 12] or VL >50 c/mL at Week 48) or a clinical event.

At BL, the median age was 43 years, 81% were male, 62.4% were White, 85.8% had a CD4 count <100 cells/mcL, and 44.6% had VL >500,000 c/mL.

### Results

BIC/FTC/TAF was non-inferior to DRV/c/FTC/TAF in the primary composite endpoint (Table 5). At Weeks 4, 8, and 12, significantly more participants achieved VL <50 c/mL in the BIC/FTC/TAF group than in the DRV/c/FTC/TAF group (each week, *P*<0.0001); a higher number of participants who received BIC/FTC/TAF achieved VL <50 c/mL at Week 48. Among participants with CD4 ≤200 cells/mcL at BL, there was no significant difference between treatment groups in the time to achieve CD4 >200 cells/mcL (aHR, 1.12; 95% CI: 0.89–1.41; *P*=0.339).

**Table 5. LAPTOP: Primary Composite Endpoint and Components (mITT Analysis)<sup>6</sup>**

Endpoint, n (%)	BIC/FTC/TAF (n=220)	DRV/c/FTC/TAF (n=222)	aHR (95% CI); P-Value
Primary composite endpoint	49 (23.8)	70 (33.9)	0.7 (0.48–1); 0.052
Virologic failure	25 (13.4)	46 (23.9)	0.54 (0.33–0.88); 0.013
Insufficient virologic response	23 (12.4)	43 (22.5)	0.53 (0.32–0.88); 0.014
Viral rebound	2 (1)	3 (1.5)	0.69 (0.12–4.15); 0.687
Clinical events	25 (11.8)	26 (12.1)	0.99 (0.57–1.72); 0.974
Any new/recurrent AIDS event within ≥28 days of therapy	7 (3.5)	15 (7.2)	0.48 (0.2–1.19); 0.114
SAE unrelated to AIDS events	11 (5.3)	5 (2.3)	2.32 (0.81–6.68); 0.119
AE that led to discontinuation	1 (0.5)	7 (3.3)	0.15 (0.02–1.18); 0.071
Death related to HIV, AIDS, or OI/BI	7 (3.3)	3 (1.4)	2.41 (0.62–9.33); 0.202

Abbreviation: mITT=modified intent-to-treat; SAE=serious adverse event.

Note: The non-inferiority margin was an HR of 1.606.

There were 5 incidences of drug-related Grade 3 or 4 AEs reported in each group ( $P=0.9931$ ). Drug-related Grade  $\geq 2$  AEs were reported in 27 participants in the BIC/FTC/TAF group and in 45 participants in the DRV/c/FTC/TAF group ( $P=0.0431$ ).

## RWD: BIC/FTC/TAF in PWH by BL CD4 Count

### BICSTaR Study<sup>7</sup>

BICSTaR is a large, ongoing, multicountry, prospective, observational cohort study in ARV-naive and TE PWH that is evaluating the efficacy, safety, and tolerability of BIC/FTC/TAF in clinical practice. Study outcomes include virologic suppression (VL  $< 50$  c/mL) by BL CD4 counts. At BL, median CD4 counts were 377 cells/mcL in the ARV-naive cohort ( $n=279$ ) and 667 cells/mcL in the TE cohort ( $n=1230$ ); of ARV-naive participants with a late HIV diagnosis and/or  $\geq 1$  AIDS-defining event, 128 participants (47.4%) had CD4  $< 350$  cells/mcL, and 74 (27.4%) had CD4  $< 200$  cells/mcL. At 12 months, virologic suppression was achieved by 90.7% of participants with BL CD4  $< 350$  cells/mcL and/or  $\geq 1$  AIDS-defining event and by 95.8% of participants with BL CD4  $\geq 350$  cells/mcL ( $P=0.117$ ). Significantly fewer participants with BL CD4  $< 200$  cells/mcL and/or  $\geq 1$  AIDS-defining event achieved virologic suppression at 12 months than participants with BL CD4  $\geq 200$  cells/mcL (85.5% vs 96.4%, respectively;  $P=0.006$ ).<sup>7</sup> Among ARV-naive participants with a late HIV diagnosis at baseline, there was no difference in the incidence of AEs between participants with CD4  $< 200$  cells/mcL and/or  $\geq 1$  AIDS-defining event (63.5%) and those with CD4  $\geq 200$  cells/mcL (53.1%;  $P=0.123$ ) or between participants with CD4  $< 350$  cells/mcL and/or  $\geq 1$  AIDS-defining event (57%) and those with CD4  $\geq 350$  cells/mcL (54.9%;  $P=0.728$ ).<sup>12</sup> Outcomes were consistent with previously published data from randomized controlled trials and observational cohort studies; no new safety signals were identified.<sup>7</sup>

### OPERA Cohort: BL CD4 $< 200$ cells/mcL<sup>8</sup>

An analysis was conducted among ARV-naive adults with CD4  $< 200$  cells/mcL in the OPERA database. Patients initiated BIC/FTC/TAF ( $n=816$ ), boosted darunavir ( $n=134$ ), DTG ( $n=253$ ), or boosted elvitegravir ( $n=146$ ) regimens. Eligible patients had  $\geq 1$  CD4 cell count and VL assessment during follow-up. BL demographics were similar between groups.

A total of 1349 PWH were included in the analysis, with varied durations of follow-up ranging from 10 to 36 months. A total of 1147 patients (85%) achieved a CD4 cell count recovery to  $\geq 200$  cells/mcL, 1147 patients (85%) achieved virologic suppression (VL  $< 200$  c/mL), and 947 patients (70%) achieved virologic undetectability (VL  $< 50$  c/mL). Patients receiving BIC/FTC/TAF were more likely to achieve a CD4 cell count  $\geq 200$  cells/mcL than patients in the other treatment groups.

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## Abbreviations

3TC=lamivudine

ABC=abacavir

AE=adverse event

aHR=adjusted hazard ratio

aIRR=adjusted incidence  
rate ratio

ARV=antiretroviral

BI=bacterial infection

BIC=bictegravir

BL=baseline

c/mL=copies/mL

CD4=cluster of  
differentiation 4

CORIS=Cohort de la Red  
de Investigación en Sida

DRV/c=darunavir/cobicistat

DTG=dolutegravir

FTC=emtricitabine

OI=opportunistic infection

OPERA=Observational  
Pharmaco-Epidemiology

Research and Analysis

PWH=people with HIV

PY=person years

RWD=real-world data

TAF=tenofovir alafenamide

TE=treatment-experienced

VL=viral load

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## Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Biktarvy US Prescribing Information available at:

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