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Efficacy and Safety of Bictegravir/Emtricitabine/Tenofovir Alafenamide in Females Living With HIV: An Integrated Analysis of 5 Trials

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Background: We characterized the efficacy and safety of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) in a broad population of pediatric/adolescent/adult/elderly females living with HIV (FWH).

Setting: Integrated analysis.

Methods: Available data from 5 trials were integrated. Week 48 virologic suppression (HIV-1 RNA <50 copies/mL), resistance, adverse events (AEs), and laboratory parameters were assessed.

Results: Three hundred and seventy-three FWH [304 virologically suppressed; 69 antiretroviral therapy (ART)-naive] received B/F/TAF [data from comparator regimens available for 306 individuals (236 virologically suppressed and 70 ART-naive participants)]. Virologic suppression rates with B/F/TAF at week 48 were high regardless of age in participants virologically suppressed at baseline (≥95%) and in ART-naive participants (≥87%). Virologic suppression rates were similar in B/F/TAF and comparator regimens (both virologically suppressed and ART-naive groups). Treatment-emergent resistance was not detected in the B/F/TAF group. AEs considered related to study drugs were experienced by 9.2% (B/F/TAF) and 5.5% (comparator regimen) of virologically suppressed participants and 15.9% (B/F/TAF) and 31.4% (comparator regimen) of ART-naive participants. For virologically suppressed and ART-naive FWH combined, only 1 of the 373 B/F/TAF–treated and 2 of the 306 comparator-regimen participants discontinued because of AEs (none were bone/renal/hepatic AEs); grade 3/4 AEs were experienced by 5.1% (B/F/TAF) and 7.8% (comparator regimen); and grade 3/4 elevation of low-density lipoprotein/total cholesterol occurred in 2.7%/0.3% (B/F/TAF) and 5.9%/2.0% (comparator regimen). At week 48, median changes from baseline estimated glomerular filtration rate in adults were <5 mL/min; results were similar in B/F/TAF and comparator-regimen groups.

Conclusion: B/F/TAF treatment was effective and well tolerated over 48 weeks, confirming B/F/TAF as an option for a broad population of FWH.

Key Words: female, bictegravir, emtricitabine, child, HIV, adolescent

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INTRODUCTION

Females living with HIV (FWH) are underrepresented in HIV trials.[1] Representation is crucial due to sex-based differences in the course of infection,[2–4] adverse drug reactions,[5] and antiretroviral therapy (ART) pharmacokinetics/pharmacodynamics.[3,6–9]

Bictegravir is an unboosted integrase strand transfer inhibitor with a high barrier to resistance[10,11] and low potential for drug–drug interactions (including no clinically significant interactions with hormonal contraceptives).[12] Bictegravir is available in a once-daily single-tablet coformulation with the nucleotide reverse transcriptase inhibitors (NRTIs) emtricitabine and tenofovir alafenamide (B/F/TAF). Phase 3 trials have demonstrated the efficacy and safety of B/F/TAF in ART-naive adult people living with HIV (PLWH), virologically suppressed adult/adolescent PLWH, and children with HIV switching from another regimen.[13–22]

The Phase 3 Study 1961 evaluated B/F/TAF in FWH and found B/F/TAF to be effective, safe, and well tolerated.[17] To further characterize the efficacy and safety of B/F/TAF in FWH, including young, elderly, and ART-naive participants, data from 5 clinical trials were analyzed.

METHODS

Study Design

Week (W) 48 data from case report forms for female (sex at birth) participants in 5 clinical trials (NCT02652624, NCT02607930, NCT02607956, NCT02881320, and NCT03405935) were integrated. Trials were selected to encompass a broad age range and sufficient numbers of treatment-naïve/virologically suppressed individuals and included registrational studies with W48 data available at the time of the analysis (excluding 2 studies in virologically suppressed individuals with very small numbers of female participants).[15–17,21–24] Studies 1489 and 1490 were randomized, double-blind comparisons of B/F/TAF with an active comparator regimen: coformulated dolutegravir/abacavir/lamivudine (DTG/ABC/3TC)[15,21] and dolutegravir plus coformulated emtricitabine/tenofovir alafenamide (DTG+F/TAF) in ART-naïve adults.[16,22] Study 1961 was randomized, active controlled, and open label, comparing B/F/TAF with baseline ART: coformulated elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF; 53%), coformulated E/C/F/tenofovir disoproxil (TDF; 42%), and atazanavir plus ritonavir and coformulated F/TDF (5%) in virologically suppressed adult FWH.[17] Studies 1474 and 4449 were open label and single arm, evaluating B/F/TAF in virologically suppressed FWH (aged 16–17 years and aged 65 years or older, respectively).[23,24]

Study designs have been reported.[15–17,21–23] Studies met institutional review board/independent ethics committee approval and conformed to Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. Participants provided written informed consent (parental consent was required for children and adolescents). B/F/TAF is indicated for HIV-1 infection in adult and pediatric patients weighing ≥25 kg.

Assessments

Parameters assessed were as follows: virologic suppression (HIV-1 RNA <50 copies/mL), treatment-emergent resistance, adverse events (AEs; Medical Dictionary for Regulatory Activities, versions 19.1/22.0), laboratory parameters, renal function [change from baseline in estimated glomerular filtration rate (eGFR; Schwartz formula for pediatrics and Cockcroft–Gault for adults)], percentage change from baseline in renal biomarkers (all adult participants and those aged 18–64 years who switched from TDF), change from baseline in bone mineral density (BMD; Study 1489), and weight.

Statistical Analysis

W48 data were grouped by previous treatment, data availability, and age. Owing to age distribution, virologically suppressed participants (Studies 1474/1961/4449) were grouped by efficacy and renal function [age in years: 6–17 (children/adolescents)/18–49 (young adults)/50–64 (older adults)/65–75 (elderly)], AEs and laboratory abnormalities (6–17/18–49/50–75 years), renal biomarkers (Studies 1961/4449), and weight change (18–64/65–75 years). ART-naive participants (Studies 1489/1490) were grouped by efficacy, AEs, laboratory abnormalities, and renal function (18–49/50–68 years), renal biomarkers and BMD (Study 1489), and weight change (18–68 years). Resistance was described for the entire population.

Statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC). Proportion with HIV RNA ≤50 copies/mL was calculated using a snapshot algorithm.[25] The medians for renal markers/weight change were compared between treatment groups using a 2-sided Wilcoxon rank sum test. The means for percentage change from baseline in BMD were compared between groups using analysis of variance.

RESULTS

In total, 373 FWH (304 virologically suppressed and 69 ART-naive participants) from Australia, Canada, Dominican Republic, Europe, Puerto Rico, Russia, South Africa, Thailand, Uganda, and the United States received B/F/TAF (baseline demographics summarized in Table 1). Data for comparator regimens were available for 306 individuals (236 virologically suppressed and 70 ART-naive participants).

In virologically suppressed participants who switched to B/F/TAF, the rate of continued virologic suppression at W48 was ≥95% across all age groups (Table 2), with consistency at all studied ages, and was similar to comparator regimens. The rate of suppression at W48 in girls and adolescents (6–17 years) was 97% with B/F/TAF (no comparator). At W48, HIV-1 RNA ≥50 copies/mL was reported in 2.1% (B/F/TAF) versus 1.5% (comparators) among participants aged 18–49 years and 0% (B/F/TAF) versus 2.5% (comparators) for those aged 50–64 years.

In ART-naive participants, virologic suppression rates at W48 were ≥87% with B/F/TAF across all age groups (Table 2). Similar proportions achieved virologic suppression with B/F/TAF versus DTG/ABC/3TC and DTG+F/TAF. Among participants aged 18–49 years, 5.6% (3/54) on B/F/TAF had HIV-1 RNA ≥50 copies/mL versus 0% (0/22) on DTG/ABC/3TC and 6.9% (2/29) on DTG+F/TAF. For

TABLE 1. Baseline Characteristics and Demographics of Females Living With HIV Included in the Integrated Analysis of 5 Clinical Trials of B/F/TAF (B/F/TAF Arms Only)

	Virologically Suppressed Participants (n = 304)					ART-Naive Participants (n = 69)		
Study age group, yrs	6–17 (n = 59)	18–49 (n = 191)	50–64 (n = 43)	65–75 (n = 11)	All patients	18–49 (n = 54)	50–68 (n = 15)	All patients
Age range, yrs	6–17	21–49	50–63	66–74	6–74	20–49	50–64	20–64
Race, n (%)								
Black	45 (76.3)	72 (37.7)	19 (44.2)	1 (9.1)	137 (45.1)	26 (48.1)	7 (46.7)	33 (47.8)
White	2 (3.4)	56 (29.3)	10 (23.3)	10 (90.9)	78 (25.7)	19 (35.2)	6 (40.0)	25 (36.2)
Asian	10 (16.9)	43 (22.5)	5 (11.6)	0	58 (19.1)	0	0	0
Other	2 (3.4)	20 (10.5)	9 (20.9)	0	31 (10.2)	9 (16.7)	2 (13.3)	11 (15.9)
Ethnicity, n (%)								
Hispanic or Latina	2 (3.4)	23 (12.0)	13 (30.2)	3 (27.3)	2 (0.7)	14 (25.9)	3 (20.0)	17 (24.6)
Median HIV-1 RNA (IQR), copies/mL	<50	<50	<50	<50	<50	4.3 (3.9–4.6)	4.3 (3.9–4.6)	<50
Median (IQR) CD4, cells/μL	848 (665–1038)	666 (531–867)	682 (554–836)	726 (511–829)	NA	411 (276–535)	522 (285–713)	NA
Median (IQR) eGFR, mL/min or mL/min/1.73 m^2 for age 6–17 yrs	147.0 (135.0–173.0)	101.4 (85.2–117.7)	86.6 (75.6–111.6)	69.6 (61.2–82.2)	NA	129.0 (104.8–163.1)	85.5 (75.4–109.0)	NA
Median (IQR) weight, kg	40.5 (29.8–49.2)	65.5 (55.2–76.5)	76.2 (63.0–92.1)	61.8 (59.0–71.0)	NA	73.3 (59.4–89.2)	73.6 (66.9–79.4)	73.5 (61.0–86.6)

ART, antiretroviral therapy; B/F/TAF, bictegravir, emtricitabine, and tenofovir alafenamide; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NA, not available.

participants aged 50–68 years, 6.7% on B/F/TAF had HIV-1 RNA ≥50 copies/mL versus 0% each with DTG/ABC/3TC and DTG+F/TAF.

Preexisting resistance data from population genotyping (treatment-naive individuals) and historical genotypes or baseline HIV DNA archive genotypes (HIV-1 RNA virologically suppressed individuals in switch studies) for 630 FWH from contributing studies showed nonnucleoside reverse transcriptase inhibitor resistance in 9.7% (61/630), NRTI resistance in 0.3% (19/630), and protease inhibitor resistance in 0.3% (17/630). Six participants (3 each for B/F/TAF and comparators) met the criteria for viral resistance testing while on treatment. No treatment-emergent resistance was identified. One woman (comparator arm; E/C/F/TAF) developed M184M/I/V in reverse transcriptase at W48 but achieved viral suppression after switching to B/F/TAF.

For B/F/TAF, 65.8% of virologically suppressed participants experienced an AE, versus 84.1% of ART-naive participants (Table 2). Grade 3/4 AEs were reported in 3.9% of virologically suppressed and 10.1% of ART-naive participants. The incidence of drug-related AEs was 9.2% in virologically suppressed and 15.9% in ART-naive participants. The most common (>10%) treatment-related AEs in girls and adolescents aged 6–17 years treated with B/F/TAF were upper respiratory tract infection (URTI), headache, cough, diarrhea, and influenza (noting that URTI/influenzas were treatment emergent but not necessarily treatment related). In adults, B/F/TAF–related AEs reported at >10% were headache, nausea, and diarrhea. Of 373 FWH treated with B/F/TAF, 1 person discontinued because of an AE (grade 2 anxiety and insomnia). Two participants (older than 65 years) receiving B/F/TAF experienced finger/bilateral traumatic wrist fractures (unrelated to treatment). Weight increase/decrease was uncommon in adults [B/F/TAF: 1.2% (4/314); comparators: <1% (2/306)]. There were no cases of Fanconi syndrome/proximal renal tubulopathy.

For comparators, 159 of the 236 (67.4%) virologically suppressed participants reported an AE versus 58 of the 70 (82.9%) ART-naive participants. AEs considered related to comparator regimen were experienced by 13 of the 236 (5.5%) virologically suppressed and 22 of the 70 (31.4%) ART-naive participants. Among comparator-regimen–treated participants, grade 3/4 AEs occurred in 14 of the 236 (5.9%) virologically suppressed and 10 of the 70 (14.3%) ART-naive participants.

For virologically suppressed and ART-naive FWH combined, 1 of the 373 B/F/TAF–treated and 2 of the 306 comparator-regimen participants discontinued because of AEs (none were bone/renal/hepatic AEs).

Low-density lipoprotein/total cholesterol levels increased in 2.7%/0.3% (B/F/TAF) and 5.9%/2.0% (comparator regimen).

In both virologically suppressed and ART-naive participants treated with B/F/TAF, small changes in eGFR (<5 mL/min in adults) were noted between baseline and W48 (Table 1); results were similar with comparators. The greatest change in eGFR (−16 mL/min/1.72 m^2) was in virologically suppressed FWH aged 6–17 years. For virologically suppressed participants aged 18–64 years, those switching from TDF to B/F/TAF or remaining on baseline regimen showed

TABLE 2. Summary of Virological Efficacy, eGFR, AEs, and Laboratory Abnormalities in FWH Included in the Integrated Analysis of 5 Clinical Trials of B/F/TAF (Results From B/F/TAF–Treated Participants Only)

	Virologically Suppressed Participants (n = 304)				ART-Naive Participants (n = 69)		
Study age group, yrs	6–17 (n = 59)	18–49 (n = 191)	50–64 (n = 43)	65–75 (n = 11)	18–49 (n = 54)	50–68 (n = 15)	
Proportion of FWH with HIV RNA <50 copies/mL at week 48	97.0	95.0*	100†	100	87.0‡	93.0§	
Study age group, yrs	6–17 (n = 58)	18–49 (n = 184)	50–64 (n = 43)	65–75 (n = 11)	18–49 (n = 49)	50–68 (n = 14)	
Median eGFR change from baseline (mL/min or mL/min/1.73 m^2 for ages 6–17 yrs) at week 48 (IQR)	−16.0 (−33.0 to −5.0)	−1.8 (−10.6 to 7.2)	−1.4 (−8.4 to 2.9)	−3.0 (−16.8 to 3.0)	−5.2 (−19.5 to 6.8)	−4.9 (−18.2 to 3.0)	
Study age group, yrs	6–17 (n = 59)	18–49 (n = 191)	50–75 (n = 54)	All patients (N = 304)	18–49 (n = 54)	50–68 (n = 15)	All patients (N = 69)
AEs, n (%)							
Any-grade AE	46 (78.0)	120 (62.8)	43 (79.6)	200 (65.8)	46 (85.2)	12 (80.0)	58 (84.1)
Study drug–related AEs	8 (13.6)	17 (8.9)	3 (5.6)	28 (9.2)	10 (18.5)	1 (6.7)	11 (15.9)
Discontinuation due to AEs	1 (1.7)	0	0	1 (0.3)	0	0	0
Any grade 3/4 AEs	1 (1.7)	10 (5.2)	1 (1.9)	12 (3.9)	7 (13.0)	0	7 (10.1)
Study drug–related grade 3/4 AEs	0	1 (0.5)	0	1 (0.3)	0	0	0
Grade 3/4 laboratory abnormalities, n (%)	20 (33.9)	36 (18.8)	6 (11.1)	62 (20.4)	9 (17.3)	3 (21.0)	12 (17.4)
Hematuria	11 (18.6)	20/160 (12.5)	1/47 (2.1)	32/297 (10.8)	1/46 (2.2)	0/7	1/53 (1.9)
Neutropenia	4 (6.8)	2 (1.0)	0	6 (2.0)	2/52 (3.8)	1/14 (7.1)	3/66 (4.3)
Elevated LDL (>4.92 mmol/L)	0	7/190 (3.7)	1 (1.9)	8 (2.6)	1/51 (2.0)	1/14 (7.1)	2/65 (2.9)
Elevated total cholesterol (>7.77 mmol/L)	0	1/190 (0.5)	0	1 (0.3)	0	0	0
Elevated triglycerides (>8.47 mmol/L)	0	0	0	0	0	0	0

*Proportion with HIV RNA <50 copies/mL at week 48 in comparator arm (n = 196): 95.0%.
†Proportion with HIV RNA <50 copies/mL at week 48 in comparator arm (n = 40): 95.0%.
‡Proportion with HIV RNA <50 copies/mL at week 48 in comparator arm (n = 51): 88.0%.
§Proportion with HIV RNA <50 copies/mL at week 48 in comparator arm (n = 19): 89.0%.
AE, adverse event; ART, antiretroviral therapy; B/F/TAF, bictegravir, emtricitabine, and tenofovir alafenamide; eGFR, estimated glomerular filtration rate; FWH, females living with HIV; IQR, interquartile range; LDL, low-density lipoprotein.

no significant difference in percentage change from baseline in urinary albumin/creatinine ratio (UACR; $P = 0.40$), but retinol-binding protein/creatinine ratio (RBP:Cr) and β2-microglobulin/creatinine ratio (β2M:Cr) decreased significantly ($P < 0.001$) after switch. The β2M:Cr increased with switch in the oldest (age 65–75 years) group. In ART-naive participants aged 18–68 years (Study 1489), changes from baseline in UACR, RBP:Cr, and β2M:Cr were not significantly different between B/F/TAF and comparators.

At W48, mean [95% confidence interval (CI)] spine BMD (Study 1489) declined by 0.5% (−1.956 to 0.910) with B/F/TAF versus 1.1% (−2.283 to 0.079) with comparators ($P = 0.52$). At W48, mean (95% CI) hip BMD decreased by 0.7% (−1.615 to 0.227) with B/F/TAF versus 1.7% (−2.741 to −0.590) with comparators ($P = 0.16$). BMD increased slightly in both arms at W144 but was not significantly different between arms (spine, $P = 0.91$; hip, $P = 0.29$).

The median [interquartile range (IQR)] baseline weight was 67 kg (56–79) for B/F/TAF–treated virologically suppressed participants aged 18–64 years (n = 229) and 68 kg (58–79) for comparator-regimen–treated participants (n = 230), with increases from baseline to W48 of 1.5 (−0.5 to 3.4) and 0.4 (−1.5 to 2.0) kg, respectively ($P < 0.001$). For B/F/TAF–treated participants aged 65–75 years (n = 11), the median (IQR) baseline weight was 62 kg (59–71); this increased by 1.0 kg (0–3.0) at W48. Among ART-naive participants aged 18–68 years, the median (IQR) baseline weight (kg) of those treated with B/F/TAF (n = 63) was 74 (61–87) compared with 84 (71–97) for DTG/ABC/3TC (n = 30) and 70 (62–90) for DTG+F/TAF (n = 32). For B/F/TAF, DTG/ABC/3TC, and DTG+F/TAF, respectively, the median (IQR) weight (kg) increase from baseline to W48 was 4.0 (0.0–6.8), 2.9 (0.9–8.5), and 3.2 (1.1–7.3) and to W144 was 5.0 (1.0–11.1), 7.9 (1.3–12.7), and 4.9 (1.6–11.0). The magnitude of weight increases with DTG/ABC/3TC and DTG+F/TAF was not significantly different from increases with B/F/TAF at W48 ($P = 0.69$ and $P = 0.79$, respectively) or W144 ($P = 0.54$ and $P = 0.77$, respectively).

DISCUSSION

This integrated analysis indicated high viral suppression rates with B/F/TAF in FWH across age ranges—in ART-naive (≥87% at W48) FWH and those with virologic suppression at baseline (97%)—with no treatment-emergent resistance. Similar rates were seen with B/F/TAF and

comparators, in agreement with individual studies.[17,21,22] The high suppression in FWH aged 6–17 years is notable, given the challenges associated with study retention/treatment adherence.[26] B/F/TAF efficacy was consistent with analyses (including both sexes) of each study.[15,16,21–24] Virologic failure was low.

B/F/TAF was well tolerated, with no unexpected AEs/laboratory findings and no clinically relevant changes in BMD relative to comparators. Safety findings were consistent with analyses for each study and did not identify any clinically relevant differences related to sex.[27] Incidence of treatment-emergent AEs was unaffected by age. In ART-naive participants, fewer drug-related AEs were reported with B/F/TAF than with comparator in Studies 1489/1490,[21,22] a trend also observed in this study. In participants with baseline virologic suppression, the incidence of drug-related AEs was higher with B/F/TAF than comparator (Study 1961[17]), as expected in an open-label study. This trend was noted across age ranges in this analysis, although sample size and absolute difference remain small. One discontinuation occurred among B/F/TAF–treated FWH. Grade 3/4 laboratory abnormalities were primarily hematuria, were mostly seen in adolescents, and may be attributable to menses.

Weight gain is ubiquitous in PLWH receiving their first ART.[28] In this study, weight gain with B/F/TAF was greater in ART-naive FWH than in virologically suppressed FWH through 48 weeks, with similar gains among ART-naive FWH on B/F/TAF and DTG-based regimens through 144 weeks. ART-naive women treated with B/F/TAF experienced no significant differences in weight gain versus comparators, including dolutegravir. Modest weight gain was observed with B/F/TAF versus comparator in participants who were virologically suppressed at baseline.

Markers of renal tubular function improved in participants switching to B/F/TAF from TDF. The observed baseline kidney function in children/adolescents aged 6–17 years with virologic suppression at baseline (median eGFR, 147 mL/min) probably represents an overestimate based on lower muscle mass, and the lower eGFR in patients aged 65–75 years with virologic suppression at baseline is consistent with expected values for healthy individuals of that age.[29] Small eGFR changes were observed with B/F/TAF, consistent with known effects of bictegravir as an inhibitor of OCT2/MATE1.[27]

The integrated analysis has limitations associated with combining data, including intrastudy differences in study designs/populations. The sample was small for some subgroups, gender identity was not incorporated, and the analysis was not adjusted for people who became pregnant. A study investigating the efficacy and safety of B/F/TAF in pregnant FWH is currently ongoing.

B/F/TAF is well tolerated and effective in a broad population of FWH (children/adolescents/adults/elderly), with high virologic suppression, no treatment-emergent resistance, and low discontinuation. Proximal renal tubular function improves with switch from TDF-based regimens. These findings confirm B/F/TAF as an important treatment option for girls and women living with HIV.

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