Phase 3 Randomized, Controlled, Clinical Trial of Bictegravir Coformulated With FTC/TAF in a Fixed-Dose Combination vs Dolutegravir + FTC/TAF in Treatment-Naïve HIV-1-Positive Adults: Week 48 Results

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Disclosures

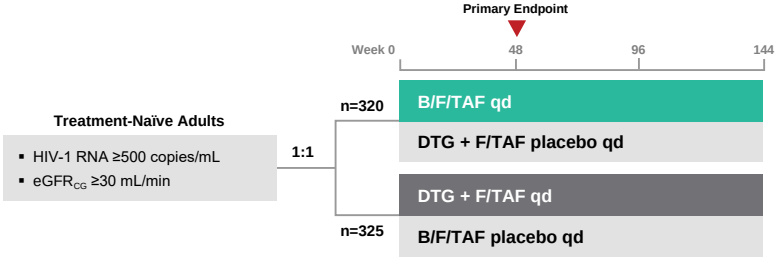
- **IW Gilead Sciences, MSD, Bristol Myers Squibb, Abbott and ViiV Healthcare**.

Introduction

- Integrase strand transfer inhibitors (INSTIs) are guideline recommended as components of 1st-line antiretroviral therapy in combination with 2 nucleoside reverse transcriptase inhibitors (NRTIs)[1-3]
- Emtricitabine (FTC, F)/tenofovir alafenamide (TAF)–based regimens have demonstrated improved bone and renal safety compared with FTC/tenofovir disoproxil fumarate–based regimens, with no discontinuations due to renal tubulopathy including Fanconi's syndrome over 3 years[4]
- Bictegravir (BIC, B) is a novel, potent INSTI with a high *in vitro* barrier to resistance and low potential for drug-drug interactions[5,6]
- BIC + F/TAF was studied in a Phase 2 trial vs dolutegravir (DTG) + F/TAF, and was safe and efficacious[7]
  - No patient developed resistance to study medications
- BIC was co-formulated into a single-tablet regimen with F/TAF (B/F/TAF) for once-daily dosing without regard to food

1. AIDSinfo. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf;
2. EACS. http://www.eacsociety.org/files/guidelines_8.2-english.pdf;
3. Gunthard HF, et al. JAMA 2016;316:191-210;
4. Arribas JR, et al. J Acquir Immune Defic Syndr 2017;75:211-8;
5. Gallant JE, et al. J Acquir Immune Defic Syndr 2017;75:61-6;
6. Tsiang M, et al. Antimicrob Agents Chemother 2016.60:7086-97;
7. Sax PE, et al. Lancet HIV 2017;4:e154-60.

Study Design:



$eGFR_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault equation.

Methods

- Phase 3, randomized, double-blind, active-controlled Study 1490 (ClinicalTrials.gov NCT02607956)
  - Stratified by HIV-1 RNA, CD4 cell count, and geographic region (USA vs ex-USA)
  - North America, Europe, Australia, and Latin America
  - Chronic hepatitis B and/or C virus (HBV/HCV) infection allowed
- Treatment-naive, HIV-infected adults with $eGFR_{CG}$ ≥30 mL/min were randomized 1:1 to receive blinded treatment with B/F/TAF (50/200/25 mg) or DTG (50 mg) + F/TAF (200/25 mg) with matching placebo once daily through Week 48
- Primary endpoint: proportion with HIV-1 RNA <50 copies/mL at Week 48
  - Non-inferiority margin of 12% based on US Food and Drug Administration-defined snapshot algorithm

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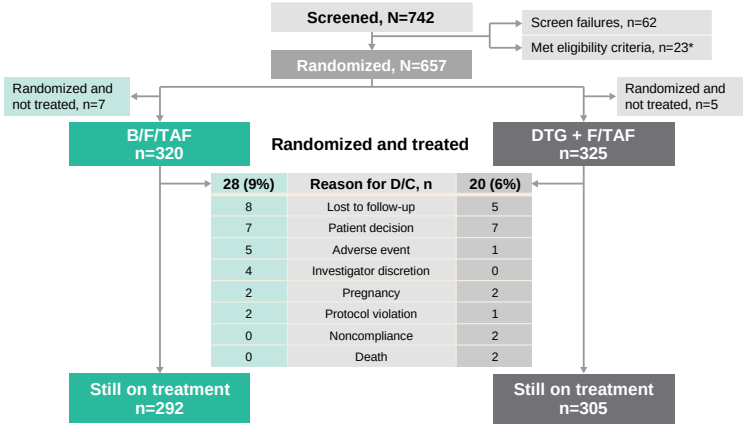
Patient Disposition



*Lost to follow-up (n=3), withdrew consent (n=14), investigator discretion (n=2), adverse event (AE; n=1), outside of visit window (n=2), and other (n=1).
D/C, discontinuation.

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Baseline Characteristics

	B/F/TAF n=320	DTG + F/TAF n=325
Median age, y (range)	33 (18–71)	34 (18–77)
Male, %	88	89
Race/ethnicity, %		
Black or African descent	30	31
Hispanic/Latino	26	25
Median HIV-1 RNA, log_{10} copies/mL (Q1, Q3)	4.43 (3.95, 4.90)	4.45 (4.03, 4.84)
HIV-1 RNA >100,000 copies/mL, %	21	17
Median CD4 cell count, cells/μL (Q1, Q3)	440 (289, 591)	441 (297, 597)
CD4 count <200 cells/μL, %	14	10
HBV*/HCV† coinfection, %	3/2	2/2
Median $eGFR_{CG}$, mL/min (Q1, Q3)	120.4 (100.8, 141.8)	120.6 (102.8, 145.1)

*Positive HBV surface antigen; isolated positive HBV core antigen, with quantifiable HBV DNA (i.e., ≥20 IU/mL) on or prior to 1st dose; †Positive HCV antibody and quantifiable HCV RNA (i.e., ≥15 IU/mL). Q, quartile.

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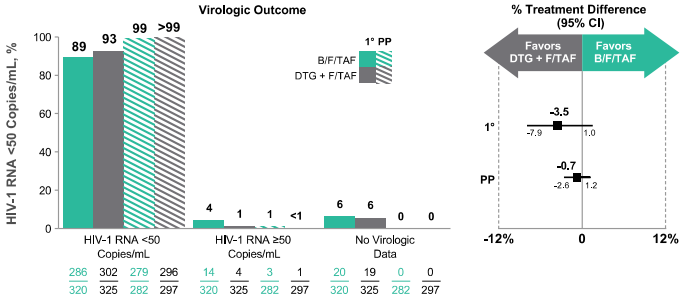
Virologic Outcome at Week 48

Snapshot Analysis



1°, primary; CI, confidence interval; PP, per protocol

- Primary endpoint of non inferiority met
- Mean CD4 changes from baseline for B/F/TAF vs DTG + F/TAF: +180 vs +201 cells/μL (p=0.10)

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Virologic Outcome at Week 48

Primary Endpoint

Patients, n (%)	B/F/TAF n=320	DTG + F/TAF n=325
HIV-1 RNA <50 copies/mL	286 (89.4)	302 (92.9)
Difference for <50 copies/mL, % (95.002% CI)	-3.5 (-7.9, 1.0; p=0.12)	
HIV-1 RNA ≥50 copies/mL	14 (4.4)	4 (1.2)
HIV-1 RNA ≥50 copies/mL	3 (0.9)	1 (0.3)
D/C due to lack of efficacy	0	0
D/C due to other reason* and last VL ≥50 copies/mL	11 (3.4)	3 (0.9)
No virologic data in Week 48 window	20 (6.3)	19 (5.8)
D/C due to AE/death	3 (0.9)	3 (0.9)
D/C due to other reason* and last VL <50 copies/mL	11 (3.4)	14 (4.3)
On study drug, but missing data in window	6 (1.9)	2 (0.6)

*Other reasons included investigator's discretion, patient decision, lost to follow-up, noncompliance with study drug, protocol violation, and pregnancy.
VL, viral load.

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Patients Discontinued for Reasons Other Than Adverse Event/Death and Last HIV-1 RNA ≥50 Copies/mL

Group	Patient	Day of Last HIV-1 RNA	Last HIV-1 RNA Copies/mL	Reason for Discontinuation
B/F/TAF	1	1 (baseline)	438*	Patient decision (did not want to participate in study)
	2	1 (baseline)	185,000*	Protocol violation (incarcerated)
	3	1 (baseline)	56,500*	Lost to follow-up (moved away)
	4	1 (baseline)	71,900*	Investigator discretion (inconsistent state of residency)
	5	1 (baseline)	17,300*	Patient decision (no reason provided)
	6	1 (baseline)	9600*	Patient decision (moved away)
	7	58	317,000	Investigator discretion (erratic behavior)
	8	62	9000	Lost to follow-up (unresponsive to contact attempts)
	9	169	23,400	Patient decision (wanted drug holiday)
	10	176	4440	Investigator discretion (multiple missed appointments)
	11	253	8630	Lost to follow-up (unresponsive to contact attempts)
DTG + F/TAF	12	10	213	Pregnancy
	13	62	22,800	Lost to follow-up (incarcerated)
	14	253	12,000	Noncompliance with study drug

*Pretreatment baseline result.

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Virologic Outcome at Week 48

Sensitivity Analyses

% With HIV-1 RNA <50 Copies/mL (n/n)	B/F/TAF	DTG + F/TAF	% Difference in Proportion (95% CI)* B/F/TAF – DTG+F/TAF
Per-protocol snapshot analysis	98.9 (279/282)	99.7 (296/297)	-0.7 (-2.6, 1.2) p=0.33
Modified snapshot analysis	91.4 (286/313)	92.9 (302/325)	-1.5 (-5.8, 2.8) p=0.48
M=F analysis	90.0 (288/320)	93.5 (304/325)	-3.4 (-7.7, 0.9) p=0.12
M=E analysis	99.0 (288/291)	99.3 (304/306)	-0.4 (-2.3, 1.6) p=0.63

*95.002% CI for per-protocol and modified snapshot analyses. M=E, missing=excluded; M=F, missing=failure.

- **Sensitivity analyses confirmed that B/F/TAF was non-inferior to DTG + F/TAF**

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Safety

- Deaths:
  - B/F/TAF: n=1 (cardiac arrest in setting of sepsis secondary to appendicitis; same patient who discontinued due to AE of cardiac arrest)
  - DTG + F/TAF: n=2 (n=1 unknown; n=1 possible pulmonary embolism)

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Virologic Resistance

	B/F/TAF n=320	DTG + F/TAF n=325
Met criteria for resistance testing*	7	5
Assay failure	0	0
NRTI resistance detected	0	0
INSTI resistance detected	0	0

*Resistance testing performed for patients with confirmed virologic rebound to >200 copies/mL after Week 8.

- **No resistance to any components of the treatment regimens occurred in either treatment group**

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All-Grade Adverse Events (≥5%) Through Week 48

Patients, %	B/F/TAF n=320	DTG + F/TAF n=325
Headache	12.5	12.3
Diarrhea	11.6	12.0
Nausea	7.8	8.9
Nasopharyngitis	6.9	9.5
Fatigue	5.9	8.0
Influenza	5.3	3.1
Lymphadenopathy	5.3	5.5
Arthralgia	5.0	2.8
Insomnia	5.0	4.3
Upper respiratory tract infection	4.7	7.1
Pyrexia	4.4	6.5
Back pain	3.4	6.2

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Adverse Events Leading to Study Drug Discontinuation

Patients, n	B/F/TAF n=320	DTG + F/TAF n=325
Any AE leading to D/C	5	1
Abdominal distention	1	0
Cardiac arrest (sepsis, appendicitis)	1	0
Chest pain	1	0
Erythema, pruritus	0	1
Paranoia, crystal methamphetamine use	1	0
Sleep disorder/insomnia/dyspepsia/tension headache/depressed mood	1	0

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Grade 3 or 4 Laboratory Abnormalities (≥2%)

Patients, %	B/F/TAF n=320	DTG + F/TAF n=325
Creatine kinase elevation	3.5	2.2
LDL elevation, fasting	3.0	3.5
ALT elevation	2.2	0.9
AST elevation	1.3	2.5
Hyperglycemia, fasting	0.3	2.2

ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDL, low-density lipoprotein.

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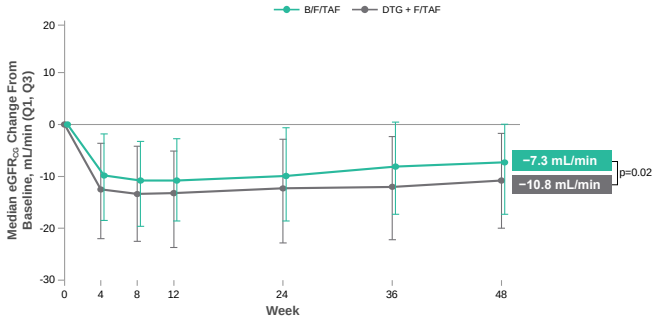
Change From Baseline in $eGFR_{CG}$



- No patients discontinued due to renal adverse events and no proximal tubulopathy occurred in either arm
- Less decrease in eGFRCG was observed with B/F/TAF vs DTG + F/TAF
  - BIC is a less potent inhibitor of serum creatinine organic cation transporter 2 than DTG

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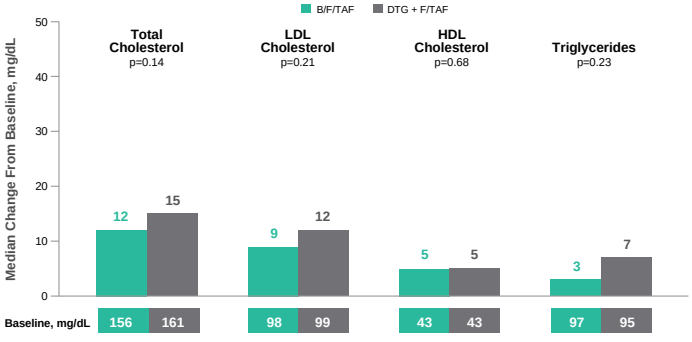
Fasting Lipid Changes at Week 48



HDL, high-density lipoprotein.

- Similar percentages of patients:
  - Were on lipid-lowering agents at baseline: B/F/TAF 6.6%, DTG + F/TAF 5.8% (p=0.75)
  - Initiated lipid-lowering agents during the study: B/F/TAF 1.6%, DTG + F/TAF 1.8% (p=1.00)

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Conclusions

- Virologic suppression at Week 48 was high in both arms, with B/F/TAF being noninferior to DTG + F/TAF in treatment-naive adults
  - Sensitivity analyses confirmed B/F/TAF was noninferior to DTG + F/TAF
  - No patient discontinued either treatment arm due to lack of efficacy
- No treatment-emergent resistance to any study medication was observed in either arm
- B/F/TAF was safe and well tolerated
- Less decrease in $eGFR_{CG}$ was observed with B/F/TAF vs DTG + F/TAF
- There were no discontinuations due to renal AEs and no cases of renal tubulopathy, including Fanconi's syndrome, in either treatment group
- Changes from baseline in lipid parameters were equivalent

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Acknowledgments

- We extend our thanks to the patients and their families, and all participating study investigators and staff. This study was funded by Gilead Sciences, Inc.

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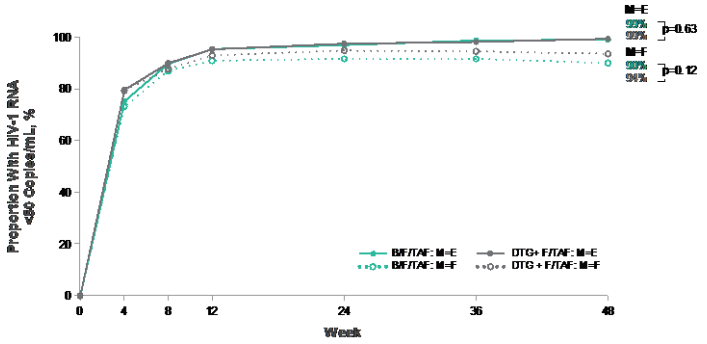
Virologic Response

Missing=Excluded and Missing=Failure Analyses



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Results

- All sensitivity analyses were pre-specified except modified snapshot analysis, which excluded all patients without post-baseline HIV-1 RNA results (7 patients excluded: 6 described above + 1 who discontinued due to AE of cardiac arrest/death in setting of sepsis/appendicitis prior to the 1st post-baseline visit)
- Per-protocol analysis excluded patients in full analysis set who were off study drug at Week 48 or had low adherence, i.e., adherence ≤2.5th percentile among those in study
- M=F and M=E analyses included patients who discontinued study drug, but remained in study, including those treated with other antiretrovirals

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