PE3/14

Long-term Efficacy and Safety of Bictegravir/Emtricitabine/Tenofovir Alafenamide in ART-Naïve Adults

Chloe Orkin,[1] Paul E. Sax,[2] Jose Arribas,[3] Samir Gupta,[4] Claudia Martorell,[5] Jeffrey L. Stephens,[6] Hans-Jürgen Stellbrink,[7] Edwin DeJesus,[8] Franco Maggiolo,[9] Hailin Huang,[10] Rima Acosta,[10] Diana M. Brainard,[10] Sean E. Collins,[10] Hal Martin,[10] on behalf of the Study 1489 and 1490 Investigators

[1]Barts Health NHS Trust, London, UK; [2]Brigham and Women's Hospital, Boston, Massachusetts, USA; [3]Hospital Universitario La Paz, Madrid, Spain; [4]Indiana University School of Medicine, Indianapolis, Indiana, USA; [5]Infectious Disease and The Research Institute, Springfield, Massachusetts; [6]Mercer University School of Medicine, Macon, Georgia, USA; [7]ICH Study Center, Hamburg, Germany; [8]Orlando Immunology Center, Orlando, Florida, USA; [9]ASST Papa Giovanni XXIII, Bergamo, Italy; [10]Gilead Sciences, Inc., Foster City, California, USA

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
800-445-3235

Introduction

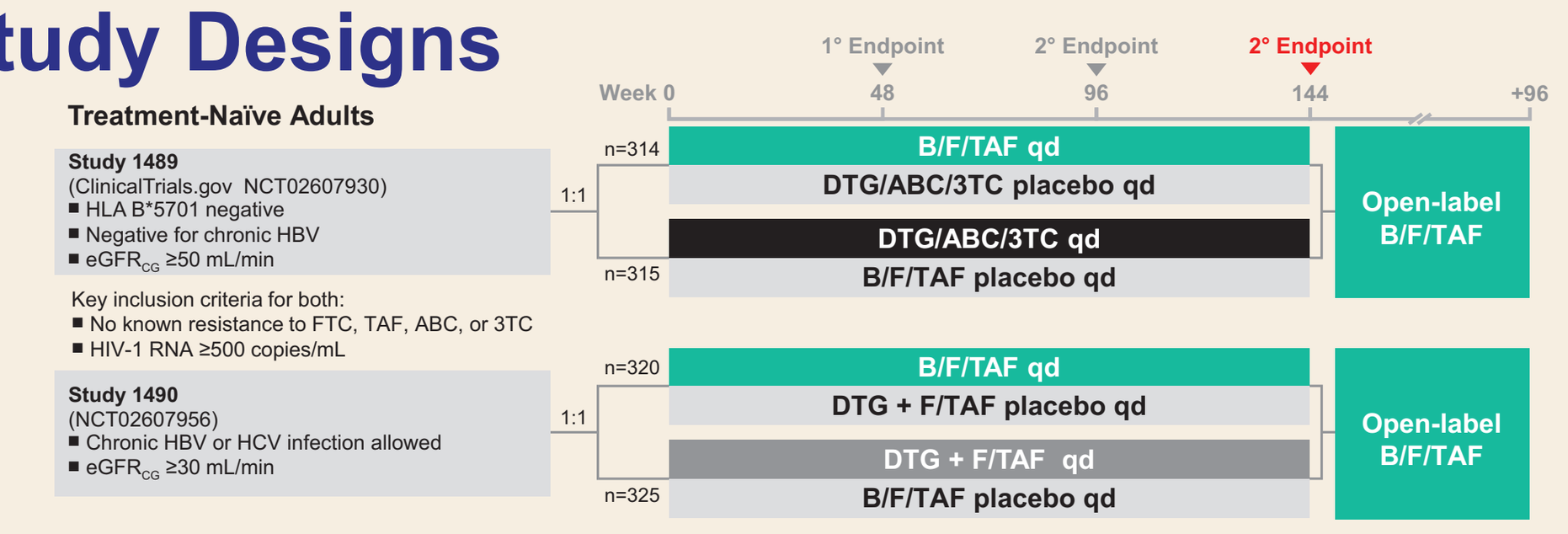
- The single-tablet regimen bictegravir (BIC; B), emtricitabine (FTC; F), and tenofovir alafenamide (TAF; B/F/TAF) is an EACS, US Dept of Health & Human Services, and International Antiviral Society–USA guidelines-recommended regimen,[1-3] with demonstrated safety and efficacy, and a high barrier to resistance
- We report long-term (Week 144) results pooled from two Phase 3 studies of treatment-naïve adults living with HIV comparing randomized treatment with B/F/TAF to 1 of 2 recommended dolutegravir (DTG)–containing regimens: DTG/abacavir (ABC)/lamivudine (3TC) in Study 1489 and DTG + F/TAF in Study 1490

Objectives

- To evaluate the safety and efficacy of B/F/TAF and DTG-containing regimens in treatment-naïve adults living with HIV based on a pooled analysis from two Phase 3 studies

Methods

Study Designs



$eGFR_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault equation; HBV, hepatitis B virus; HCV, hepatitis C virus; HLA, human leukocyte antigen.

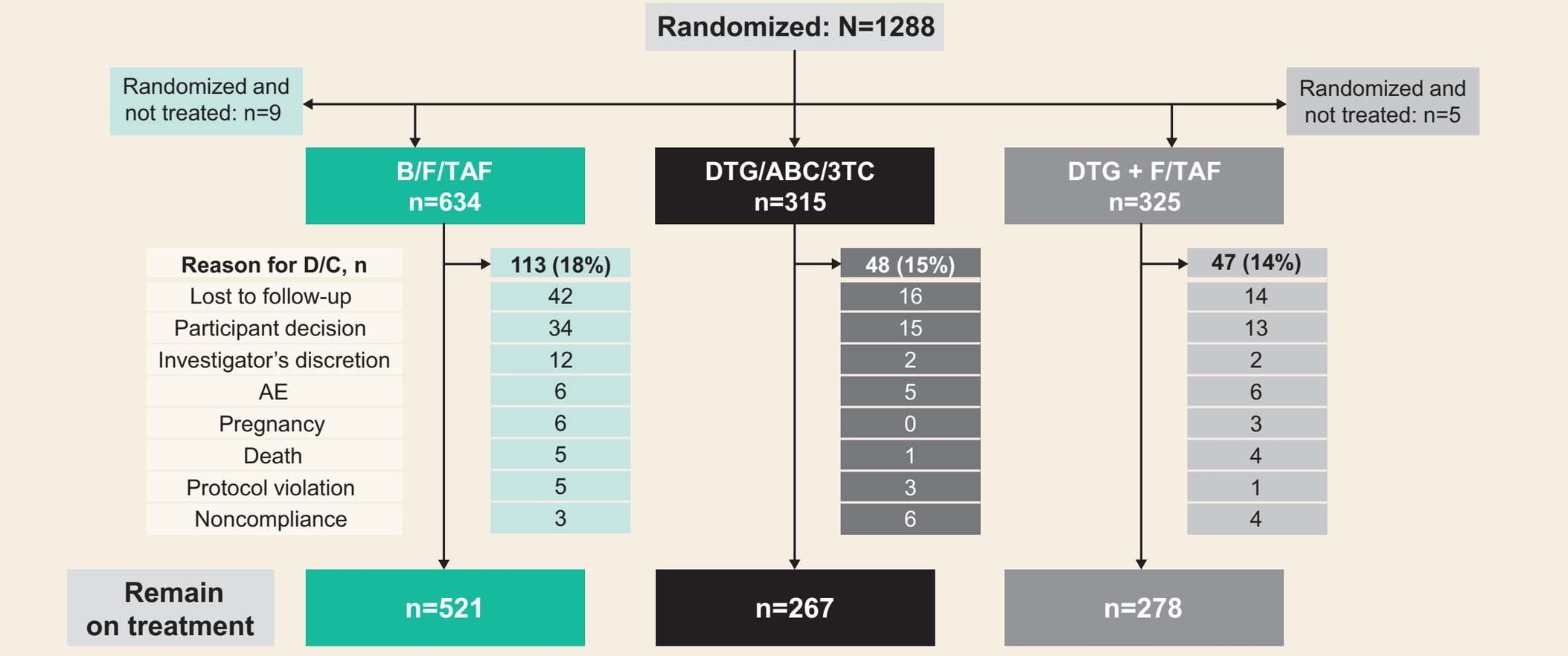
Results

Baseline Characteristics

	Pooled	Study 1489		Study 1490	
	B/F/TAF n=634	B/F/TAF n=314	DTG/ABC/3TC n=315	B/F/TAF n=320	DTG + F/TAF n=325
Median age, y (range)	32 (18–71)	31 (18–71)	32 (18–68)	33 (18–71)	34 (18–77)
Men, %	89	91	90	88	89
Race/ethnicity, %					
Black or African descent	33	36	36	30	31
Hispanic/Latino	24	23	21	26	25
Median HIV-1 RNA, log_{10} copies/mL (IQR)	4.4 (4.0–4.9)	4.4 (4.0–4.9)	4.5 (4.0–4.9)	4.4 (4.0–4.9)	4.5 (4.0–4.8)
HIV-1 RNA >100,000 copies/mL, %	19	17	16	21	17
Median CD4 cell count, cells/µL (IQR)	442 (293–590)	443 (299–590)	450 (324–608)	440 (289–591)	441 (297–597)
CD4 count <200 cells/µL, %	13	11	10	14	10
Asymptomatic HIV infection, %	90	91	91	89	89
Median $eGFR_{CG}$, mL/min (IQR)	122 (104–143)	126 (108–146)	123 (107–144)	120 (101–142)	121 (103–145)

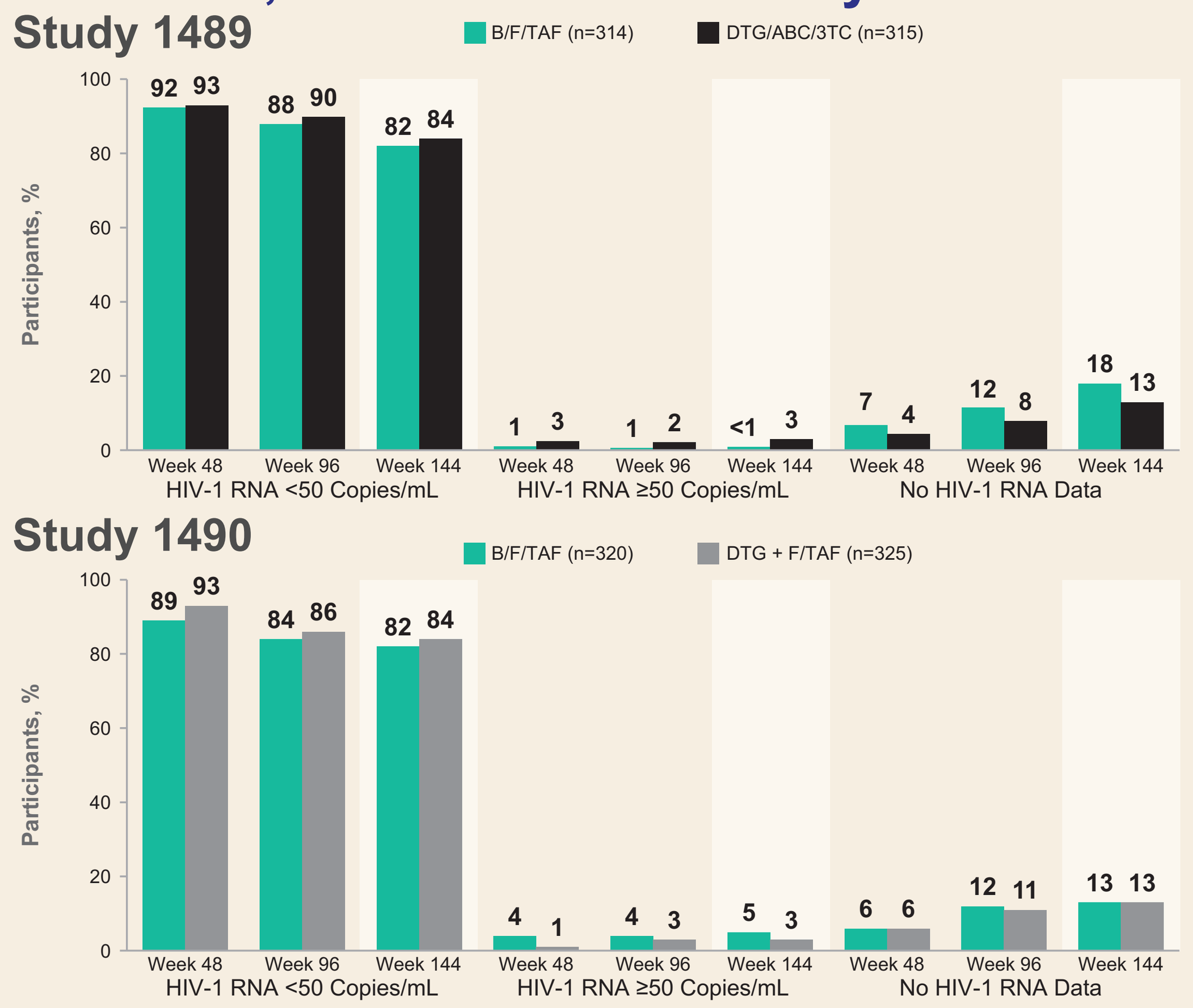
CD4, cluster of differentiation-4; IQR, interquartile range.

Pooled Participant Disposition From Baseline to Week 144



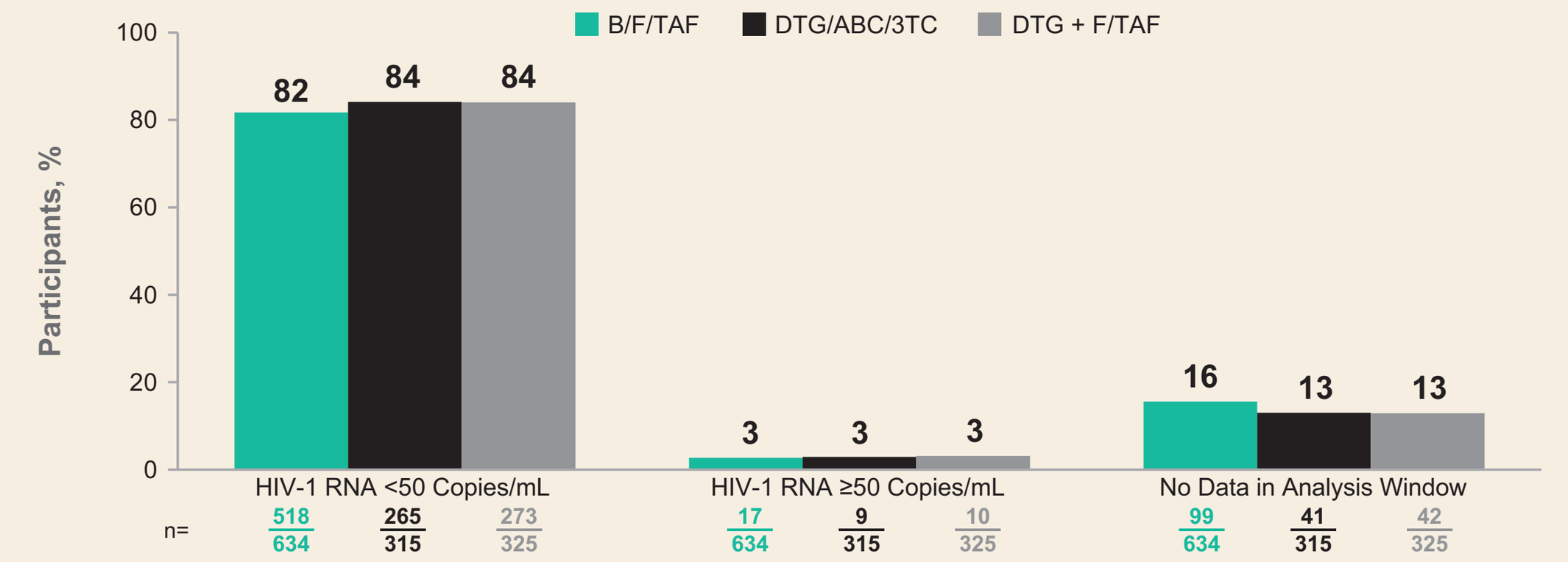
AE, adverse event; D/C, discontinuation.

Virologic Outcome by FDA Snapshot at Weeks 48, 96 and 144: Full Analysis Set



- Differences in HIV-1 RNA <50 copies/mL by FDA Snapshot at Week 144:
  - Study 1489: -2.6% (95% confidence interval [CI] -8.5%, 3.4%)
  - Study 1490: -1.9% (-7.8%, 3.9%)
- B/F/TAF was noninferior to DTG-containing regimens in each of the individual studies

Pooled Virologic Outcomes by FDA Snapshot at Week 144



- Per-protocol analysis of HIV-1 RNA <50 copies/mL:
  - Overall population: B/F/TAF 100% vs DTG/ABC/3TC 99% vs DTG + F/TAF 99%
  - HIV RNA >100,000 copies/mL at baseline: B/F/TAF 100% vs DTG/ABC/3TC 97% vs DTG + F/TAF 100%
  - CD4 <200 cells/µL at baseline: B/F/TAF 100% vs DTG/ABC/3TC 92% vs DTG + F/TAF 100%

Virologic Resistance Results at Week 144

	Overall		
Participants, n	B/F/TAF n=634	DTG/ABC/3TC n=315	DTG + F/TAF n=325
Met criteria for resistance testing*	8	6	7
NRTI resistance detected	0	0	0
INSTI resistance detected	0	0	0

*Performed for participants with confirmed HIV-1 RNA ≥50 copies/mL, with confirmation sample being ≥200 copies/mL or ≥200 copies/mL at last visit, and no resuppression of HIV-1 RNA to <50 copies/mL while on study drug. INSTI, integrase strand transfer inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor.

- No treatment-emergent resistance to any components of the regimens was detected in any treatment group
- 1 participant with baseline DTG resistance (Q148H + G140S) was randomized to B/F/TAF, suppressed <50 copies/mL at Week 4, and remained suppressed at Week 144

Adverse Events Through Week 144

	Overall		
All Grades	B/F/TAF n=634	DTG/ABC/3TC n=315	DTG + F/TAF n=325
≥10% of any group			
Diarrhea	19	18	16
Headache	16	18	18
Nasopharyngitis	14	17	19
Upper respiratory tract infection	14	19	16
Nausea*	11	24	13
Syphilis	11	16	10
Back pain	10	12	12
Fatigue	10	12	11
Insomnia	9	11	7
Oropharyngeal pain	7	11	6
Any drug-related AE*	26	42	29
AEs occurring in ≥5% of any group			
Nausea*	4	18	5
Headache	5	5	3
Diarrhea	5	4	3

*p <0.001: B/F/TAF vs DTG/ABC/3TC based on Fisher exact test.

- B/F/TAF had lower rates of study drug-related AEs, nausea, and study drug-related nausea than DTG/ABC/3TC (p <0.001)

Adverse Events Leading to Discontinuation Through Week 144

Overall		
B/F/TAF n=634	DTG/ABC/3TC n=315	DTG + F/TAF n=325
n=6 (1%)	n=5 (2%)	n=6 (2%)
Cardiac arrest (Day 28)	Nausea and generalized rash (Day 4)*	Erythema and pruritus (Day 112)
Atypical chest pain (Day 31)*	Thrombocytopenia (Day 50)*	Depression (Day 420)*
Sleep disorder, dyspepsia, tension headache, depressed mood, and insomnia (Day 65)*	Steatorrhea (Day 134)*	Lipoatrophy (Day 464)*
Paranoia (Day 302)	Depression (Day 248)*	Depression (Day 532)*
Abdominal distension (Day 304)*	Renal failure (Day 621)	Supraventricular tachycardia (Day 597)
Depression (Day 337)*		Large B-cell lymphoma (Day 1009)
6 deaths reported: • Cardiac arrest during septic shock (Day 28) • Gastric adenocarcinoma (Day 376) • Hypertensive heart disease and congestive heart failure (Day 412) • Suicide (Day 656) • Recreational drug overdose (Day 771) • Sudden cardiac death (Day 1060)	**1 death reported:** • Recreational drug overdose (Day 812)	**4 deaths reported:** • Unknown cause (Day 174) • Pulmonary embolism (Day 266) • Lymphoma (Day 422) • Unknown cause (Day 771)

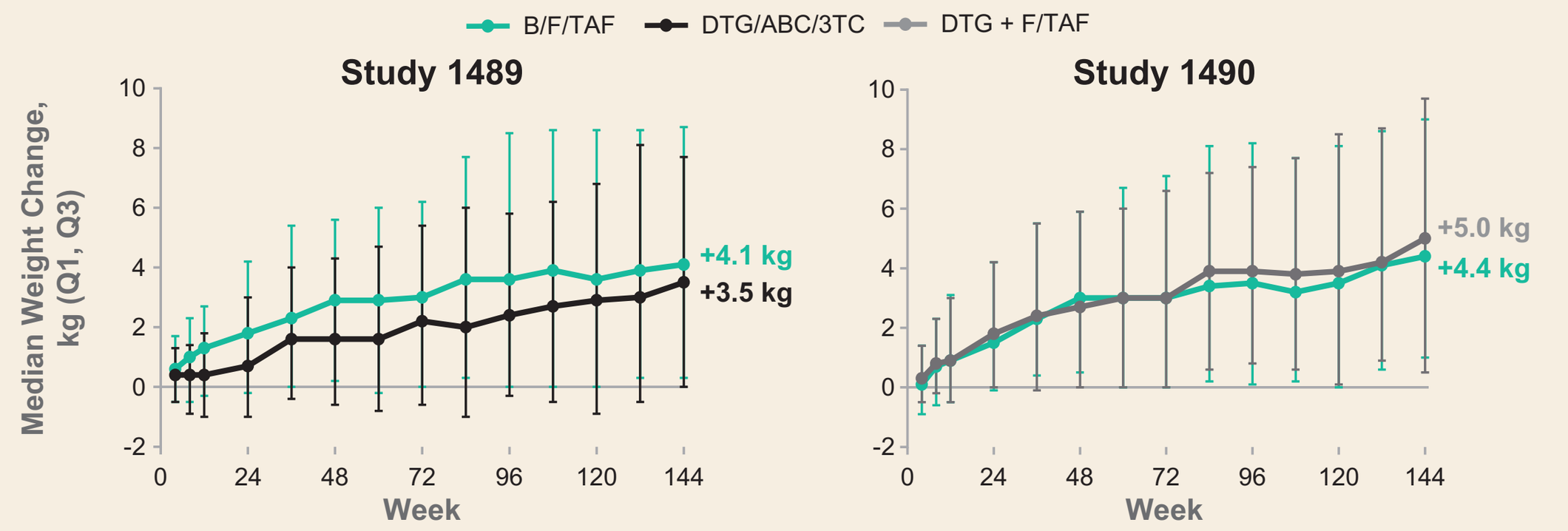
*Considered study drug-related by investigator.

Laboratory Abnormalities Through Week 144

	Overall		
≥5% of Any Overall Group, %	B/F/TAF n=634	DTG/ABC/3TC n=315	DTG + F/TAF n=325
Any Grade 3 or 4 lab abnormality	26	25	23
Increased creatine kinase	7	8	4
Increased fasting LDL	4	5	6

LDL, low-density lipoprotein.

Weight Change Through Week 144

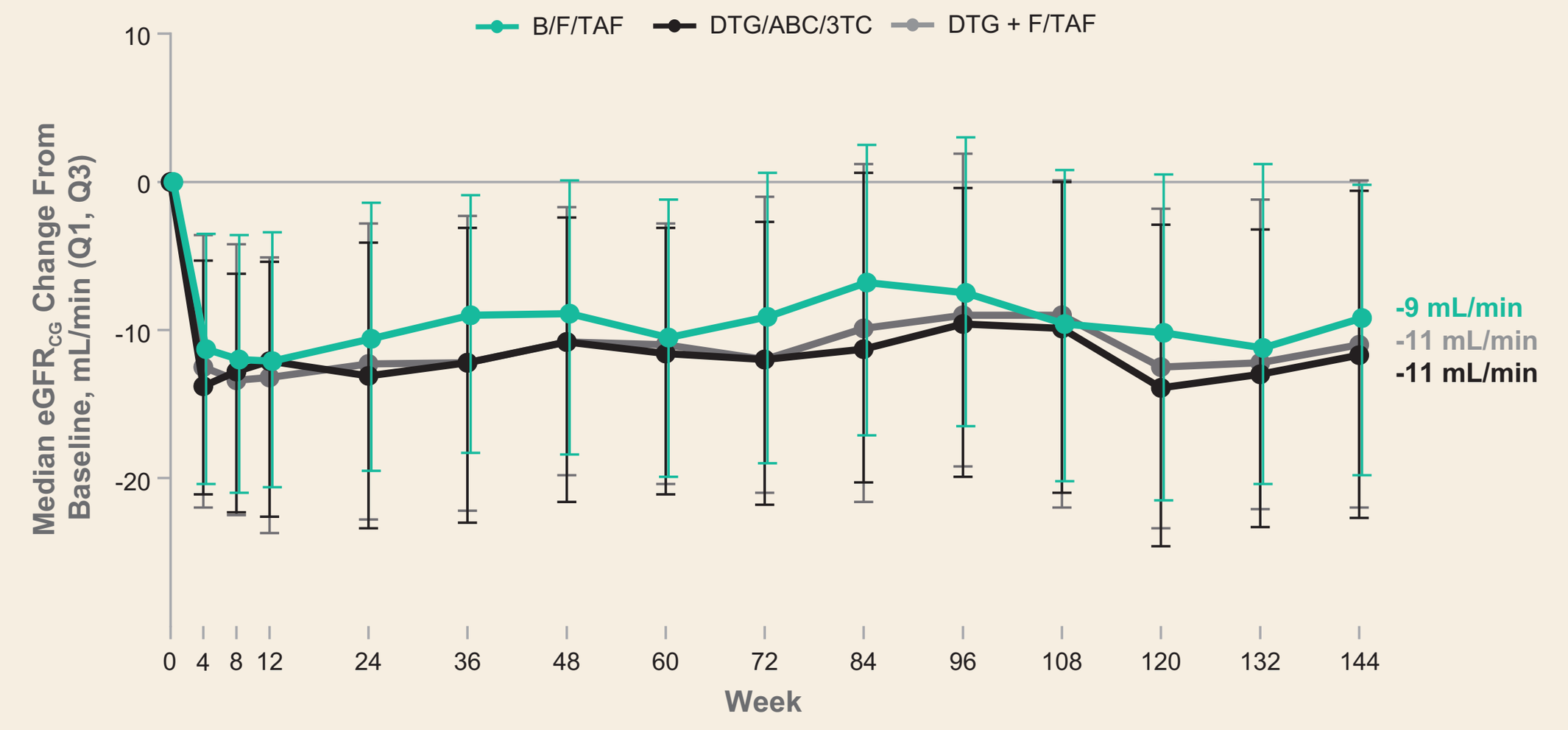


	Study 1489		Study 1490	
Week 144	B/F/TAF n=314	DTG/ABC/3TC n=315	B/F/TAF n=320	DTG + F/TAF n=325
Participants, %				
≥5% weight gain	52	48	53	55
≥10% weight gain	29	25	30	32
Weight loss or no change from baseline	24	26	21	22
Mean weight change from baseline, kg (SD)	5.3 (9.2)	4.3 (7.8)	5.6 (8.3)	5.7 (7.8)

Q, quartile; SD, standard deviation.

- An AE of weight increase was reported for B/F/TAF 3%, DTG/ABC/3TC 4%, and DTG + F/TAF 3%, and weight decrease for B/F/TAF 1%, DTG/ABC/3TC 1%, and DTG + F/TAF 3%

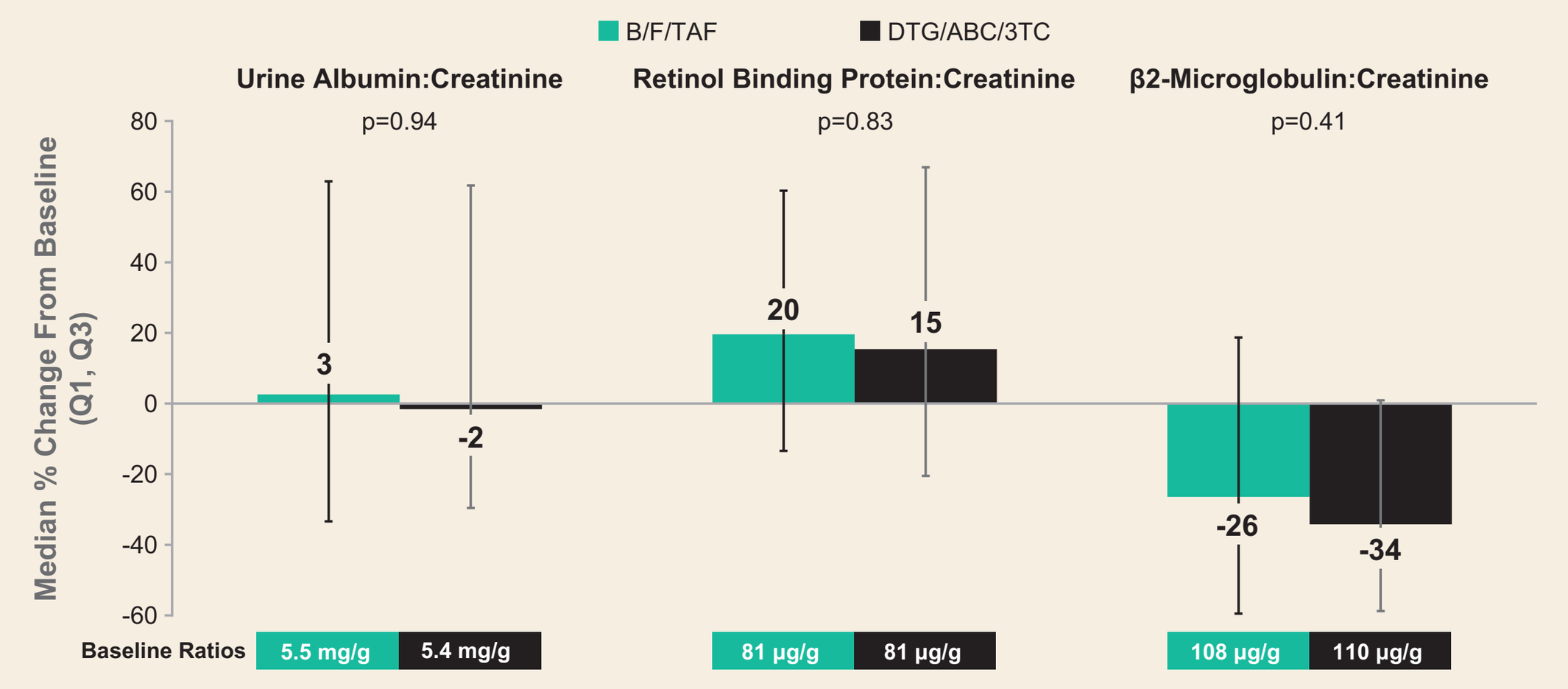
Change From Baseline in eGFR Through Week 144: Overall



Differences at Week 144 between B/F/TAF and DTG/ABC/3TC, p=0.13; and B/F/TAF vs DTG + F/TAF, p=0.28; p-values from 2-sided Wilcoxon rank-sum test.

- Changes in eGFR were consistent with inhibition of tubular creatinine secretion via organic cation transporter-2 by DTG or BIC
- There were no D/Cs due to renal AEs in B/F/TAF or DTG + F/TAF group
- There was 1 D/C due to renal failure in DTG/ABC/3TC group not attributed to study drug

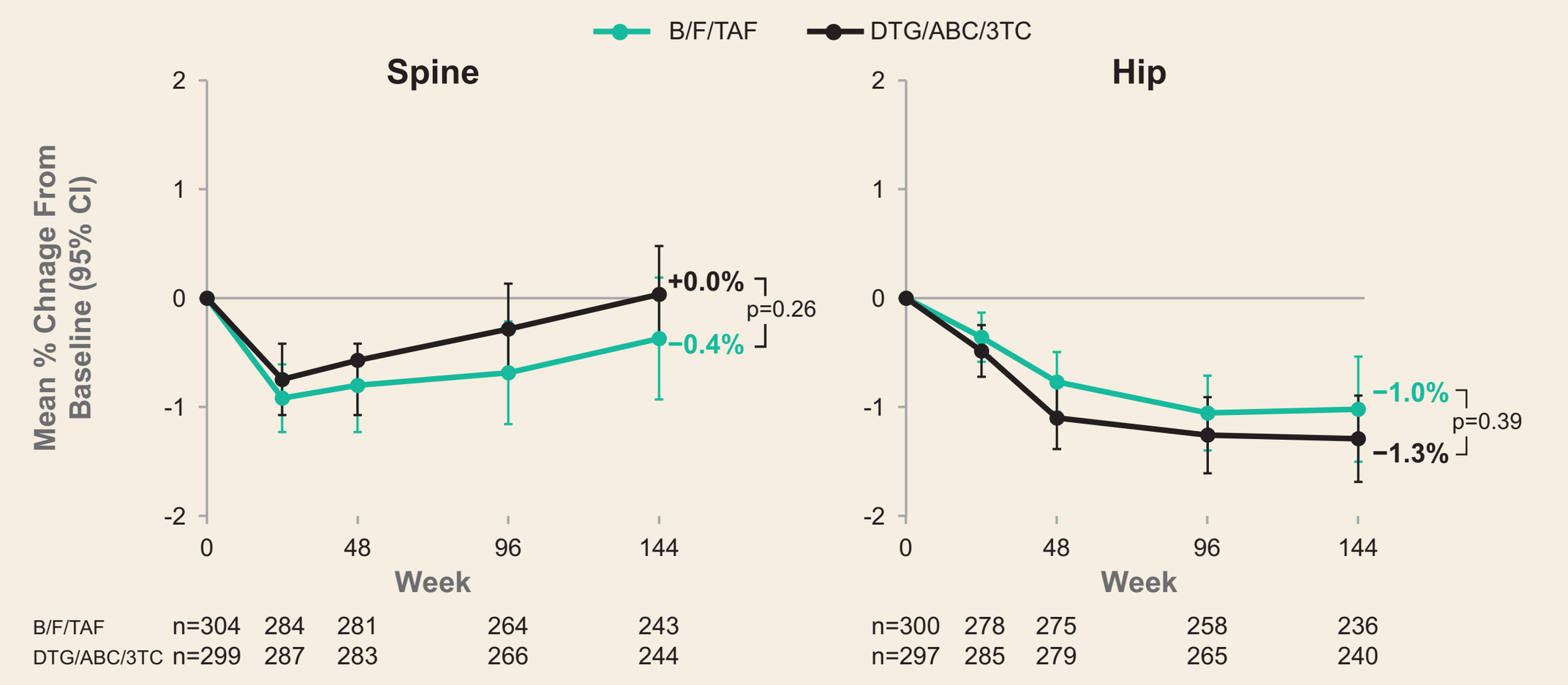
% Change From Baseline in Quantitative Proteinuria at Week 144: Study 1489



Difference in % change from baseline for each marker tested between treatment groups by Wilcoxon rank sum test; urine protein tests performed for Study 1489 only.

- There were no cases of proximal renal tubulopathy reported in any group

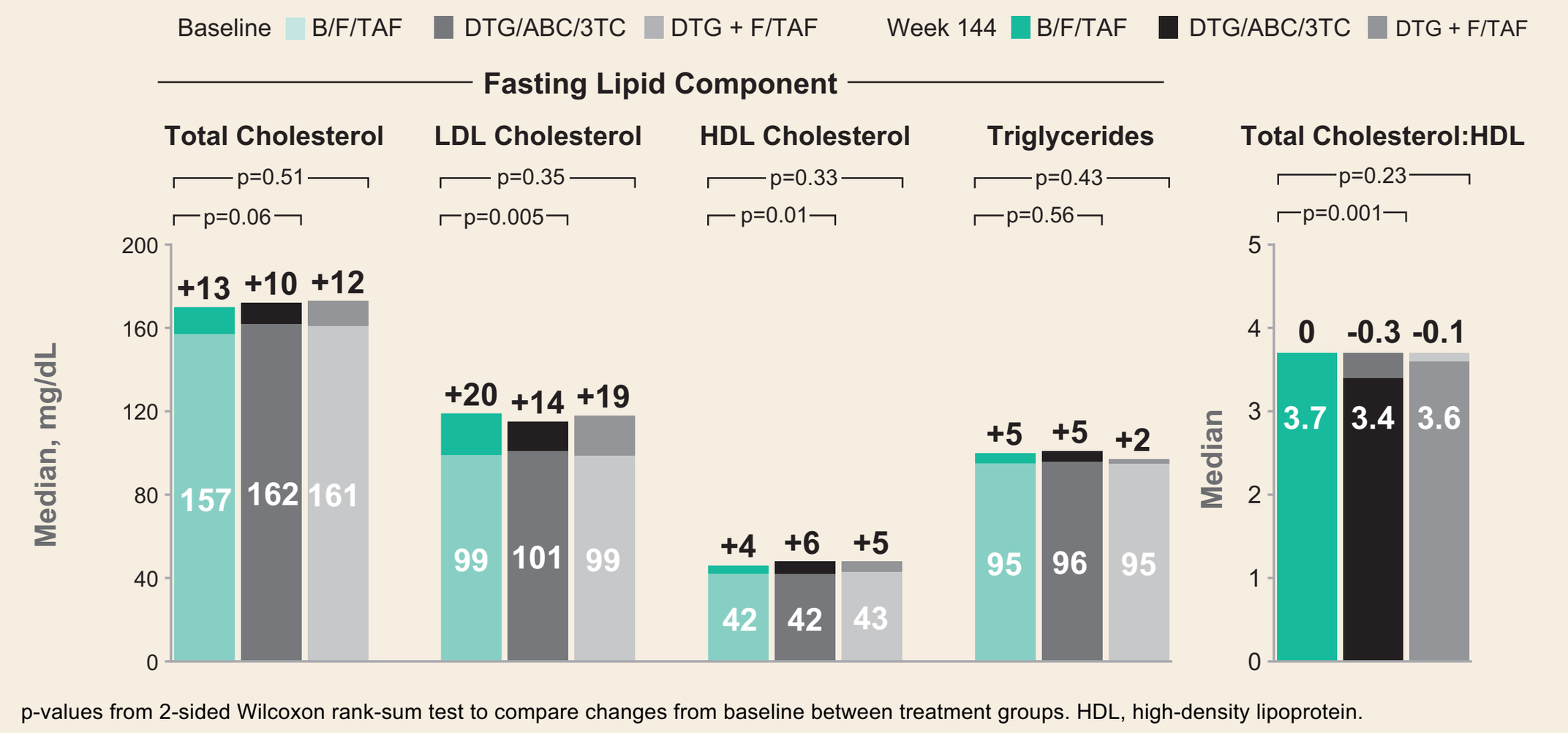
% Change in Spine and Hip BMD Through Week 144: Study 1489



Comparison of B/F/TAF vs DTG/ABC/3TC at Week 144 by analysis of variance model; bone mineral density (BMD) measured by dual-energy x-ray absorptiometry in Study 1489 only.

- Changes in BMD from baseline were similar between groups

Change From Baseline in Fasting Lipids at Week 144: Overall



p-values from 2-sided Wilcoxon rank-sum test to compare changes from baseline between treatment groups. HDL, high-density lipoprotein.

- Fasting lipids increased in all groups after treatment initiation
- Differences between groups in changes from baseline in fasting lipids were not clinically relevant
- Similar percentages of participants in each group received lipid-modifying agents at study entry (B/F/TAF 5.0%, DTG/ABC/3TC 2.2%, and DTG + F/TAF 5.5%) and initiated treatment during the study (B/F/TAF 4.7%, DTG/ABC/3TC 5.1%, and DTG + F/TAF 4.9%)

Conclusions

- At Week 144, B/F/TAF remained noninferior to either DTG-based triple therapy regimen in treatment-naïve participants with high rates of virologic suppression in all treatment arms
- There was no treatment-emergent resistance to any of these triple-therapy treatment regimens
- B/F/TAF was associated with fewer treatment-related AEs than DTG/ABC/3TC (p <0.001)
  - Nausea and treatment-related nausea were less common with B/F/TAF vs DTG/ABC/3TC (p <0.001)
- Changes from baseline in BMD and renal markers for B/F/TAF were similar to DTG/ABC/3TC
  - There were no cases of proximal renal tubulopathy in any treatment arm
  - No participant discontinued B/F/TAF due to renal or bone-related AEs
- There were no clinically relevant differences between arms in median changes from baseline in fasting lipids and no differences in proportions initiating lipid-lowering medications
- This 3-year long-term follow-up demonstrates treatment with B/F/TAF was effective, and may offer better safety and tolerability over other guideline-recommended regimens

References: 1. EACS European AIDS Clinical Society. Guidelines Version 9.1, October 2018. https://www.eacsociety.org/files/2018_guidelines-9.1-english.pdf; 2. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Dep of Health and Human Services. https://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL003510.pdf; 3. Saag MS, et al. JAMA 2018;320:379-96.

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