SWITCHING TO THE 2-DRUG REGIMEN OF DOLUTEGRAVIR/LAMIVUDINE (DTG/3TC) FIXED-DOSE COMBINATION IS NON-INFERIOR TO CONTINUING A 3-DRUG REGIMEN THROUGH 48 WEEKS IN A RANDOMIZED CLINICAL TRIAL (SALSA)

Josep M. Llibre,[1] Carlos Alves Brites,[2] Chien-Yu Cheng,[3,4] Olayemi Osiyemi,[5] Carlos Galera,[6] Laurent Hocqueloux,[7] Franco Maggiolo,[8] Olaf Degen,[9] Libby Blair,[10] Brian Wynne,[10] James Oyee,[11] Mark Underwood,[10] Lloyd Curtis,[11] Gilda Bontempo,[10] Jean van Wyk[12]

[1]Hospital Universitari Germans Trias i Pujol, Barcelona, Spain; [2]Universidade Federal da Bahia, Salvador, Brazil; [3]Department of Infectious Diseases, Taoyuan General Hospital, Ministry of Health and Welfare, Taoyuan, Taiwan; [4]School of Public Health, National Yang-Ming University, Taipei, Taiwan; [5]Triple O Research Institute PA, West Palm Beach, FL, USA; [6]Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain; [7]Centre Hospitalier Régional d'Orléans, Orléans, France; [8]ASST Papa Giovanni XXIII, Bergamo, Italy; [9]Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; [10]ViiV Healthcare, Research Triangle Park, NC, USA; [11]GlaxoSmithKline, Uxbridge, UK; [12]ViiV Healthcare, Brentford, UK

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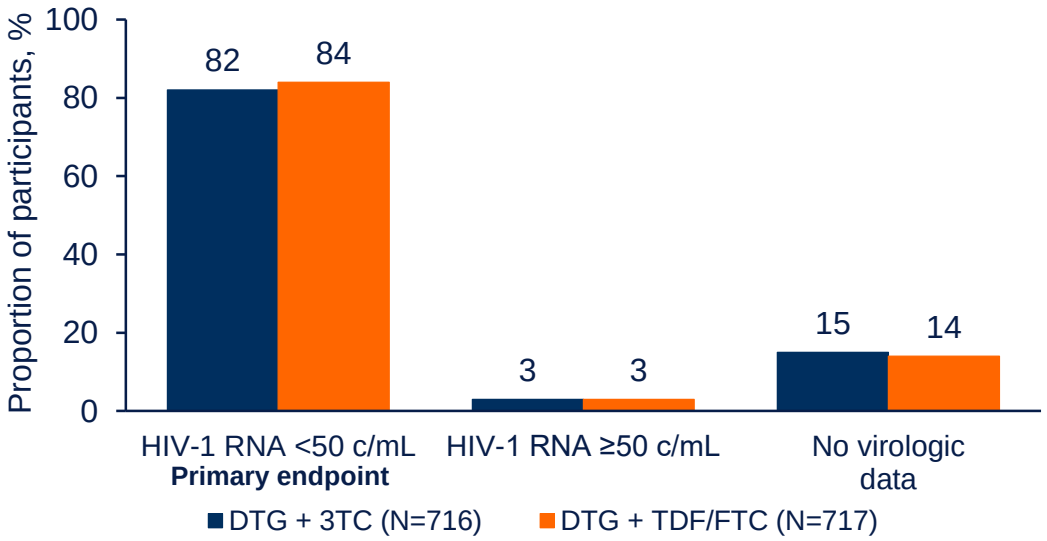
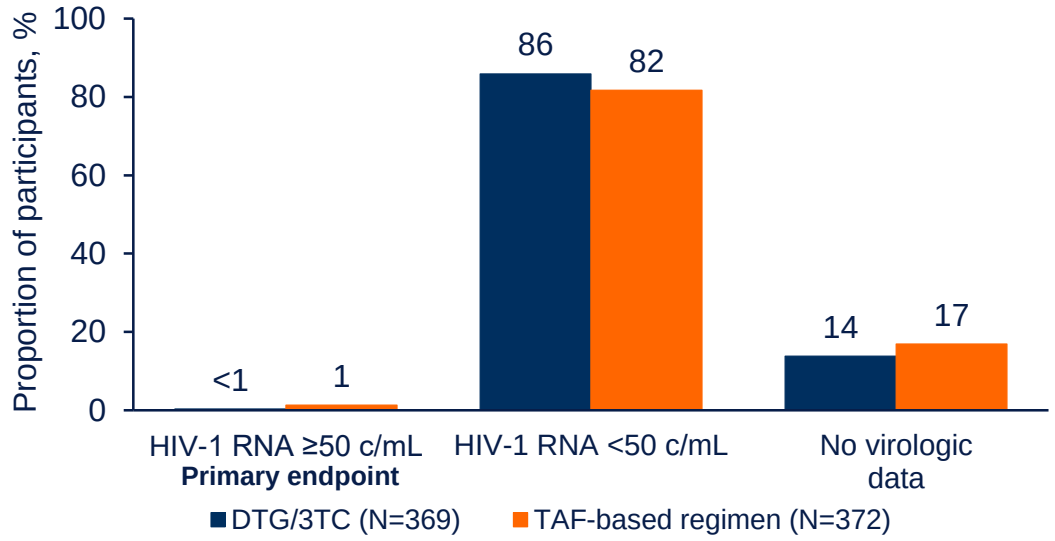
Introduction

- 2DRs have reduced the number of antiretroviral agents taken by individuals who need lifelong ART[1]
- DTG/3TC has demonstrated long-term non-inferior efficacy, a good safety profile, and a high barrier to resistance through Week 144 in treatment-naive individuals in the GEMINI studies (vs DTG + TDF/FTC)[2-4] and treatment-experienced, virologically suppressed individuals in the TANGO study (vs continuing TAF-based regimens)[5-7]

GEMINI-1 and GEMINI-2, Week 144
Virologic Outcomes (Snapshot)[4]



TANGO, Week 144
Virologic Outcomes (Snapshot)[7]



1. Back. *Germs*. 2017;7:113-114. **2.** Cahn et al. *Lancet*. 2019;393:143-155. **3.** Cahn et al. *J Acquir Immune Defic Syndr.* 2020;83:310-318. **4.** Cahn et al. HIV Glasgow 2020; Virtual. Poster P018. **5.** van Wyk et al. *Clin Infect Dis*. 2020;71:1920-1929. **6.** van Wyk et al. HIV Glasgow 2020; Virtual. Slides O441. **7.** van Wyk et al. IAS 2021; Virtual. Poster PEB164.

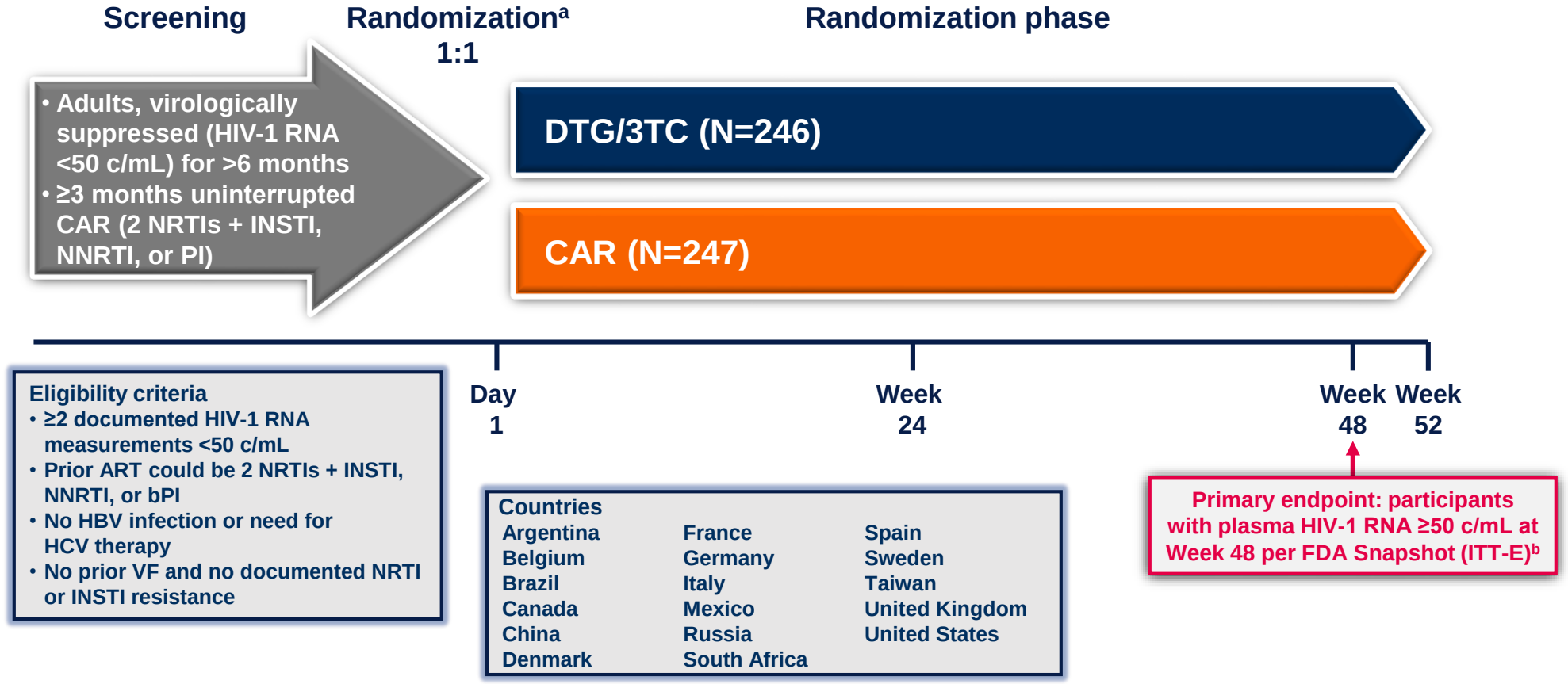
Introduction (cont)

- The TANGO study included only individuals treated with TAF-based regimens, mostly EVG/c/TAF/FTC and RPV/TAF/FTC[1]
- To broaden the scope of data beyond comparison with TAF-based regimens (TANGO), the objective of SALSA was to evaluate efficacy and safety of switching to the 2-drug regimen of DTG/3TC FDC compared with continuing any current 3- or 4-drug ART regimen (CAR) in adults with HIV-1 over 48 weeks

1. van Wyk et al. *Clin Infect Dis*. 2020;71:1920-1929.

SALSA Phase III Study Design

Randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study



[a]Stratified by baseline third agent class (PI, INSTI, or NNRTI). [b]5% non-inferiority margin.

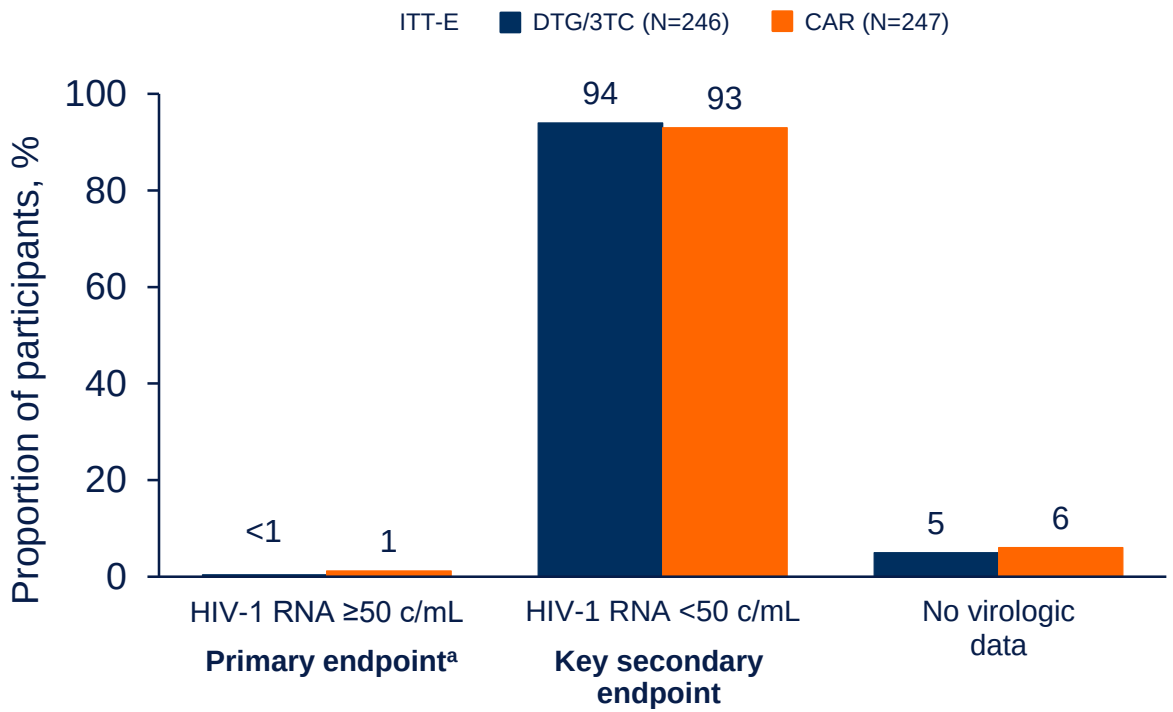
Demographics and Baseline Characteristics: ITT-E Population

Characteristic	DTG/3TC (N=246)	CAR (N=247)
Age		
Median (range), y	45 (22-74)	45 (23-83)
Age ≥50 y, n (%)	98 (40)	95 (38)
Female, n (%)	108 (44)	84 (34)
Race, n (%)		
African American/African heritage	45 (18)	48 (19)
Asian	31 (13)	39 (16)
White	149 (61)	144 (58)
CD4+ cell count, median (range), cells/mm^3	675 (154-2089)	668 (94-1954)
CD4+ cell count, cells/mm^3, n (%)		
<350	21 (9)	17 (7)
≥350	224 (91)	230 (93)
Duration of ART before Day 1, median (range), mo	63 (4-240)	71 (12-253)
Baseline third agent class, n (%)		
INSTI	98 (40)	98 (40)
NNRTI	123 (50)	124 (50)
PI	25 (10)	25 (10)
NRTIs received at screening in ≥30% of participants		
FTC	149 (61)	156 (63)
TDF[a]	109 (44)	109 (44)
3TC	96 (39)	89 (36)
TAF	83 (34)	91 (37)
Weight, median (range), kg	73 (43-154)	75.0 (36-160)
BMI, median (range), kg/m^2	25 (17-51)	26 (14-69)

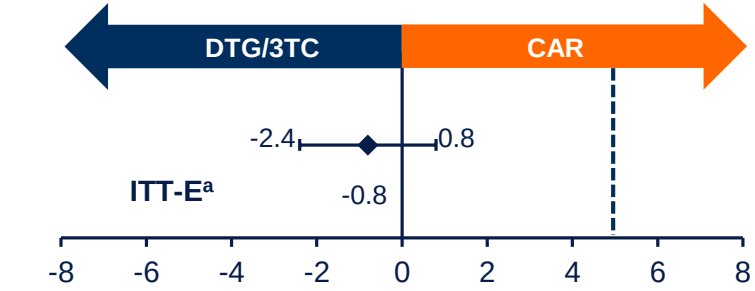
[a]Includes tenofovir disoproxil succinate (DTG/3TC, n=1; CAR, n=3).

DTG/3TC Is Non-Inferior to CAR at Week 48

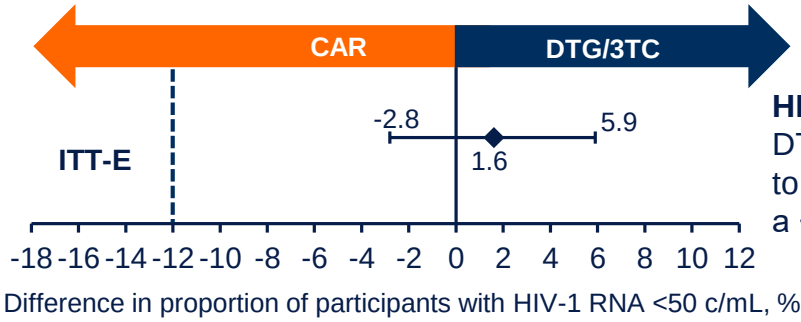
Virologic outcomes (Snapshot analysis)



Adjusted treatment difference (95% CI)[b]



HIV-1 RNA ≥50 c/mL
DTG/3TC is non-inferior to CAR at Week 48 based on a 5% non-inferiority margin



HIV-1 RNA <50 c/mL
DTG/3TC is non-inferior to CAR at Week 48 based on a −12% non-inferiority margin

- In the per-protocol population, 1/222 (0.5%) in the DTG/3TC group and 3/234 (1.3%) in the CAR group had HIV-1 RNA ≥50 c/mL at Week 48 (adjusted difference, −0.8%; 95% CI, −2.5% to 0.9%)

[a]Primary endpoint (Snapshot virologic non-response, ITT-E). [b]Based on Cochran-Mantel-Haenszel stratified analysis (DTG/3TC − CAR) adjusting for baseline third agent class.

Snapshot Outcomes at Week 48: ITT-E Population

n (%)	DTG/3TC (N=246)	CAR (N=247)
HIV-1 RNA <50 c/mL	232 (94)	229 (93)
HIV-1 RNA ≥50 c/mL	1 (<1)	3 (1)
Data in window and HIV-1 RNA ≥50 c/mL	1 (<1)[a]	1 (<1)[b]
Discontinued for lack of efficacy	0	2 (<1)
Discontinued for other reason and HIV-1 RNA ≥50 c/mL	0	0
Change in ART	0	0
No virologic data	13 (5)	15 (6)
Discontinued because of AE or death[c]	5 (2)	2 (<1)
Discontinued for other reasons[d]	7 (3)	10 (4)
On study but missing data in window[e]	1 (<1)	3 (1)

[a]1 participant had VL of 53 c/mL at Week 48, followed by 2 retests and was withdrawn with VL <40 c/mL after Week 52. [b]1 participant had VL of 90 c/mL at Week 36 and was withdrawn during Week 48 window with VL of 68 c/mL. [c]Reasons for discontinuations due to AEs in DTG/3TC group: insomnia (n=2), alcohol abuse/anxiety (n=1), weight increased (n=1), and unknown cause of death (n=1); in CAR group: ulcerative colitis and post-operative complications (n=1 each); last on-treatment VLs were all <50 c/mL. [d]Other reasons for discontinuation included protocol deviation (n=6), participant withdrawal (n=6), pregnancy (n=2), physician decision (n=2), and lost to follow-up (n=1). [e]Missing data in window was due to COVID-19 pandemic in 2 participants in the CAR group only.

Confirmed Virologic Withdrawals Through Week 48

Confirmed virologic withdrawal (CVW), n (%)	DTG/3TC (N=246)	CAR (N=247)
Week 48	0	0

- Zero resistance mutations were observed as zero participants met confirmed virologic withdrawal criteria

Confirmed virologic withdrawal criteria defined as one assessment of HIV-1 RNA ≥200 c/mL after Day 1 with an immediately prior HIV-1 RNA ≥50 c/mL.

Summary of Adverse Events and Weight Changes Through Week 48: Safety Population

n (%)	DTG/3TC (N=246)	CAR (N=247)
Any AE	180 (73)	172 (70)
AEs occurring in ≥7% of participants in either group		
Headache	16 (7)	17 (7)
Weight increased	20 (8)	5 (2)
Any grade 2-5 AE	88 (36)	105 (43)
Grade 2-5 AEs occurring in ≥3% of participants in either group		
COVID-19	7 (3)	4 (2)
Headache	1 (<1)	9 (4)
Syphilis	7 (3)	1 (<1)
Drug-related AEs	48 (20)	16 (6)
Drug-related AEs occurring in ≥3% of participants in either group		
Weight increased	14 (6)	0
Insomnia	7 (3)	1 (<1)
Dizziness	7 (3)	0
AEs leading to withdrawal from the study	5 (2)	3 (1)
Drug-related AEs leading to withdrawal from the study	4 (2)	1 (<1)
Any SAE	7 (3)	16 (6)
Drug-related SAEs	0	0

Data in the table are cumulative through Week 48.

- Adjusted mean change in weight from baseline to Week 48 was 2.1 kg in the DTG/3TC group and 0.6 kg in the CAR group
- Adjusted mean change in BMI from baseline to Week 48 was 0.7 kg/m^2 in the DTG/3TC group and 0.2 kg/m^2 in the CAR group

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Adverse Events Leading to Withdrawal Through Week 48: Safety Population

n (%)	DTG/3TC (N=246)	CAR (N=247)
AEs leading to withdrawal from the study	5 (2)	3 (1)
Psychiatric	3 (1)	1 (<1)
Insomnia	2 (<1)	0
Alcohol abuse	1 (<1)	0
Anxiety	1 (<1)	0
Suicidal ideation	0	1 (<1)
Gastrointestinal disorders	0	1 (<1)
Colitis ulcerative[a]	0	1 (<1)
General disorders and administration site conditions	1 (<1)	0
Death[a]	1 (<1)	0
Injury, poisoning, and procedural complications	0	1 (<1)
Post-procedural complication[a]	0	1 (<1)
Investigations	1 (<1)	0
Weight increased	1 (<1)	0

[a]Considered unrelated to study treatment.

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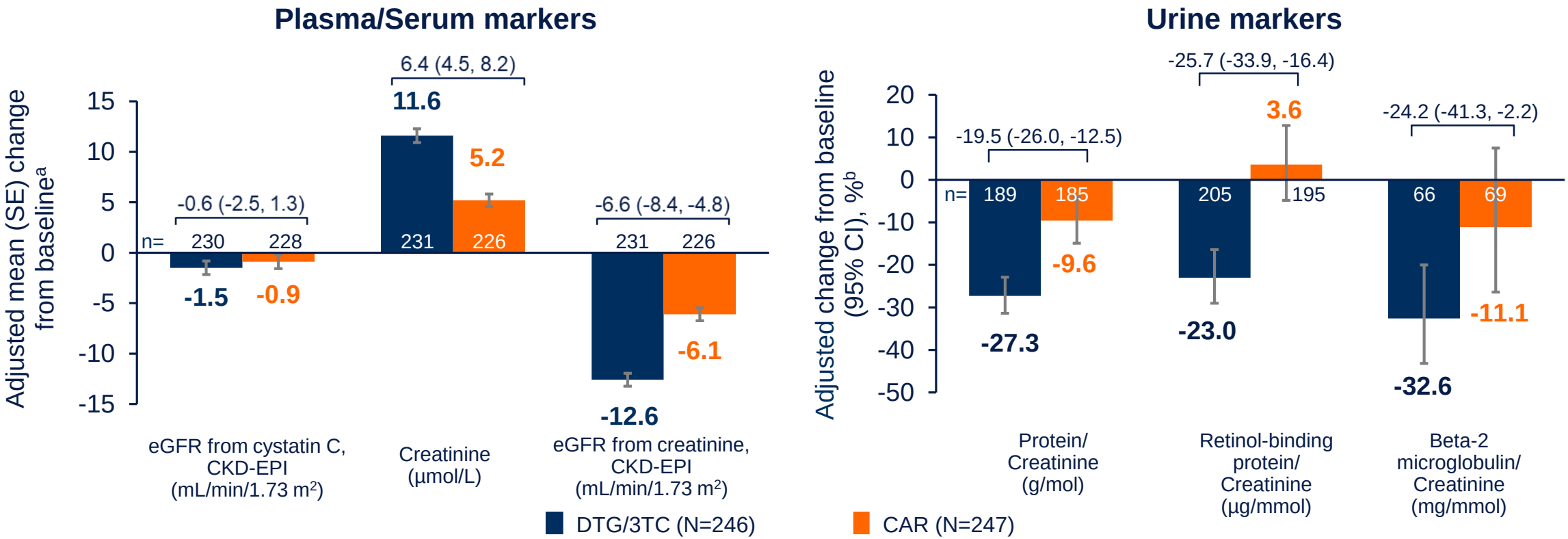
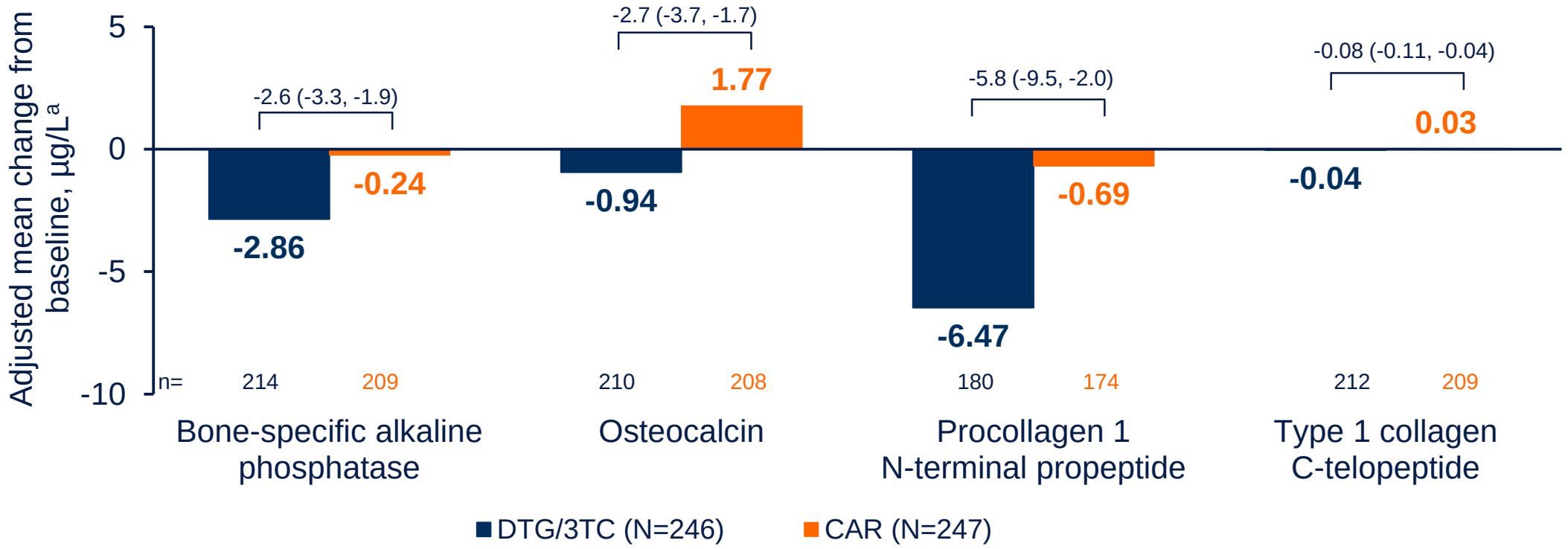
Change in Renal Biomarkers at Week 48: Safety Population



- Similar small changes in eGFR from cystatin C were observed in both treatment groups; decreases in eGFR by creatinine were observed in both treatment groups, with a greater decrease with DTG/3TC
- Improvements in markers for proximal tubular renal function were observed with DTG/3TC

Adjusted mean treatment difference (95% CI) displayed above treatment groups.
[a]Estimated mean change from baseline at Week 48 in each group calculated from MMRM adjusting for treatment, visit, baseline third agent class, CD4+ cell count (continuous), age (continuous), sex, race, BMI (continuous), presence of diabetes mellitus, presence of hypertension, baseline biomarker value (continuous), treatment-by-visit interaction, and baseline value-by-visit interaction, with visit as the repeated factor. [b]Based on estimated geometric means ratio of Week 48 vs baseline. Based on the same model as plasma/serum markers except adjusting for $\log_e$-transformed baseline biomarker value. n = number of participants with non-missing data at baseline and Week 48.

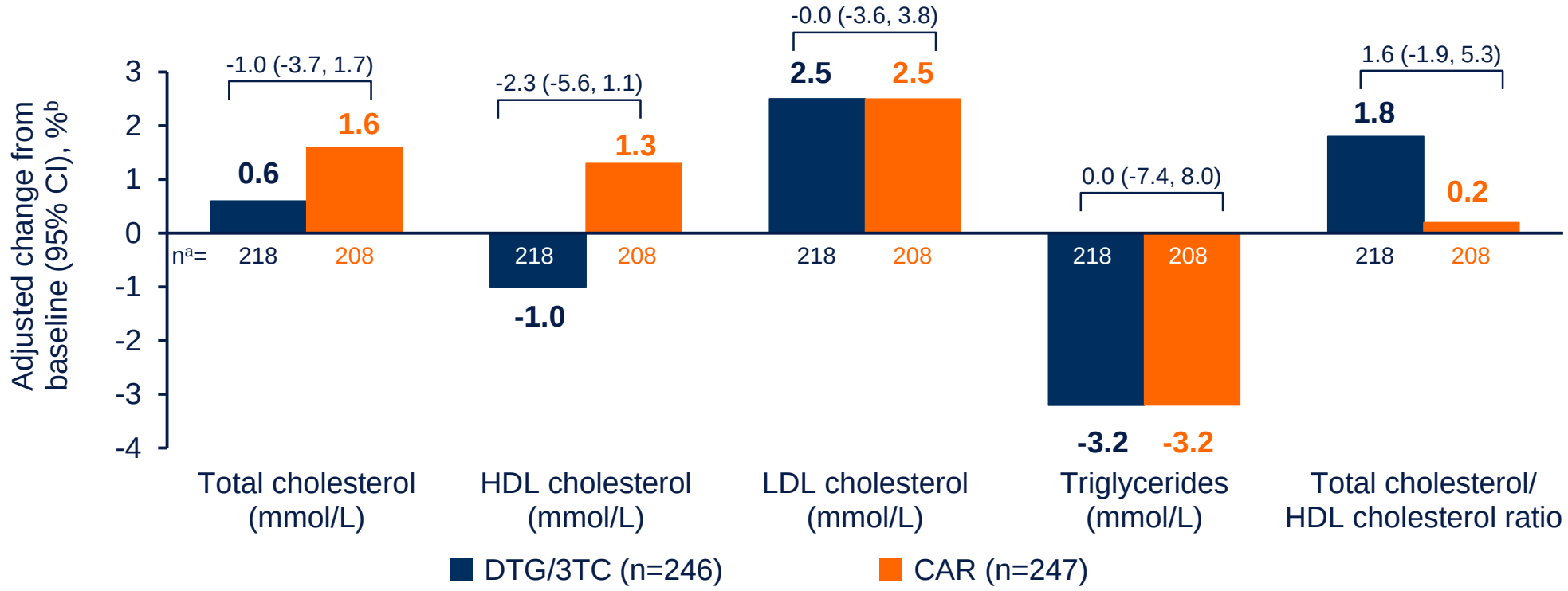
Change in Bone Biomarkers at Week 48: Safety Population



- Improvements in markers of bone turnover were observed after switching to DTG/3TC

Adjusted mean treatment difference (95% CI) displayed above treatment groups.
[a]Estimated mean change from baseline at Week 48 in each group calculated from MMRM adjusting for treatment, visit, baseline third agent class, CD4+ cell count (continuous), age (continuous), sex, race, BMI (continuous), smoking status, baseline biomarker value (continuous), treatment-by-visit interaction, and baseline value-by-visit interaction, with visit as the repeated factor.

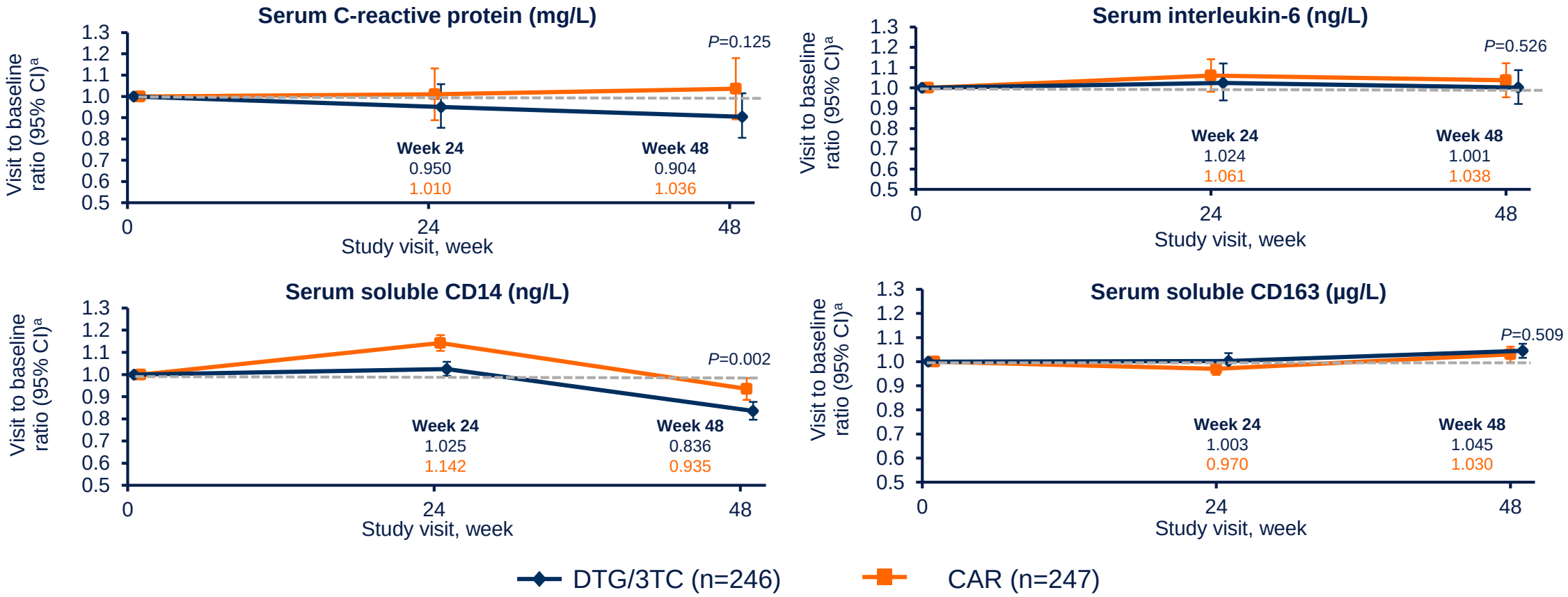
Change in Serum Lipids at Week 48: Safety Population



- Small and similar changes between treatment groups were observed at Week 48 across lipid parameters

Adjusted mean treatment difference (95% CI) displayed above treatment groups.
[a]n = number of participants with non-missing fasting lipid data at baseline and Week 48, removing those with lipid-modifying agent administered at baseline (lipid data collected after initiation of a lipid-modifying agent were censored and multiple imputation was applied). [b]Percent change from baseline based on adjusted ratio (Week 48 to baseline) in each group calculated from a multiple imputation model applied to change from baseline in $\log_e$-transformed data adjusting for treatment, visit, baseline third agent class, CD4+ cell count (continuous), age (continuous), sex, race, $\log_e$-transformed baseline value (continuous), treatment-by-visit interaction, and $\log_e$-transformed baseline value-by-visit interaction, with visit as the repeated factor.

Change in Inflammatory Biomarkers at Week 48: Safety Population



MMRM analysis was not performed for D-dimer due to high proportion of participants with D-dimer < LLQ in both treatment groups. Baseline geometric mean values (DTG/3TC group; CAR group): C-reactive protein (1.34; 1.27), interleukin-6 (1.73; 1.68), soluble CD14 (1.55×10^6; 1.46×10^6), and soluble CD163 (538.18; 541.70).

[a]Ratio is the estimated adjusted ratio (Week 144 to baseline) in each group calculated using MMRM applied to change from baseline in $\log_e$-transformed data adjusting for treatment, visit, baseline third agent class, CD4+ cell count (continuous), age (continuous), sex, race, BMI (continuous), smoking status, HCV co-infection status, $\log_e$-transformed baseline biomarker value (continuous), treatment-by-visit interaction, and baseline value-by-visit interaction, with visit as the repeated factor.

Conclusions

- Switching to DTG/3TC FDC in virologically suppressed adults on a 3- or 4-drug regimen demonstrated non-inferior virologic efficacy to a variety of ART regimens through 48 weeks of treatment
- Zero confirmed virologic withdrawals were observed in either treatment group, with no viral resistance
- DTG/3TC FDC had a good safety and tolerability profile through Week 48
  - Rate of AEs leading to study withdrawal was low in both treatment groups; a higher rate of drug-related AEs was observed in the DTG/3TC group, as expected with an open-label switch study
  - Changes in proximal tubular renal function and bone biomarkers favored the DTG/3TC group, whereas changes in eGFR by cystatin C and lipids were similar between treatment groups; changes in inflammatory biomarkers were also generally similar between groups, with the exception of soluble CD14 changes favoring DTG/3TC
- These data build upon the previous TANGO study and support DTG/3TC as a robust switch option with high levels of efficacy, good safety and tolerability, and a high barrier to resistance

Acknowledgments

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