

# DURABLE EFFICACY OF DOLUTEGRAVIR (DTG) PLUS LAMIVUDINE (3TC) IN ANTIRETROVIRAL TREATMENT-NAIVE ADULTS WITH HIV-1 INFECTION—3-YEAR RESULTS FROM THE GEMINI STUDIES

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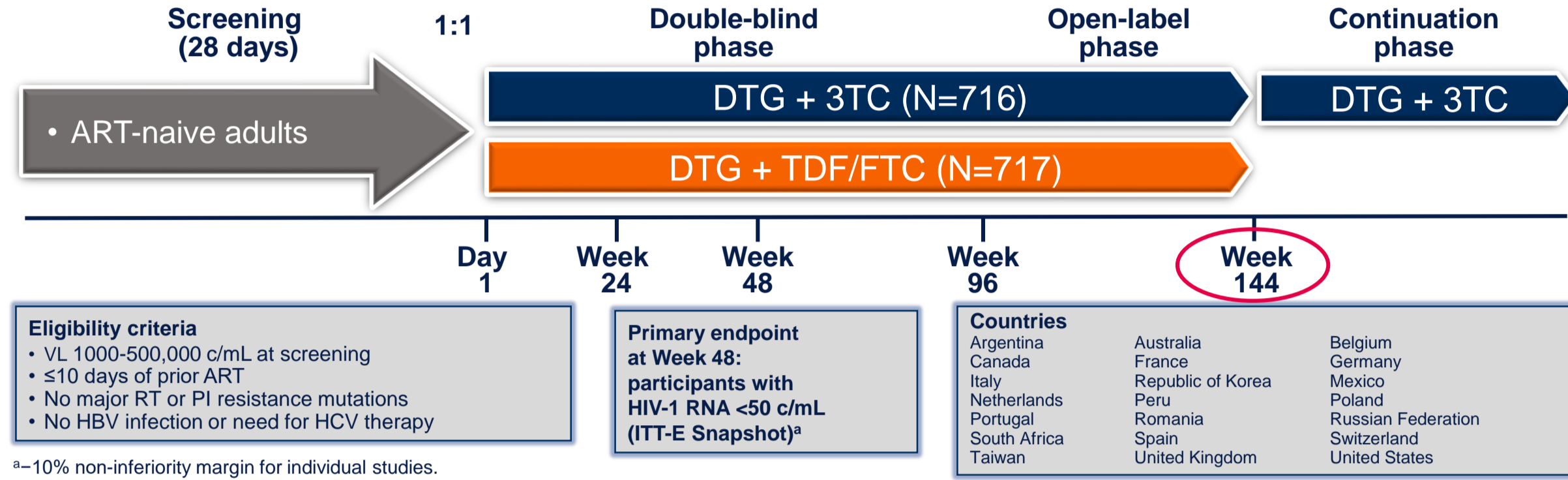
## Introduction

- Two-drug regimens (2DRs) have been investigated as a means for reducing the number of ARV agents taken by individuals who need lifelong ART.<sup>1,2</sup>
- In the primary analysis of the GEMINI-1 and GEMINI-2 studies at Week 48, the 2DR DTG + 3TC was non-inferior to the 3-drug regimen DTG + TDF/FTC in the treatment of ART-naive adults with HIV-1.<sup>3</sup>
- DTG + 3TC maintained non-inferior efficacy over 96 weeks vs DTG + TDF/FTC in ART-naive adults, with low rates of confirmed virologic withdrawal (CVW), and no resistance development in either treatment group.<sup>4</sup>
- DTG + 3TC is recommended as an initial ART regimen for most PLWH, with exceptions for individuals with HIV-1 RNA >500,000 c/mL, HBV co-infection, or in whom therapy is started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available.<sup>5,6</sup>
- We present data from the prespecified Week 144 secondary endpoint analyses of GEMINI-1 and GEMINI-2 evaluating durability after 3 years of therapy with DTG + 3TC

## Methods

- GEMINI-1 and GEMINI-2 (ClinicalTrials.gov identifiers, NCT02831673 and NCT02831764, respectively) are identically designed, randomized, double-blind, parallel-group, multicenter, phase III, non-inferiority studies<sup>3</sup> (Figure 1)
- Participants with HIV-1 RNA ≤500,000 c/mL at screening were randomized 1:1 (stratified by plasma HIV-1 RNA and CD4+ cell count) to once-daily treatment with DTG + 3TC or DTG + TDF/FTC
- The primary endpoint was proportion of participants with plasma HIV-1 RNA <50 c/mL at Week 48 (Snapshot algorithm in the intention-to-treat-exposed [ITT-E] population)<sup>3</sup>

Figure 1. GEMINI-1 and GEMINI-2 Study Design



## Results

### Participants

- 1433 participants in GEMINI-1 and GEMINI-2 were randomized and received ≥1 dose of study medication (DTG + 3TC, N=716; DTG + TDF/FTC, N=717)
- At baseline, 20% (n=293) of participants had HIV-1 RNA >100,000 c/mL and 8% (n=118) had CD4+ cell count ≤200 cells/mm<sup>3</sup> (Table 1)

Table 1. Demographic and Baseline Characteristics of the Pooled GEMINI-1 and GEMINI-2 Population<sup>4</sup>

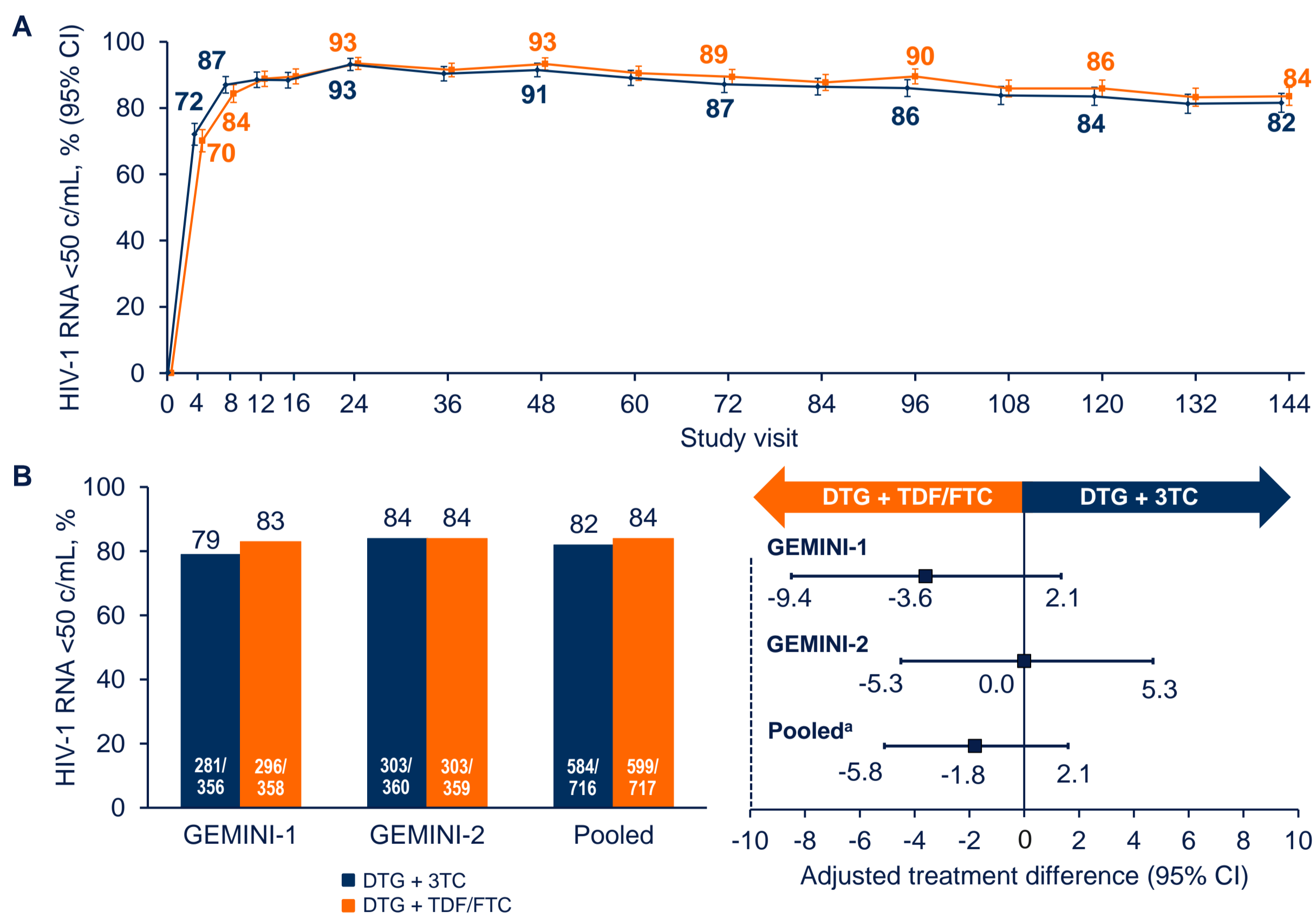
Characteristic	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
Age, median (range), y	32 (18-72)	33 (18-70)
Female, n (%)	113 (16)	98 (14)
Race, n (%)		
African American/African heritage	90 (13)	71 (10)
Asian	71 (10)	72 (10)
White	484 (68)	499 (70)
Other	71 (10)	75 (10)
HIV-1 RNA >100,000 c/mL, n (%) <sup>a</sup>	140 (20)	153 (21)
CD4+ cell count ≤200 cells/mm <sup>3</sup> , n (%)	63 (9)	55 (8)

<sup>a</sup>2% of participants in each group had baseline HIV-1 RNA ≥500,000 c/mL and were included in the ITT-E analysis.

### Efficacy

- DTG + 3TC was non-inferior to DTG + TDF/FTC in Snapshot HIV-1 RNA <50 c/mL for GEMINI-1, GEMINI-2, and the pooled population at Week 144 (Figure 2)

Figure 2. Snapshot Analysis of the Proportion of Participants With Plasma HIV-1 RNA <50 c/mL Through Week 144 (A) by Visit in the Pooled ITT-E Population and (B) in the GEMINI-1, GEMINI-2, and Pooled ITT-E Populations



- The proportion of participants with HIV-1 RNA ≥50 c/mL was low and similar between treatment groups (3% in both groups; Table 2)
- The majority of Snapshot failures were due to non-virologic reasons

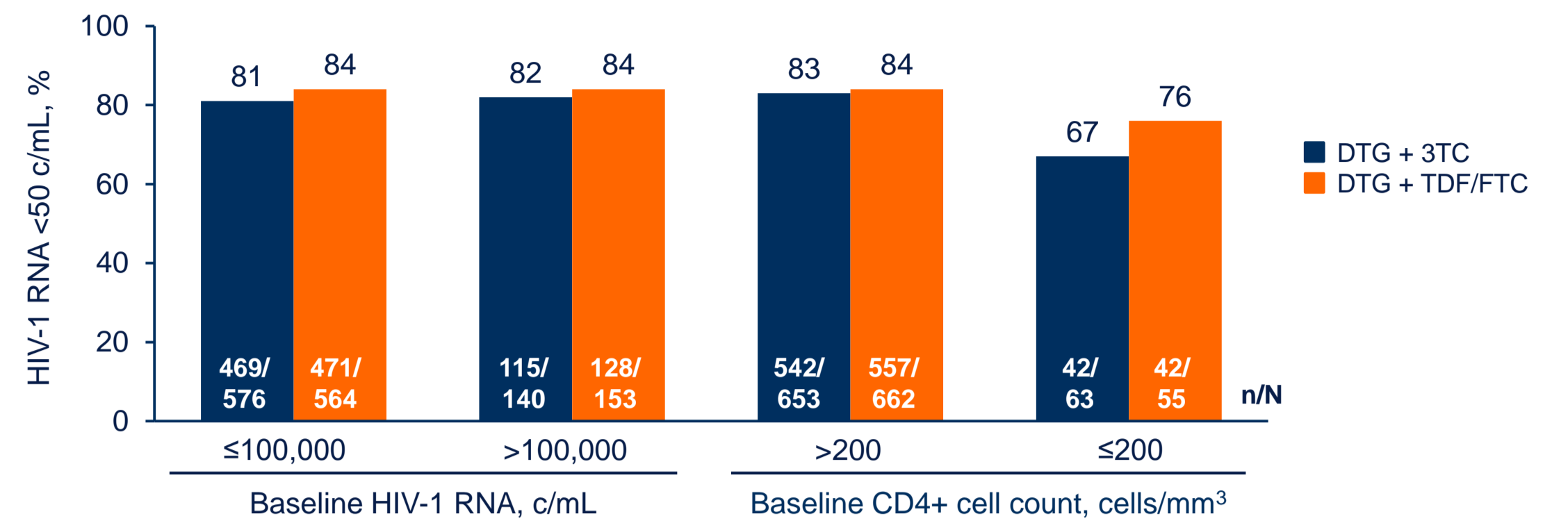
Table 2. Summary of Study Outcomes at Week 144: Snapshot Analysis (ITT-E Population)

Snapshot outcome, n (%)	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
HIV-1 RNA <50 c/mL	584 (82)	599 (84)
HIV-1 RNA ≥50 c/mL	23 (3)	21 (3)
Data in window and HIV-1 RNA ≥50 c/mL	4 (<1)	5 (<1)
Discontinued for lack of efficacy	10 (1)	4 (<1)
Discontinued for other reason and HIV-1 RNA ≥50 c/mL	7 (1)	11 (2)
Change in ART	2 (<1)	1 (<1)
No virologic data	109 (15)	97 (14)
Discontinued study due to AE or death	29 (4)	32 (4)
Discontinued study for other reasons <sup>a</sup>	78 (11)	64 (9)
On study but missing data in window	2 (<1)	1 (<1)

<sup>a</sup>Other reasons for discontinuation at Week 144 included protocol deviation, lost to follow-up, physician decision, withdrawal by participant, and lack of efficacy (in 1 participant in each treatment group in GEMINI-2).

- At Week 144, in participants with baseline HIV-1 RNA >100,000 c/mL, 82% and 84% in the DTG + 3TC and DTG + TDF/FTC groups, respectively, achieved HIV-1 RNA <50 c/mL; among participants with baseline CD4+ cell count ≤200 cells/mm<sup>3</sup>, 67% in the DTG + 3TC group and 76% in the DTG + TDF/FTC group achieved HIV-1 RNA <50 c/mL (Figure 3)
- The corresponding proportions were 81% and 84%, respectively, for those with baseline HIV-1 RNA ≤100,000 c/mL and 83% and 84%, respectively, for those with baseline CD4+ cell count >200 cells/mm<sup>3</sup>

Figure 3. Proportion of Participants With HIV-1 RNA <50 c/mL by Baseline Viral Load and CD4+ Cell Count at Week 144: Snapshot Analysis for the Pooled Population



- Across both studies, 12 participants (2%) in the DTG + 3TC group (1 since Week 96) and 9 participants (1%) in the DTG + TDF/FTC group (2 since Week 96) met protocol-defined CVW criteria<sup>3</sup> through Week 144
- None of these participants had treatment-emergent INSTI or NRTI resistance mutations
- 1 non-CVW participant with reported non-adherence in the DTG + 3TC group developed M184V at Week 132 (HIV-1 RNA 61,927 c/mL) and R263R/K at Week 144 (HIV-1 RNA 135 c/mL), conferring a 1.8-fold change in susceptibility to DTG
- Baseline HIV-1 RNA: 93,515 c/mL; CD4+ cell count: 393 cells/mm<sup>3</sup>
- Suppressed to HIV-1 RNA <50 c/mL from Week 4 through Week 120; HIV-1 RNA 61,927 c/mL detected at Week 132, with successive HIV-1 RNA of <50, 135, and 61 c/mL after Week 132
- Withdrawn due to lack of efficacy after Week 144, switched to DTG once daily + DRV/COBI, and regained virologic suppression

### Safety

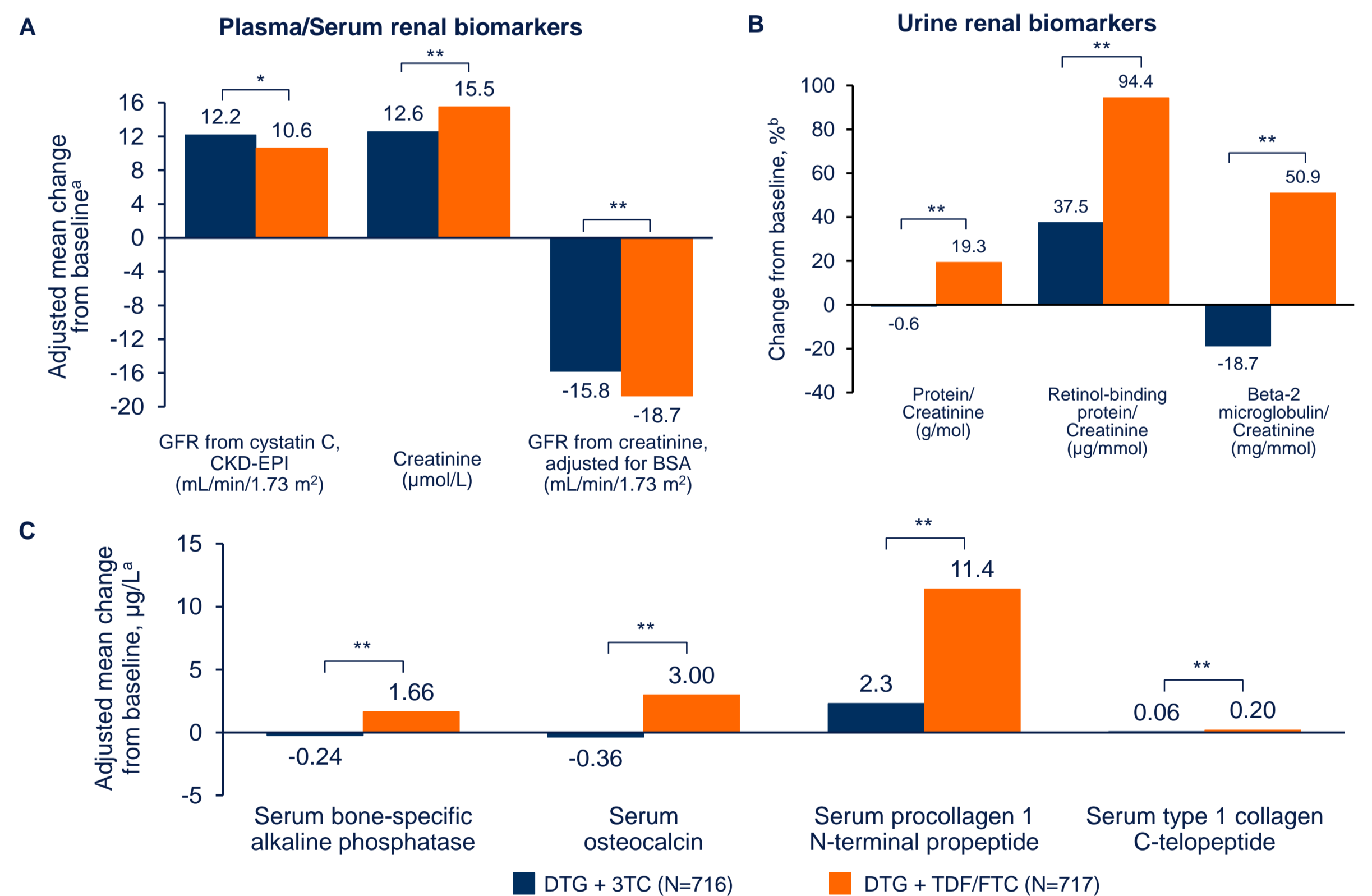
- Through Week 144, overall AE profiles were similar between treatment groups
- Participants in the DTG + 3TC group had a significantly lower risk of drug-related AEs (20%) compared with the DTG + TDF/FTC group for the pooled population (27%; relative risk, 0.76 [95% CI, 0.63-0.92]; Table 3)
- Overall, 4 deaths occurred (3 in the DTG + 3TC group and 1 in the DTG + TDF/FTC group), all considered unrelated to the study drug regimen
- Overall mean weight change from baseline to Week 144 was 3.7 kg with DTG + 3TC and 2.4 kg with DTG + TDF/FTC

Table 3. Summary of AEs in the Pooled Safety Population From GEMINI-1 and GEMINI-2

AE, n (%)	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
Any AE	613 (86)	625 (87)
AEs occurring in ≥10% of participants in either group		
Diarrhea	99 (14)	106 (15)
Nasopharyngitis	93 (13)	127 (18)
Headache	84 (12)	91 (13)
Upper respiratory tract infection	84 (12)	61 (9)
Syphilis	64 (9)	70 (10)
Drug-related AEs	146 (20)	192 (27)
Any grade 2-5 drug-related AE	58 (8)	69 (10)
Grade 2-5 drug-related AEs occurring in ≥1% of participants		
Headache	8 (1)	8 (1)
AEs leading to withdrawal from the study	31 (4)	33 (5)
AEs of interest leading to withdrawal from the study		
Psychiatric disorders	11 (2)	8 (1)
Renal related	2 (<1)	12 (2)
Osteoporosis	0	2 (<1)
Any serious AE	76 (11)	85 (12)

- Changes from baseline in renal biomarkers favored DTG + 3TC vs DTG + TDF/FTC through Week 144 (Figure 4A-B)
- Increase from baseline in bone turnover markers was lower with DTG + 3TC than DTG + TDF/FTC (Figure 4C)
- Changes in lipid parameters generally favored DTG + TDF/FTC through Week 144
- Adjusted mean change from baseline at Week 144 in the DTG + 3TC vs DTG + TDF/FTC group: total cholesterol, 0.365 vs -0.027 mmol/L, P<0.001; HDL-C, 0.180 vs 0.095 mmol/L, P<0.001; LDL-C, 0.158 vs -0.095 mmol/L, P<0.001; triglycerides, 0.100 vs -0.079 mmol/L, P=0.002; TC/HDL-C ratio, -0.237 vs -0.377, P=0.008

Figure 4. Adjusted Mean Change From Baseline in (A) Serum or Plasma Renal Biomarkers, (B) Ratios of Urine Renal Biomarkers, and (C) Serum Bone Turnover Biomarkers at Week 144



<sup>a</sup>Week 144 analysis used a mixed-effect repeated-measures model. Mean change from baseline adjusted for study, treatment, visit, baseline HIV-1 RNA, baseline CD4+ cell count, age, sex, race, baseline biomarker value, treatment-by-visit interaction, and baseline biomarker value-by-visit interaction. For renal biomarkers, mean change from baseline was also adjusted for presence of diabetes and presence of hypertension. For bone biomarkers, mean change was also adjusted for BMI, smoking status, and current vitamin D use. \*Estimated from geometric mean ratios for baseline and Week 144. Based on the same model as plasma/serum markers except adjusting for log<sub>e</sub>-transformed baseline biomarker. \*P<0.01. \*\*P<0.001.

## Conclusions

- DTG + 3TC maintained non-inferior efficacy vs DTG + TDF/FTC in ART-naive adults and demonstrated a high barrier to resistance, with low rates of CVW through Week 144
- 1 non-CVW participant in the DTG + 3TC group with reported non-adherence developed M184V at Week 132 (HIV-1 RNA 61,927 c/mL) and R263R/K at Week 144 (HIV-1 RNA 135 c/mL), conferring a 1.8-fold change in DTG susceptibility; the participant was withdrawn for lack of efficacy after Week 144, switched to DTG once daily + DRV/COBI, and regained virologic suppression
- Overall safety and tolerability were comparable between groups. There was a lower risk of drug-related AEs with DTG + 3TC than with DTG + TDF/FTC
- Changes in renal and bone biomarkers generally favored DTG + 3TC
- These results confirm the durable efficacy, tolerability, and high barrier to resistance of DTG + 3TC, further supporting the 2DR DTG + 3TC as a first-line treatment option for PLWH

**Acknowledgments:** This study was funded by ViiV Healthcare. We thank the study participants; their families and caregivers; investigators and site staff who participated in the study; and the ViiV Healthcare, GlaxoSmithKline, Pharmaceutical Product Development, and Parexel study team members. Editorial assistance and graphic design support for this poster were provided under the direction of the authors by MedThink SciCom and funded by ViiV Healthcare.

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