Initial Viral Load Decline and Response Rates by Baseline Viral Load Strata With Dolutegravir Plus Lamivudine Versus Dolutegravir Plus Tenofovir Disoproxil Fumarate/Emtricitabine: Pooled Results From the GEMINI Studies

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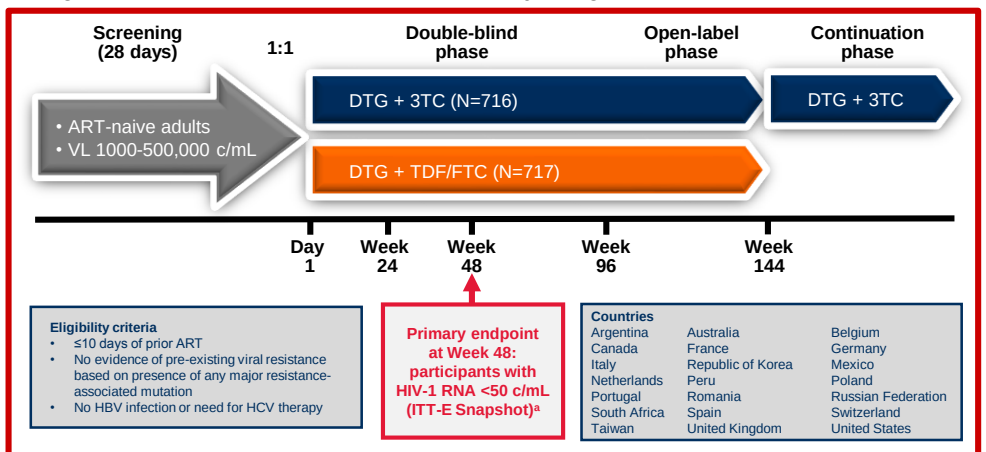
Introduction

- The requirement for lifelong antiretroviral therapy (ART) for HIV infection has heightened interest in 2-drug regimens (2DRs) to minimize cumulative drug exposure[1]
- GEMINI-1 and -2 demonstrated non-inferior virologic efficacy for the 2DR dolutegravir + lamivudine (DTG + 3TC) vs the 3DR DTG + tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) at Week 48 for treatment-naive participants with HIV-1 viral load (VL) ≤500,000 c/mL at screening[2]
- Response rate in participants with high baseline VL is a key test of potency of ART regimens
- We describe the initial VL decline, time to suppression, and Week 48 efficacy outcomes by baseline VL strata

Methods

- GEMINI-1 and GEMINI-2 are identically designed, double-blind, multicenter, randomized (1:1) phase III studies of DTG 50 mg + 3TC 300 mg once daily vs DTG 50 mg + TDF 300 mg/ FTC 200 mg once daily in treatment-naive adults with HIV-1 infection (ClinicalTrials.gov: NCT02831673, NCT02831764; Figure 1)[2]
  - The primary endpoint was proportion of participants with HIV-1 RNA <50 c/mL at Week 48
  - Potency analyses included initial VL decline and time to suppression in participants with baseline HIV-1 RNA >100,000 c/mL, as well as proportions of participants with plasma HIV-1 RNA <50 c/mL at Week 48 (using Snapshot) by baseline HIV-1 RNA strata ≤100,000, >100,000, >250,000, >400,000, and >500,000 c/mL

Figure 1. GEMINI-1 and GEMINI-2 Phase III Study Designs



Baseline stratification factors: plasma HIV-1 RNA (≤100,000 vs >100,000 c/mL) and CD4+ cell count (≤200 vs >200 cells/mm^3).

[a]−10% non-inferiority margin for individual studies.

Results

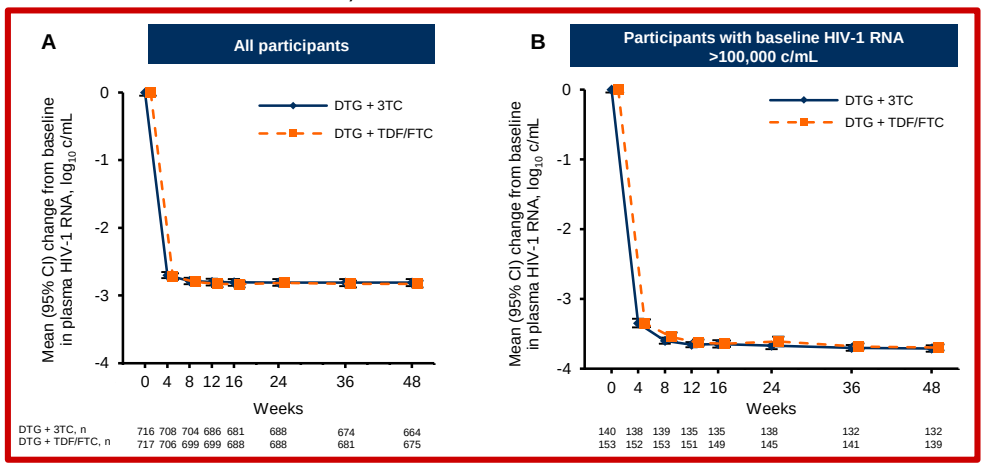
- 1433 participants were enrolled in GEMINI-1 and GEMINI-2; demographics and baseline characteristics were balanced across treatment groups (Table 1)

Table 1. Demographics and Baseline Characteristics for the Pooled GEMINI-1 and GEMINI-2 Populations[2]

Characteristic	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
Age, median (range), y	32.0 (18-72)	33.0 (18-70)
Female, n (%)	113 (16)	98 (14)
Race, n (%)		
White	480 (67)	497 (69)
African American/African heritage	99 (14)	76 (11)
Asian	71 (10)	72 (10)
Other	66 (9)	72 (10)
HIV-1 RNA, median (range), $\log_{10}$ c/mL	4.43 (1.59-6.27)	4.46 (2.11-6.37)
≤100,000	576 (80)	564 (79)
>100,000[a]	140 (20)	153 (21)
>250,000	51 (7)	46 (6)
>400,000	18 (3)	24 (3)
>500,000[b]	13 (2)	15 (2)
CD4+ cell count, median (range), cells/mm^3	427.0 (19-1399)	438.0 (19-1497)
≤200	63 (9)	55 (8)
>200	653 (91)	662 (92)

[a]2% of participants in each group had baseline HIV-1 RNA >500,000 c/mL and were included in the ITT-E analysis. [b]Participants were required to have HIV-1 RNA ≤500,000 c/mL at screening. Other than 1 participant enrolled without meeting study entry criteria, these participants had an observed increase in HIV-1 RNA between screening and baseline.

Figure 2. Viral Load Decline Through 48 Weeks in (A) All Participants and (B) Participants With Baseline HIV-1 RNA >100,000 c/mL



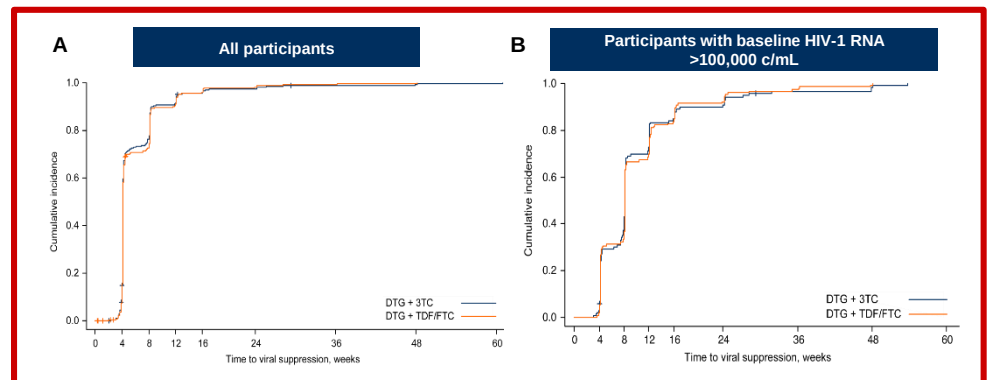
Snapshot analysis in pooled ITT-E population

- At Week 48, 91% (655/716) of participants in the DTG + 3TC group vs 93% (669/717) in the DTG + TDF/FTC group achieved HIV-1 RNA <50 c/mL (adjusted treatment difference, −1.7%; 95% CI, −4.4 to 1.1)

Potency analysis in pooled ITT-E population

- Rapid VL log decline was observed in both treatment groups overall (median change from baseline at Week 4, −2.77 $\log_{10}$ c/mL in the DTG + 3TC group and −2.80 $\log_{10}$ c/mL in the DTG + TDF/FTC group) and in participants with baseline VL >100,000 c/mL (−3.38 $\log_{10}$ c/mL and −3.40 $\log_{10}$ c/mL, respectively; Figure 2)
- Time to viral suppression was similar for the DTG + 3TC and DTG + TDF/FTC groups in all participants (hazard ratio, 1.01; 95% CI, 0.91 to 1.12) and in participants with baseline HIV-1 RNA >100,000 c/mL (hazard ratio, 1.00; 95% CI, 0.79 to 1.26; Figure 3)

Figure 3. Time to Viral Suppression in (A) All Participants and (B) Participants With Baseline HIV-1 RNA >100,000 c/mL



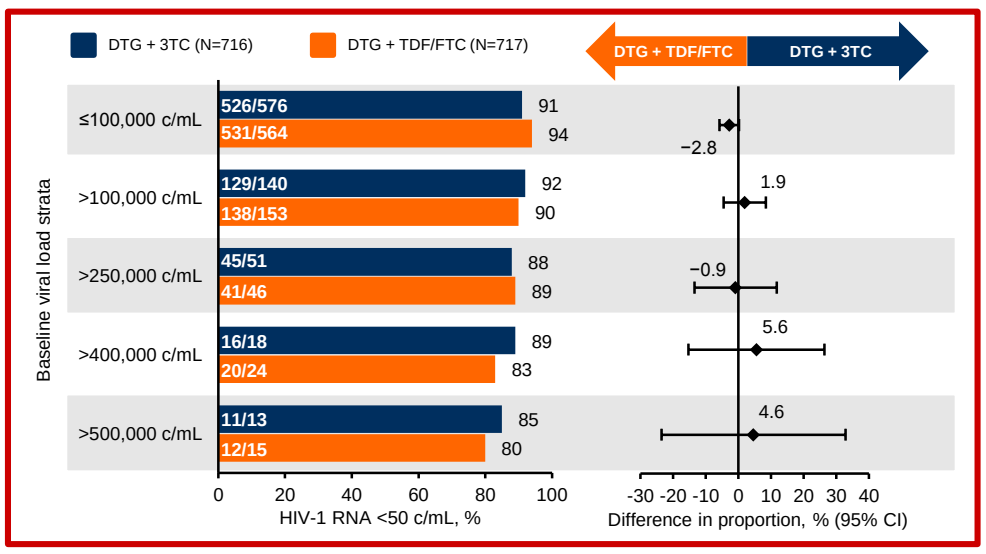
Time to viral suppression	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
Median (95% CI), days	29.0 (NE-NE)	29.0 (NE-NE)
Hazard ratio (95% CI)	1.01 (0.91-1.12)	

Time to viral suppression	DTG + 3TC (N=140)	DTG + TDF/FTC (N=153)
Median (95% CI), days	57.0 (56.0-57.0)	57.0 (NE-NE)
Hazard ratio (95% CI)	1.00 (0.79-1.26)	

NE, not estimable.

- High rates of virologic success were observed in participants with baseline HIV-1 RNA ≤100,000 and >100,000 c/mL (Figure 4)
  - Rates of virologic success were similar in both treatment groups for all baseline VL strata

Figure 4. Proportion of Participants With Plasma HIV-1 RNA <50 c/mL at Week 48 (Snapshot Analysis) by Baseline Plasma HIV-1 RNA



Conclusions

- The magnitude and speed of VL decline with DTG + 3TC were comparable to those with DTG + TDF/FTC, irrespective of baseline VL
- Time to viral suppression with DTG + 3TC was comparable to that with DTG + TDF/FTC, irrespective of baseline VL
- Response rates in participants with baseline VL >100,000 c/mL (including those with baseline VL >500,000 c/mL) were high with DTG + 3TC and similar to those with DTG + TDF/FTC
- These data further demonstrate the high potency of DTG + 3TC and support the efficacy of this 2DR for the treatment of HIV-1 infection

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References: 1. Kelly et al. *Drugs*. 2016;76:523-531. **2.** Cahn et al. *Lancet*. 2019;393:143-155.