Two-Drug Regimen of Dolutegravir Plus Lamivudine (DTG + 3TC) Is Non-Inferior to Dolutegravir Plus Tenofovir/Emtricitabine (DTG + TDF/FTC) at 48 Weeks in Antiretroviral Treatment–Naive Adults With HIV-1 Infection: Subgroup Analyses in the GEMINI Studies

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Introduction

- Two-drug regimens (2DRs) are being evaluated against standard 3-drug regimens for their potential to reduce cumulative drug exposure and drug–drug interactions during lifelong antiretroviral therapy (ART) in people living with HIV
- We evaluated the 2DR of DTG + 3TC in 2 identical global, double-blind, multicenter, phase III studies GEMINI-1 and -2 (ClinicalTrials.gov: NCT02831673/NCT02831764)
  - Primary endpoint results were previously presented: DTG + 3TC was non-inferior to DTG + TDF/FTC at Week 48. No participants who met protocol-defined virologic withdrawal criteria had treatment-emergent INSTI or NRTI resistance mutations[1]

Methods

- **Study design:** Phase III, randomized (1:1), double-blind, parallel-group
  - Participants received either DTG + 3TC (N=716) or DTG + TDF/FTC (N=717)
- **Stratification:** By Screening plasma HIV-1 RNA (≤100,000 vs >100,000 c/mL) and CD4+ cell count (≤200 vs >200 cells/mm^3)
- **Key eligibility criteria:** ≥18 years of age; ART naive (≤10 days of prior ART); no evidence of pre-existing major resistance-associated mutations; no hepatitis B virus infection; HIV-1 RNA 1000 to 500,000 c/mL
- **Primary endpoint:** Proportion with plasma HIV-1 RNA <50 c/mL at Week 48 using snapshot algorithm; −10% non-inferiority margin
- **Subgroup analyses:** Snapshot outcomes and adverse event (AE) frequencies by demographics and Baseline HIV-1 RNA and CD4+ cell count
- **Statistical analysis:** For the primary endpoint, estimates and confidence intervals (CIs) were based on a stratified analysis using Cochran–Mantel–Haenszel weights. The subgroup analyses were unadjusted

Results

Study Population

- 1433 adults from 21 countries were randomized and treated in GEMINI-1 and -2

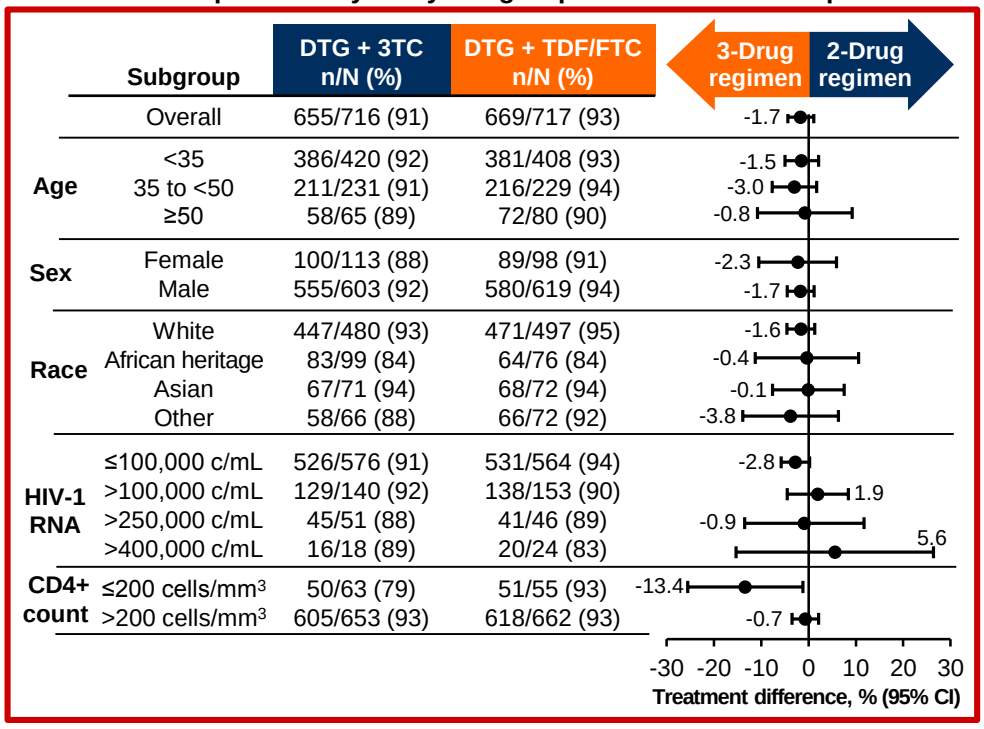
Table 1. Demographics and Baseline Characteristics: Pooled ITT–E Population

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 (%)		
African heritage	99 (14)	76 (11)
Asian	71 (10)	72 (10)
White	480 (67)	497 (69)
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, n (%)	140 (20)	153 (21)
CD4+ cell count, median (range), cells/mm^3	427.0 (19-1399)	438.0 (19-1497)
≤200, n (%)	63 (9)	55 (8)

Efficacy

- Subgroup analyses of efficacy based on baseline disease and demographic characteristics were generally consistent with overall study results (Figure)

Figure. Proportion of Participants With Plasma HIV-1 RNA <50 c/mL at Week 48: Snapshot Analysis by Subgroups—Pooled ITT–E Population



- In the CD4+ count ≤200 cells/mm^3 subgroup, most reasons for snapshot non-response were not related to efficacy or treatment (eg, non–treatment-related AEs; Table 2)

Table 2. Snapshot Non-Response in Participants With Baseline CD4+ Cell Count ≤200 cells/mm^3

Participant	Snapshot outcome at Week 48	Clinical reason for study DC	Study day of DC	Last study VL, c/mL
DTG + 3TC				
1	VL ≥50 c/mL	NA: continued in study	NA	≥50[a,b]
2	VL ≥50 c/mL	NA: continued in study	NA	<50[a]
3	VL ≥50 c/mL	NA: continued in study	NA	<50[a]
4	VL ≥50 c/mL	Protocol-defined virologic withdrawal	205	362
5	No virologic data	AE: pulmonary TB	206	<50
6	No virologic data	AE: cerebral chagoma	164	507,564[c]
7	No virologic data	Treatment for HCV infection	165	<50
8	No virologic data	Withdrew consent	115	<50
9	VL ≥50 c/mL	NA: unplanned change in ART	NA	≥50[a,b]
10	VL ≥50 c/mL	PV: randomized in error[d]	15	102
11	No virologic data	PV: randomized in error[e]	28	1,848,435[f]
12	VL ≥50 c/mL	Lost to follow-up	356	64,366
13	No virologic data	Lost to follow-up	100	<50
DTG + TDF/FTC				
14	VL ≥50 c/mL	NA: continued in study	NA	<50[a]
15	No virologic data	Withdrew consent	342	<50
16	VL ≥50 c/mL	Investigator discretion: incarceration	76	384
17	No virologic data	Lost to follow-up	175	<50

AE, adverse event; DC, discontinuation; HBV, hepatitis B virus; HCV, hepatitis C virus; NA, not applicable; PV, protocol violation; TB, tuberculosis; VL, viral load. [a]VL results from Week 60 shown for participants who continued the study beyond Week 48. [b]Value not provided due to potential for unblinding. [c]Participant had discontinued study treatment prior to study DC. [d]Enrolled with HBV coinfection. [e]Enrolled with Screening VL of >500,000 c/mL. [f]VL result available from Day 1 only.

Safety

- Overall rates of AEs were similar between arms. Rates of withdrawals due to AEs were low (DTG + 3TC, 15/716 [2%] vs DTG + TDF/FTC, 16/717 [2%]), with withdrawals due to psychiatric disorders in 10/1433 (0.7%) overall
- Numerically, more participants on DTG + TDF/FTC reported drug-related AEs (169/717 [24%]) than did those on DTG + 3TC (126/716 [18%])
- The analysis of AE frequencies by subgroups of age, gender, Baseline HIV-1 RNA, and CD4+ cell count demonstrated no notable differences between treatment arms or across subgroups compared with the overall frequencies

Results of efficacy and safety subgroup analyses were similar in the individual studies compared with pooled results

Conclusions

- In GEMINI-1 and -2, DTG + 3TC demonstrated non-inferior efficacy to DTG + TDF/FTC in treatment-naive adults with Screening HIV-1 RNA ≤500,000 c/mL at Week 48. Both regimens were well tolerated
- Subgroup analyses of efficacy and AEs performed based on baseline disease and demographic characteristics were generally consistent with overall study results
  - Response rates in participants with Baseline HIV-1 RNA >100,000 c/mL were high and similar between arms
  - Response rates in participants with Baseline CD4+ ≤200 cells/mm^3 were lower in the DTG + 3TC arm compared with DTG + TDF/FTC; however, snapshot failures were predominantly for reasons unrelated to efficacy or treatment
- DTG + 3TC is a robust option for treatment of HIV-infected patients across a spectrum of disease characteristics and patient populations
- The studies are ongoing to explore long-term durability and safety

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Reference: 1. Cahn P, Madero JS, Arribas J, et al. Non-inferior efficacy of dolutegravir (DTG) plus lamivudine (3TC) versus DTG plus tenofovir/emtricitabine (TDF/FTC) fixed-dose combination in antiretroviral treatment-naive adults with HIV-1 infection: 48-week results from the GEMINI studies. Presented at: 22nd International AIDS Conference; July 23-27, 2018; Amsterdam, the Netherlands. Abstract TUAB0106LB.