

# Durable Efficacy of Dolutegravir Plus Lamivudine in Antiretroviral Treatment–Naive Adults With HIV-1 Infection: 96-Week Results From the GEMINI-1 and GEMINI-2 Randomized Clinical Trials

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**Background:** The 2-drug regimen dolutegravir + lamivudine was noninferior to dolutegravir + tenofovir disoproxil fumarate/emtricitabine in achieving HIV-1 RNA <50 copies/mL in treatment-naive adults in the 48-week primary analysis of the GEMINI trials. We present results from the prespecified 96-week secondary analyses.

**Setting:** One hundred eighty-seven centers in 21 countries.

**Methods:** GEMINI-1 and GEMINI-2 are identical, double-blind phase III studies. Participants with screening HIV-1 RNA ≤500,000 copies/mL were randomized 1:1 to once-daily dolutegravir + lamivudine or dolutegravir + tenofovir disoproxil fumarate/emtricitabine.

**Results:** At week 96, dolutegravir + lamivudine (N = 716) was noninferior to dolutegravir + tenofovir disoproxil fumarate/emtricitabine (N = 717) in achieving HIV-1 RNA <50 copies/mL (Snapshot algorithm; −10% noninferiority margin) in the pooled analysis (proportion of responders, 86.0% vs 89.5%, respectively; adjusted treatment difference [95% CI], −3.4% [−6.7 to 0.0007]), GEMINI-1 (−4.9% [−9.8 to 0.03]), and GEMINI-2 (−1.8% [−6.4 to 2.7]). Proportions of participants in the HIV-1 RNA ≥50 copies/mL Snapshot category were largely unchanged from week 48 to 96. Eleven participants taking dolutegravir + lamivudine and 7 taking dolutegravir + tenofovir disoproxil fumarate/emtricitabine met confirmed virologic withdrawal criteria through week 96; none had treatment-emergent

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resistance mutations. Dolutegravir + lamivudine had a lower rate of drug-related adverse events than dolutegravir + tenofovir disoproxil fumarate/emtricitabine (19.6% vs 25.0%; relative risk ratio, 0.78; 95% CI: 0.64 to 0.95). Renal and bone biomarker changes favored dolutegravir + lamivudine.

**Conclusions:** Consistent with 48-week data, dolutegravir + lamivudine demonstrated long-term, noninferior efficacy vs dolutegravir + tenofovir disoproxil fumarate/emtricitabine without increased risk of treatment-emergent resistance, supporting its use in treatment-naïve HIV-1-infected individuals.

**Key Words:** 2DR, dolutegravir, integrase strand transfer inhibitor, nucleoside reverse transcriptase inhibitor, treatment-naïve

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## INTRODUCTION

Two-drug regimens (2DRs) can potentially reduce long-term cumulative drug exposure and decrease treatment-associated costs for HIV-1-infected individuals, who require lifelong therapy.<sup>1</sup> The core antiretroviral agent in a 2DR must have high potency and a high barrier to resistance.<sup>1</sup> As such, early studies investigating 2DRs as initial or maintenance therapy for HIV infection evaluated the pairing of the potent, well-tolerated nucleoside reverse transcriptase inhibitor (NRTI) lamivudine with pharmacologically boosted protease inhibitors (PIs), which have a high barrier to resistance.<sup>2–6</sup> Although noninferior efficacy was shown against 3-drug regimens (3DRs), PIs are associated with adverse metabolic effects, long-term toxicities, and drug–drug interactions, limiting their appeal as components of lifelong therapy.<sup>7,8</sup> Thus, a need remains for well-tolerated, potent 2DRs with a high barrier to resistance.

The integrase strand transfer inhibitor (INSTI) dolutegravir has a high barrier to resistance, making it a well-suited candidate for inclusion in a 2DR,<sup>9</sup> particularly when paired with lamivudine,<sup>10</sup> as previously observed.<sup>11,12</sup> In primary week 48 analyses of the 2 phase III studies GEMINI-1 and GEMINI-2 in treatment-naïve adults, dolutegravir + lamivudine was noninferior to dolutegravir + tenofovir disoproxil fumarate/emtricitabine in achieving HIV-1 RNA <50 copies/mL according to the US Food and Drug Administration (FDA) Snapshot algorithm.<sup>13</sup> Importantly, resistance mutations associated with INSTIs or NRTIs did not emerge in the few participants who had virologic failure. These data led to the approval of the fixed-dose combination of dolutegravir/lamivudine as a once-daily, single-tablet 2DR by the FDA and the European Medicines Agency.<sup>14,15</sup> In addition, the 2019 update to the US Department of Health and Human Services treatment guidelines for HIV-1 infection supports the use of dolutegravir + lamivudine as initial treatment in patients for whom abacavir, tenofovir disoproxil fumarate, or tenofovir alafenamide either cannot be used or are not optimal.<sup>16</sup> European AIDS Clinical Society guidelines also indicate that when preferred regimens are not feasible or available,<sup>17</sup> dolutegravir + lamivudine can be used. Both guidelines indicated the need for longer-term data to support the use of dolutegravir + lamivudine in a broader patient

population. Here, we report longer-term results from the GEMINI-1 and GEMINI-2 planned secondary analyses at 96 weeks.

## METHODS

### Study Design

GEMINI-1 (NCT02831673) and GEMINI-2 (NCT02831764) are ongoing, identically designed, phase III, randomized, double-blind, noninferiority studies conducted at 187 centers in 21 countries. This report describes results through the final visit of the double-blind randomized phase at week 96. Protocols for GEMINI-1 and GEMINI-2 are available at <https://www.viiv-clinicalstudyregister.com/study/204861#ps> and <https://www.viiv-clinicalstudyregister.com/study/205543#ps>, respectively. Methods, including information regarding ethical compliance, have previously been described.<sup>13</sup>

### Participants and Study Treatment

Eligible participants were aged  $\geq 18$  years with HIV-1 infection,  $\leq 10$  days of previous antiretroviral therapy (ART), and screening plasma HIV-1 RNA 1000 to 500,000 copies/mL. Women of reproductive potential were eligible if they were not pregnant or lactating and using highly effective contraception (defined by study protocol). Exclusion criteria included presence of pre-existing major viral resistance mutations to NRTIs, non-NRTIs, or PIs<sup>18</sup> and active Centers for Disease Control and Prevention stage 3 HIV disease<sup>19</sup> (except for cutaneous Kaposi sarcoma and CD4<sup>+</sup> cell count <200 cells/mm<sup>3</sup>). Participants were assessed for eligibility during a screening period of  $\leq 35$  days. Eligible participants were randomized 1:1 to receive a once-daily 2DR of dolutegravir 50 mg plus lamivudine 300 mg or a once-daily 3DR of dolutegravir 50 mg plus tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg. Participants were stratified by screening HIV-1 RNA ( $\leq 100,000$  or  $>100,000$  copies/mL) and screening CD4<sup>+</sup> cell count ( $\leq 200$  or  $>200$  cells/mm<sup>3</sup>) and treated in a double-blind randomized phase from day 1 to week 96 during which lamivudine and tenofovir disoproxil fumarate/emtricitabine tablets were provided overencapsulated to visually match each other, followed by an open-label randomized phase from week 96 to 148.

### Assessments

Study visits were planned at baseline (day 1) and weeks 4, 8, 12, 16, 24, 36, 48, and every 12 weeks thereafter until week 144. Plasma for quantitative HIV-1 RNA analysis and storage was collected at all visits and quantitated using the Abbott RealTime HIV-1 assay (lower limit of quantitation, 40 copies/mL; Abbott Molecular, Des Plaines, IL). For participants with HIV-1 RNA  $\geq 50$  copies/mL at weeks 24, 48, or 96, a retest was conducted at weeks 28, 52, or 100, respectively. Participants met confirmed virologic withdrawal (CVW) criteria if a second and consecutive HIV-1 RNA value met any of the following definitions: decrease from baseline

in HIV-1 RNA  $<1 \log_{10}$  copies/mL, unless HIV-1 RNA  $<200$  copies/mL, by week 12; confirmed plasma HIV-1 RNA  $\geq 200$  copies/mL at or after week 24; or HIV-1 RNA  $\geq 200$  copies/mL after confirmed consecutive HIV-1 RNA  $<200$  copies/mL. These participants were discontinued from the study, and plasma samples from day 1 and the initial elevated, and therefore suspected, viral load were used for genotypic and phenotypic resistance tests (Monogram Biosciences, San Francisco, CA).

Adverse events (AEs), concomitant medications, and symptom-directed physical examinations were assessed at all study visits. AEs were coded using MedDRA, version 21.0. The maximum toxicity of AEs was graded using guidelines from the Division of AIDS, version 2.0.<sup>20</sup> Testing for fasting lipids and glucose, urinalysis, and renal and bone biomarkers was conducted at baseline and weeks 24, 48, 96, and 144. Renal biomarkers included estimated glomerular filtration rate (based on Chronic Kidney Disease Epidemiology Collaboration equation [CKD-EPI] creatinine and CKD-EPI cystatin C), serum creatinine, urine protein/creatinine ratio, urine retinol-binding protein/creatinine ratio, and urine beta-2 microglobulin/creatinine ratio. Bone biomarkers included serum bone-specific alkaline phosphatase, serum osteocalcin, serum procollagen 1 N-terminal propeptide, and serum type 1 collagen C-telopeptide. The Columbia Suicide-Severity Rating Scale was used to monitor suicidal ideation and behavior starting from day 1.

## Outcomes

The primary endpoint of each GEMINI study was the proportion of participants with plasma HIV-1 RNA  $<50$  copies/mL at week 48 using the FDA Snapshot algorithm<sup>21</sup> in the intention-to-treat–exposed (ITT-E) population. Endpoints for the week 96 secondary analysis included proportion of participants with HIV-1 RNA  $<50$  copies/mL at week 96, change in CD4<sup>+</sup> cell count from baseline, incidence of emergent mutations conferring genotypic and/or phenotypic resistance to dolutegravir + lamivudine or dolutegravir + tenofovir disoproxil fumarate/emtricitabine in participants meeting criteria for CVW, and proportion of participants with HIV-1 RNA  $<50$  copies/mL in participant subgroups defined by demographic and baseline disease characteristics, including plasma viral load and CD4<sup>+</sup> cell count. Safety endpoints included incidence and severity of AEs and proportion of participants who discontinued treatment because of AEs. Renal and bone biomarkers and lipids were monitored by assessing changes from baseline at week 96 (see Supplemental Digital Content 1, <http://links.lww.com/QAI/B418> for complete list of secondary endpoints).

## Statistical Analysis

All randomized participants who received  $\geq 1$  dose of study medication were included in the ITT-E population, which was used for the efficacy analyses. The safety population included all participants who received  $\geq 1$  dose of study medication and was analyzed according to actual treatment received. Week 96 secondary analyses of the

individual studies as well as a pooled analysis were prespecified. The proportion of participants with HIV-1 RNA  $<50$  copies/mL at week 96 was analyzed using a Cochran–Mantel–Haenszel test stratified by baseline plasma HIV-1 RNA ( $\leq 100,000$  vs  $>100,000$  copies/mL), baseline CD4<sup>+</sup> cell count ( $\leq 200$  vs  $>200$  cells/mm<sup>3</sup>), and individual study (GEMINI-1 vs GEMINI-2). Baseline characteristics, response rates by study visit or participant subgroup (using Snapshot algorithm), and AEs were summarized using descriptive statistics. Treatment-related discontinuation equals failure (TRDF) was a preplanned analysis at week 96 that accounted for CVW, withdrawal due to lack of efficacy, withdrawal due to treatment-related AE, and participants who met protocol-defined stopping criteria. The proportion of participants without TRDF was estimated using the Kaplan–Meier nonparametric method. Change from baseline at week 96 in CD4<sup>+</sup> cell count was analyzed using a mixed-effect repeated-measures model adjusting for study, treatment, visit, baseline plasma HIV-1 RNA, baseline CD4<sup>+</sup> cell count, treatment-by-visit interaction, and baseline CD4<sup>+</sup> cell count-by-visit interaction, with visit as the repeated factor. Changes in body weight and body mass index (BMI) from baseline to week 96 were summarized, and ad hoc summaries by sex are also presented. Change from baseline in lipids was analyzed using repeated-measures model adjusting for study, treatment, visit, baseline plasma HIV-1 RNA, baseline CD4<sup>+</sup> cell count, age, baseline value, treatment-by-visit interaction, and baseline value-by-visit interaction, with visit as the repeated factor.

## RESULTS

In GEMINI-1 and GEMINI-2, 1433 participants were randomized and received  $\geq 1$  dose of study medication (dolutegravir + lamivudine, N = 716; dolutegravir + tenofovir disoproxil fumarate/emtricitabine, N = 717; see Figure, Supplemental Digital Content 2, <http://links.lww.com/QAI/B418>). As previously reported, baseline characteristics were well balanced between treatment groups.<sup>13</sup> The majority of participants were male (85.3%; n = 1222) and white (68.6%; n = 983; Table 1). Overall, 20.4% (n = 293) of participants had baseline HIV-1 RNA  $>100,000$  copies/mL, and 8.2% (n = 118) had CD4<sup>+</sup> cell count  $\leq 200$  cells/mm<sup>3</sup>.

At the cutoff date for the 96-week analysis (April 4, 2019), 85.5% (n = 612) in the dolutegravir + lamivudine group and 88.8% (n = 637) in the dolutegravir + tenofovir disoproxil fumarate/emtricitabine group remained on study. The most common reasons for study discontinuation were withdrawal of consent (2DR, 3.5% [n = 25]; 3DR, 2.9% [n = 21]), AE (2DR, 3.1% [n = 22]; 3DR, 2.2% [n = 16]), and lost to follow-up (2DR, 3.1% [n = 22]; 3DR, 2.0% [n = 14]; see Figure, Supplemental Digital Content 2, <http://links.lww.com/QAI/B418>).

Analysis of virologic outcomes by visit through week 96 shows a similar proportion of participants with HIV-1 RNA  $<50$  copies/mL in either treatment group at each visit (Fig. 1A). At week 96, 86.0% (616/716) of participants in the dolutegravir + lamivudine group and 89.5% (642/717) in the dolutegravir + tenofovir disoproxil fumarate/emtricitabine

group achieved HIV-1 RNA <50 copies/mL (Snapshot algorithm; pooled analysis of the ITT-E population) for an adjusted treatment difference (95% CI) of -3.4% (-6.7 to 0.0007; Figs. 1B, C). Based on a prespecified -10% noninferiority margin, dolutegravir + lamivudine remained noninferior to dolutegravir + tenofovir disoproxil fumarate/emtricitabine at week 96 because the lower bound of the 95% CI for the adjusted treatment difference was greater than -10%. In GEMINI-1, HIV-1 RNA <50 copies/mL was achieved in 84.3% (300/356) of participants in the dolutegravir + lamivudine group and 89.4% (320/358) in the dolutegravir + tenofovir disoproxil fumarate/emtricitabine group at week 96 (adjusted treatment difference [95% CI] was -4.9% [-9.8 to 0.03]); the corresponding numbers in GEMINI-2 were 87.8% (316/360) vs 89.7% (322/359; adjusted treatment difference [95% CI], -1.8% [-6.4 to 2.7]; see Table, Supplemental Digital Content 3, <http://links.lww.com/QAI/B418>). In the week 96 pooled analysis, proportions of participants in the HIV-1 RNA ≥50 copies/mL Snapshot category were 3.1% in the dolutegravir + lamivudine group and 2.0% in the dolutegravir + tenofovir disoproxil fumarate/emtricitabine group and were largely unchanged from week 48 to week 96 in both groups; 10.9% and 8.5%, respectively, had no virologic data (Fig. 1B).

Most Snapshot failures that occurred after week 48 in both groups were discontinuations for nonvirologic or non-treatment-related reasons, including withdrawal of consent, lost to follow-up, protocol deviation, and physician decision (see Table, Supplemental Digital Content 3, <http://links.lww.com/QAI/B418>); this was most notable in the dolutegravir + lamivudine group in GEMINI-1. In the prespecified TRDF Kaplan-Meier analysis at week 96, 96.4% of participants in the dolutegravir + lamivudine group and 96.2% in the dolutegravir + tenofovir disoproxil fumarate/emtricitabine group did not discontinue for treatment-related reasons (unadjusted treatment difference [95% CI], 0.2% [-1.8 to 2.2]). In the ITT-E population, adjusted mean change from baseline to week 96 in CD4+ cell count was 269.0 cells/mm<sup>3</sup> in the dolutegravir + lamivudine group and 259.2 cells/mm<sup>3</sup> in the dolutegravir + tenofovir disoproxil fumarate/emtricitabine group.

Few participants met the prespecified criteria for CVW through week 96, with 11 participants (1.5%) in the dolutegravir + lamivudine group and 7 (1.0%) in the dolutegravir + tenofovir disoproxil fumarate/emtricitabine group (see Table, Supplemental Digital Content 4, <http://links.lww.com/QAI/B418>). Viral loads ranged from 206 to 87,794 copies/mL at the visit where CVW criteria were met and from <50 to 3011 copies/mL at the follow-up withdrawal visits (in those with a separate withdrawal visit). Of these, 5 participants in the dolutegravir + lamivudine group and 2 in the dolutegravir + tenofovir disoproxil fumarate/emtricitabine group met CVW criteria between weeks 48 and 96 and 1 participant in the dolutegravir + tenofovir disoproxil fumarate/emtricitabine group met CVW criteria at week 12 but was not reported in the week 48 analysis because of a laboratory reporting error. The latter participant remained in the study and had HIV-1 RNA <50 copies/mL at week 96.

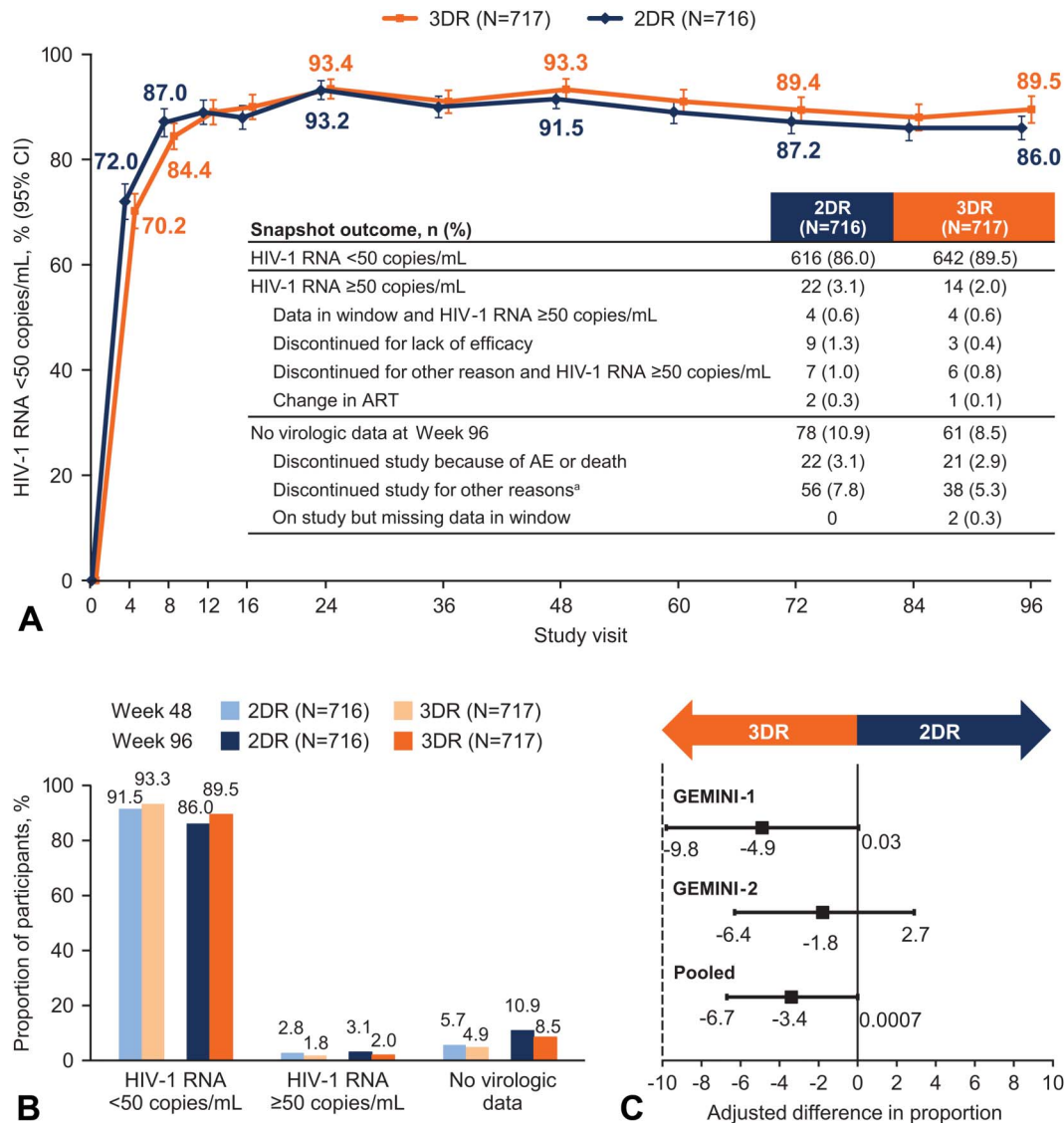
No INSTI or NRTI resistance mutations emerged during treatment among any participants who met CVW criteria.

Proportion of participants with HIV-1 RNA <50 copies/mL in key subpopulations including race, sex, and age was generally comparable across treatment groups, consistent with the overall results (see Figure, Supplemental Digital Content 5, <http://links.lww.com/QAI/B418>). In participants with baseline HIV-1 RNA >100,000 copies/mL, 83.6% (117/140) and 86.3% (132/153) in the dolutegravir + lamivudine and dolutegravir + tenofovir disoproxil fumarate/emtricitabine groups, respectively, achieved HIV-1 RNA <50 copies/mL at week 96 (Fig. 2); the corresponding proportions were 86.6% (499/576) and 90.4% (510/564) for those with baseline HIV-1 RNA ≤100,000 copies/mL and 87.7% (573/653) and 89.7% (594/662) for those with baseline CD4+ cell count >200 cells/mm<sup>3</sup>. Among participants with baseline CD4+ cell count ≤200 cells/mm<sup>3</sup>, 68.3% (43/63) in the dolutegravir + lamivudine group and 87.3% (48/55) in the dolutegravir + tenofovir disoproxil fumarate/emtricitabine group achieved HIV-1 RNA <50 copies/mL at week 96. Of note, the higher rate of Snapshot virologic nonresponse in the baseline CD4+ cell count ≤200 cells/mm<sup>3</sup> group on dolutegravir + lamivudine was primarily due to non-treatment-related reasons (see Table, Supplemental Digital Content 6, <http://links.lww.com/QAI/B418>). Consequently, there was little difference in the TRDF analysis at week 96 where rates of participants without treatment-related discontinuations with baseline CD4+ cell count ≤200 cells/mm<sup>3</sup> were 92.6% in the dolutegravir + lamivudine group and 96.2% in the dolutegravir + tenofovir disoproxil fumarate/emtricitabine group. Furthermore, the number of participants

**TABLE 1.** Demographics and Clinical Baseline Characteristics in the Pooled ITT-E Population From GEMINI-1 and GEMINI-2\*

Demographic/Characteristic	2DR (N = 716)	3DR (N = 717)
Sex, n (%)		
Female	113 (15.8)	98 (13.7)
Male	603 (84.2)	619 (86.3)
Ethnicity, n (%)		
Hispanic or Latino	215 (30.0)	232 (32.4)
Not Hispanic or Latino	501 (70.0)	485 (67.6)
Race, n (%)		
White	484 (67.6)	499 (69.6)
Black or African American	90 (12.6)	71 (9.9)
Asian	71 (9.9)	72 (10.0)
American Indian/Alaskan Native	52 (7.3)	57 (7.9)
Multiracial	17 (2.4)	17 (2.4)
Native Hawaiian or Pacific Islander	2 (0.3)	1 (0.1)
HIV-1 RNA, mean (SD), log <sub>10</sub> copies/mL	4.42 (0.66)	4.45 (0.65)
≤100,000 copies/mL, n (%)	576 (80.4)	564 (78.7)
>100,000 copies/mL, n (%)	140 (19.6)	153 (21.3)
CD4+ cell count, mean (SD), cells/mm <sup>3</sup>	462.0 (219.2)	461.3 (213.1)
≤200, n (%)	63 (8.8)	55 (7.7)
>200, n (%)	653 (91.2)	662 (92.3)

\*Analyses were pooled from the GEMINI-1 and GEMINI-2 studies.  
2DR, 2-drug regimen (dolutegravir + lamivudine); 3DR, 3-drug regimen (dolutegravir + tenofovir disoproxil fumarate/emtricitabine).

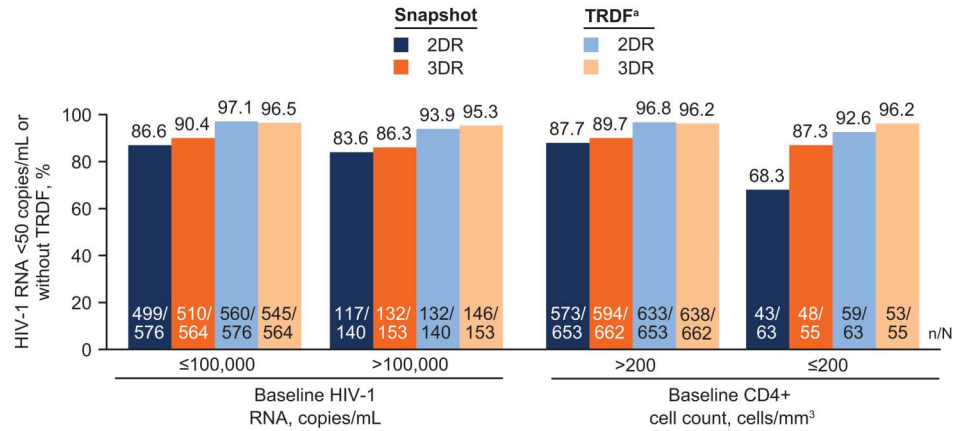


**FIGURE 1.** Snapshot analysis of the proportion of participants with plasma HIV-1 RNA <50 copies/mL (A) by visit and (B) at weeks 48 and 96 in the pooled ITT-E population. C, Adjusted treatment differences at week 96 of the Snapshot analysis in the ITT-E populations of the individual trials and the pooled analysis. <sup>a</sup>Other reasons for discontinuing study included (2DR, n [%] vs 3DR, n [%]) protocol deviation (10 [1.4%] vs 8 [1.1%]), lost to follow-up (18 [2.5%] vs 10 [1.4%]), physician decision (10 [1.4%] vs 4 [0.6%]), withdrew consent (18 [2.5%] vs 15 [2.1%]), and protocol-defined CVW (0 [0%] vs 1 [0.1%]). 2DR, 2-drug regimen (dolutegravir + lamivudine); 3DR, 3-drug regimen (dolutegravir + tenofovir disoproxil fumarate/emtricitabine).

meeting CVW criteria in this group was 3 and 2 in the 2DR and 3DR groups, respectively (see Table, Supplemental Digital Content 4, <http://links.lww.com/QAI/B418>). Although participants with screening HIV-1 RNA >500,000 copies/mL were excluded from the study, 2% of participants had HIV-1 RNA >500,000 copies/mL at the baseline visit (which was after the screening visit). Of these, 69.2% (9/13) in the dolutegravir + lamivudine group and 80.0% (12/15) in the dolutegravir + tenofovir disoproxil fumarate/emtricitabine group achieved HIV-1 RNA <50 copies/mL at week 96; most Snapshot failures in both groups were due to discontinuations for nonvirologic or non-treatment-related reasons (see Table, Supplemental Digital Content 7, <http://links.lww.com/QAI/B418>).

Through week 96, overall AE profiles were similar between treatment groups (relative risk [95% CI], 0.97 [0.93 to 1.02]). Consistent with week 48 results,<sup>13</sup> the most common AEs in the pooled safety population were diarrhea, headache, nasopharyngitis, and upper respiratory tract infection (Table 2). Participants in the dolutegravir + lamivudine group had a lower rate of drug-related AEs compared with the dolutegravir + tenofovir disoproxil fumarate/emtricitabine group (19.6% [140/716] vs 25.0% [179/717], respectively, relative risk [95% CI], 0.78 [0.64 to 0.95]); these differences were driven primarily by larger numbers of participants reporting drug-related grade 1 events, notably nausea, in the dolutegravir + tenofovir disoproxil fumarate/emtricitabine group. Rates of SAEs were similar between groups:

**FIGURE 2.** Snapshot and TRDF analyses of the proportion of participants with HIV-1 RNA <50 copies/mL or without TRDF at week 96 by baseline viral load and CD4+ cell count in the pooled ITT-E population from GEMINI-1 and GEMINI-2. 2DR, 2-drug regimen (dolutegravir + lamivudine); 3DR, 3-drug regimen (dolutegravir + tenofovir disoproxil fumarate/emtricitabine). <sup>a</sup>TRDF was a preplanned analysis at week 96. Percentages estimated from the TRDF Kaplan–Meier analysis.



dolutegravir + lamivudine, 8.9% (n = 64); dolutegravir + tenofovir disoproxil fumarate/emtricitabine, 9.3% (n = 67). Five participants in the dolutegravir + lamivudine group (suicidal ideation, n = 2; psychotic disorder, n = 1; substance-induced psychotic disorder, n = 1; and hepatotoxicity, n = 1) and 4 in the dolutegravir + tenofovir disoproxil fumarate/emtricitabine group (suicidal ideation, n = 1; suicide attempt, n = 1; cholelithiasis, n = 1; and rhabdomyolysis, n = 1) experienced drug-related SAEs. Three fatal AEs occurred in the dolutegravir + lamivudine group, which were considered unrelated to study treatment (acute myocardial infarction, n = 1; Burkitt lymphoma, n = 1; and coronary artery disease, n = 1). AEs leading to withdrawal were reported in 3.4% of participants in the dolutegravir + lamivudine group (n = 24) and 3.2% in the dolutegravir + tenofovir disoproxil fumarate/emtricitabine group (n = 23; Table 2). Increased weight was reported as an AE in 1.8% (n = 13) of participants in the dolutegravir + lamivudine group and 1.4% (n = 10) in the dolutegravir + tenofovir disoproxil fumarate/emtricitabine group. Overall mean (SD) change in weight from baseline was 3.1 (5.7) kg in the dolutegravir + lamivudine group and 2.1 (7.4) kg in the dolutegravir + tenofovir disoproxil fumarate/emtricitabine group, and mean change in BMI was 1.04 and 0.67 kg/m<sup>2</sup>, respectively. Few participants with normal BMI at baseline became obese at week 96 (dolutegravir + lamivudine, 3; dolutegravir + tenofovir disoproxil fumarate/emtricitabine, 4; see Figure, Supplemental Digital Content 8, <http://links.lww.com/QAI/B418>). Mean change in weight from baseline was comparable between groups for female (dolutegravir + lamivudine, 1.50 kg; dolutegravir + tenofovir disoproxil fumarate/emtricitabine, 1.56 kg) and male participants (dolutegravir + lamivudine, 3.43 kg; dolutegravir + tenofovir disoproxil fumarate/emtricitabine, 2.18 kg). Similarly, mean change in BMI from baseline to week 96 was also comparable between groups for female (dolutegravir + lamivudine, 0.62 kg/m<sup>2</sup>; dolutegravir + tenofovir disoproxil fumarate/emtricitabine, 0.60 kg/m<sup>2</sup>) and male participants (dolutegravir + lamivudine, 1.11 kg/m<sup>2</sup>; dolutegravir + tenofovir disoproxil fumarate/emtricitabine, 0.69 kg/m<sup>2</sup>).

Overall, 6 pregnancies were reported on study, 2 since the week 48 analysis. Two pregnancies resulted in live births of healthy infants (1 at 39 weeks of gestation and 1 unknown

gestation duration), 2 resulted in spontaneous abortions at 7 weeks and 4–5 weeks of gestation, and 2 resulted in elective abortions, both at 6 weeks of gestation. No apparent congenital abnormalities were reported.

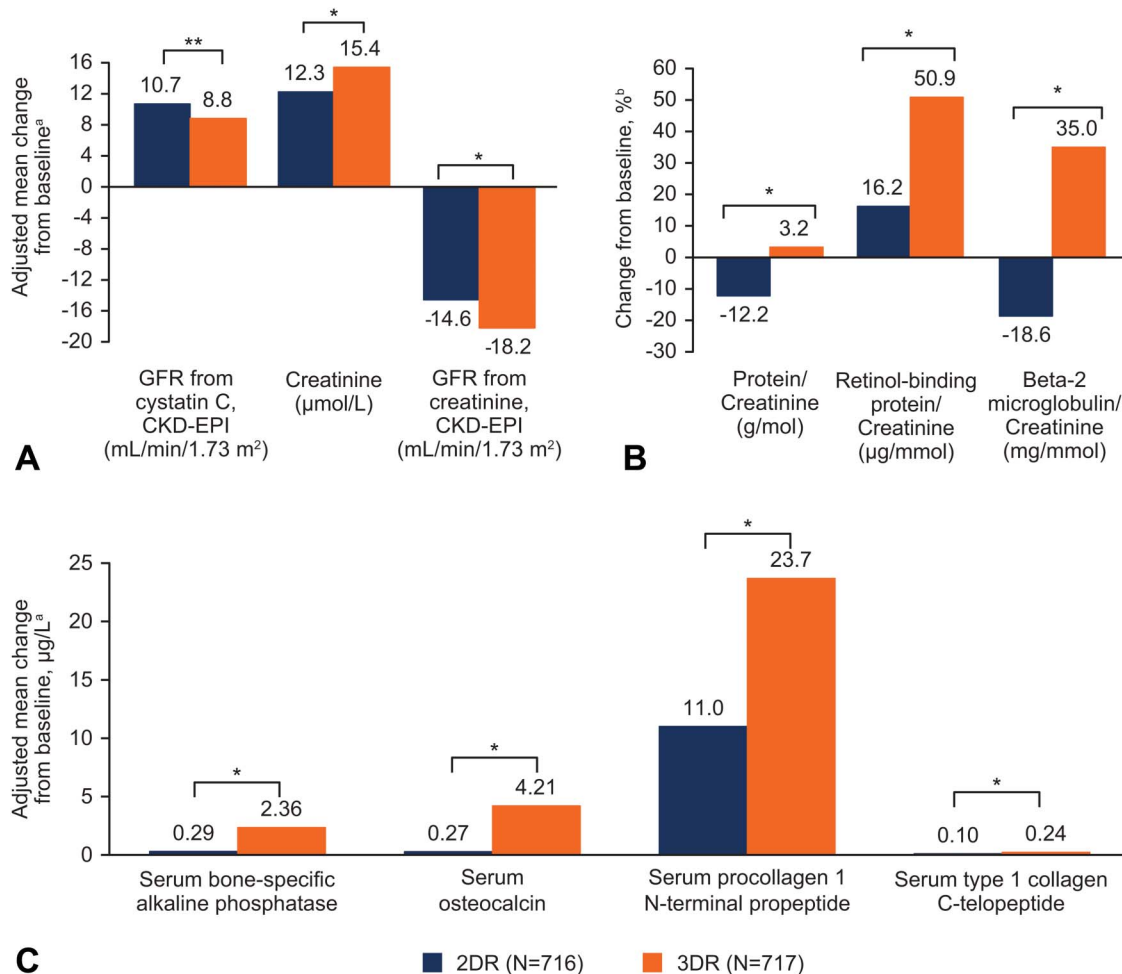
At week 96, changes in renal biomarkers significantly favored dolutegravir + lamivudine (Figs. 3A, B). Bone turnover biomarkers also favored dolutegravir + lamivudine, with significant increases observed with dolutegravir + tenofovir

**TABLE 2.** Summary of AEs in the Pooled Safety Population From GEMINI-1 and GEMINI-2

n (%)	2DR (N = 716)	3DR (N = 717)
Any AE	591 (82.5)	609 (84.9)
AEs occurring in ≥5% of participants in either group		
Diarrhea	89 (12.4)	93 (13.0)
Headache	79 (11.0)	87 (12.1)
Nasopharyngitis	71 (9.9)	114 (15.9)
Upper respiratory tract infection	70 (9.8)	56 (7.8)
Syphilis	49 (6.8)	52 (7.3)
Pharyngitis	47 (6.6)	48 (6.7)
Back pain	41 (5.7)	39 (5.4)
Bronchitis	36 (5.0)	30 (4.2)
Influenza	35 (4.9)	36 (5.0)
Insomnia	34 (4.7)	56 (7.8)
Nausea	29 (4.1)	58 (8.1)
Arthralgia	20 (2.8)	38 (5.3)
Drug-related AEs	140 (19.6)	179 (25.0)
Grade 2–5 AEs occurring in ≥1% of participants		
Headache	8 (1.1)	8 (1.1)
Serious AEs	64 (8.9)	67 (9.3)
AEs leading to withdrawal from treatment and study	24 (3.4)	23 (3.2)
AEs of interest leading to withdrawal from the study		
Neuropsychiatric	10 (1.4)	5 (0.7)
Renal-related	2 (0.3)	7 (1.0)
Osteoporosis	0	2 (0.3)

2DR, 2-drug regimen (dolutegravir + lamivudine); 3DR, 3-drug regimen (dolutegravir + tenofovir disoproxil fumarate/emtricitabine).





**FIGURE 3.** Profiles of renal and bone biomarkers. Adjusted mean change from baseline in (A) serum or plasma renal biomarkers and (B) ratios of urine renal biomarkers at week 96. C, Adjusted mean change from baseline in bone turnover biomarkers at week 96. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; 2DR, 2-drug regimen (dolutegravir + lamivudine); 3DR, 3-drug regimen (dolutegravir + tenofovir disoproxil fumarate/emtricitabine); GFR, glomerular filtration rate. <sup>a</sup>The 96-week analysis used mixed-effect model repeat measurement. Mean change from baseline adjusted for study, treatment, visit, baseline viral load, baseline CD4<sup>+</sup> 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. No assumptions were made about the correlations between participant readings of biomarkers (the correlation matrix for within-participant errors was unstructured). <sup>b</sup>Estimated from geometric means ratio for baseline and week 96. \**P* < 0.001. \*\**P* < 0.005.

disoproxil fumarate/emtricitabine vs dolutegravir + lamivudine for all biomarkers (Fig. 3C). There were also fewer renal function-related AEs (2DR, *n* = 2; 3DR, *n* = 7). There were no osteoporosis AEs with the 2DR and 2 osteoporosis AEs with the 3DR that led to treatment discontinuation (Table 2). Changes in lipid parameters at week 96 were consistent with week 48 results.<sup>13</sup> Total cholesterol, low-density lipoprotein cholesterol, and triglycerides increased in the dolutegravir + lamivudine group and decreased in the dolutegravir + tenofovir disoproxil fumarate/emtricitabine group (see Figure, Supplemental Digital Content 9, <http://links.lww.com/QAI/B418>). Importantly, in both groups, increases in high-density lipoprotein (HDL) cholesterol with resultant decreases in total cholesterol/HDL cholesterol ratio were observed. Significant differences between

treatment groups in adjusted mean change from baseline were observed for all lipid parameters. Forty participants (5.6%) in the 2DR group and 16 (2.2%) in the 3DR group initiated lipid-modifying agents after baseline.

At week 96, changes from baseline in EQ-5D-5L utility score, visual analog scale, and health state utility score were similar between groups (see Table, Supplemental Digital Content 10, <http://links.lww.com/QAI/B418>).

## DISCUSSION

The week 96 analysis of the GEMINI studies demonstrates the long-term virologic efficacy of the 2DR dolutegravir + lamivudine, as evidenced by its continued noninferiority vs

dolutegravir + tenofovir disoproxil fumarate/emtricitabine, as initial therapy for HIV-1–infected individuals. High proportions of participants had HIV-1 RNA <50 copies/mL at week 96 in both the dolutegravir + lamivudine and dolutegravir + tenofovir disoproxil fumarate/emtricitabine groups, and response rates were similar between groups regardless of baseline viral load (including those with baseline HIV-1 RNA >500,000 copies/mL). Importantly, the proportion of participants with HIV-1 RNA  $\geq$ 50 copies/mL at week 96 remained low and similar between treatment groups and from week 48 to 96. Most Snapshot failures that occurred after week 48 in both groups were discontinuations for nonvirologic or non-treatment-related reasons.

Consistent with the 48-week results, a lower rate of participants with baseline CD4<sup>+</sup> cell count  $\leq$ 200 cells/mm<sup>3</sup> had HIV-1 RNA <50 copies/mL at week 96 in the dolutegravir + lamivudine group. Interpretation of this finding is limited by the relatively small number of participants in this subgroup (n = 118; 8% of the pooled ITT-E population). Nevertheless, most of the reasons for the lower response rate in this 2DR subset were not related to lack of efficacy or adverse drug reactions (see Table, Supplemental Digital Content 6, <http://links.lww.com/QAI/B418>). This is reflected in the results of the TRDF analysis, which show a high and similar proportion of participants without treatment-related discontinuations between treatment groups in the baseline CD4<sup>+</sup> cell count  $\leq$ 200 cells/mm<sup>3</sup> subgroup.

One important question that has arisen during the development of dolutegravir-based 2DRs is the durability of the high barrier to resistance compared with dolutegravir-based 3DRs. This week 96 analysis has addressed this question and demonstrated that dolutegravir + lamivudine sustains a high barrier to resistance, with low numbers of participants experiencing CVW and zero emergence of resistance to INSTIs or NRTIs in either group. The lack of resistance development with the 2DR of dolutegravir + lamivudine over a prolonged treatment period is a very important finding because preservation of future treatment options for people with HIV, who can conceivably be on therapy for decades, is critical.

Safety results from the week 96 analysis of GEMINI-1 and GEMINI-2 were consistent with week 48 results.<sup>13</sup> Overall, there were few treatment-related discontinuations and a lower rate of drug-related AEs with the 2DR vs the 3DR. No new safety signals were observed between weeks 48 and 96. Although mean weight increased in both groups from baseline, no participants discontinued the study because of weight-related AEs. Changes in lipid parameters at week 96 relative to baseline generally were in favor of the dolutegravir + tenofovir disoproxil fumarate/emtricitabine group, consistent with the known effect of tenofovir disoproxil fumarate on cholesterol.<sup>22</sup> The total cholesterol/HDL ratio, which is often used to estimate long-term cardiovascular risk, decreased in both groups over 96 weeks, although the difference between groups significantly favored the tenofovir disoproxil fumarate–containing regimen. Notably, a greater proportion of participants initiated lipid-lowering agents in the 2DR group than in the 3DR group. The favorable effects on renal and bone biomarkers observed for dolutegravir + lamivudine vs dolutegravir + tenofovir disoproxil fumarate/emtricitabine in the

week 48 analysis were maintained through week 96. Consistent with these trends, there were fewer renal-related and osteoporosis AEs with the 2DR that led to treatment discontinuation. These treatment group differences might be attributed to the known effects of tenofovir disoproxil fumarate on renal and bone health.<sup>23,24</sup> Tenofovir alafenamide may have fewer renal and bone toxicities than tenofovir disoproxil fumarate, but due to consideration of standard of care and availability in participating countries at the time of study setup, the GEMINI trials used tenofovir disoproxil fumarate in the 3DR.<sup>25</sup>

Limitations of the GEMINI trials include the demographics of the study population, which was predominantly white (69%), male (85%), and aged <50 years at enrollment (90%), and may limit the generalizability of the results. However, virologic efficacy in key subpopulations including race, sex, and age was generally comparable across treatment groups. As described above, a low number of participants were enrolled with baseline CD4<sup>+</sup> cell count  $\leq$ 200 cells/mm<sup>3</sup>, limiting the interpretability of the results in this population with advanced HIV disease. Notably, there were no restrictions based on baseline viral load or CD4<sup>+</sup> cell count in the approvals from the FDA and the European Medicines Agency.<sup>14,15</sup> Few participants had very high viral loads (HIV-1 RNA >500,000 copies/mL) at treatment initiation since participants with screening HIV-1 RNA >500,000 copies/mL were excluded from the study. Participants with evidence of hepatitis B virus infection (since lamivudine monotherapy is generally not considered an adequate therapy for hepatitis B) and those with any major drug-resistance mutations were also excluded.

GEMINI-1 and GEMINI-2 are the largest phase III trials of a 2DR in ART-naive individuals with HIV-1 infection, which resulted in high precision of the noninferiority analysis. Results through 96 weeks demonstrate long-term durability with continued absence of treatment-emergent resistance and sustained noninferiority of dolutegravir + lamivudine compared with a standard and potent 3DR of dolutegravir + tenofovir disoproxil fumarate/emtricitabine. In conclusion, the week 96 results of the GEMINI-1 and GEMINI-2 trials provide further support for use of this 2DR as a treatment option for ART-naive people with HIV-1 infection.

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