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Dolutegravir Plus Abacavir/Lamivudine for the Treatment of HIV-1 Infection in Antiretroviral Therapy-Naive Patients: Week 96 and Week 144 Results From the SINGLE Randomized Clinical Trial

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Abstract: The SINGLE study was a randomized, double-blind, noninferiority study that evaluated the safety and efficacy of 50 mg dolutegravir + abacavir/lamivudine versus efavirenz/tenofovir/emtricitabine in 833 ART-naive HIV-1 + participants. Of 833 randomized participants, 71% in the dolutegravir + abacavir/lamivudine arm and 63% in the efavirenz/tenofovir/emtricitabine arm maintained viral loads of <50 copies per milliliter through W144 (P = 0.01). Superior efficacy was primarily driven by fewer discontinuations due to adverse events in the dolutegravir + abacavir/lamivudine arm [dolutegravir + abacavir/lamivudine arm, 13 (3%); efavirenz/tenofovir/emtricitabine arm, 48 (11%)] through W144. No treatment-emergent integrase or nucleoside resistance was observed in dolutegravir + abacavir/lamivudine recipients through W144.

Key Words: dolutegravir, abacavir, lamivudine, HIV

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INTRODUCTION

SINGLE is an ongoing, phase 3, multicenter, randomized, double-blind, noninferiority study involving treatment-naive HIV-infected participants. The study was designed to assess the safety and efficacy of dolutegravir 50 mg plus a fixed-dose combination of abacavir 600 mg/lamivudine 300 mg once daily compared with fixed-dose efavirenz 600 mg/tenofovir disoproxil fumarate (tenofovir DF) 300 mg/emtricitabine 200 mg once daily. The primary analysis occurred at week (W) 48. A full description of the study design, methods, and power calculation has been published.[1] Eligible participants were 18 years of age or older, had HIV-1 infection, had not previously received antiretroviral therapy, had plasma HIV-1 RNA levels (pVL) of at least 1000 copies per milliliter without genotypic evidence of HIV-1 protease and reverse transcriptase resistance mutations at screening, and were negative for the *HLA-B*5701* allele. Randomization was stratified according to the pVL at screening (≤100,000 copies/mL vs. >100,000 copies/mL) and the $CD4^+$ T-cell count (≤200 per mm^3 vs. >200 per mm^3). The trial continued double-blinded to participants and site staff with a secondary analysis conducted at W96. A protocol amendment added an open-label phase (maintaining original randomization) to both treatment groups from W96 to W144 to collect long-term efficacy and safety data. Participants and investigators were made aware of the study results, and participants had to reconsent to participate in the third year of the trial. The additional duration of therapy was conducted with an open-label design due to the superior efficacy results of the dolutegravir + abacavir/lamivudine arm at W48. The blinded W96 and unblinded W144 results of the study are presented here.

Study Endpoints and Statistical Analysis

The primary efficacy endpoint was the proportion of participants with pVL of <50 copies per milliliter at W48, as determined with the Food and Drug Administration Snapshot algorithm with a prespecified noninferiority margin of −10% using stratum-adjusted Cochran–Mantel–Haenszel weights. Secondary efficacy endpoints included proportion of participants with pVL <50 copies per milliliter at W96 and W144, time to viral suppression (ie, pVL of <50 copies/mL; analyzed using a Wilcoxon test), and change from baseline in $CD4^+$ T-cell count (analyzed using a repeated measures mixed model). Other secondary endpoints included safety profile, health outcomes, and incidence of the development of genotypic and phenotypic resistance to dolutegravir + abacavir/lamivudine and efavirenz/tenofovir DF/emtricitabine during treatment. Details of the statistical plan have been previously published.[1]

Study Population

A total of 833 participants were randomized (1:1) and received at least 1 dose of study medication (dolutegravir + abacavir/lamivudine, 414; efavirenz/tenofovir DF/emtricitabine, 419). Baseline demographics and disease characteristics of participants were comparable between arms. Median age of participants was 35 years; 16% of participants were women, 24% were black, and 4% were in class C of the Centers for Disease Control and Prevention HIV classification system. Median pVL at baseline was 4.68 $\log_{10}$ copies per milliliter, and median $CD4^+$ T-cell count was 338 per cells per cubic millimeter.[1]

Of 833 participants, 342 (83%) in the dolutegravir + abacavir/lamivudine arm and 310 (74%) in the efavirenz/tenofovir DF/emtricitabine arm completed the double-blind phase to W96. Main reasons for withdrawal were adverse events (AEs), which occurred in 13 (3%) and 48 (11%), and lack of efficacy, which occurred in 18 (4%) and 14 (3%), whereas categories of lost to follow up, withdrew consent, protocol deviations, and investigator discretion were fewer and similar between arms. After participants were unblinded and reconsented at W96, 341 (82%) and 309 (74%) entered the open-label phase, respectively. One participant in each arm declined to participate in the open-label phase. Overall, 317 (77%) and 278 (66%) participants completed the open-label phase to W144. Reasons for withdrawal by W144 were similar between treatment arms.

Efficacy

In the primary analysis, a higher proportion of participants in the dolutegravir + abacavir/lamivudine arm (88%) responded with pVL of <50 copies per milliliter compared with the efavirenz/tenofovir DF/emtricitabine arm (81%) through W48 [difference: 7.4%; 95% confidence interval (CI): 2.5% to 12.3%; $P = 0.003$]. A higher proportion of participants in the dolutegravir + abacavir/lamivudine arm than in the efavirenz/tenofovir DF/emtricitabine arm maintained pVL of <50 copies per milliliter through W96 (80% vs. 72%; $P = 0.006$); this difference was maintained at W144 (71% vs. 63%; $P = 0.01$ for dolutegravir + abacavir/lamivudine arm and efavirenz/tenofovir DF/emtricitabine arms, respectively; Figure 1).

As observed at W48, differences in the virological response rate were driven by a lower rate of discontinuations due to AEs or deaths in the dolutegravir + abacavir/lamivudine arm than in the efavirenz/tenofovir DF/emtricitabine arm [W96: 13/414 (3%) vs. 48/419 (11%); at W144: 16/414 (4%) vs. 58/419 (14%), respectively]. At W144, 30 (7%) of participants in the efavirenz/tenofovir DF/emtricitabine arm were virological nonresponders (defined as viral load not <50 copies per milliliter or discontinued for lack of efficacy or for other reasons without being suppressed) according to the Snapshot algorithm, compared with 43 (10%) in the dolutegravir + abacavir/lamivudine arm.

Thirty percent (124) of participants in the efavirenz/tenofovir DF/emtricitabine arm and 18% (75) of those in the dolutegravir + abacavir/lamivudine arm lacked virological data at the W144 visit and were considered nonresponders. This included participants who discontinued due to AEs or death, had missing data during the Snapshot window, or discontinued due to other reasons.

Treatment response among participants with low baseline pVL (≤100,000 copies/mL) at W96 and W144 was 237/280 (85%) and 204/280 (73%), respectively, in the dolutegravir + abacavir/lamivudine arm and 209/288 (73%) and 185/288 (64%), respectively, in the efavirenz/tenofovir DF/

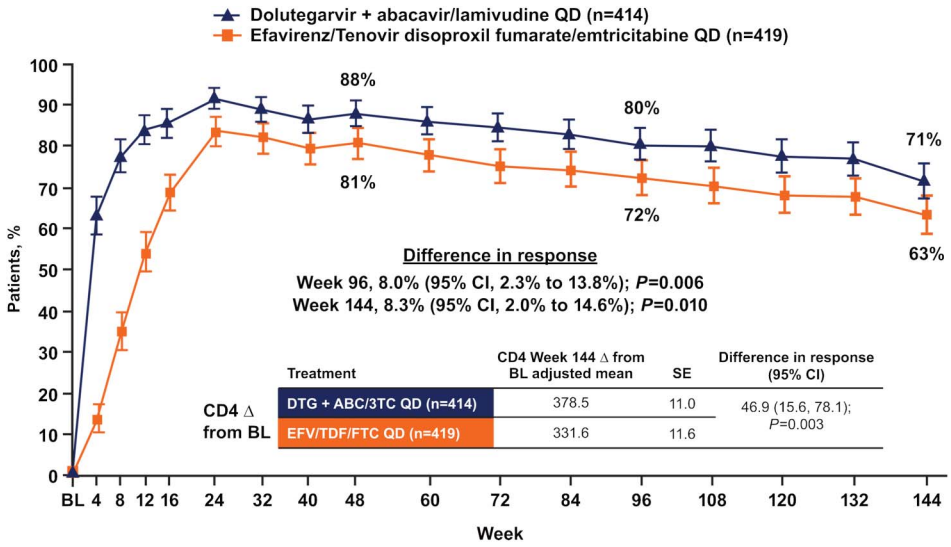

FIGURE 1. Proportion <50 copies per milliliter (95% CI) and CD4 change from baseline. BL, baseline; DTG + ABC/3 TC, dolutegravir + abacavir/lamivudine; EFV/TDF/FTC, efavirenz/tenofovir disoproxil fumarate/emtricitabine; QD, once daily; SE, standard error.

emtricitabine arm. In the high baseline pVL subgroup (>100,000 copies/mL), response rates were 95/134 (71%) at W96 and 92/134 (69%) at W144 in the dolutegravir + abacavir/lamivudine arm and 94/131 (72%) at W96 and 80/131 (61%) at W144 in the efavirenz/tenofovir DF/emtricitabine arm. Less pronounced response in the high baseline pVL subgroup at W96 in the dolutegravir + abacavir/lamivudine arm was due to withdrawals for reasons unrelated to treatment such as protocol deviation, loss to follow up, and withdrawal of consent. By W144, these subgroup responses were consistent with overall response rates.

Change from baseline in $CD4^+$ cell counts was consistently greater in the dolutegravir + abacavir/lamivudine arm than in the efavirenz/tenofovir DF/emtricitabine arm {W96: +325 cells/mm^3 vs. +281 cells/mm^3; difference and 95% CI: 44.0 [14.3 to 73.6 cells/mm^3 ($P = 0.004$)]; W144: +378 cells/mm^3 vs. +332 cells/mm^3; difference and 95% CI: 46.9 [15.6 to 78.2 cells/mm^3 ($P = 0.003$)]}. The incidence of HIV disease progression was comparable and low between arms (Figure 1).

Safety

The safety profile of dolutegravir + abacavir/lamivudine through W96 and W144 was similar to W48 and was generally favorable compared with the efavirenz/tenofovir DF/emtricitabine arm throughout. The most common drug-related AEs in the efavirenz/tenofovir DF/emtricitabine arm, which differed by more than 2% from the dolutegravir + abacavir/lamivudine arm, were dizziness [140 (33%) vs. 29 (7%)], abnormal dreams [67 (16%) vs. 27 (7%)], and rash [34 (8%) vs. 4 (<1%)]. The drug-related AE of insomnia was more commonly reported in the dolutegravir + abacavir/lamivudine arm (n = 41, 10%) than in the efavirenz/tenofovir DF/emtricitabine arm (n = 28, 7%; Table 1).

The overall incidence of serious adverse events (SAEs) was low and comparable across the dolutegravir + abacavir/lamivudine and efavirenz/tenofovir DF/emtricitabine arms through W96 [44 (11%) vs. 51 (12%) overall, respectively] and W144 [65 (16%) vs. 60 (14%), respectively]. Nine (2%) drug-related SAEs occurred in the efavirenz/tenofovir DF/emtricitabine arm compared with 2 (<1%) in the dolutegravir + abacavir/lamivudine arm through W144. During the double-blind phase, abacavir hypersensitivity was reported in 5 (1%) of participants in the efavirenz/tenofovir DF/emtricitabine arm and in 2 (0.5%) of participants in the dolutegravir + abacavir/lamivudine arm. Two fatalities were previously reported in the W48 analysis[1]; no additional fatalities occurred through W144. Two new drug-related SAEs occurred, 1 in the efavirenz/tenofovir DF/emtricitabine arm (renal failure between W48 and W96) and 1 in the dolutegravir + abacavir/lamivudine arm (osteonecrosis between W96 and W144).

No new clinically significant differences in laboratory parameters between the arms emerged since W48. The mean changes in low-density lipoprotein and total cholesterol were small and not statistically significant. A greater increase in high-density lipoprotein cholesterol for the efavirenz/tenofovir DF/emtricitabine arm compared with the dolutegravir + abacavir/lamivudine arm was seen through W144; overall, both groups showed a small increase in the ratio of total cholesterol to high-density lipoprotein cholesterol. A comparable and modest rise in mean total triglycerides was seen through W96 in both groups; however, the increase in triglycerides in the efavirenz/tenofovir DF/emtricitabine arm was greater than in the dolutegravir + abacavir/lamivudine arm at W144. Mean serum creatinine level in participants who received dolutegravir + abacavir/lamivudine remained stable through W144 after the expected, small, nonprogressive, nonclinically significant increase that was seen after treatment initiation. Five participants presented with grade 2 elevations in creatinine levels in the dolutegravir + abacavir/lamivudine arm on a single occasion through W144. There was 1 grade 3 elevation in the efavirenz/tenofovir DF/emtricitabine arm. Overall, there was a low rate of elevated

TABLE 1. Safety Data for Study ING114467 Through Weeks 96 and 144

	Dolutegravir + Abacavir/Lamivudine QD (n = 414)		Efavirenz/Tenofovir Disoproxil Fumarate/ Emtricitabine QD (n = 419)	
	Wk 96	Wk 144	Wk 96	Wk 144
Common drug-related AEs (reported in >5% of subjects in either treatment), %				
Any	44	+1	67	+1.2
Dizziness	7	+0	33	+0.2
Abnormal dreams	7	+0	16	+0.2
Nausea	11	+0.2	12	+0
Insomnia	10	+0	6	+0.7
Diarrhea	6	+0	8	+0
Fatigue	7	+0	7	+0
Headache	6	+0	7	+0
Rash	<1	+0	8	+0

	Dolutegravir + Abacavir/Lamivudine QD (n = 414)	Efavirenz/Tenofovir Disoproxil Fumarate/ Emtricitabine QD (n = 419)
SAEs at wk 144, n (%)		
Serious–any event	65 (16)	60 (14)
Serious drug-related–any event	2 (<1)*	9 (2)†
Fatal AEs	0	2 (<1)‡

*Dolutegravir + abacavir/lamivudine: 1 HSR, 1 osteonecrosis (new since week 96 analysis).
†Efavirenz/Tenofovir disoproxil fumarate/emtricitabine QD: 4 psychiatric, 2 syncopes, 1 cerebrovascular accident, 1 HSR, 1 renal failure.
‡One related to IP (renal failure); 1 not related to IP (pneumonia).
HSR, hypersensitivity reaction; IP, investigational product; QD, once daily.

liver enzymes in both treatment groups across the study period. Six participants (1%) had Grade 3/4 alanine aminotransferase (ALT) elevations in the dolutegravir + abacavir/lamivudine arm. Three were due to acute hepatitis C virus (HCV) infections, and 3 to concurrent use of hepatotoxic drugs (anabolic steroids, naltrexone, and duloxetine). Three grade 3/4 ALT elevations were observed in the efavirenz/tenofovir DF/emtricitabine arm (<1%); 2 of these were due to acute HCV infections, and 1 to use of anabolic steroids. Two participants with acute HCV infections were withdrawn from the study, 1 in each study arm.

Virology

The proportion of subjects who met criteria for protocol-defined virological failure (defined as 2 consecutive HIV-1 RNA values of ≥50 copies per milliliter on or after week 24) was low and similar across both the dolutegravir + abacavir/lamivudine and efavirenz/tenofovir DF/emtricitabine arms [39 (9%) vs. 33 (8%)] from baseline through W144. Of these, most participants had low-level viremia, ie, pVL <200 copies per milliliter (29 [74%] vs. 23 [70%] in the dolutegravir + abacavir/lamivudine and efavirenz/tenofovir DF/emtricitabine arms, respectively) at the time of failure. There were small numbers of participants whose pVL was 1000 copies per milliliter or above: 5 participants in the dolutegravir + abacavir/lamivudine arm and 2 participants in the efavirenz/tenofovir DF/emtricitabine arm. Resistance testing was attempted on the first suspected virological failure sample (regardless of pVL) for those participants with confirmed virological failure. No resistance mutation occurred in the dolutegravir + abacavir/lamivudine arm, whereas 7 participants developed resistance mutations in the efavirenz/tenofovir DF/emtricitabine arm (2 additional cases after W48). Of those, 6 had nonnucleoside reverse transcriptase inhibitor (NRTI) resistance mutations (K101E, K103K/N, and G190G/A), and 1 had the treatment-emergent NRTI resistance mutation K65K/R detected at the time of virological failure.

Health Outcomes

Patient-reported health outcome measures (Symptom Distress Module and EuroQol EQ-5D) were included at W48 and W96 to assess changes in subject-perceived symptom distress and health-related quality of life after initiation of study treatment. No statistically different responses in health outcomes endpoints were found at W48 or W96 between the arms.

DISCUSSION/CONCLUSIONS

This report describes results through W144 in the SINGLE trial and represents the longest duration of efficacy and safety data currently available for dolutegravir + abacavir/lamivudine. Dolutegravir + abacavir/lamivudine has been part of US Department of Health and Human Services initial antiretroviral treatment option recommendations for all patients regardless of baseline pVL or CD4 cell count since May 2014.[2] These data demonstrate that dolutegravir + abacavir/lamivudine is statistically superior

to standard of care fixed-dose combination efavirenz/tenofovir DF/emtricitabine with respect to the Snapshot algorithm through 144 weeks of treatment. Superiority continued to be driven by fewer participants discontinuing treatment due to AEs or death in the dolutegravir + abacavir/lamivudine arm.

Dolutegravir + abacavir/lamivudine were well tolerated through 144 weeks with no additional AE or SAE profile. No new clinically significant changes in clinical chemistry, hematology, or lipid safety parameters emerged in either group after W48. Most drug-related AEs and withdrawals due to AEs occurred during the initial 48 weeks of the study.

The nonprogressive, nonclinically meaningful initial increases in serum creatinine levels by dolutegravir have now been observed to remain stable for up to 3 years and have been described in other dolutegravir studies.[3–6] This is due to the inhibition of creatinine secretion and not associated with renal insufficiency.

The lack of treatment-emergent resistance mutations in the dolutegravir + abacavir/lamivudine arm to either the NRTI or integrase inhibitor class while resistance was observed in the comparator arm is consistent with in vitro data, suggesting that dolutegravir has a high barrier to resistance. The durability of the virological response and resistance advantage seen through 144 weeks supports a dolutegravir + abacavir/lamivudine regimen as a first-line option for treatment-naive patients with HIV.

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