Efficacy and Safety of Lersivirine (UK-453,061) Versus Efavirenz in Antiretroviral Treatment–Naive HIV-1–Infected Patients: Week 48 Primary Analysis Results From an Ongoing, Multicenter, Randomized, Double-Blind, Phase IIb Trial

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Objective: A 96-week clinical study was planned to estimate the antiviral activity and safety of lersivirine in treatment-naive HIV-1–infected patients.

Methods: This ongoing international, multicenter, double-blind, randomized, Phase IIb exploratory study evaluates the efficacy and safety of 2 doses of lersivirine or 1 of efavirenz, each combined with tenofovir disoproxil fumarate/emtricitabine. Patients were randomized 1:1:1 to receive lersivirine (500 or 750 mg once daily) or efavirenz (600 mg once daily), each administered with tenofovir disoproxil fumarate/emtricitabine (300 mg/200 mg, once daily). The primary endpoint is the proportion of patients with HIV-1 RNA <50 copies per milliliter (missing/discontinuation = failure) at week 48.

Results: For the 193 patients in the study, baseline mean plasma HIV-1 RNA was 4.7 $\log_{10}$ copies per milliliter, and median $CD4^+$ cell count was 312 cells per cubic millimeter. At week 48, the percentage of patients with HIV-1 RNA <50 copies per milliliter was 78.5% (51/65), 78.5% (51/65), and 85.7% (54/63) in the lersivirine 500 mg, 750 mg, and efavirenz groups, respectively. $CD4^+$ cell count changes from baseline were similar across groups. Virologic failure occurred in 7 patients (11%) in each of the lersivirine groups and 3 patients (5%) in the efavirenz group. The pattern of lersivirine resistance was distinct from other nonnucleoside reverse transcriptase

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inhibitors. Overall incidences of all-causality treatment-related or grade 3/4 adverse events (AEs) or AE-related discontinuations were lower with lersivirine than with efavirenz, and serious AEs occurred at similar rates across treatment groups.

Conclusions: Both lersivirine doses showed broadly comparable efficacy to efavirenz over 48 weeks in treatment-naive patients, with different AE profiles from efavirenz.

Key Words: efavirenz, HIV, lersivirine, treatment naive

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INTRODUCTION

There remains a need for newer antiretroviral drugs that address the limitations of currently available agents for the treatment of HIV-1 infection. According to current guidelines, the preferred first-line agent within the nonnucleoside reverse transcriptase inhibitor (NNRTI) class is efavirenz or nevirapine, administered in combination with 2 nucleoside reverse transcriptase inhibitors. However, the use of efavirenz or other first-generation NNRTIs is limited by adverse events (AEs) such as neuropsychiatric disorders, rash, hepatotoxicity, and dyslipidemia, and by the emergence of resistance.[1–6] Furthermore, efavirenz is associated with a number of pharmacokinetic interactions[2] and is not recommended during early pregnancy. The agent is classified as US Food and Drug Administration Pregnancy Category D and may cause fetal harm if administered during the first trimester.[1,7–9] All of these factors hamper first-generation NNRTI use in particular patient populations. There is, therefore, a requirement for newer NNRTIs with improved tolerability, efficacy against NNRTI-resistant virus, and with the potential for administration in a broader cohort of patients.

Lersivirine is a next-generation NNRTI that exhibits a distinct resistance profile due to its novel binding in the NNRTI-binding pocket[10] and demonstrates potent in vitro antiretroviral activity against wild-type virus and a number of clinically relevant NNRTI-resistant strains.[11,12] In a randomized, double-blind, placebo-controlled, 7-day monotherapy study in HIV-1–infected treatment-naive patients, lersivirine demonstrated potent antiretroviral activity, and was safe and generally well tolerated at doses of 500 mg once daily or greater.[13]

The primary objective of the Phase IIb trial reported in this article was to evaluate the efficacy of 2 doses of lersivirine (500 or 750 mg once daily) compared with efavirenz 600 mg once daily [each in combination with tenofovir disoproxil fumarate (DF)/emtricitabine], as measured by the percentage of patients with HIV-1 RNA <50 copies per milliliter at week 48.

METHODS

Study Patients

HIV-1–infected patients aged ≥ 18 years with plasma HIV-1 RNA ≥ 1000 copies per milliliter and $CD4^+$ cell count ≥ 200 cells per cubic millimeter at screening were eligible. Key exclusion criteria included the following: prior antiretroviral therapy for >14 cumulative days; active opportunistic infection during screening; suspected acute HIV-1 infection; acute hepatitis B or C infection (chronic infection was permitted provided patients were clinically stable and did not require treatment during the study); clinical or laboratory evidence of significant impairment in hepatic or renal function; pregnancy or breastfeeding; or documented genotypic resistance to efavirenz, tenofovir DF, or emtricitabine. Exclusionary NNRTI resistance–associated mutations included A98G, L100I, K101E/P, K103N/S/T, V106A/M, V108I, E138K, V179D/E/F, Y181C/I/V, Y188C/H/L, G190A/E/Q/S, H221Y, P225H, F227C/L, M230L/I, L234I, and K238T/N.

Study Design

Study A5271015 (NCT00824421) is an ongoing, 96-week, international, double-blind, randomized, placebo-controlled, Phase IIb trial conducted at 29 centers in 9 countries (Argentina, Australia, Canada, Italy, Mexico, Poland, South Africa, Switzerland, and the United Kingdom). Screening occurred 4–6 weeks before the start of the 96-week treatment period. Eligible patients were randomized according to a computer-generated pseudorandom code using the method of permutated blocks, balanced within each randomization stratum, and assigned at day 1 using a web/telephone computer-based telerandomization system. Randomization was stratified by plasma HIV-1 RNA ($<100{,}000$ or $\geq 100{,}000$ copies/mL) at screening and geographic region [Region A: European Union, Latin America (Argentina), Australia, Canada; Region B: South Africa]. South Africa was defined as a distinct region based on geography and the predominance of Clade C HIV-1.

Patients were randomized 1:1:1 to receive lersivirine at doses of 500 mg or 750 mg once daily or efavirenz 600 mg once daily, each administered with tenofovir DF/emtricitabine 300 mg/200 mg once daily. Lersivirine or efavirenz (together with an appropriate matched placebo to maintain blinding) were administered without food at bedtime, and tenofovir DF/emtricitabine was taken with the evening meal. Adherence was assessed by monitoring the number of tablets in study drug containers and variation in plasma HIV-1 RNA, and potential noncompliance was followed up. The use of other antiretroviral agents or substitutions for any of the treatment components was not permitted. After initiation of treatment, patients were evaluated at weeks 2 and 4, every 4 weeks through week 16, then every 8 weeks through week 48.

Treatment failure was defined as meeting any of the following criteria (all confirmed by a second consecutive measurement collected within 14 days): failure to achieve HIV-1 RNA <50 copies per milliliter at week 24 or thereafter; decrease from baseline in HIV-1 RNA of <1.0 $\log_{10}$ copies per milliliter at week 4 or thereafter; increase in HIV-1 RNA to at least 3 times the baseline level at week 2 or thereafter; or increase in HIV-1 RNA to detectable levels (≥ 50 copies/mL) in patients previously confirmed to have undetectable levels (<50 copies/mL).

Safety and tolerability assessments included monitoring of vital signs, physical examination results, safety laboratory tests, AEs at all study visits, and 12-lead electrocardiogram at selected visits. The investigator determined causality of AEs

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and applied the Division of AIDS reference table to describe their severity.[14]

Ethical Approval

The study was approved by the appropriate Institutional Review Board or Independent Ethics Committee at each center and conducted in compliance with principles derived from the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice guidelines, and local regulatory requirements. All patients provided written informed consent.

Measurements

Initially, HIV-1 RNA measurements were performed using the Roche COBAS AmpliPrep/COBAS TaqMan test (Roche, Basel, Switzerland). However, shortly after the study commenced, the assay was changed to the Roche Amplicor HIV-1 Monitor test (Version 1.5) as detection frequency at the lower limit of quantification was considered more accurate.[15,16] At the time of the change, 43 samples had been assayed using the TaqMan assay; all were obtained before treatment administration (39 at screening, 3 at randomization, and 1 on day 1). These results were included in the calculation of baseline HIV-1 RNA, which was derived by averaging all available ~~pre-dose~~ values obtained with either assay.

Resistance genotyping was performed for all patients at screening using the Monogram Biosciences GenSeq assay. Resistance testing (both genotyping and phenotyping) was performed on day 1 (predose) and at the time of treatment failure in patients who met any of the treatment failure criteria, using the Monogram Biosciences PhenoSenseGT assay (San Francisco, CA).

Efficacy Endpoints and Data Analysis

The primary analysis was performed when all patients had been treated for 48 weeks or had discontinued before week 48. Efficacy data were analyzed in the modified intent-to-treat (mITT) population, which included all randomized patients who received at least 1 dose of study medication regardless of adherence to protocol requirements.

The primary efficacy endpoint was the proportion of patients who achieved plasma HIV-1 RNA <50 copies per milliliter at week 48. Missing values within the week 48 window or discontinuation before or within the week 48 visit window were imputed as treatment failures (missing/discontinuation = failure; MD = F) for the primary missing data imputation method. Any patient with plasma HIV-1 RNA <50 copies per milliliter at week 48 but who discontinued within the same visit window was considered a failure.

As this was an estimation study, it was not powered for formal hypothesis testing of efficacy comparisons between lersivirine and efavirenz. Two-sided 80% confidence intervals (CIs) for the difference in proportions between each lersivirine treatment group and the efavirenz treatment group were formed using the normal approximation to the binomial with continuity correction. The analysis was adjusted using the Cochran-Mantel-Haenszel method[17,18] based on the randomization strata. Predefined subgroup analyses were performed, including plasma HIV-1 RNA concentration at screening ($<100{,}000$ or $\geq 100{,}000$ copies/mL) and geographic region as stratification factors.

A formal interim analysis was undertaken at week 24 to evaluate the lersivirine arms for futility. Futility of the lersivirine dose group was to be claimed if the lower bound of the 2-sided 80% CI for the difference between a lersivirine group and the efavirenz group in the proportion of patients with plasma HIV-1 RNA <50 copies per milliliter in the mITT population (MD = F) was <-0.20 at week 24. Investigators, site staff, and patients remained blinded until the week 96 visit was completed for each individual patient, whilst the sponsor was unblinded at the week 24 interim analyses.

Secondary efficacy evaluations included the percentage of patients achieving plasma HIV-1 RNA <400 ~~copies/mL~~ (MD = F) and change from baseline (defined as the average of all the values obtained before day 1 dosing) in $CD4^+$ cell counts. Last observation carried forward was used to impute missing values for the $CD4^+$ cell count. An analysis of covariance model was used to analyze the change from baseline in $CD4^+$ cell counts. Baseline $CD4^+$ cell count and stratification factors were covariates. Additional secondary endpoints included assessment of genotypic and phenotypic susceptibility at treatment failure. Two-sided 80% CIs were calculated where applicable. No adjustments were made for multiple comparisons.

The identification of samples for virologic analysis was based on an assessment of plasma HIV-1 RNA concentration over time. Virologic failures were identified using the time to loss of virologic response algorithm, based on the limit of quantification (plasma HIV-1 RNA ≥ 50 copies/mL). Samples were planned to be analyzed only if plasma HIV-1 RNA was >500 copies per milliliter, the technical limit required for a valid analysis to be performed. On occasion, plasma samples with HIV-1 RNA <500 copies per milliliter were submitted as either part of the treatment failure confirmation visit or the early termination visit and tested successfully. These results were also included in the virology analysis. Failures also included patients who discontinued early for nonvirologic reasons. Both virologic and nonvirologic failures were assessed if they discontinued therapy early or reached week 48 with sufficient plasma HIV-1 RNA for evaluation. The genotypic and phenotypic changes from day 1 (predose) through week 48 were examined.

Efficacy and virology analyses included all observations through day 378, the upper limit of the week 48 visit window.

Safety Endpoints and Data Analysis

Secondary endpoints include assessment of safety and tolerability in all patients who were randomized and received at least 1 dose of study medication. The change from baseline in fasting metabolic endpoints [total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, and glucose] at week 48 were analyzed using an analysis of covariance model with the baseline value and stratification factors as covariates. Baseline was the last fasting measurement before day 1 dosing. Missing

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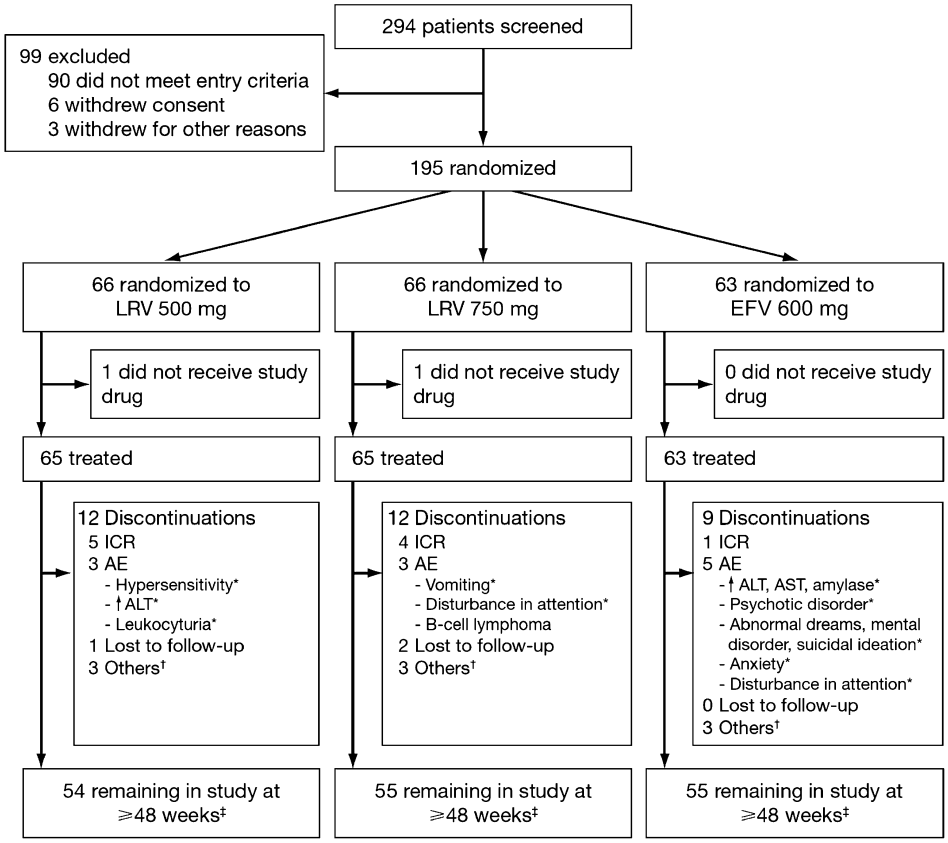

FIGURE 1. Disposition of patients through week 48. *Considered by investigator to be at least possibly related to study drug. "Others" included patients no longer willing to participate in study, withdrawn due to pregnancy, death, relocation, and imprisonment. †Four patients (1 in LRV 500 mg, 2 in LRV 750 mg, and 1 in EFV) completed the week 48 visit but discontinued thereafter within the visit window. ALT, alanine aminotransferase; AST, aspartate aminotransferase; EFV, efavirenz; ICR, insufficient clinical response; LRV, lersivirine.

data were ignored. A 2-sided P value of <0.2 was considered to indicate a potential trend. Safety data included all observations through day 378, the upper limit of the week 48 visit window. Periodic reviews of safety and efficacy data were performed by an independent Data Monitoring Committee.

RESULTS

Patient Disposition and Baseline Characteristics

Patients were recruited between February 9 and October 29, 2009. In total, 294 patients were screened, of whom 195 were randomized, 193 received treatment and were included in the mITT analyses, and 164 (85%) completed 48 weeks of treatment (Fig. 1). The percentage of patients who discontinued treatment was similar between the lersivirine and efavirenz groups; 11 patients were discontinued due to AEs [3 (5%), 3 (5%), and 5 (8%) in the lersivirine 500 mg, lersivirine 750 mg, and efavirenz groups, respectively] and 10 due to insufficient clinical response [5 (8%), 4 (6%), and 1 (2%) in the lersivirine 500 mg, lersivirine 750 mg, and efavirenz groups, respectively].

Demographic and baseline disease characteristics were similar across groups (see **Table S1, Supplemental Digital Content,** http://links.lww.com/QAI/A364). The majority of patients in each group were male (71%–75%) and white (54%–62%), with a mean age of 36 years. Approximately 33% of patients were black and were enrolled primarily in Region B (South Africa). Overall, 61.7% of patients had Clade B HIV-1 infection and 31.6% had Clade C HIV-1 infection. Other HIV-1 subtypes were reported for 6.7% of patients. Of 64 patients randomized in South Africa, 60 had Clade C infection (93.8%). At screening, plasma HIV-1 RNA concentration was ≥100,000 copies per milliliter in 33% of patients and median $CD4^+$ cell counts ranged from 317 to 323 cells per cubic millimeter.

Virologic and Immunologic Response

At the week 24 interim analysis, the percentages of patients with plasma HIV-1 RNA <50 copies per milliliter (MD = F, mITT) were 83%, 83%, and 87% for lersivirine 500 mg, lersivirine 750 mg, and efavirenz, respectively. The lower limits of the 2-sided 80% CI for the differences in the percentage of patients with plasma HIV-1 RNA <50 copies per milliliter at week 24 (MD = F, mITT) were −14% (lersivirine 500 mg versus efavirenz) and −13% (lersivirine 750 mg versus efavirenz), which were above the prespecified margin of −20%, thus did not cross the boundary of futility. Therefore, a further larger study was warranted.

At week 48, 51 of 65 (78.5%) patients in each of the lersivirine groups and 54 of 63 (85.7%) patients in the efavirenz group achieved plasma HIV-1 RNA <50 copies per milliliter (mITT, MD = F) (Table 1, Fig. 2). Within the week 48 window, 2 patients in the lersivirine 750 mg group achieved plasma HIV-1 RNA <50 copies per milliliter but discontinued therapy for other reasons (one due to imprisonment and one lost to follow-

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TABLE 1. Week 48 Virologic (MD = F, mITT) and Immunologic (LOCF, mITT) Response

	Lersivirine 500 mg (n = 65)	Lersivirine 750 mg (n = 65)	Efavirenz 600 mg (n = 63)
Plasma HIV-1 RNA <50 copies/mL, n (%)	51 (78.5)	51 (78.5)	54 (85.7)
80% CI of difference LRV - EFV	−18.1, 0.8	−17.0, 1.2	NA
Plasma HIV-1 RNA <400 copies/mL, n (%)	53 (81.5)	52 (80.0)	54 (85.7)
80% CI of difference LRV - EFV	−14.9, 3.4	−15.4, 2.8	NA
Mean change from baseline in $CD4^+$ cell count, LSM* (SE)	194.2 (20.3)	199.4 (19.8)	196.7 (20.1)

*LSM was adjusted for randomization stratification variables of plasma HIV-1 RNA level at screening (<100,000 versus ≥100,000 copies/mL), geographic region (group A versus B), and the baseline absolute $CD4^+$ cell count. The baseline for $CD4^+$ cell count was defined as the average of all the values obtained before day 1 dosing.

Cochran-Mantel-Haenszel estimates for the 80% CI of difference between lersivirine and EFV adjusted for randomization stratification variables of HIV-1 RNA level at screening (<100,000 versus ≥100,000 copies/mL) and geographic region (group A versus group B). Difference is the percentage difference between the lersivirine and EFV groups. EFV, efavirenz; LOCF, last observation carried forward; LSM, least squares mean; MD = F, missing/discontinuation = failure; NA, not applicable.

up); these were considered failures. The percentage of patients achieving plasma HIV-1 RNA <400 copies per milliliter at week 48 (mITT, MD = F) and mean changes from baseline in absolute $CD4^+$ cell counts at week 48 (mITT, last observation carried forward) were similar between the 3 treatment groups (Table 1, Fig. 2).

Observed response rates according to the 2 stratification factors, plasma HIV-1 RNA at screening and geographic region, are shown in Figure 3. Within the subgroup of patients with HIV-1 RNA <100,000 copies per milliliter at screening, responses were broadly similar among the 3 treatment groups; within the subgroup of patients with HIV-1 RNA ≥100,000 copies per milliliter at screening, the response in the lersivirine 750 mg group was lower than in the other treatment groups. Responses in the lersivirine groups were lower in Region B (South Africa), where patients had predominantly Clade C HIV-1, than in Region A (European Union, Latin America, Australia, Canada). Within Region A, response rates were comparable for patients with plasma HIV-1 RNA <100,000 copies per milliliter and ≥100,000 copies per milliliter at screening for each of the treatment groups.

Failure occurred in 14 (21.5%) patients in each of the lersivirine groups and 9 (14.3%) patients in the efavirenz group. Half of the failures occurring in the lersivirine 750 mg group (n = 7/14) were enrolled in South Africa, and the majority of these (n = 5/7) had plasma HIV-1 RNA ≥100,000 copies per milliliter at screening. Four of these 5 patients were reported to be nonadherent (compliance by pill count of <95% for any treatment component) at one or more study visits.

Resistance Analysis

Paired baseline (day 1 predose) and on-treatment analyses were successfully performed on plasma HIV-1 RNA from 12 patients (lersivirine 500 mg, n = 4; lersivirine 750 mg, n = 5; efavirenz, n = 3). Five of the samples from lersivirine-treated patients did not have any emergent resistance-associated mutations. Of the other 4, although selected mutations (K101E/V108I/H221Y; Y188H/F227L/L234I; F227C; V106M/F227L) were associated with resistance to lersivirine (36-fold to 114-fold change), the change in susceptibility to efavirenz was 1.6-fold to 11-fold. M184V or M184I mutations also emerged in these samples, and resistance to emtricitabine was observed.

In 1 patient treated with efavirenz, a K103N mutation emerged. There was a 11-fold change in susceptibility to efavirenz with no change in susceptibility to lersivirine.

Virus from one patient who was randomized to the lersivirine 500 mg treatment group in error had a detectable reverse transcriptase mutation, M230I, at screening. This mutation was included among the protocol exclusion criterion. On treatment failure, emergent nucleoside reverse transcriptase inhibitor and NNRTI RAMs were observed; however, the M230I mutation was not detectable.

Safety and Tolerability

Overall, the incidence of both all-causality and treatment-related AEs was slightly lower in each of the lersivirine groups compared with efavirenz (Table 2). The majority of AEs in all treatment groups were mild to moderate in severity, and the most commonly reported AEs (all causality) included diarrhea, nausea, vomiting, upper respiratory tract infection, dizziness, headache, and abnormal dreams (reported by more than 15% of patients in any treatment group). The incidence of nausea was numerically greater in the lersivirine 500 mg (23.1%) and 750 mg (41.5%) treatment groups versus efavirenz (12.7%), whereas a numerically greater number of patients treated with efavirenz compared with lersivirine 500 mg and 750 mg experienced dizziness (20.6% versus 7.7% and 6.2%, respectively) and abnormal dreams (19.0% versus 7.7% and 7.7%, respectively). The incidence of discontinuations as a result of any AE, and of serious AEs, was similarly low in each treatment group (Table 2). There was 1 death in the lersivirine 750 mg group due to a motor vehicle accident, considered unrelated to lersivirine.

The overall incidence of grade 2–4 AEs considered to be at least possibly related to treatment (including relatedness to the investigational treatment and/or background antiretroviral drugs) was numerically lower in each of the lersivirine groups compared with efavirenz (Table 2). There were no apparent dose-related effects with respect to treatment-related grade 2–4 AEs in the lersivirine groups with the exception of nausea, which was reported at the highest rates in the lersivirine 750 mg group. Median times to nausea were 2, 2, and 6 days in the lersivirine 500 mg, 750 mg, and efavirenz groups, respectively, whereas the corresponding median durations of nausea were 16, 29, and 13 days. Nausea did not result in treatment or study discontinuation, though 1 patient in the lersivirine 750 mg group discontinued due to vomiting (grade 2). Overall, treatment-related grade 2–4 neuropsychiatric AEs including abnormal dreams, nightmare, suicidal ideation, headache, and vertigo were reported slightly more frequently in the

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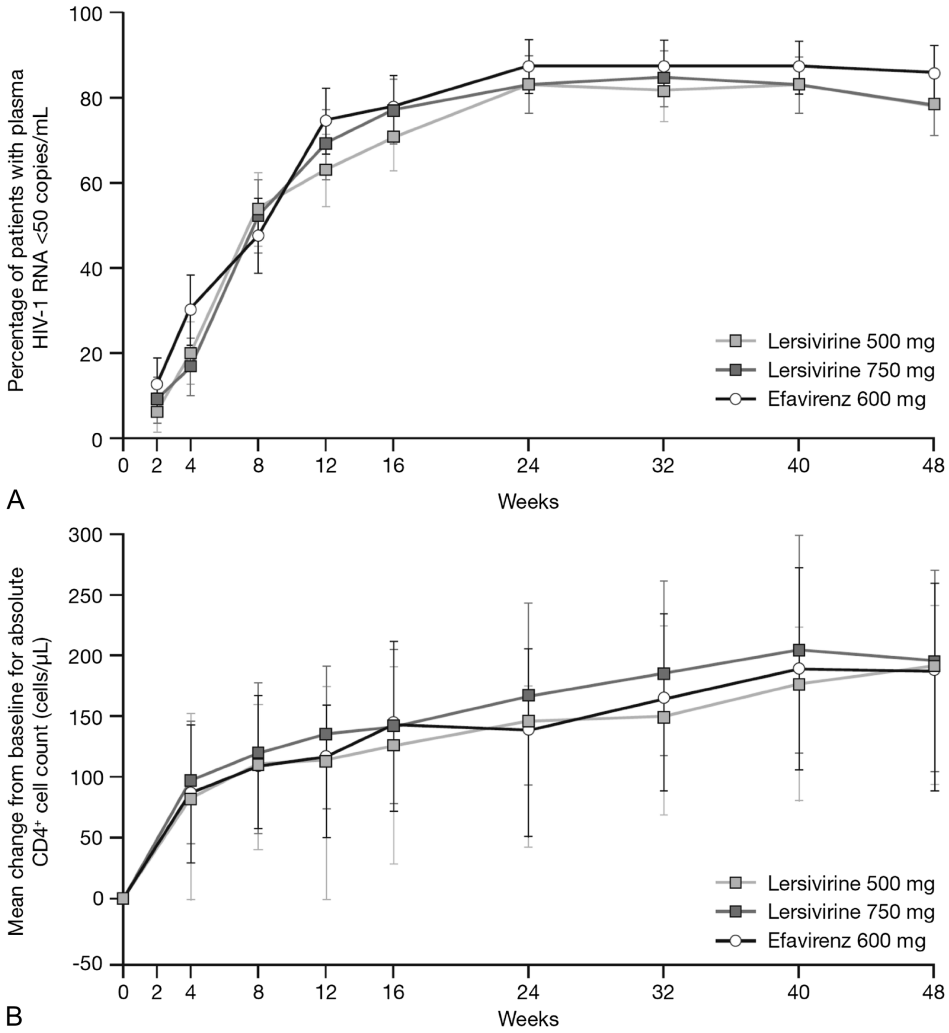

FIGURE 2. Virologic and immunologic efficacy through week 48. A, Percentage of patients with HIV-1 RNA <50 copies per milliliter, MD = F, mITT. B, Mean change from baseline in absolute $CD4^+$ cell count (cells/μL), LOCF, mITT. Error bars represent the following: A, 80% confidence intervals; and B, interquartile ranges. The baseline for $CD4^+$ cell count was defined as the average of all the values obtained before day 1 dosing. LOCF, last observation carried forward; MD = F, missing/discontinuation = failure.

efavirenz group (Table 2). One case of hypersensitivity with rash and fever (grade 2) was reported in a patient enrolled in the lersivirine 500 mg group after receiving a single dose of lersivirine and resulted in treatment discontinuation with subsequent resolution of symptoms.

The incidence of grade 3–4 laboratory abnormalities was similar across treatment groups, with no apparent trends exhibited by any 1 group (Table 2). One patient in the lersivirine 500 mg group experienced grade 3 and 4 abnormalities in transaminases and elevated total bilirubin that were associated with concurrent acute hepatitis A infection. In the lersivirine 750 mg group, grade 3 or 4 elevations in aspartate aminotransferase and in alanine aminotransferase were each reported in 2 patients. These resolved without discontinuation of lersivirine. In 1 patient, elevations were associated with exercise and protein supplementation.

Mean changes from baseline in total cholesterol, LDL-C, and HDL-C were numerically lower in both lersivirine groups than in the efavirenz group, and in triglycerides, numerically lower in the lersivirine 750 mg group than in the efavirenz group (Table 2).

DISCUSSION

In this randomized, double-blind, Phase IIb, estimation study, both doses of lersivirine (500 mg and 750 mg once daily) demonstrated rates of viral suppression and increases in $CD4^+$ cell count that were broadly comparable to those demonstrated with efavirenz over 24 and 48 weeks in HIV-1–infected treatment-naive patients. This trial was not designed to assess noninferiority to efavirenz, as testing of such a hypothesis would require a larger sample size. Rather, it was conceived to estimate whether antiviral efficacy can be considered similar to that of efavirenz. Results indicated that this was indeed the case, with a difference of response (plasma HIV-1 RNA <50 copies/mL) of only 3 patients between the lersivirine and efavirenz arms at week 48.

Responses stratified by plasma HIV-1 RNA at screening and geographic region on response were also comparable in the lersivirine 500 mg and efavirenz groups. In the lersivirine 750 mg group, response rates were lower in the upper stratum (≥100,000 copies/mL), compared with the lower stratum of plasma HIV-1 RNA (<100,000 copies/mL), and in geographic Region B (South Africa) compared with Region A (the

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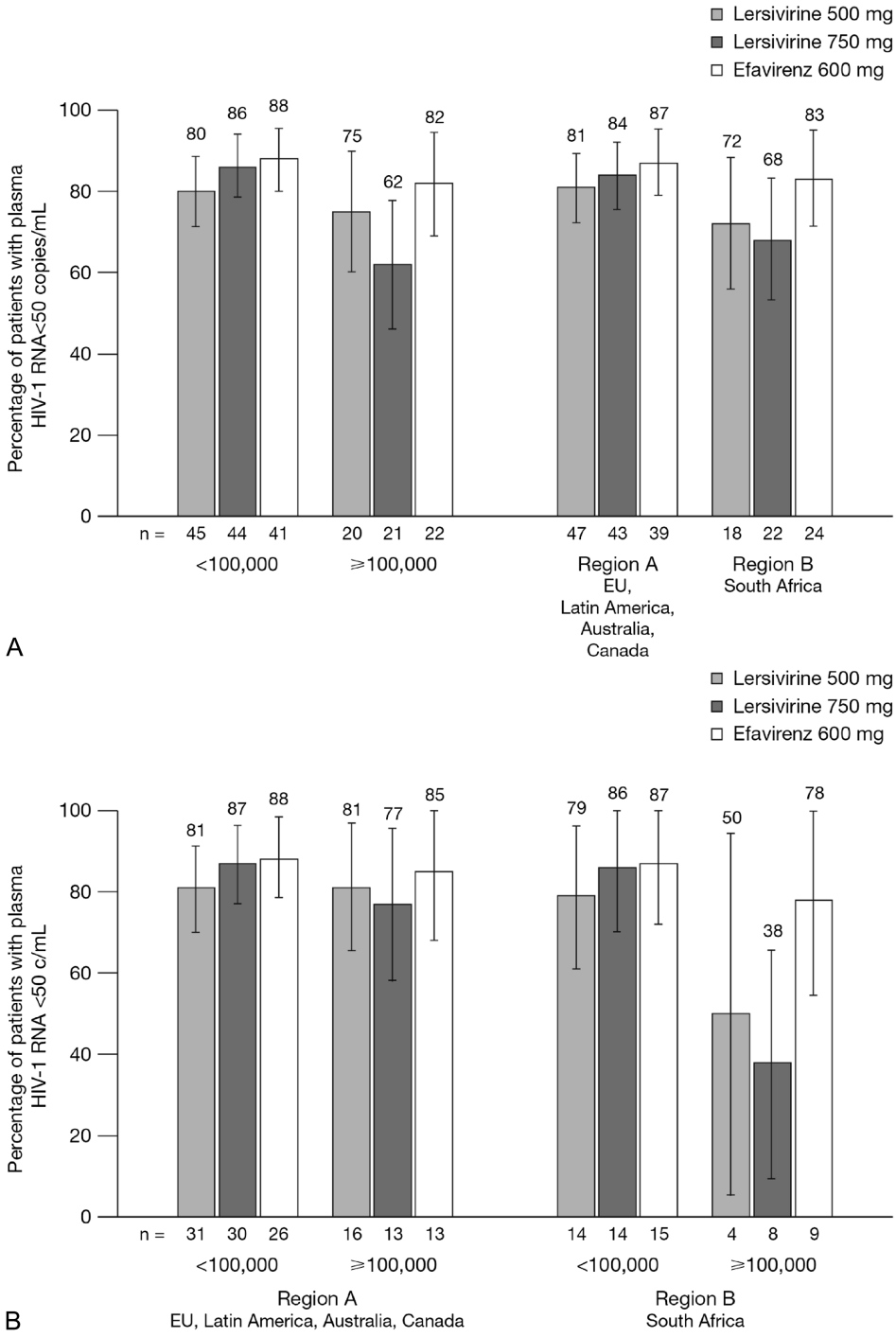

FIGURE 3. A, Efficacy at week 48 by plasma HIV-1 RNA at screening and geographic region (mITT, MD = F), and B, efficacy in regions A and B by plasma HIV-1 RNA at screening (mITT, MD = F). Error bars represent 80% confidence intervals. MD = F, missing/discontinuation = failure.

European Union, Latin America, Australia, and Canada). However, within Region A, response rates were comparable for patients enrolled in both plasma HIV-1 RNA strata for each of the 3 treatment groups. The lower response rates observed in the lersivirine 750 mg group for patients in the higher stratum seemed to be driven primarily by lower response rates among patients enrolled in South Africa. Although race and Clade were confounding factors among the 64 patients enrolled from South Africa (94% were black and had Clade C HIV-1), preclinical studies have shown lersivirine to be fully active against Clade C infection in vitro,[12] and the most likely reason for failure in this group is considered to be nonadherence, as noted in 4 of 5 Region B patients in the upper stratum who did not respond to treatment. However, due to the relatively small number of patients enrolled in each subgroup, the results of these analyses should be interpreted with caution and no definitive conclusions can be made.

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TABLE 2. Summary of Treatment-Emergent AEs, Laboratory Abnormalities, and Change From Baseline in Lipid Parameters and Glucose

Number (%) of Patients		Lersivirine 500 mg (n = 65)	Lersivirine 750 mg (n = 65)	Efavirenz 600 mg (n = 63)
With AEs	All causality	52 (80)	56 (86)	58 (92)
	Treatment related	40 (62)	40 (62)	45 (71)
With SAEs	All causality	4 (6)	5 (8)	4 (6)
Discontinued due to AEs	All causality	3 (5)	3 (5)	5 (8)
With DAIDS grade 3 or 4 AEs	All causality	4 (6)	9 (14)	14 (22)
	Treatment related	2 (3)	3 (5)	8 (13)
DAIDS grade 2–4 treatment-related AEs (>2% in any treatment group)				
Total		14 (22)	12 (18)	25 (40)
Abdominal pain		1 (2)	1 (2)	3 (5)
Abnormal dreams		1 (2)	0	4 (6)
ALT increased		1 (2)	0	3 (5)
AST increased		1 (2)	0	2 (3)
Asthenia		1 (2)	1 (2)	2 (3)
Blood cholesterol increased		0	0	2 (3)
Diarrhea		2 (3)	0	0
Disturbance in attention		0	2 (3)	1 (2)
Headache		0	1 (2)	3 (5)
Insomnia		1 (2)	2 (3)	3 (5)
Lipase increased		2 (3)	0	0
Nausea		2 (3)	4 (6)	0
Nightmare		0	1 (2)	2 (3)
Pruritus		0	0	2 (3)
Rash*		0	0	3 (5)
Suicidal ideation		0	0	2 (3)
Vertigo		1 (2)	0	3 (5)
Vomiting		0	2 (3)	1 (2)
Grade 3 or 4 laboratory abnormalities (occurring in ≥2 patients in any treatment group)				
Total		4 (6)	6 (9)	6 (10)
ALT ≥ 5 × ULN		1 (2)	2 (3)	2 (3)
AST ≥ 5 × ULN		1 (2)	2 (3)	1 (2)
Creatine kinase ≥ 10 × ULN		1 (2)	2 (3)	2 (3)
LDL-C > 190 mg/dL		0	0	2 (3)
Change from baseline in fasting lipid parameters and fasting glucose, LSM (SE)				
N		48	51	48
Total cholesterol, mg/dL		0.9 (3.7)†	−4.2 (3.5)†	15.5 (3.6)
HDL-C, mg/dL		2.8 (1.3)†	1.2 (1.3)†	9.3 (1.3)
LDL-C, mg/dL		−1.7 (3.0)†	−4.6 (2.9)†,‡	4.0 (2.9)
Triglycerides, mg/dL		−1.5 (8.2)	−3.1 (7.8)†	10.6 (7.8)
N		51	53	50
Fasting glucose, mg/dL		1.8 (1.3)†	4.1 (1.2)†	7.9 (1.2)

*Does not include rash observed with case of hypersensitivity (a separate term of rash was not reported for this case).
†$P < 0.2$, for comparison of lersivirine versus EFV.
‡N = 50.
Baseline for the fasting lipid parameters and fasting glucose was the last fasting measurement before day 1 dosing. Treatment-related AEs included all events related to investigational product (ie, lersivirine or EFV) and/or background antiretroviral drugs (ie, tenofovir DF/emtricitabine).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; DAIDS, division of acquired immunodeficiency syndrome; EFV, efavirenz; LSM, least squares mean; SAE, serious adverse event; SE, standard error; ULN, upper limit of normal.

Among the few patients who met the criteria for virologic failure and could undergo virologic assessment, the observed patterns of resistance for lersivirine-treated patients were distinct from those of first-generation NNRTIs and consistent with in vitro findings.[11,12]

Overall, in this trial, lersivirine exhibited an AE rate that was at least comparable to that of efavirenz, with few AEs leading to discontinuation. Compared with efavirenz, the incidence of both all-causality and treatment-related AEs of any severity was slightly lower in both lersivirine groups, although the incidence of serious AEs was similar between treatment groups. In total, grade 3 and 4 AEs were also reported at slightly lower frequencies in patients receiving lersivirine than those receiving efavirenz.

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Nausea was among the most common AEs and was experienced by a greater proportion of patients treated with either dose of lersivirine than with efavirenz. Lersivirine 500 mg seemed to be better tolerated than lersivirine 750 mg with regard to the lower overall rates of nausea that were observed. The large majority of nausea events occurring in either group were mild in severity (no grade 3 or 4 nausea) and self-limiting. Discontinuation due to a gastrointestinal AE (vomiting) occurred in one patient, in the lersivirine 750 mg group. It has been suggested that there may be an association between nausea and high lersivirine maximum plasma concentration, however ongoing investigation of the formulation aims to address this.

Although regimens containing efavirenz provide effective treatment options for treatment-naive patients, administration of efavirenz may be associated with neuropsychiatric AEs, rash, elevated transaminases, and hyperlipidemia, and may not be considered suitable in certain populations due to pharmacokinetic interactions and teratogenicity. In this trial, grade 2–4 neuropsychiatric events typically associated with efavirenz, such as abnormal dreams, nightmare, suicidal ideation, and vertigo, were less frequently reported with either dose of lersivirine than efavirenz in total, although incidences of individual events were low. Lersivirine also had a neutral effect on lipids between baseline and week 48. Numerically greater increases in all measured lipid parameters, including total cholesterol, LDL-C, HDL-C, and triglycerides, were observed in the efavirenz group than in either of the lersivirine groups (with the exception of triglycerides in the lersivirine 500 mg group). In addition, lersivirine was associated with a smaller increase in glucose relative to efavirenz.

In summary, results of this study demonstrate that lersivirine at doses of 500 mg or 750 mg once daily was effective when administered in combination with tenofovir DF/emtricitabine in treatment-naive individuals infected with HIV-1 and resulted in few AE-related treatment discontinuations. With the current safety and efficacy profile observed in this small Phase IIb estimation study, lersivirine may have the potential to provide an alternative to efavirenz where neuropsychiatric events or pharmacokinetic interactions are a concern. Before confirmation of these results in larger Phase III studies, potential modifications of the current lersivirine formulation will be explored to assess whether the observed rates of gastrointestinal-related AEs can be reduced.

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