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GENERIC DRUG NAME / COMPOUND NUMBER: Lersivirine / UK-453,061

PROTOCOL NO.: A5271015

PROTOCOL TITLE: A Phase 2b Multicenter, Randomized, Double-Blind, Comparative Trial of UK-453,061, in Combination With Tenofovir DF and Emtricitabine Versus Efavirenz in Combination With Tenofovir DF and Emtricitabine for the Treatment of Antiretroviral-Naive HIV-1 Infected Subjects

Study Center(s): Twenty nine centers took part in the study and randomized subjects. 1 each in Argentina and Mexico, 3 each in Australia, Canada, Italy, and Switzerland, 4 in Poland, 5 in United Kingdom, and 6 in South Africa.

Study Initiation Date and Final Completion Date: 11 February 2009 to 14 October 2011

Phase of Development: Phase 2

Note: Lersivirine is an investigational drug and not approved for use in any country.

Study Objective(s):

Primary Objective: The primary objective was to assess the efficacy of lersivirine when used in combination with tenofovir disoproxil fumarate (DF)/emtricitabine, as measured by the percentage of subjects with human immunodeficiency virus (Type 1) (HIV-1) ribonucleic acid (RNA) <50 copies/mL at 48 weeks.

Secondary Objectives:

- To assess efficacy as measured by the percentage of subjects with HIV-1 RNA <50 copies/mL at 24 and 96 weeks.
- To assess efficacy as measured by the percentage of subjects with HIV-1 RNA <400 copies/mL at 24, 48, and 96 weeks.
- To assess change from Baseline in $\log_{10}$ transformed HIV-1 RNA level at 24, 48, and 96 weeks.
- To assess safety and tolerability of lersivirine.
- To assess pharmacokinetic (PK) parameters of lersivirine; area under the concentration-time curve from time 0 to 24 hours (AUC_{24}), maximum plasma

concentration (C_{max}) and plasma concentration at the 24-hour time point (C_{24}) (PK sub-study).

METHODS

Study Design: This study was a 96-week, multicenter, multinational, double-blind, randomized, comparative, Phase 2b study to assess the antiviral activity and safety of lersivirine in combination with tenofovir DF/emtricitabine compared to efavirenz in combination with tenofovir DF/emtricitabine in HIV-1 infected, antiretroviral treatment-naive subjects.

Treatment with lersivirine and efavirenz was blinded, and treatment with tenofovir DF/emtricitabine was open label.

Subjects underwent a Screening visit approximately 6 weeks before dosing with study treatment. Those subjects found to be eligible were enrolled in the study and returned for scheduled visits at prespecified times (Table 1).

The Sponsor study team conducted the Week 24 interim analysis and the Week 48 primary analysis in an unblinded manner; however, investigators and subjects were to remain blinded to the treatments until all outcome analyses (efficacy and safety) had been completed and the database had been locked for the End-of-Study analysis at Week 96 with the following exception: subsequent to the primary analysis at Week 48, individuals completing 96 weeks of treatment could have been unblinded as long as all subjects had reached the Week 48 visit. The total duration of this study was 2 years, 8 months, and 4-days. The schedule of activities is presented in Table 1.

Table 1. Schedule of Activities

Procedures	Screening (Day -42 to Day -8)	Day 1[a]/ Randomization	Week 2[b]	Weeks 4, 8, 12, 16, 32, 40, 60, 72, 84[b]	Weeks 24, 48, 96 or Early Termination[b]
Informed consent	X				
Review inclusion/exclusion criteria	X	X[c]			
Medical history (including alcohol/smoking/exposure category)		X			
Physical examination/vital signs		X			X
Targeted physical examination/vital signs				X[d]	
Waist/hip lipodystrophy measurements		X			X
Assessment of signs, symptoms and adverse events		X	X	X	X
Concomitant medications	X	X	X	X	X
Chemistry	X	X	X	X[e]	X
Hematology	X	X	X	X[e]	X
Urinalysis	X	X	X	X	X
Fasting metabolic assessment (total cholesterol, HDL, LDL, triglycerides, glucose)		X			X
12-Lead electrocardiogram[f]	X	X	X	Weeks 4 and 8	X[g]
PK sampling[h]			X	X	Weeks 24 and 48
PK substudy[i]				Week 4	
Hepatitis screen (B core Ab, sAg, sAb, cAb)	X				
Hepatitis C virus RNA[j]		X		Week 12	X
Hepatitis C genotype		X[k]			
CD4+ (absolute and percentage)	X	X		X	X
Plasma HIV-1 RNA (viral load)[l]	X	X	X	X	X
Pregnancy test[m]	X	X	X	X	X
Plasma and PBMC (proviral DNA) samples[n]		X			X
Virus susceptibility (genotype, phenotype)	X[o]			X[p]	X[p, q]
Lersivirine phenotypic susceptibility		X[r]		X[p,s]	X[p, q]
Molecular profiling (host genotyping)		X[t]			
Free T4, TSH		X		Week 12	X
Assess dosing compliance			X[u]	X	X
Dispense study treatment		X		X	X[v]

Table 1. Schedule of Activities

Procedures	Screening (Day -42 to Day -8)	Day 1[a]/ Randomization	Week 2[b]	Weeks 4, 8, 12, 16, 32, 40, 60, 72, 84[b]	Weeks 24, 48, 96 or Early Termination[b]

Abbreviations: Ab = antibody; cAb = core antibody; CD = cluster of differentiation; DNA = deoxyribonucleic acid; HDL = high density lipoprotein; HIV-1 = human autoimmune deficiency virus Type 1; IEC = Independent Ethics Committee; IRB = Institutional Review Board; LDL =low density lipoprotein; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; QTc = corrected time between the start of the Q wave and the end of the T wave; RNA = ribonucleic acid; sAb = surface antibody; sAg = surface antigen; T4 = thyroid hormone 4; TSH = thyroid stimulating hormone.

a. Prior to dosing.
b. All visits had to occur within ±2 days.
c. Prior to randomization.
d. Head and neck, heart, lung, abdominal, brief neurologic, and skin.
e. Excluding Week 12.
f. If the QTc interval was >500 msec and/or the change in QTc interval was >60 msec from Baseline, the Principal Investigator was required to notify the Sponsor.
g. Excluding Week 96.
h. Two 5 mL PK samples, >60 minutes apart were required at Weeks 2 and 24. One 5 mL PK sample was required at Weeks 4, 8, 12, 16, 32, 40, and 48. Subjects participating in the PK substudy did not have the Week 4 PK sample taken.
i. Only at selected sites for subjects who consented to participate.
j. If hepatitis C antibody was positive at Screening, performed at Day 1, Weeks 12, 24, 48, and 96 or early termination.
k. If hepatitis C antibody was positive at Screening.
l. If a subject met ≥1 studydefined failure criteria, a confirmatory HIV-1 RNA level was obtained within 14 days of the first measurement.
m. For women of childbearing potential, serum pregnancy test at Screening and urine tests were performed at all visits. A positive urine test had to be confirmed with a serum test.
n. Two whole blood samples for plasma aliquots and PBMC (proviral DNA) preparation were collected at Day 1 and at Weeks 24, 48, 96, or at early termination upon treatment failure only, 1 whole blood sample for the preparation of two 1 mL plasma aliquots (frozen) and 1 whole blood (17 mL) sample at ambient temperature for PBMC preparation to be stored for future analysis.
o. Genotype only.
p. Only for subjects who required a second measurement of HIV-1 RNA to confirm treatment failure. Taken at the time of collection of the second HIV-1 RNA sample.
q. At the early termination visit only, for subjects discontinuing due to treatment failure. Samples for viral (phenotype and genotype) and lersivirine-phenotypic susceptibility were not collected if already collected at the time of confirmation of treatment failure (ie, when the second HIV-1 RNA sample was taken).
r. A 10 mL sample of blood for lersivirine phenotypic susceptibility was to be stored for future analysis.
s. Only for subjects with HIV-1 RNA >500 copies/mL at Week 8 (to be stored for future analysis).
t. Requiring separate IRB/IEC approval and subject consent.
u. Subjects participating in the PK substudy were reminded to self-administer lersivirine/matched placebo in the morning (rather than at bedtime) starting 7 days before the Week 4 visit.
v. Except Week 96 or early termination visit.

Number of Subjects (Planned and Analyzed): A total of 189 subjects (63 subjects per group) were planned to be randomized in a 1:1:1 ratio into each of the 3 treatment arms. 195 subjects were randomized; 4 in Argentina, 17 in Australia, 19 in Canada, 12 in Italy, 6 in Mexico, 42 in Poland, 65 in South Africa, 15 in Switzerland, and 15 in United Kingdom. A total of 294 subjects were screened from 9 countries. Ninety-nine (99) subjects failed Screening and were not randomized into the study (90 [90.9%] subjects did not meet entrance criteria; 6 [6.1%] subjects were no longer willing to participate in the study; and 3 [3.0%] subjects failed Screening due to "other" reasons). Of the 195 randomized subjects; 66, 66, and 63 subjects were randomized in the lersivirine 500 mg, lersivirine 750 mg, and efavirenz groups, respectively. Among the randomized subjects, a total of 193 subjects (65, 65, and 63 subjects in lersivirine 500 mg, lersivirine 750 mg, and efavirenz groups, respectively) received at least 1 dose of study medication and were included in the analyses.

Diagnosis and Main Criteria for Inclusion: The study included male or female subjects ≥18 years of age available for a follow-up period of at least 96 weeks, were required to have HIV-1 RNA viral load of >1,000 copies/mL and women of child bearing age with a negative urine pregnancy test at the Day 1 visit prior to receiving the first dose of study treatment and effective barrier contraception for men and women of child bearing potential.

Exclusion Criteria: Subjects with suspected or documented active, untreated HIV-1 related opportunist infection or other condition requiring acute therapy at the time of randomization, subjects on therapy for hepatitis B, subjects with acute Hepatitis B and/or C within 30 days of randomization, and subjects with absolute Cluster of differentiation (CD) 4+ count <200 cells/mm^3.

Study Treatment:

Subjects were randomized to 1 of the lersivirine groups or the efavirenz group in a 1:1:1 ratio, administered orally once daily (QD):

- Lersivirine 500 mg: lersivirine 500 mg+tenofovir DF 300 mg/emtricitabine 200 mg;
- Lersivirine 750 mg: lersivirine 750 mg+tenofovir DF 300 mg/emtricitabine 200 mg; or
- Efavirenz: efavirenz 600 mg+tenofovir DF 300 mg/emtricitabine 200 mg.

Blinded lersivirine, efavirenz and their corresponding matched placebo were provided as tablets. Open-label tenofovir DF/emtricitabine was provided as tablets, with each tablet containing 300 mg of tenofovir DF (which is equivalent to 245 mg of tenofovir disoproxil) and 200 mg of emtricitabine.

Subjects enrolled in the PK substudy were self-administered lersivirine or its matched placebo in the morning for 7 days prior to the Week 4 visit and for 1 day following the Week 4 visit. On the day following the Week 4 visit, a morning and evening dose of lersivirine or its matched placebo was taken to avoid a dose interval of >24 hours. Evening dosing of lersivirine or its matched placebo was continued for the remainder of the study. Efavirenz or its matched placebo was continued to be taken without food at bedtime and

tenofovir DF/emtricitabine was continued to be taken with food at the evening meal during the PK substudy and throughout the study.

The study was subject, investigator, and Sponsor blinded until the Week 24 analysis, after which the Sponsor study team was unblinded. The study remained subject and investigator blinded until all outcome analyses (efficacy and safety) were completed and the database was locked at Week 96 with the following exception: after the primary analysis at Week 48, individual subjects who completed 96 weeks of treatment were unblinded once all subjects reached the Week 48 visit. In addition, subjects could be unblinded if they were in a lersivirine treatment group that was discontinued following the Week 24 interim analyses.

Efficacy, Pharmacokinetic, and Pharmacodynamic Endpoints:

Primary Endpoint: The percentage of subjects with HIV-1 RNA <50 copies/mL at 48 weeks.

Secondary Endpoints:

- The percentage of subjects with HIV-1 RNA <50 copies/mL at 24 and 96 weeks.
- The percentage of subjects with HIV-1 RNA <400 copies/mL at 24, 48 and 96 weeks.
- The change from Baseline in $\log_{10}$ transformed HIV-1 RNA levels at 24, 48 and 96 weeks.
- The time-averaged difference (TAD) in $\log_{10}$ transformed HIV-1 RNA levels at 24, 48 and 96 weeks.
- The percentage of subjects with time to loss of virologic response 50 (TLOVR) virologic response at 24, 48 and 96 weeks. The TLOVR50 virologic response was derived based on Food and Drug Administration's (FDA) time to loss of virologic response algorithm.
- Outcomes of treatment (snapshot – based on HIV-1 RNA level and subject summary) at 24, 48 and 96 Weeks.
- Outcomes of treatment (TLOVR50) at 24, 48 and 96 Weeks.
- Change from Baseline in CD4+ counts (absolute and percentage) at 24, 48 and 96 weeks.
- Genotypic and phenotypic susceptibility at the time of treatment failure.
- Safety and tolerability as measured by spontaneous adverse event (AE) reports, serious adverse events (SAE) and safety laboratory tests.
- Lersivirine PK parameters AUC_{24}, C_{max} and C_{24} (PK sub-study).

Safety Evaluations: Safety evaluations included AE & SAE monitoring, clinical laboratory testing, electrocardiogram (ECG), physical examination, and vital signs measurement. These safety evaluations were conducted at different intervals as detailed in Table 1.

Statistical Methods:

Efficacy tables were based on the full analysis set (FAS) and per protocol analysis set as applicable. Safety tables were based on the safety population, which was defined the same as the FAS.

Full Analysis Set: The FAS consisted of all randomized subjects who received at least 1 dose of study medication. The "FAS analyzed as randomized" was referred as "Intent-to-Treat" (ITT).

Safety Analysis Set: Safety tables were based on the safety population, ie, safety analysis set, which was defined the same as the FAS, but analyzed as treated.

Efficacy Evaluations: Binary endpoints were subjects with HIV-1 RNA level <50 copies/mL at Week 24, 48, and 96; subjects with HIV-1 RNA level <400 copies/mL at Week 24, 48, and 96; and TLOVR50 responders at Week 24, 48, and 96.

The number and percentage of subjects with the binary response were tabulated. Two-sided 80% confidence intervals (CIs) were formed for the proportion of subjects with the binary response using the normal approximation to the binomial with continuity correction. Two-sided 80% CIs for the difference in the proportions between each lersivirine group and the efavirenz group were formed using the normal approximation to the binomial with continuity correction. The analysis was adjusted using the Cochran-Mantel-Haenszel (CMH) method based on the randomization strata.

Continuous endpoints were change from Baseline in $\log_{10}$ transformed HIV-1 RNA level at Week 24, 48, and 96; TAD in $\log_{10}$ transformed HIV-1 RNA level at Week 24, 48, and 96; change from Baseline in CD4+ cell count (absolute and percentage) at Week 24, 48, and 96.

Continuous endpoints were analyzed using an analysis of covariance model with the randomization stratification variables, continuous Baseline measurements, and treatment group as the main effects. The least squares mean (LSM) and its 80% CI were provided. Two-sided 80% CI for the treatment difference between each lersivirine group and the efavirenz group were presented.

The continuous endpoint was summarized descriptively (N, mean, standard deviation, coefficient of variation [CV], median, minimum and maximum).

The analysis of genotypes included an assessment of the HIV-1 reverse transcriptase (RT) encoding region sequenced (codons 1 through 305) compared with the assay reference sequence and with the pre-treatment genotype. From the reported RT variants, RAMs included in the International acquired immunodeficiency syndrome (AIDS) Society-United States of America resistance tables in addition to specific lersivirine Resistance-associated mutation (RAM) (based on pre-clinical data) were assessed. Genotypic and phenotypic susceptibility at the time of treatment failure were summarized descriptively through Week 96.

Pharmacokinetic Evaluations: The following PK parameters were determined for lersivirine for the PK substudy analysis set: C_{24}, C_{max} and the first time of its occurrence (T_{max}) were obtained directly from the recorded data. AUC_{24} was calculated using the linear-log trapezoidal method. The PK parameters C_{24}, C_{max}, T_{max} and AUC_{24} were summarized descriptively by treatment.

For AUC_{24}, C_{max}, and C_{24}, individual subject parameters were plotted by treatment group. Concentrations were listed and summarized descriptively using PK sampling time and treatment group. Individual subject and median profiles of the concentration-time data were to be plotted by treatment group. For summary statistics and median plots by sampling time, the nominal PK sampling time was used. For individual subject plots by time, the actual PK sampling time was used.

Safety Evaluations: Safety assessments (AEs, laboratory tests, vital signs and ECG) were listed and summarized in accordance with the Sponsor reporting standards.

RESULTS

Subject Disposition and Demography: Subject dispositions for Weeks 24, 48, and 96 are presented in Table 2. Demographic characteristics are presented in Table 3.

Table 2. Subject Disposition

Number (%) of Subjects	Week 24			Week 48			Week 96		
	Lersivirine 500 mg	Lersivirine 750 mg	Efavirenz	Lersivirine 500 mg	Lersivirine 750 mg	Efavirenz	Lersivirine 500 mg	Lersivirine 750 mg	Efavirenz
Screened 294									
Randomized	66	66	63	66	66	63	66	66	63
Treated	65	65	63	65	65	63	65	65	63
Ongoing at date of cutoff[a]/Completed[b]	54 (83.1)	53 (81.5)	55 (87.3)	53 (81.5)	53 (81.5)	54 (85.7)	49 (75.4)	44 (67.7)	49 (77.8)
Discontinued at date of cutoff[c]	11 (16.9)	12 (18.5)	8 (12.7)	12 (18.5)	12 (18.5)	9 (14.3)	16 (24.6)	21 (32.3)	14 (22.2)
Subject died[c]	0	1 (1.5)	0	0	1 (1.5)	0	0	1 (1.5)	0
Relation to study drug not defined									
Insufficient clinical response	4 (6.2)	4 (6.2)	1 (1.6)	5 (7.7)	4 (6.2)	1 (1.6)	5 (7.7)	7 (10.8)	4 (6.3)
Lost to follow-up	1 (1.5)	1 (1.5)	0	1 (1.5)	2 (3.1)	0	2 (3.1)	3 (4.6)	0
Subject no longer willing to participate in study	1 (1.5)	2 (3.1)	3 (4.8)	1 (1.5)	1 (1.5)	3 (4.8)	2 (3.1)	3 (4.6)	3 (4.8)
Other	1 (1.5)	1 (1.5)	0	1 (1.5)	1 (1.5)	0	0	1 (1.5)[d]	0
Withdrawn due to pregnancy	1 (1.5)	0	0	1 (1.5)	0	0	1 (1.5)	0	1 (1.6)
Related to study drug									
Adverse event	3 (4.6)	2 (3.1)	4 (6.3)	3 (4.6)	2 (3.1)	5 (7.9)	4 (6.2)	2 (3.1)	6 (9.5)
Not related to study drug									
Adverse event	0	1 (1.5)	0	0	1 (1.5)	0	2 (3.1)	4 (6.2)	0
Analyzed for efficacy									
FAS (ie, ITT)	65 (100)	65 (100)	63 (100.0)	65 (100)	65 (100)	63 (100)	65 (100)	65 (100)	63 (100)
TLOVR50 responders	54 (83.1)	54 (83.1)	55 (87.3)	51 (78.46)	51 (78.46)	54 (85.71)	NA	NA	NA
TLOVR50 failures	11 (16.9)	11 (16.9)	8 (12.7)	14 (21.54)	14 (21.54)	9 (14.29)	NA	NA	NA
Analyzed for PK	65 (100)	65 (100)	0	63 (96.9)	65 (100)	0	NA	NA	NA
PK sub-study	7 (10.8)	6 (9.2)	NA	7 (10.8)	6 (9.2)	NA	NA	NA	NA
Analyzed for safety									
AEs	65 (100)	64 (98.5)	63 (100.0)	65 (100)	64 (98.5)[e]	63 (100)	65 (100)	65 (100)	63 (100)
Laboratory data	64 (98.5)[f]	65 (100)	63 (100.0)	64 (98.5)[f]	65 (100)	63 (100)	64 (98.5)[f]	65 (100)	63 (100)
Vital signs	65 (100)	65 (100)	63 (100.0)	65 (100)	65 (100)	63 (100)	65 (100)	65 (100)	63 (100)
Electrocardiogram	65 (100)	65 (100)	63 (100.0)	65 (100)	65 (100)	63 (100)	65 (100)	65 (100)	63 (100)

Abbreviations: AE = adverse event; FAS = full analysis set; NA = not available; ITT = intent-to-treat, PK = pharmacokinetic; TLOVR = time to loss of virologic response.

Table 2. Subject Disposition

Number (%) of Subjects	Week 24			Week 48			Week 96		
	Lersivirine 500 mg	Lersivirine 750 mg	Efavirenz	Lersivirine 500 mg	Lersivirine 750 mg	Efavirenz	Lersivirine 500 mg	Lersivirine 750 mg	Efavirenz

a. Applicable for Week 24 and Week 48.
b. Applicable for Week 96.
c. One subject in lersivirine 750 mg group died due to a car accident which was considered to be not related to study treatment.
d. One subject in lersivirine 750 mg group was withdrawn due to imprisonment (not related to study treatment).
e. One subject did not experience any AE up to Week 48 and a blank AE record was not entered into the oracle clinical database. However, this subject was included in all the AE analyses.
f. One subject was lost to follow-up after Day 1, and had no on-study data. This subject was not analyzed for laboratory data.

Table 3. Demographic Characteristics- ITT

	Lersivirine 500 mg	Lersivirine 750 mg	Efavirenz
Number of subjects	65	65	63
Gender, n (%)			
Female	16 (24.6)	19 (29.2)	17 (27.0%)
Male	49 (75.4)	46 (70.8)	46 (73.0%)
Age (years)			
Mean (SD)	36.5 (8.0)	35.7 (8.2)	36.3 (8.7)
Range	24-61	22-62	21-61
Race, n (%)			
White	40 (61.5)	38 (58.5)	34 (54.0)
Black	18 (27.7)	22 (33.8)	24 (38.1)
Asian	6 (9.2)	0	2 (3.2)
Other	1 (1.5)	5 (7.7)	3 (4.8)

Abbreviations: ITT = intent-to-treat; n = number of subjects; SD = standard deviation.

Efficacy and Pharmacokinetic Results:

Efficacy Results:

Primary Efficacy Evaluations:

The Percentage of Subjects with HIV-1 RNA Level <50 copies/mL at Week 48: The percentage of subjects with HIV-1 RNA level <50 copies/mL at Week 48 (snapshot non-completer = failure; ITT) was similar between each lersivirine group and efavirenz. The statistical analysis of the difference in the percentage of subjects with HIV-1 RNA level <50 copies/mL at Week 48, in the ITT population is presented in Table 4.

Table 4. Statistical Analysis (CMH) of Difference in the Percentage of Subjects With HIV-1 RNA Level <50 copies/mL at Week 48 - ITT - Non-Completer = Failure[a]

	Lersivirine 500 mg	Lersivirine 750 mg	Efavirenz
N	65	65	63
n	51	51	54
%	78.5	78.5	85.7
Difference (SE)[b], (%)	-8.6 (6.7)	-7.9 (6.5)	NA
80% CI for difference, (%)	-18.1, 0.8	-17.0, 1.2	NA

Group A included European Union, Latin America, Australia, and Canada and Group B included South Africa.
Abbreviations: CI = confidence interval; CMH = Cochran-Mantel-Haenszel; HIV = human immunodeficiency virus; ITT = intent-to-treat; n = number of subjects with HIV-1 RNA level <50 copies/mL at Week 48; N = number of subjects in the ITT population; NA = not applicable; RNA = ribonucleic acid; SE = standard error.
a. Missing Data Imputation: Subjects who were discontinued from the study, were lost to follow-up, or had missing HIV-1 RNA level data at 48 weeks were considered to have HIV-1 RNA levels ≥50 copies/mL. Such subjects were also referred to as noncompleters = failures.
b. Cochran-Mantel-Haenszel estimates adjusted for randomization stratification variables of Screening HIV-1 RNA level (<100,000 copies/mL) and geographic region (Group A versus B). Difference is the percentage difference between the lersivirine and efavirenz groups.

Secondary Efficacy Evaluations:

The Percentage of Subjects with HIV-1 RNA Level <50 copies/mL at Week 24 and Week 96: The percentages of subjects with HIV-1 RNA level <50 copies/mL at Week 24 and Week 96 is presented in Table 5.

At Week 24, the lower limits of the two-sided 80% CI for the differences in the percentage of subjects with HIV-1 RNA level <50 copies/mL at Week 24 were -13.9% (lersivirine 500 mg versus efavirenz) and -13.4% (lersivirine 750 mg versus efavirenz), which were above the pre-specified margin of -20%, thus meeting the criterion of non-inferiority (ie, meeting the main objective of the Week 24 interim analysis).

At Week 96, the 2-sided 80% CIs for the difference in the percentage of subjects with HIV-1 RNA level <50 copies/mL at Week 96 were (-19.6%, 1.4%) (lersivirine 500 mg versus efavirenz) and (-21.4%, -0.5%) (lersivirine 750 mg versus efavirenz). These results indicated that the antiviral efficacy of both dose groups of lersivirine studied can be considered broadly comparable to that of efavirenz through 96 weeks in the context of this Phase 2b estimation study.

Table 5. Statistical Analysis of Difference in Percentage of Subjects With HIV-1 RNA Level <50 Copies/mL at Week 24 and Week 96 – ITT – Non-Completer=Failure[a]

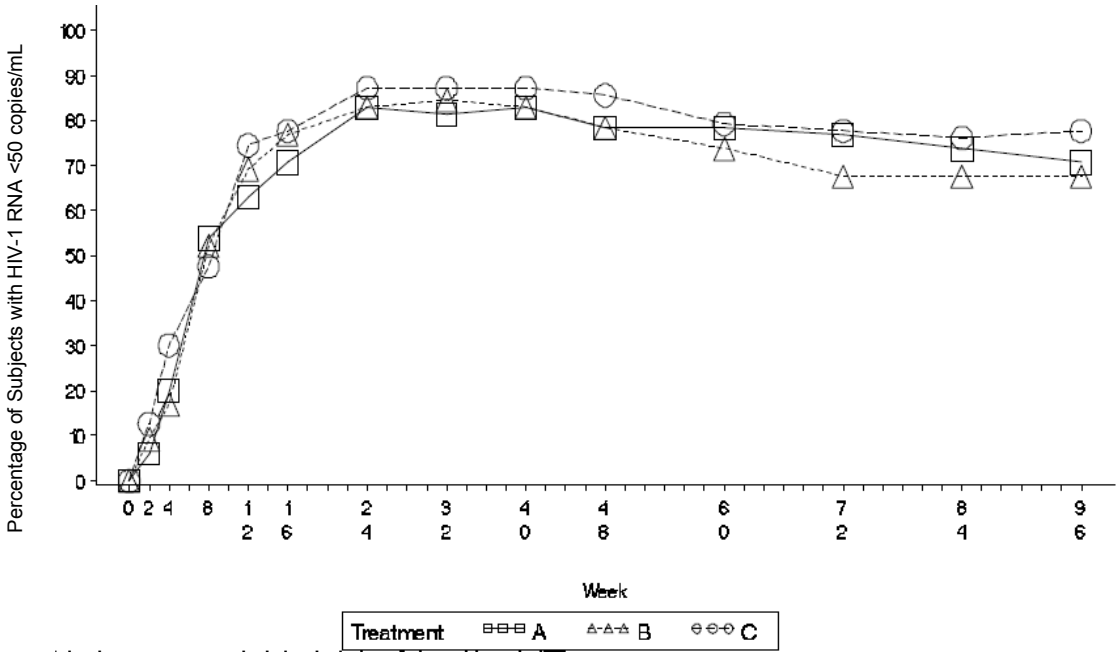
	Lersivirine 500 mg	Lersivirine 750 mg	Efavirenz
Week 24			
N	65	65	63
n	54	54	55
%	83.1	83.1	87.3
Difference (SE)[b], (%)	-5.0 (6.3)	-4.6 (6.2)	NA
80% CI for difference (%)	-13.9, 3.8	-13.4, 4.1	NA
Week 96			
N	65	65	63
n	46	44	49
%	70.8	67.7	77.8
Difference (SE)[b], (%)	-9.1 (7.5)	-11.0 (7.6)	NA
80% CI for difference, (%)	-19.6, 1.4	-21.4, -0.5	NA

Group A included European Union, Latin America, Australia, and Canada and Group B included South Africa.
Abbreviations: CI = confidence interval; HIV-1 = human immunodeficiency virus Type 1; ITT = intent-to-treat; n = number of subjects with HIV-1 RNA level <50 copies/mL; N = number of subject in each treatment group; NA = not applicable; RNA = ribonucleic acid; SE = standard error.
a. Missing Data Imputation: Subjects who were discontinued from the study, were lost to follow-up, or had missing HIV-1 RNA level data at a visit of interest (ie, 24 and 96 weeks, respectively) were considered to have HIV-1 RNA levels ≥50 copies/mL. Such subjects were also referred to as noncompleters = failures.
b. Cochran-Mantel-Haenszel estimates adjusted for randomization stratification variables of Screening HIV-1 RNA level (<100,000 versus ≥100,000 copies/mL) and geographic region (Groups A versus B). Difference was the percentage difference between lersivirine and efavirenz.

The percentage of subjects with HIV-1 RNA Level <50 copies/mL through Week 96 (non-completer = failure; ITT) is presented in Figure 1. Overall, response rates (percentage

of subjects with HIV-1 RNA level <50 copies/mL) were broadly similar between each lersivirine group and efavirenz across visits.

Figure 1. Line Plot of Percentage of Subjects with HIV-1 RNA Level <50 copies/mL by Visit – ITT Non-Completer = Failure



Treatment groups: A = lersivirine 500 mg (65 subjects); B = lersivirine 750 mg (65 subjects); C = efavirenz (63 subjects). Missing Data Imputation: Subjects who were discontinued from the study, were lost to follow-up, or had missing HIV-1 RNA level data at a visit of interest were considered to have HIV-1 RNA levels ≥50 copies/mL. Such subjects were also referred to as non-completers = failures.
Abbreviations: HIV-1 = human immunodeficiency virus Type 1; ITT = intent-to-treat; RNA = ribonucleic acid.

The percentage of subjects with HIV-1 RNA <400 copies/mL at 24, 48 and 96 weeks: Results of the analysis of the difference in the percentage of subjects with HIV-1 RNA level <400 copies/mL at Week 24, 48, and 96 in the ITT population are presented in Table 6.

Table 6. Statistical Analysis of Difference in Percentage of Subjects With HIV-1 RNA Level <400 copies/mL at Week 24, 48 and 96 – ITT – Non-Completer=Failure[a]

	Lersivirine 500 mg	Lersivirine 750 mg	Efavirenz
Week 24			
N	65	65	63
n	55	57	57
%	84.6	87.7	90.5
Difference (SE)[b], (%)	-6.4 (6.0)	-2.8 (5.6)	NA
80% CI, %	-14.8, 2.1	-10.7, 5.2	NA
Week 48			
N	65	65	63
n	53	52	54
%	81.5	80.0	85.7
Difference (SE)[b], (%)	-5.7 (6.5)	-6.3 (6.5)	NA
80% CI for difference, (%)	-14.9, 3.4	-15.4, 2.8	NA
Week 96			
N	65	65	63
n	48	44	49
%	73.8	67.7	77.8
Difference (SE)[b], (%)	-6.0 (7.4)	-11.0 (7.6)	NA
80% CI for difference, (%)	-16.3, 4.3	-21.4, -0.5	NA

Group A included European Union, Latin America, Australia, and Canada and Group B included South Africa.
Abbreviations: CI=confidence interval; HIV=human immunodeficiency virus; ITT=intent-to-treat; N=number of subjects in the ITT; n=number of subjects with HIV-1 RNA level <400 copies/mL; NA=not applicable; RNA=ribonucleic acid; SE=standard error.
a. Missing Data Imputation: Subjects who were discontinued from the study, were lost to follow-up, or had missing HIV-1 RNA level data at a visit of interest (ie, 24, 48 and 96 weeks, respectively) were considered to have HIV-1 RNA levels ≥400 copies/mL. Such subjects were also referred to as non-completers = failures.
b. Cochran-Mantel-Haenszel estimates adjusted for randomization stratification variables of Screening HIV-1 RNA level (<100,000 versus ≥100,000 copies/mL) and geographic region (Groups A versus B). Difference is the percentage difference between lersivirine and efavirenz.

Change From Baseline in Log_{10} Transformed HIV-1 RNA Level at Week 24, 48 and 96:

Results of the statistical analysis of the change from Baseline in log_{10} HIV-1 RNA level at Week 24, 48, and 96 are presented in Table 7.

Table 7. Statistical Analysis of Change From Baseline in log_{10} Transformed HIV-1 RNA Level (log_{10} copies/mL) at Week 24, 48 and 96 – ITT – Missing Data Method 1[a]

	Lersivirine 500 mg	Lersivirine 750 mg	Efavirenz
Week 24			
N	65	65	63
LSM (SE)	-2.41 (0.14)	-2.55 (0.14)	-2.63 (0.14)
LSM Difference (SE)	0.22 (0.18)	0.08 (0.18)	NA
80% CI	-0.0, 0.5	-0.1, 0.3	NA
Week 48			
N	65	65	63
LSM (SE)	-2.25 (0.16)	-2.20 (0.16)	-2.42 (0.16)
LSM difference (SE)	0.17 (0.21)	0.22 (0.21)	NA
80% CI	-0.1, 0.4	-0.1, 0.5	NA
Week 96			
N	65	65	63
LSM (SE)	-2.06 (0.18)	-1.84 (0.18)	-2.18 (0.18)
LSM difference (SE)	0.11 (0.24)	0.34 (0.24)	NA
80% CI	-0.20, 0.42	0.03, 0.64	NA

LSM was adjusted for randomization stratification variables of Screening HIV-1 RNA level (<100,000 versus ≥100,000 copies/mL) and geographic region (Group A versus B) and the Baseline log_{10} HIV-1 RNA level.
The Baseline for log_{10} HIV-1 RNA was calculated as the mean of all predose measurements.
Group A included European Union, Latin America, Australia, and Canada and Group B included South Africa.
Abbreviations: CI = confidence interval; HIV = human immunodeficiency virus Type 1; ITT = intent-to-treat; LSM = least squares mean; N = number of subjects in the ITT population; NA = not applicable; RNA = ribonucleic acid; SE = standard error.
a. Imputation Method 1: Subjects who discontinued the study before a visit of interest (ie, Week 24, Week 48 and Week 96, respectively) had their final values imputed as Baseline. For subjects who had not discontinued and the observation at a visit of interest was missing, then the last observation carried forward was used. No change from Baseline was imputed for subjects with missing Baseline or no HIV-1 RNA level assessment on treatment.

Time-Averaged Difference (TAD) in Log_{10} Transformed HIV-1 RNA Levels at Week 24, 48 and 96.

Results of the statistical analysis of the TAD in log_{10} transformed HIV-1 RNA level at Week 24, 48 and 96 are presented in Table 8.

Table 8. Statistical Analysis of TAD (log_{10} copies/mL) in Log_{10} Transformed HIV-1 RNA Levels at Week 24, 48 and 96 – ITT

	Lersivirine 500 mg	Lersivirine 750 mg	Efavirenz
Week 24			
N	65	65	63
LSM (SE)	-2.13 (0.12)	-2.21 (0.12)	-2.34 (0.12)
LSM Difference (SE)	0.21 (0.16)	0.14 (0.16)	NA
80% CI	0.0, 0.4	-0.1, 0.3	NA
Week 48			
N	65	65	63
LSM (SE)	-2.15 (0.15)	-2.12 (0.15)	-2.31 (0.15)
LSM difference (SE)	0.16 (0.20)	0.18 (0.20)	NA
80% CI	-0.1, 0.4	-0.1, 0.4	NA
Week 96			
N	65	65	63
LSM (SE)	-2.03 (0.18)	-1.78 (0.18)	-2.12 (0.17)
LSM difference (SE)	0.08 (0.23)	0.34 (0.23)	NA
80% CI	-0.21, 0.38	0.04, 0.64	NA

Group A included EU, Latin America, Australia, and Canada and Group B included South Africa.
LSM was adjusted for randomization stratification variables of Screening HIV-1 RNA level (<100,000 versus ≥100,000 copies/mL) and geographic region (Group A versus B) and the Baseline log_{10} HIV-1 RNA level.
The Baseline for log_{10} HIV-1 RNA was calculated as the mean of all predose measurements.
Abbreviations: CI = confidence interval; EU = European Union; HIV-1 = human immunodeficiency virus Type 1; ITT = intent-to-treat; LSM = least squares mean; N = number of subjects in the ITT population; NA = not applicable; SE = standard error; TAD = time-averaged difference.

TLOVR50 Response at Week 24, 48, and 96:

Results of the analysis of the difference in the percentage of TLOVR50 responders at Week 24, 48, and 96, in the ITT population (noncompleter = failure) are presented in Table 9.

Table 9. Statistical Analysis (CMH) of Difference in Percentage of TLOVR50 Responders at Week 24, 48, and 96 - ITT - Non-Completer = Failure[a]

	Lersivirine 500 mg	Lersivirine 750 mg	Efavirenz
Week 24			
N	65	65	63
n	54	54	55
%	83.1	83.1	87.3
Difference (SE)[b], (%)	-5.0 (6.3)	-4.6 (6.2)	NA
80% CI for difference (%)	-13.9, 3.8	-13.4, 4.1	NA
Week 48			
N	65	65	63
n	51	51	54
%	78.5	78.5	85.7
Difference (SE)[b], (%)	-8.6 (6.7)	-7.9 (6.5)	NA
80% CI for difference, (%)	-18.1, 0.8	-17.0, 1.2	NA
Week 96			
N	65	65	63
n	44	44	48
%	67.7	67.7	76.2
Difference (SE)[b], (%)	-10.5 (7.8)	-9.3 (7.7)	NA
80% CI for difference, (%)	-21.2, 0.3	-19.9, 1.4	NA

Group A included European Union, Latin America, Australia, and Canada and Group B included South Africa.
Abbreviations: CI = confidence interval; CMH = Cochran-Mantel-Haenszel; HIV = human immunodeficiency virus Type 1; ITT = intent-to-treat; n = number of TLOVR50 responders; N = number of subjects in the ITT population; NA = not applicable; RNA = ribonucleic acid; SE = standard error.
a. TLOVR50 responders were derived using the FDA's time to loss of virologic response algorithm (see description below). Missing Data Imputation: Subjects who were discontinued from the study, were lost to follow-up, or had missing HIV-1 RNA level data at a visit of interest (ie, 24, 48 and 96 weeks, respectively) were considered a TLOVR50 failure. Such subjects were also referred to as non-completers = failures.
b. CMH estimates adjusted for randomization stratification variables of Screening HIV-1 RNA level (<100,000 copies/mL versus ≥100,000 copies/mL) and geographic region (Group A versus B). Difference was the percentage difference between the lersivirine and efavirenz groups.

Outcomes of Treatment: A TLOVR50 failure was defined as follows:

- If a subject did not have a confirmed HIV-1 RNA level of <50 copies/mL for 2 consecutive tests before the following events, then the subject was considered to have failed at Time 0 (ie, Day 1) due to the following reasons:
  - Death;
  - Permanent discontinuation of the study treatment or loss to follow-up;
  - Last available visit ("Visit" means a visit with an observed HIV-1 RNA level. HIV-1 RNA level data from all available visits, including unplanned visits, were included for the calculation.);
  - Meeting the protocol-defined treatment-failure criteria.

- If a subject had a confirmed HIV-1 RNA level of <50 copies/mL for 2 consecutive tests, the time of failure was the earliest time of:
  - Death;
  - Permanent discontinuation of the study treatment or loss to follow-up;
  - Meeting the protocol-defined treatment-failure criteria;
  - Confirmed HIV-1 RNA level ≥50 copies/mL, defined as HIV-1 RNA level from 2 consecutive tests ≥50 copies/mL or test ≥50 copies/mL followed by permanent discontinuation of study treatment or loss to follow-up.
- If the time of TLOVR50 failure defined above was immediately preceded by a single missed scheduled visit or multiple consecutive missed scheduled visits, then the time of TLOVR50 failure was replaced by the first time of a missed visit.
- If a subject did not have any postdose HIV-1 RNA measurement, then the subject was considered a TLOVR50 failure at Time 0 (ie, Day 1).

Subjects were classified as either a TLOVR50 failure or TLOVR50 responder at a visit of interest (ie, Week 24, Week 48 and Week 96, respectively). Any subject who discontinued prematurely or had a missing value was considered a TLOVR50 failure.

There are 2 Outcomes of Treatment summaries: One based on snapshot (ie, HIV-1 RNA level and subject summaries), and the other based on TLOVR50 outcomes; results are presented in Table 10, Table 11.

Table 10. Outcomes of Treatment (Snapshot - Based on HIV-1 RNA Level and Subject Summary) at Week 24, 48, and 96 – ITT – Non Completer=Failure[a]

Outcome, n (%)	Lersivirine 500 mg N=65	Lersivirine 750 mg N=65	Efavirenz N=63
Week 24			
Subjects who completed the Week 24 visit	57 (87.7)	60 (92.3)	57 (90.5)
HIV-1 RNA level <50 copies/mL at Week 24	54 (83.1)	54 (83.1)	55 (87.3)
HIV-1 RNA level ≥50 copies/mL at Week 24	2 (3.1)	3 (4.6)	2 (3.2)
Other[b]	1 (1.5)	3 (4.6)	0
Subjects who died or discontinued before Week 24	8 (12.3)	5 (7.7)	6 (9.5)
Death	0	0	0
Discontinuation before Week 24	8 (12.3)	5 (7.7)	6 (9.5)
Due to insufficient clinical response	3 (4.6)	1 (1.5)	0
Due to AE	2 (3.1)	3 (4.6)	4 (6.4)
Due to other reason	3 (4.6)	1 (1.5)	2 (3.2)
Week 48			
Subjects who completed the Week 48 Visit	54 (83.1)	55 (84.6)	55 (87.3)
HIV-1 RNA level <50 copies/mL at Week 48	51 (78.5)	51 (78.5)	54 (85.7)
HIV-1 RNA level ≥50 copies/mL at Week 48	3 (4.6)	2 (3.1)	1 (1.6)
Other[c]	0	2 (3.1)	0
Subjects who died or discontinued before Week 48	11 (16.9)	10 (15.4)	8 (12.7)
Death	0	1 (1.5)	0
Discontinuations before Week 48	11 (16.9)	9 (13.9)	8 (12.7)
Due to insufficient clinical response	4 (6.2)	4 (6.2)	1 (1.6)
Due to AEs	3 (4.6)	3 (4.6)	4 (6.4)
Due to other reasons	4 (6.2)	2 (3.1)	3 (4.8)
Week 96			
Subjects who completed the Week 96 Visit	49 (75.4)	44 (67.7)	49 (77.8)
HIV-1 RNA level <50 copies/mL at Week 96	46 (70.8)	44 (67.7)	49 (77.8)
HIV-1 RNA level ≥50 copies/mL at Week 96	3 (4.6)	0	0
Subjects who died or discontinued before Week 96	16 (24.6)	21 (32.3)	14 (22.2)
Death	0	1 (1.5)	0
Discontinuations before Week 96	16 (24.6)	20 (30.8)	14 (22.2)
Due to insufficient clinical response	5 (7.7)	7 (10.8)	4 (6.4)
Due to AEs	6 (9.2)	6 (9.2)	6 (9.5)
Due to other reasons	5 (7.7)	7 (10.8)	4 (6.4)

If there were multiple reasons for discontinuation, then the following order of preference was used: death > insufficient clinical response > AE > other.
Abbreviations: AE = adverse event; HIV = human immunodeficiency virus Type 1; ITT = intent-to-treat; n = number of subjects meeting the criterion; N = number of subjects in the ITT population; RNA = ribonucleic acid.
a. Missing Data Imputation: Subjects who were discontinued from the study, were lost to follow-up, or had missing HIV-1 RNA level data at a visit of interest (ie, 24, 48 and 96 weeks, respectively) were considered to have HIV-1 RNA levels ≥50 copies/mL. Such subjects were also referred to as noncompleters = failures.
b. "Other" included subjects who completed the Week 24 visit but discontinued or died or had missing HIV-1 RNA level within the visit Week 24 window.
c. 'Other' included a subject who completed the Week 48 visit and had an HIV-1 RNA level <50 copies/mL but discontinued or died, or who completed the Week 48 visit but had a missing HIV-1 RNA level within the Week 48 visit window.

Table 11. Outcomes of Treatment (TLOVR50) at Week 24, 48, and 96 – ITT - Non Completer=Failure[a]

Outcome, n (%)	Lersivirine 500 mg N=65	Lersivirine 750 mg N=65	Efavirenz N=63
Week 24			
Subjects who completed the Week 24 visit	57 (87.7)	60 (92.3)	57 (90.5)
TLOVR50 responders at Week 24	54 (83.1)	54 (83.1)	55 (87.3)
TLOVR50 failures at Week 24	3 (4.6)	6 (9.2)	2 (3.2)
TLOVR50 rebounder	0	1 (1.5)	1 (1.6)
TLOVR50 never-suppressed	2 (3.1)	4 (6.2)	1 (1.6)
TLOVR50 non-responder	0	0	0
Other	1 (1.5)	1 (1.5)	0
Subjects who died or discontinued prematurely before Week 24	8 (12.3)	5 (7.7)	6 (9.5)
Death	0	0	0
Discontinuations before Week 24	8 (12.3)	5 (7.7)	6 (9.5)
Due to TLOVR50 virologic failure	3 (4.6)	1 (1.5)	0
TLOVR50 rebounder	0	0	0
TLOVR50 non-responder	3 (4.6)	1 (1.5)	0
Due to adverse events	2 (3.1)	3 (4.6)	4 (6.4)
Due to other reasons	3 (4.6)	1 (1.5)	2 (3.2)
Week 48			
Subjects who completed the Week 48 visit	54 (83.1)	55 (84.6)	55 (87.3)
TLOVR50 responders at Week 48	51 (78.5)	51 (78.5)	54 (85.7)
TLOVR50 failures at Week 48	3 (4.6)	4 (6.2)	1 (1.6)
Rebounder	3 (4.6)	1 (1.5)	1 (1.6)
Never-suppressed	0	1 (1.5)	0
Non-responder	0	0	0
Other[b]	0	2 (3.1)	0
Subjects who died or discontinued before Week 48	11 (16.9)	10 (15.4)	8 (12.7)
Death	0	1 (1.5)	0
Discontinuations before Week 48	11 (16.9)	9 (13.9)	8 (12.7)
Due to TLOVR50 virologic failures	4 (6.2)	5 (7.7)	2 (3.2)
Rebounder	0	1 (1.5)	1 (1.6)
Never-suppressed	1 (1.5)	3 (4.6)	1 (1.6)
Non-responder	3 (4.6)	1 (1.5)	0
Due to AEs	3 (4.6)	3 (4.6)	4 (6.4)
Due to other reasons	4 (6.2)	1 (1.5)	2 (3.2)
Week 96			
Subjects who completed the Week 96 visit	49 (75.4)	44 (67.7)	49 (77.8)
TLOVR50 responders at Week 96	44 (67.7)	44 (67.7)	48 (76.2)
TLOVR50 failures at Week 96	5 (7.7)	0	1 (1.6)
Rebounder	5 (7.7)	0	1 (1.6)
Subjects who died or discontinued before Week 96	16 (24.6)	21 (32.3)	14 (22.2)
Death	0	1 (1.5)	0
Discontinuations before Week 96	16 (24.6)	20 (30.8)	14 (22.2)
Due to TLOVR50 virologic failures	6 (9.2)	8 (12.3)	6 (9.5)
Rebounder	2 (3.1)	6 (9.2)	5 (7.9)
Nonresponder	4 (6.2)	2 (3.1)	1 (1.6)
Due to AEs	5 (7.7)	3 (4.6)	5 (7.9)
Due to other reasons	5 (7.7)	9 (13.9)	3 (4.8)

Table 11. Outcomes of Treatment (TLOVR50) at Week 24, 48, and 96 – ITT - Non Completer=Failure[a]

Outcome, n (%)	Lersivirine 500 mg N=65	Lersivirine 750 mg N=65	Efavirenz N=63

If a subject had multiple reasons for TLOVR50 failure then the following order of preference was used: death > TLOVR50 virologic failure (rebounder > never-suppressed > non-responder) > discontinuation due to AE > discontinuation due to other reasons.
Abbreviations: AE = adverse event; HIV = human immunodeficiency virus Type 1; ITT = intent-to-treat; n = number of subjects meeting the criterion; N = number of subjects in the ITT population; RNA = ribonucleic acid; TLOVR = time to loss of virologic response.
a. TLOVR50 responders were derived using the FDA's time to loss of virologic response algorithm. Missing Data Imputation: Subjects who were discontinued from the study, were lost to follow-up, or had missing HIV-1 RNA level data at a visit of interest (ie, 24, 48 and 96 weeks, respectively) were considered a TLOVR50 failure. Such subjects were also referred to as noncompleters = failures.
b. 'Other' included a subject who completed the Week 48 visit and had an HIV-1 RNA level <50 copies/mL but discontinued or died, or who completed the Week 48 visit and had a missing HIV-1 RNA level within the Week 48 visit window.

Change From Baseline in CD4+ Cell Counts (Absolute and Percentage) at Week 24, 48 and 96:

Results of the statistical analysis of absolute CD4+ cell count at Week 24, 48 and 96 are presented in Table 12. Results of the statistical analysis of percentage CD4+ cell count at Week 24, 48 and 96 are not presented.

Table 12. Statistical Analysis of the Change From Baseline in CD4+ Cell Count (cells/µL) (Absolute) at Week 24, 48 and 96 – LOCF - ITT

	Lersivirine 500 mg	Lersivirine 750 mg	Efavirenz
Week 24			
N	65	65	63
LSM (SE)	143.4 (17.3)	166.3 (17.0)	139.6 (17.2)
LSM Difference (SE)	3.8 (23.4)	26.7 (23.3)	NA
80% CI	-26.3, 33.9	-3.3, 56.7	NA
Week 48			
N	65	65	63
LSM (SE)	194.2 (20.3)	199.4 (19.8)	196.7 (20.1)
LSM difference (SE)	-2.4 (27.3)	2.7 (27.3)	NA
80% CI	-37.6, 32.7	-32.4, 37.8	NA
Week 96			
N	65	65	63
LSM (SE)	204.5 (23.2)	224.7 (22.7)	214.6 (23.0)
LSM difference (SE)	-10.1 (31.3)	10.2 (31.3)	NA
80% CI	-50.4, 30.2	-30.0, 50.3	NA

Group A included EU, Latin America, Australia, and Canada and Group B included South Africa.
Baseline absolute CD4+ cell count was calculated as the mean of all predose measurements.
LSM was adjusted for randomization stratification variables of Screening HIV-1 RNA level (<100,000 versus ≥100,000 copies/mL), geographic region (Group A versus B), and the Baseline absolute CD4+ cell count.
LSM difference is the difference between each of the lersivirine groups and efavirenz.
Abbreviations: CD = cluster of differentiation; CI = confidence interval; EU = European Union; HIV-1 = human immunodeficiency virus Type 1; ITT = intent-to-treat; LOCF = last observation carried forward; LSM = least squares mean; N = number of subjects in the ITT population; NA = not applicable; RNA = ribonucleic acid; SE = standard error.

Genotypic and Phenotypic Findings:

The on-treatment virology findings are summarized in Table 13.

Table 13. Treatment-Emergent Nucleoside and Non-Nucleoside Reverse Transcriptase Inhibitor Resistance-Associated Mutations and Fold-Change of Drug Susceptibility through Week 96 in Evaluated Failure Population

Serial Number	Failure Category/Test Day	Genotype	IC_{50} Fold-Change[a]			
			Lersivirine	Efavirenz	Emtricitabine	Tenofovir
Lersivirine 500 mg						
1	Rebound/723	NM	1.19/2.25	1.10/1.28	1.22/0.98	0.96/1.13
2[b]	Rebound/337	NM	NR/0.81	NR/0.61	NR/1.25	NR/1.03
3	Nonresponse/74	M184M/I/V, K101E, V108I, H221H/Y	1.54/56	0.65/3.94	0.95/>MAX[c]	0.73/0.58
4[d]	Nonresponse/ 122	M184M/I/V, [M230M/I], Y188Y/H, F227F/L, L234L/I	4.13/36	2.00/1.62	1.04/>MAX[c]	0.99/0.50
5	Nonresponse/ 132	M184V, V90I, F227C	2.12/69	1.43/5.23	1.37/>MAX[c]	1.31/0.61
Lersivirine 750 mg						
1	Rebound/559	NM	1.29/1.26	0.9/0.95	0.85/0.91	1.11/1.29
2	Rebound/193	NM	0.38/0.53	0.51/0.51	0.92/1.17	0.73/0.84
3	Rebound/381	NM	1.21/1.30	0.81/0.71	1.11/1.34	0.93/1.07
4	Rebound/479	NM	1.65/1.25	0.93/1.01	1.04/1.18	0.94/0.71
5	Nonresponse /421	M184V, V106M, F227L	0.83/114	0.42/11	1.01/>MAX[c]	0.7/0.36
6	Rebound/538	NM	1.66/1.33	1.17/1.11	0.88/1.21	0.89/0.91
7	Rebound/113	NM	0.83/0.93	0.86/0.87	1.0/0.93	0.76/0.82
8[b]	Nonresponse /140	NM	NA/3.63	NA/2.31	NA/0.80	NA/1.11
Efavirenz						
1	Rebound/520	NM	0.52/0.76	0.52/0.69	0.81/0.94	0.81/1.4
2	Rebound/360	NM	0.66/0.75	0.33/0.40	0.93/1.15	0.91/1.04
3	Rebound/500	NM	0.71/0.90	0.85/0.90	1.15/1.27	0.95/1.39
4	Rebound/598	NR	1.58/0.99	1.07/0.77	1.36/0.84	0.90/1.58
5	Nonresponse /109	K103N	0.61/1.33	0.68/11.0	0.92/1.28	0.99/1.27
6	Non-virologic failure/71	NM	0.50/0.76	0.59/0.59	1.09/0.96	0.78/0.94

Abbreviations: HIV-1 = human immunodeficiency virus Type 1; IC 50 = half maximal inhibitory concentration; MAX = maximum; NA = not available; NM = no mutation; NR=not reportable; RAM=resistance-associated mutation; TLOVR = time to loss of virologic response.

a. Fold-change to wild-type reference strain.
b. TLOVR50 Evaluated Failure without Baseline phenotype.
c. The virus is highly resistant to the drug, with IC 50 above the upper limit for the assay.
d. Virus from this subject had the NNRTI RAM M230M/I present at screening but not on-treatment.

Pharmacokinetic Results: PK parameters are summarized descriptively in Table 14. Lersivirine peak plasma concentrations were achieved within 0.483 to 2.00 hours postdose (median T_{max}=1.00 hour) for the lersivirine 500 mg group and 0.500 to 8.00 hours postdose (median T_{max}=2.00 hours) for the lersivirine 750 mg group.

Geometric means for C_{max} were 1056 and 1354 ng/mL for the lersivirine 500 mg and 750 mg groups respectively, and declined gradually over time with C_{24} of at least 5-fold the protein-adjusted in vitro 90% inhibitory concentration (IC_{90}; 5.3 ng/mL) for wild-type virus with lersivirine. The C_{24} ranged between 26.9 and 178 ng/mL for the lersivirine 500 mg group and between 43.4 and 101 ng/mL for the lersivirine 750 mg group.

Inter-subject variabilities in lersivirine exposures based on geometric CV% values were moderate, with AUC_{24} and C_{max} CV% values of 30% and 41%, respectively for the lersivirine 500 mg group and 21% and 31%, respectively for the lersivirine 750 mg group.

Overall exposures (as measured by the geometric means of AUC_{24} and C_{max}) for the QD oral doses of lersivirine were 6002 ng·hr/mL (AUC_{24}) and 1056 ng/mL (C_{max}) for the lersivirine 500 mg group and 8677 ng·hr/mL (AUC_{24}) and 1354 ng/mL (C_{max}) for the lersivirine 750 mg group.

Table 14. Summary of Plasma Lersivirine Pharmacokinetic Parameter Values Following Single Daily Oral Doses of Lersivirine at Week 4 - PK Sub-Study

	Parameter Summary[a] Statistics	
Parameter, units	**Lersivirine 500 mg**	**Lersivirine 750 mg**
N	7	6
C_{max}, ng/mL	1056 (41)	1354 (31)
T_{max}, hour	1.00 (0.483-2.00)	2.00 (0.500-8.00)
AUC_{24}, ng•hr/mL	6002 (30)	8677 (21)
C_{24}, ng/mL	49.56 (73)	57.70 (34)

Abbreviations: AUC_{24} = area under the plasma concentration-time profile from time 0 to 24 hours postdose, C_{24} = plasma concentration at the 24 hour time point, C_{max} = maximum plasma concentration, N = number of subjects in the evaluable population; PK = pharmacokinetic, T_{max} = time at which C_{max} occurred.
a. Geometric mean (%CV) for all except median (range) for T_{max}.

Safety Results: The overall incidence of treatment emergent adverse events (TEAEs) (all causality and treatment-related) by treatment group is presented in Table 15. Overall, 80%, 89.2%, and 93.7% subjects in the lersivirine 500 mg, lersivirine 750 mg, and efavirenz groups, respectively, reported at least 1 TEAE.

Table 15. Incidence of Treatment-Emergent Adverse Events (All Causality and Treatment-Related)

		Lersivirine 500 mg (N = 65)	Lersivirine 750 mg (N = 65)	Efavirenz (N = 63)
Number of AEs	All causality	359	386	433
	Treatment-related	101	114	145
Number (%) of subjects:				
With AEs	All causality	52 (80.0)	58 (89.2)	59 (93.7)
	Treatment-related	37 (56.9)	40 (61.5)	41 (65.1)
With SAEs	All causality	6 (9.2)	7 (10.8)	6 (9.5)
	Treatment-related	2 (3.1)	0	1 (1.6)
With Grade 3 or 4 AEs	All causality	6 (9.2)	12 (18.5)	17 (27.0)
	Treatment-related	2 (3.1)	2 (3.1)	10 (15.9)
Discontinued due to AEs	All causality	6 (9.2)	6 (9.2)	6 (9.5)
	Treatment-related	4 (6.2)	2 (3.1)	6 (9.5)
Discontinued lersivirine/efavirenz due to AEs	All causality	6 (9.2)	6 (9.2)	6 (9.5)
	Treatment-related	4 (6.2)	2 (3.1)	6 (9.5)
Discontinued emtricitabine/tenofovir due to AEs	All causality	5 (7.7)	6 (9.2)	5 (7.9)
	Treatment-related	3 (4.6)	2 (3.1)	5 (7.9)
Who temporarily discontinued lersivirine/efavirenz due to AEs	All causality	0	2 (3.1)	1 (1.6)
	Treatment-related	0	2 (3.1)	0
Who temporarily discontinued emtricitabine/tenofovir due to AEs	All causality	1 (1.5)	2 (3.1)	1 (1.6)
	Treatment-related	0	2 (3.1)	0
With dose reduction of lersivirine/efavirenz due to AEs	All causality	0	0	0
	Treatment-related	0	0	0
With dose reduction of emtricitabine/tenofovir due to AEs	All causality	0	0	0
	Treatment-related	0	0	0

Abbreviations: AE = adverse event; N = number of subjects in the evaluable population; SAE = serious adverse event.
Except for the number of AEs, subjects are counted only once per treatment in each row.
SAEs are presented according to the Investigator's assessment.

Treatment-emergent non serious AEs (all causalities) are presented in Table 16. The most commonly reported preferred term (PT) all-causality TEAEs (>15%) were headache, nausea, diarrhea, and upper respiratory tract infection in the lersivirine 500 mg group; nausea, headache, upper respiratory tract infection, diarrhea, and vomiting in the lersivirine 750 mg group; and dizziness, diarrhea, upper respiratory tract infection, abnormal dreams, headache, and vomiting in the efavirenz group.

Table 16. Treatment-Emergent Non Serious Adverse Events Reported for ≥5% of Subjects in any Treatment Group (All Causalities)

AEs by MedDRA Preferred Term	Lersivirine 500 mg (N = 65) n (%)	Lersivirine 750 mg (N = 65) n (%)	Efavirenz (N = 63) n (%)
Vertigo	4 (6.2)	1 (1.5)	5 (7.9)
Diarrhoea	12 (18.5)	12 (18.5)	14 (22.2)
Nausea	16 (24.6)	28 (43.1)	8 (12.7)
Bronchitis	4 (6.2)	9 (13.8)	5 (7.9)
Gastroenteritis	5 (7.7)	5 (7.7)	5 (7.9)
Influenza	5 (7.7)	7 (10.8)	8 (12.7)
Nasopharyngitis	8 (12.3)	3 (4.6)	4 (6.3)
Sinusitis	4 (6.2)	2 (3.1)	1 (1.6)
Syphilis	6 (9.2)	1 (1.5)	3 (4.8)
Tinea pedis	4 (6.2)	1 (1.5)	0
Upper respiratory tract infection	10 (15.4)	13 (20.0)	14 (22.2)
Arthralgia	5 (7.7)	3 (4.6)	3 (4.8)
Back pain	5 (7.7)	4 (6.2)	6 (9.5)
Dizziness	5 (7.7)	5 (7.7)	15 (23.8)
Headache	19 (29.2)	14 (21.5)	11 (17.5)
Abnormal dreams	5 (7.7)	5 (7.7)	12 (19.0)
Insomnia	7 (10.8)	9 (13.8)	8 (12.7)
Proteinuria	4 (6.2)	2 (3.1)	1 (1.6)
Erectile dysfunction	5 (7.7)	1 (1.5)	2 (3.2)
Cough	5 (7.7)	4 (6.2)	3 (4.8)
Acne	4 (6.2)	2 (3.1)	0
Conjunctivitis	3 (4.6)	5 (7.7)	2 (3.2)
Abdominal distension	2 (3.1)	4 (6.2)	3 (4.8)
Abdominal pain	2 (3.1)	8 (12.3)	8 (12.7)
Vomiting	3 (4.6)	12 (18.5)	11 (17.5)
Fatigue	2 (3.1)	4 (6.2)	3 (4.8)
Influenza like illness	3 (4.6)	5 (7.7)	2 (3.2)
Herpes zoster	1 (1.5)	4 (6.2)	0
Myalgia	1 (1.5)	4 (6.2)	2 (3.2)
Skin papilloma	3 (4.6)	5 (7.7)	0
Anxiety	0	5 (7.7)	5 (7.9)
Asthenia	2 (3.1)	2 (3.1)	4 (6.3)
Pharyngitis	2 (3.1)	2 (3.1)	8 (12.7)
Alanine aminotransferase increased	1 (1.5)	1 (1.5)	4 (6.3)
Aspartate aminotransferase increased	1 (1.5)	1 (1.5)	4 (6.3)
Blood creatine phosphokinase increased	2 (3.1)	1 (1.5)	4 (6.3)
Weight decreased	2 (3.1)	1 (1.5)	5 (7.9)
Oropharyngeal pain	1 (1.5)	2 (3.1)	4 (6.3)
Night sweats	1 (1.5)	0	4 (6.3)
Rash	2 (3.1)	1 (1.5)	5 (7.9)

Table 16. Treatment-Emergent Non Serious Adverse Events Reported for ≥5% of Subjects in any Treatment Group (All Causalities)

AEs by MedDRA Preferred Term	Lersivirine 500 mg (N = 65) n (%)	Lersivirine 750 mg (N = 65) n (%)	Efavirenz (N = 63) n (%)

Subjects were only counted once per treatment for each row.
Included data up to 999 days after last dose of study drug.
MedDRA (Version 14.1) coding dictionary applied.
Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects in each treatment group; n = number of subjects with AEs.

Treatment-related TEAEs reported for ≥2% of subjects in any treatment group are summarized in Table 17. The most commonly reported PT treatment-related TEAEs (>15%) were nausea (14 [21.5%] subjects) in the lersivirine 500 mg group; nausea (26 [40.0%] subjects) and vomiting (11 [16.9%] subjects each) in the lersivirine 750 mg group; and dizziness (14 [22.2%] subjects) and abnormal dreams (12 [19.0%] subjects) in the efavirenz group.

Table 17. Treatment-Emergent Adverse Events Reported for ≥2% of Subjects in any Treatment Group–Treatment-Related

AEs by MedDRA Preferred Term	Lersivirine 500 mg (N = 65) n (%)	Lersivirine 750 mg (N = 65) n (%)	Efavirenz (N = 63) n (%)
Vertigo	3 (4.6)	1 (1.5)	5 (7.9)
Diarrhoea	8 (12.3)	5 (7.7)	4 (6.3)
Nausea	14 (21.5)	26 (40.0)	4 (6.3)
Blood creatinine phosphokinase increased	2 (3.1)	0	1 (1.6)
Dizziness	3 (4.6)	5 (7.7)	14 (22.2)
Headache	5 (7.7)	9 (13.8)	6 (9.5)
Abnormal dreams	5 (7.7)	5 (7.7)	12 (19.0)
Insomnia	2 (3.1)	5 (7.7)	6 (9.5)
Proteinuria	4 (6.2)	1 (1.5)	0
Rash-related events[a]	2 (3.1)	0	6 (9.5)
Abdominal distention	1 (1.5)	3 (4.6)	2 (3.2)
Abdominal pain	1 (1.5)	5 (7.7)	4 (6.3)
Vomiting	1 (1.5)	11 (16.9)	5 (7.9)
Asthenia	1 (1.5)	2 (3.1)	3 (4.8)
Fatigue	0	1 (1.5)	2 (3.2)
Alanine aminotransferase increased	1 (1.5)	0	3 (4.8)
Aspartate aminotransferase increased	1 (1.5)	0	3 (4.8)
Back pain	1 (1.5)	0	3 (4.8)

AEs and SAEs are not separated out.
MedDRA (Version 14.1) coding dictionary applied.
Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects in each treatment group; n = number of subjects with AEs; SAE = serious AE.
a. Rash-related events refered to the combined TEAEs of drug eruption, rash, rash macular, rash maculopapular, rash erythematous, rash papular and rash pruritic.

Three Category C AIDS-defining events were reported in 2 subjects in the lersivirine 750 mg group (diffuse large B-cell lymphoma [Grade 4 severity] and hepatic lesion [Grade 4 severity; suspected lymphoma] in 1 subject and Kaposi's varicelliform eruption [Grade 2 severity] in another subject). Another subject in the efavirenz group was diagnosed with basal cell carcinoma (Grade 3 severity) during the study.

Treatment emergent SAEs (all causality) is presented in Table 18 and treatment emergent SAEs (treatment related) is presented in Table 19.

Table 18. Treatment-Emergent Serious Adverse Events (All Causality)

AEs by MedDRA Preferred Term	Lersivirine 500 mg (N = 65) n (%)	Lersivirine 750 mg (N = 65) n (%)	Efavirenz (N = 63) n (%)
Gastrointestinal disorders	0	0	1 (1.6)
Rectal ulcer	0	0	1 (1.6)
Immune system disorders	1 (1.5)	0	0
Hypersensitivity	1 (1.5)	0	0
Infections and infestations	3 (4.6)	2 (3.1)	1 (1.6)
Bronchitis	1 (1.5)	0	0
Bronchopneumonia	1 (1.5)	0	0
Cellulitis	0	1 (1.5)	0
Folliculitis	0	1 (1.5)	0
Groin abscess	0	1 (1.5)	0
Hepatitis A	0	1 (1.5)	0
Pyelonephritis	2 (3.1)	0	0
Syphilis	1 (1.5)	0	1 (1.6)
Injury, poisoning and procedural complications	1 (1.5)	2 (3.1)	1 (1.6)
Head injury	1 (1.5)	0	0
Injury	0	1 (1.5)	0
Meniscus lesion	0	0	1 (1.6)
Multiple fractures	0	1 (1.5)	0
Musculoskeletal and connective tissue disorders	1 (1.5)	0	1 (1.6)
Intervertebral disc disorder	1 (1.5)	0	0
Tendonitis	0	0	1 (1.6)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	1 (1.5)	0
Diffuse large B-cell lymphoma	0	1 (1.5)	0
Nervous system disorders	0	0	1 (1.6)
Sciatica	0	0	1 (1.6)
Psychiatric disorders	1 (1.5)	1 (1.5)	2 (3.2)
Depression	0	1 (1.5)	0
Mental disorder	0	0	1 (1.6)
Psychotic disorder	0	0	1 (1.6)
Suicide attempt	1 (1.5)	0	0
Renal and urinary disorders	2 (3.1)	1 (1.5)	0
Leukocyturia	1 (1.5)	0	0
Nephrolithiasis	0	1 (1.5)	0
Renal impairment	1 (1.5)	0	0
Renal papillary necrosis	1 (1.5)	0	0

MedDRA (Version 14.1) coding dictionary applied.
Subjects were only counted once per treatment for each row.
Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects in each treatment group; n = number of subjects with AEs.

Table 19. Treatment-Emergent Serious Adverse Events (Treatment-Related)

Serial Number	MedDRA Preferred Termd[a]	Causality[b]	Clinical Outcome	Seriousness
1	Hypersensitivity	Related	Resolved	Hospitalization; important medical event
2	Leukocyturia	Related/ Unrelated[c]	Resolved	Hospitalization
	Leukocyturia	Related/ Unrelated[c]	Resolved	Hospitalization
3	Psychotic disorder	Related	Resolving	Hospitalization; important medical event

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.
a. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 14.1).
b. Causality (relationship to the study treatment) as assessed by the Investigator.
c. Causality (relationship to the study treatment) as assessed by the Sponsor.

Details of the TEAEs leading to permanent discontinuation from the study are summarized in Table 20. Six (6) subjects in each of the lersivirine 500 mg, lersivirine 750 mg, and efavirenz groups discontinued the study due to TEAEs.

Table 20. Treatment-Emergent Adverse Events Leading to Discontinuation From the Study

Serial Number	MedDRA[a] PT (Severity)	Start Day[b]	Stop Day[b]	Last-Dose Day	Causality	Outcome
Lersivirine 500 mg						
1	Depressed mood (Grade 2)	1	>505	507	Treatment-related	Still present
2	Hypersensitivity[c] (Grade 2)	1	5	1	Treatment-related	Resolved with sequelae
3	Suicide attempt[c] (Grade 4)	575	580	574	Other – overdose of recreational drugs	Resolved
4	ALT increased (Grade 4)	103	>177	174	Treatment-related	Still present
5	Leukocyturia[c] (Grade 3)	56	101	56	Treatment-related	Resolved
6	Hepatitis C (Grade 3)	434	>457	434	Other – unknown	Still present
Lersivirine 750 mg						
1	Major depression (Grade 3)	444	>559	556	Other – major depression second to job loss	Still present
2	Multiple fractures[c] (Grade 4)	502	>542	502	Other – subject was hit by a car	Still present
3	Hepatitis A[c] (Grade 4)	502	827	510	Other illness – viral infection	Resolved
4	Vomiting (Grade 2)	98	101	100	Treatment-related	Resolved
5	Disturbance in attention (Grade 2)	10	127	112	Treatment-related	Resolved
6	Diffuse large B-cell lymphoma[c] (Grade 4)	42	>55	54	Other illness – lymphoma	Still present
Efavirenz						
1	ALT increased (Grade 3)	29	>71	73	Treatment-related	Still present
	AST increased (Grade 2)	29	>71	73	Treatment-related	Still present
	Blood amylase increased (Grade 3)	1	>71	73	Treatment-related	Still present
2	Psychotic disorder[c] (Grade 3)	310	>360	310	Treatment-related	Still present
3	Abnormal dreams (Grade 2)	1	13	5	Treatment-related	Resolved
	Mental disorder (Grade 2)	1	13	5	Treatment-related	Resolved
	Suicidal ideation (Grade 2)	1	13	5	Treatment-related	Resolved
4	Anxiety (Grade 3)	85	108	100	Treatment-related	Resolved
5	AST increased (Grade 3)	160	>492	491	Treatment-related	Still present
6	Disturbance in attention (Grade 3)	29	105	70	Treatment-related	Resolved

For all stop day results with a leading ">" the stop-day value was imputed from incomplete dates and times.
Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term.

a. AEs were coded using the MedDRA (Version 14.1).
b. Start day and stop day were the start and stop of the AE relative to the start of the treatment (Day 1).
c. Serious adverse event (according to Investigators assessment).

Details of the TEAEs leading to temporary discontinuation or dose reduction during the study are summarized in Table 21. The number of subjects who temporarily discontinued the

study or had dose reductions due to all causality TEAEs was comparable across the treatment groups (1, 2, and 1 subject in the lersivirine 500 mg, lersivirine 750 mg, and efavirenz groups, respectively).

Table 21. Treatment-Emergent Adverse Events Leading to Temporary Discontinuation or Dose Reduction During the Study

Serial Number	MedDRA[a] PT (Severity)	Start Day[b]	Stop Day[b]	Causality	Outcome
Lersivirine 500 mg					
1	Pyelonephritis[c] (Grade 3)	24	101	Other illness – bacterial infection	Resolved
Lersivirine 750 mg					
2	Vomiting (Grade 2)	85	94	Treatment-related	Resolved
3	Gastritis (Grade 1)	47	48	Other illness – psychosomatic (under stressing situation)	Resolved
	Gastritis (Grade 1)	443	445	Treatment-related	Resolved
	Bronchospasm (Grade 1)	553	557	Other illness – allergic diseases (previous medical history of allergic diseases as rhinitis)	Resolved
Efavirenz					
4	Oropharyngeal pain (Grade 1)	662	678	Concomitant treatment – tonsillectomy	Resolved

Abbreviations: AE = adverse event; PT = preferred term.
a. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 14.1).
b. Start day and stop day were the start and stop of the AE relative to the start of the treatment (Day 1).
c. Serious adverse event (according to investigator's assessment).

One subject (lersivirine 750 mg group) died during the study. This subject died on Day 286, due to an injury suffered in a car accident. The event was assessed by the Investigator as not treatment related.

Overall laboratory results are summarized in Table 22. Overall, the incidence of laboratory abnormalities was comparable in all 3 groups in terms of any division of acquired immunodeficiency syndrome grade. The most frequently reported laboratory abnormality in the lersivirine 500 mg and lersivirine 750 mg groups was proteinuria; in the efavirenz group, the most frequently reported laboratory abnormalities were alanine aminotransferase (ALT) and aspartate aminotransferase abnormalities.

Table 22. Overall Summary of Laboratory Results

	Lersivirine 500 mg	Lersivirine 750 mg	Efavirenz
Number of subjects evaluable for labs, N	64	65	63
Number of laboratory abnormalities	232	164	229
Number (%) of subjects with:			
Laboratory abnormalities	59 (92.2)	58 (89.2)	57 (90.5)
Grade 3 or 4 laboratory abnormalities	7 (10.9)	7 (10.8)	9 (14.3)

Abbreviations: DAIDS = Division of acquired immunodeficiency syndrome; N = number of subjects in the evaluable population.
Abnormality referred to a DAIDS Grade 1 or greater.
For number of laboratory abnormalities, subjects with multiple occurrences of the same laboratory parameter were counted only once.

There were no notable mean changes from Baseline in any of the vital signs parameters (supine or standing) at any time point in the study between the lersivirine groups and the efavirenz group, and no notable mean changes from Baseline in anthropometric measurements.

CONCLUSIONS:

24 Week:

- The percentages of subjects with HIV-1 RNA level <50 copies/mL at Week 24 were 83.1%, 83.1% and 87.3% for the lersivirine 500 mg, lersivirine 750 mg and efavirenz groups, respectively. The lower limits of the two-sided 80% CI for the differences in the percentage of subjects with HIV-1 RNA level <50 copies/mL at Week 24 were -13.9% (lersivirine 500 mg versus efavirenz) and -13.4% (lersivirine 750 mg versus efavirenz), which were above the pre-specified margin of -20%, thus meeting the criterion of non-inferiority (ie, meeting the main objective of the Week 24 interim analysis). The lersivirine 500 mg and lersivirine 750 mg groups appeared to have similar efficacy.

- The efficacy, as measured by percentage of subjects with HIV-1 RNA level <400 copies/mL, was comparable between each lersivirine group and the efavirenz group.

- The decrease from Baseline in $\log_{10}$ transformed HIV-1 RNA level at Week 24 was comparable between each lersivirine group and the efavirenz group.

- Mean changes from Baseline in absolute CD4+ cell counts at Week 24 were comparable between each lersivirine group and the efavirenz group.

Week 48:

- Both lersivirine doses showed similar efficacy to efavirenz over 48 weeks in treatment-naive subjects. The percentage of subjects with HIV-1 RNA level

<50 copies/mL at Week 48 were 78.5%, 78.5%, and 85.7% in the lersivirine 500 mg, lersivirine 750 mg, and efavirenz groups, respectively.

- Mean changes from Baseline in absolute CD4+ cell count at Week 48 were similar between each of the lersivirine groups and the efavirenz group.

- The efficacy as measured by secondary endpoints of percentage of subjects with HIV-1 RNA level <400 copies/mL at Week 48, decreases in Baseline in $\log_{10}$ transformed HIV-1 RNA level at Week 48, and TAD in $\log_{10}$ transformed HIV-1 RNA level at Week 48 was similar across the treatment groups.

- Virologic failure occurred in 7 (10.8%) subjects in each of the lersivirine groups and 3 (4.8%) subjects in the efavirenz group.

- In the PK sub-study, the lersivirine C_{24} ranged between 26.9 and 178 ng/mL for the lersivirine 500 mg group and between 43.4 and 101 ng/mL for the lersivirine 750 mg group which were at least 5-fold the protein-adjusted in vitro 90% inhibitory concentration (IC_{90}: 5.3 ng/mL) for wild-type virus. Exposures as measured by geometric mean values for C_{max} and AUC_{24} were 1056 ng/mL and 6002 ng·hr/mL for the lersivirine 500 mg group and 1354 ng/mL and 8677 ng·hr/mL for the lersivirine 750 mg group.

Week 96:

- Both lersivirine doses showed broadly similar efficacy to efavirenz over 96 weeks in treatment-naive subjects in the context of this Phase 2b estimation study. The percentage of subjects with HIV-1 RNA level <50 copies/mL at Week 96 was 70.8%, 67.7%, and 77.8% in the lersivirine 500 mg, lersivirine 750 mg, and efavirenz groups, respectively.

- The mean increase from Baseline in absolute CD4+ cell count (last observation carried forward) at Week 96 was comparable across all treatment groups.

- Efficacy as measured by secondary endpoints of percentage of subjects with HIV-1 RNA level <400 copies/mL at Week 96, decreases in Baseline in $\log_{10}$ transformed HIV-1 RNA level at Week 96, and TAD in $\log_{10}$ transformed HIV-1 RNA level at Week 96 was broadly similar across the treatment groups.

- The virologic results from this Week 96 report are consistent with preclinical findings in relation to lersivirine virologic characteristics.

- In total, paired predose and on-treatment analyses were successfully performed using population genotype on 18, and using phenotype on 17 plasma sets (pre- and posttreatment).

- There were 3 of 5 (60%) tested subjects in the lersivirine 500 mg group and 1 of 8 (12.5%) tested subjects in the lersivirine 750 mg group whose virus selected nucleoside reverse transcriptase inhibitor RAMs (all 4 subjects had a M184V or I variant) and

NNRTI RAMs. None of these posttreatment viruses had the signature efavirenz or nevirapine mutations K103N or Y181C. One of 5 subjects tested in the efavirenz treated group selected K103N.

- Overall, lersivirine was generally well tolerated and had a different AE profile compared with efavirenz. One subject died during the study (in a nontreatment-related injury suffered in a car accident). The number of subjects reporting SAEs was comparable across the treatment groups. Six subjects in each treatment group discontinued the study due to TEAEs.

- The majority of TEAEs were mild (Grade 1) or moderate (Grade 2) in severity. Grade 2 (moderate), Grade 3 (severe), or Grade 4 (potentially life-threatening) TEAEs were reported less frequently in the lersivirine groups compared with the efavirenz group. Grade 3 or 4 AEs were reported less frequently in the lersivirine 500 mg and 750 mg groups (6 [9.2%] and 12 [18.5%], respectively) compared with the efavirenz group (17 [27.0%] subjects).

- There was a higher incidence of nausea reported in both lersivirine groups compared with the efavirenz group. However, the incidence of vomiting was lower in the lersivirine 500 mg group compared with the lersivirine 750 mg and efavirenz groups. The incidence of headache was higher in both lersivirine groups compared with the efavirenz group, but the rate of Grade 2 (moderate) to 4 (very severe) headache was similar between the lersivirine 500 mg and efavirenz groups and was higher than in the lersivirine 750 mg group. There was a lower incidence of certain NNRTI related TEAEs (abnormal dreams, dizziness, rash, and increased ALT) in both lersivirine groups compared with the efavirenz group.

- There were few Category C events and malignancies reported in the study.

- A similar number of subjects reported Grade 3 or 4 laboratory abnormalities across groups (7, 7, and 9 subjects in the lersivirine 500 mg, lersivirine 750 mg, and efavirenz groups, respectively). The incidence of Grade 3 and Grade 4 transaminase abnormalities was low and similar across treatment groups.

- Overall, the findings at Week 96 were consistent with those of the primary analysis at Week 48, demonstrating durability of clinical response.