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

PROTOCOL NO.: A5271022

PROTOCOL TITLE: A Phase 2b Multicenter, Randomized, Comparative Trial of UK-453,061 Versus Etravirine in Combination With Darunavir/Ritonavir and a Nucleotide/Nucleoside Reverse Transcriptase Inhibitor for the Treatment of Antiretroviral Experienced HIV-1 Infected Subjects With Evidence of NNRTI Resistant HIV-1

Study Centers: A total of 39 centers took part and randomized subjects in this study; Brazil (6 centers), Germany (1 center), Malaysia (2 centers), Poland (1 center), Portugal (3 centers), Puerto Rico (2 centers), South Africa (7 centers), Taiwan (1 center), Ukraine (2 centers), United Kingdom (2 centers), and United States (12 centers).

Study Initiation, Primary Completion and Final Completion Dates:
Study Initiation Date: 25 March 2009, Primary Completion Date: 08 December 2011, and Final Completion Date: 18 October 2012.

The study was terminated prematurely by the Sponsor.

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

Phase of Development: Phase 2b

Study Objectives:

Primary Objective: The primary objective was to assess the efficacy of lersivirine when used in combination with darunavir/ritonavir and an optimized nucleoside reverse transcriptase inhibitor (NRTI) for the treatment of subjects with prior non-nucleoside reverse transcriptase inhibitor (NNRTI) use and documented evidence of NNRTI resistance associated mutations (RAMs). Efficacy was measured by the percentage of subjects with human immunodeficiency virus (HIV)-1 ribonucelic acid (RNA) level <50 copies/mL at 24 weeks.

Secondary Objectives:

- To assess efficacy as measured by percentage of subjects with HIV-1 RNA level <50 copies/mL at 48 and 96 weeks.
- To assess efficacy as measured by percentage of subjects with HIV-1 RNA level <400 copies/mL.

- To assess efficacy as measured by change from Baseline in log 10 transformed HIV-1 RNA levels.

- To assess the pharmacokinetics (PK) and pharmacokinetic/pharmacodynamics (PD).

- PK/PD-relationship of lersivirine.

- To assess safety and tolerability of lersivirine.

METHODS

Study Design: This study was a 96-week, multi-center, multi-national, randomized, comparative, Phase 2b study to assess the antiviral activity and safety of lersivirine (750 mg once daily [QD] and 1000 mg QD) compared to etravirine, each given in combination with darunavir/ritonavir and an optimized NRTI. As the primary objective of this study was not met at the time of the Week 24 analysis, the decision was made to terminate the study early. All the subjects had either discontinued the study prematurely, or had completed at least 48 weeks of treatment at the time of the study termination.

Two doses of lersivirine were administered in a blinded fashion. Subjects randomized to the 750 mg QD treatment group received 3 lersivirine 250 mg tablets and 1 matching placebo tablet; subjects randomized to the 1000 mg QD treatment group received 4 lersivirine 250 mg tablets. The optimized NRTI, darunavir/ritonavir, and etravirine were administered as open-label treatment. Subjects who were on a stable antiretroviral (ARV) regimen for at least 4 weeks prior to the Screening visit were required to remain on their existing regimen during the Screening period. Subjects not on ARV therapy for 4 weeks prior to the Screening visit remained off therapy until the Day-1 visit. Subjects who had never received an NNRTI based regimen but had NNRTI RAMs were excluded.

All enrolled subjects were required to have HIV-1 with evidence of virologic failure (HIV-1 RNA ≥500 copies/mL) at Screening, single NNRTI regimen experience, and the presence of NNRTI RAMs (documented either at Screening or by historical genotype) with or without prior protease inhibitor (PI) experience and /or resistance.

Investigators optimized the background NRTI (branded, open-label agents) on the basis of susceptibility testing, treatment history and safety/adverse event (AE) considerations. After the Day 1 visit, changes to the chosen NRTI may only have been made after consultation with the medical monitor and under the following circumstances:

1. Toxicity attributed to the optimized NRTI. A drug of the same class could have been substituted.

2. Documented human error in interpretation of NRTI screening resistance test results after the Day 1 Visit, but no later than Week 2 Visit. A drug of the same class could have been substituted without requiring the subject to be discontinued from study drug.

3. Dose adjustments could have been made to existing NRTI due to the addition of a required concomitant agent that results in an anticipated new drug interaction. Such changes were only permissible if confirmed by the manufacturer's label.

Experimental ARV agents available through pre-approval access programs or by other means were not appropriate for use as part of background therapy.

Randomization was stratified by Screening plasma HIV-1 RNA level (<100,000 versus ≥100,000 copies/mL plasma) and by subject sub-population (PI naïve and absence of PI resistance mutations versus PI experienced or presence of PI resistance mutations) to form a total of 4 strata.

Table 1 describes the schedule of activities.

Table 1. Schedule of Activities

Procedures	Screening (Day -42 to Day -28)	Randomization (Day -7 to -1)	Day 1[a]	Week 2[b]	Week 4, 8, 12, 16, 32, 40, 60, 72, 84[b]	Week 24, 48, 96 or Early Termination[b]
Informed consent	X					
Medical history (including alcohol/smoking/exposure category)			X			
Review inclusion/exclusion criteria	X	X	X			
Transcribe NNRTI and PI genotype results[c]		X				
Physical exam/vital signs			X			X
Targeted physical exam/vital signs					X	
Waist/hip lipodystrophy measurements			X			X
Adverse events		X	X	X	X	X
Concomitant medications	X	X	X	X	X	X
Chemistry	X		X	X	X[d]	X
Hematology	X		X	X	X[d]	X
Urinalysis	X		X	X	X	X
Fasting metabolic assessment (total cholesterol, HDL/LDL, triglycerides, glucose)			X			X
12-lead electrocardiogram[e]	X		X	X	Weeks 4 and 8	X[f]
PK sampling[g]				X	X	Weeks 24 and 48
Hepatitis screen (HB core Ab, sAg, sAb, HC Ab)	X					
Hepatitis C virus RNA			X[h]		Week 12[h]	X[h]
Hepatitis C genotype			X[i]			
CD4+ lymphocyte count (absolute and percentage)	X		X		X	X
Plasma HIV-1 RNA level (viral load)	X		X	X	X	X
Pregnancy test[j]	X		X	X	X	X
Plasma and PBMC (proviral DNA) samples[k]			X			X
Virus susceptibility (phenotype, genotype) and lersivirine phenotypic susceptibility	X		X[l]		X[m, n]	X[m,o]
Host genotyping			X[p]			
Free T4, TSH			X		Week 12	X
Prescribe optimized NRTI		X				

Table 1. Schedule of Activities

Procedures	Screening (Day -42 to Day -28)	Randomization (Day -7 to -1)	Day 1[a]	Week 2[b]	Week 4, 8, 12, 16, 32, 40, 60, 72, 84[b]	Week 24, 48, 96 or Early Termination[b]
Assess dosing compliance				X	X	X
Dispense study medication			X		X	X[q]

CD4=cluster of differentiation 4; CRF=case report form; DNA=deoxyribonucleic acid; HB core Ab=hepatitis B core antibody; HC Ab=hepatitis C antibody; HDL=high density lipoprotein; HIV-1=human immunodeficiency virus-1; IEC=independent Ethics Committee; IRB=institutional Review Board; LDL=low density lipoprotein; NNRTI=non-nucleoside reverse transcriptase inhibitor; PBMC=peripheral blood mononuclear cell; PI=protease inhibitor; PK=pharmacokinetic; QTc=QT interval corrected; RNA=ribonucelic acid; sAb=surface antibody; sAg=surface antigen; T4=thyroxine; TSH=thyroid-stimulating hormone; NRTI=nucleoside reverse transcriptase inhibitor.

a. All procedures had to be completed prior to dosing.
b. All visits had to occur within ±2 days.
c. Transcribe/record documented historical HIV-1 resistance testing results (NNRTI and PI genotype) on CRF only for subjects whose screening results failed to qualify for enrollment but who had qualifying documented mutations on historical genotype (at any time in the past).
d. Excluding Week 12.
e. If the change in QTc interval was >60 msec from Baseline (Day 1) or the QTc interval was >500 msec, the principal investigator was required to notify the sponsor.
f. Excluding Week 96.
g. Two 5 mL PK samples were required at Weeks 2 and 24 and had to be collected at least 60 minutes apart. One 5 mL PK sample was required at other visits, through Week 48.
h. If hepatitis C antibody was positive at Screening visit, it was to be performed at Day 1,Weeks 12, 24, 48 and 96, or Early Termination.
i. If hepatitis C antibody was positive at Screening.
j. For women of child bearing potential. Serum pregnancy test at Screening and urine tests at all visits except Randomization. A positive urine test had to be confirmed with a serum test. If urine test was positive then study medication was not to be dispensed unless the results of the confirmatory serum pregnancy test were negative.
k. Whole blood samples for plasma aliquots and PBMCs (proviral DNA) were collected at Day 1 and at Weeks 24, 48, 96 or Early Termination upon treatment failure only (to be stored for future analysis).
l. A 10 mL sample for phenotypic and genotypic susceptibility and 10 mL sample for lersivirine phenotypic susceptibility to be stored for future analysis.
m. Only for subjects who required a second measurement of HIV-1 RNA to confirm treatment failure. Taken at the time of collection of second HIV-1 RNA sample.
n. 10 mL samples taken only at Week 12 and only if subject had viral load >500 at Week 8 (to be stored for future analysis).
o. At the Early Termination visit for treatment failure only: Samples for viral (phenotype and genotype) and lersivirine phenotypic susceptibility were not collected if already collected at the time of confirmation of treatment failure (when second sample for HIV-1 RNA was taken).
p. Requiring separate IRB/IEC approval and subject consent as per Molecular Profiling Supplement of the protocol.
q. Except Week 96 or Early Termination.

Number of Subjects (Planned and Analyzed):

A total of 90 subjects (30 subjects per treatment group) were planned to be randomized in this study. A total of 105 subjects were randomized (35 subjects each were assigned to lersivirine 750 mg QD treatment group, lersivirine 1000 mg QD treatment group, and etravirine 200 mg twice daily [BID] treatment group, respectivel); 33 in Brazil, 1 in Germany, 2 in Malaysia, 1 in Poland, 3 in Portugal, 4 in Puerto Rico, 33 in South Africa, 2 in Taiwan, 3 in Ukraine, 3 in United Kingdom, and 20 in United States. Among the randomized subjects, a total of 97 subjects (31, 32 and 34 subjects in Lersivirine 750 mg QD treatment group, Lersivirine 1000 mg QD treatment group, and Etravirine 200 mg BID treatment group, respectively) received at least one dose of study medication and were included in the analyses.

Diagnosis and Main Criteria for Inclusion: Subjects were male or female subjects at least 18 years of age available for a follow-up period of at least 96 weeks, with HIV 1 RNA viral load of >500 copies/mL measured by the Roche Amplicor® HIV 1 Monitor test (Version 1.5) at the Screening visit. All subjects were required to have virologically failed a single NNRTI-based regimen with documented evidence of NNRTI resistance mutations at Screening or on historical genotype (with or without PI experience/resistance). Women of child bearing potential were required to have negative urine pregnancy test the Day-1 visit, prior to receiving the first dose of study medication.

Exclusion Criteria: Subjects with suspected or documented active, untreated HIV-1 related opportunistic 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 previous use of darunavir or etravirine.

Study Treatment: Subjects were randomized to 1 of the following 3 treatment groups in a 1:1:1 ratio, administered orally:

- Lersivirine 750 mg QD +1 optimized NRTI + darunavir/ritonavir 600/100 mg BID.
- Lersivirine 1000 mg QD +1 optimized NRTI + darunavir/ritonavir 600/100 mg BID.
- Etravirine 200 mg BID +1 optimized NRTI + darunavir/ritonavir 600/100 mg BID.

Lersivirine was taken with evening meals. Darunavir / ritonavir and etravirine were taken with breakfast and with evening meals. NRTIs were taken as per the individual prescribing information.

Efficacy and Safety Endpoints:

Primary Endpoint:

- The percentage of subjects with HIV-1 RNA level <50 copies/mL at 24 weeks.

Secondary Endpoints:

- The percentage of subjects with HIV-1 RNA level <50 copies/mL at 48 and 96 weeks.
- The percentage of subjects with HIV-1 RNA level <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 and 48 weeks.
- The percentage of TLOVR Responders at 24 and 48 weeks.
- Change from Baseline in $CD4^+$ lymphocyte counts (absolute and percentage) at 24, 48 and 96 weeks.
- Genotypic and phenotypic resistance to lersivirine, etravirine, darunavir and NRTIs at the time of treatment failure.
- Safety and tolerability as measured by spontaneous adverse event reports, serious adverse events and safety laboratory test.

As the primary objective of this study was not met at the time of the Week 24 analysis, the decision was made to terminate the study early. This report presents a summary of the Week 24 data as well as Week 48 data and includes partial data beyond Week 48 through End of Study as a result of the early termination.

Safety Evaluations: Safety evaluation included AEs, serious adverse events (SAEs), safety laboratory tests, physical examinations, electrocardiograms (ECGs), and vital signs (blood pressure and pulse rate). Category C acquired immunodeficiency syndrome (AIDS)-defining illnesses were included in the assessment of AEs and SAEs.

Safety evaluations were conducted at different time points as detailed in Table 1.

Statistical Methods:

Analysis Sets:

Full Analysis Set: The full analysis set (FAS) consisted of all randomized subjects who received at least 1 dose of study medication. The 'FAS set 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 Analyses: Efficacy analyses were performed on the FAS and PPS.

The number and percentage of subjects with the HIV-1 RNA <50 copies/mL at Week 48 were tabulated. Two-sided 80% confidence intervals (CIs) were formed for the percentage of subjects with HIV-1 RNA <50 copies/mL using the normal approximation to the binomial. Two-sided 80% CIs for the difference in the proportions between each lersivirine dose group and the etravirine treatment group were formed using the normal approximation to the binomial with continuity correction. The analysis was adjusted using the Cochran-Mantel-Haenszel method based on the randomization strata. For the primary analysis at Week 24 and the main analyses at Weeks 48 and 96, subjects who had discontinued from the study, were lost to follow-up, or had switched to an ARV drug or changed the dose of ARV not allowed by the protocol, or had missing HIV-1 RNA data at Week 48 were considered to have HIV-1 RNA ≥50 copies/mL. This imputation was referred to as 'missing/switch/discontinuation = failure' (MSDF).

Percentages of subjects with HIV-1 RNA <400 copies/mL and TLOVR50 response at each visit of interest were analyzed similarly to the primary/main analyses on the ITT population.

The change from Baseline in $\log_{10}$ transformed HIV-1 RNA level, the TAD in $\log_{10}$ transformed HIV-1 RNA level, and the change from Baseline in $CD4^+$ cell counts (absolute and percentage) at each visit of interest were analyzed on the ITT population using an analysis of covariance model with the randomization stratification variables, continuous Baseline measurements and treatment group as the main effects. The Baseline was defined as the average of all predose values. The least square mean (LSM) and its 80% CI were provided for each treatment group. Two-sided 80% CI for the treatment difference between each lersivirine dose group and etravirine was presented.

Genotypic and phenotypic resistance to NNRTIs based on International AIDS Society, United States of America RAM guidelines were evaluated using Monogram Biosciences PhenoSenseGT assay at Baseline. This was then repeated for all subjects with HIV-1 viral load >500 copies/mL at treatment failure, up to Week 48. The virology analysis set included a subset of participants from TLOVR50 failures who had both valid genotypic or phenotypic susceptibility testing results and plasma HIV-1 RNA >500 copies/mL at Baseline and treatment failure.

Safety Analyses: Safety analyses were performed on the safety population. Safety analyses were descriptive in nature.

RESULTS

Subject Disposition and Demography: Disposition of subjects is presented in Table 2 (Week 24 analysis) and Table 3 (final analysis).

Table 2. Subject Disposition - Week 24[a]

Number of Subjects	Lersivirine 750 mg QD	Lersivirine 1000 mg QD	Etravirine 200 mg BID
Screened 549			
Assigned to treatment	35	35	35
Treated	31	32	34
Completed at ≥24 weeks of study	22	25	30
Discontinued	13	10	6
Relation to study drug not defined	13	9	4
Insufficient clinical response	8	4	2
Lost to follow-up	1	0	0
No longer willing to participate in study	2	3	1
Other	1	0	1
Protocol violation	1	1	0
Withdrawn due to pregnancy	0	1	0
Related to study drug	0	0	2
Adverse event	0	0	2
Not related to study drug	0	1	0
Adverse event	0	1	0
Discontinued prior to Week 24 (Days <141)	9	7	4
Discontinued within Week 24 (Days 141-196)	4	3	2
Ongoing beyond Day 196	18	22	28

BID = twice daily; QD = once daily.

a. Week 24 was the primary analysis time point. The primary analysis was conducted when all subjects had completed the Week 24 visit or discontinued from study prior to Week 24.

Table 3. Subject Disposition - Final Analysis[a]

Number of Subjects	Lersivirine 750 mg QD	Lersivirine 1000 mg QD	Etravirine 200 mg BID
Screened 549			
Assigned to study treatment	35	35	35
Treated	31	32	34
Completed	6	3	11
Discontinued (total)	20	24	16
Discontinued (through Week 48)	17	20	13
Relation to study drug not defined	17	19	10
Insufficient clinical response	11	13	8
Lost to follow-up	2	1	0
No longer willing to participate in study	2	3	1
Other	1	0	1
Protocol violation	1	1	0
Withdrawn due to pregnancy	0	1	0
Related to study drug	0	0	2
Adverse event	0	0	2
Not related to study drug	0	1	1
Adverse event	0	1	1
Discontinued (post Week 48)	3	4	3
Relation to study drug not defined	3	3	2
Insufficient clinical response	2	3	1
No longer willing to participate in study	0	0	1
Other	1	0	0
Related to study drug	0	1	1
Adverse event	0	1	1
Early termination following the decision to terminate the A5271022 study early[b]	5	5	7

BID = twice daily; QD = once daily.

a. The final analysis included all the data for Week 48 and beyond through End of Study.

b. Among the subjects who terminated early following the decision to termination the A5271022 study, the termination days of 4 subjects were within the Week 96 visit window defined for reporting purposes in the statistical analysis plan.

Data Sets Analyzed are presented in Table 4.

Table 4. Data Sets Analyzed

Number of Subjects	24 Week			Final Analysis		
	Lersivirine 750 mg QD	Lersivirine 1000 mg QD	Etravirine 200 mg BID	Lersivirine 750 mg QD	Lersivirine 1000 mg QD	Etravirine 200 mg BID
Analyzed for efficacy						
Per protocol set	28	32	34	27	32	34
Full analysis set (ie, ITT)	31	32	34	31	32	34
Analyzed for pharmacokinetics[a]	28	31	0	28	31	0
Analyzed for safety						
Adverse events	31[b]	32[b]	34	31	32	34
Laboratory data[c]	29	31	34	29	31	34
ECG	31	32	34	31	32	34
Vital signs	31	32	34	31	32	34

AE = adverse event; BID = twice daily; ECG = electrocardiogram; ITT = intent to treat; QD = once daily.

a. Four subjects not included in the pharmacokinetic analysis because they discontinued prior to Week 2.

b. All subjects who were randomized and received at least 1 dose of study medication were included in the AE analysis. However, for lersivirine 750 mg QD and lersivirine 1000 mg QD 28 and 29 subjects, respectively were shown in the Clinical Study Report table due to a few subjects who did not have AEs at the time of database cut.

c. Three subjects not included in the laboratory analysis because there were no postbaseline data.

Demographic and Baseline clinical characteristics are presented in Table 5.

Table 5. Demographic and Baseline Clinical Characteristics - All Treated Subjects in ITT

	Lersivirine 750 mg QD (N=31)	Lersivirine 1000 mg QD (N=32)	Etravirine 200 mg BID (N=34)
Gender, n (%)			
Male	16 (51.6)	14 (43.8)	16 (47.1)
Female	15 (48.4)	18 (56.2)	18 (52.9)
Age (years)			
Mean (SD)	41.1 (8.9)	40.0 (8.7)	41.9 (9.1)
Range	26-63	20-56	24-66
Race, n (%)			
White	13 (41.9)	17 (53.1)	20 (58.8)
Black	17 (54.8)	11 (34.4)	11 (32.4)
Asian	1 (3.2)	2 (6.3)	2 (5.9)
Other	0	2 (6.3)	1 (2.9)
HIV-1 subtype, n (%)			
B	12 (38.7)	15 (46.9)	21 (61.8)
C	13 (41.9)	8 (25.0)	9 (26.5)
Other[a]	6 (19.4)	9 (28.1)	4 (11.8)
Screening HIV-1 RNA level (copies/mL), n (%)			
<100000	21 (67.7)	20 (62.5)	21 (61.8)
≥100000	10 (32.3)	12 (37.5)	13 (38.2)
Screening $\log_{10}$ HIV-1 RNA ($\log_{10}$ copies/mL)			
Mean (SD)	4.35 (0.94)	4.67 (0.85)	4.62 (0.87)
Range	2.70-5.82	3.07-6.14	2.76-6.53
Baseline[b] CD4+ cell count (cells/µL), n (%)			
<200	10 (32.3)	12 (37.5)	16 (47.1)
200-350	12 (38.7)	10 (31.3)	14 (41.2)
>350-500	8 (25.8)	6 (18.8)	2 (5.9)
>500	1 (3.2)	4 (12.5)	2 (5.9)
Mean (SD)	247 (143)	259 (187)	227 (146)
Range	5-590	1-624	3-670
Baseline hepatitis[c], n (%)			
B	1 (3.2)	1 (3.1)	2 (5.9)
C	5 (16.1)	2 (6.3)	4 (11.8)
B/C	0	0	1 (2.9)
None	25 (80.6)	29 (90.6)	27 (79.4)
Screening PI experience or resistance[d], n (%)			
Prior PI experience or resistance	12 (38.7)	16 (50.0)	16 (47.1)
No prior PI experience or resistance	19 (61.3)	16 (50.0)	18 (52.9)
Time from HIV diagnosis, n (%)			
<5 years	12 (38.7)	11 (34.4)	7 (20.6)
5-10 years	9 (29.0)	8 (25.0)	14 (41.2)
>10 years	10 (32.3)	13 (40.6)	13 (38.2)

Prior PI experience or resistance = PI experienced or presence of PI resistance mutations.
No prior PI experience or resistance = PI naïve and absence of PI resistance mutations.
BID = twice daily; CD4 = cluster of differentiation 4; HIV = human immunodeficiency virus; ITT = intent-to-treat; N = total number of subjects in ITT; n = number of evaluable subjects in the numerator or in a sub-category; PI = protease inhibitor; QD = once daily; RNA = ribonucleic acid; SD = standard deviation.

a. HIV-1 subtype of 'other' included any subtype that was not either pure B or pure C.
b. Baseline CD4+ cell count was calculated as the mean of all predose measurements.
c. Hepatitis testing was performed only for the detection of hepatitis B and C. None indicated negative

Table 5. Demographic and Baseline Clinical Characteristics - All Treated Subjects in ITT

	Lersivirine 750 mg QD (N=31)	Lersivirine 1000 mg QD (N=32)	Etravirine 200 mg BID (N=34)

testing for hepatitis B and C.
d. These were realized categories formed using major PI resistance mutations only (rather than both major and minor mutations).

Efficacy Results:

As the primary objective of this study was not met at the time of the Week 24 analysis, the decision was made to terminate the study early.

Primary Efficacy Endpoint:

Percentage of Subjects With HIV-1 RNA <50 Copies/mL at Week 24: The percentage of subjects with HIV-1 RNA <50 copies/mL at Week 24 (snapshot, MSDF; ITT) was 48.4%, 43.8% and 67.6% for lersivirine 750 mg QD, lersivirine 1000 mg QD and etravirine 200 mg BID, respectively (Table 6).

Table 6. Statistical Analysis (CMH) of Difference in the Percentage of Subjects With HIV-1 RNA <50 Copies/mL at Week 24 – MSDF - ITT

	Lersivirine 750 mg QD	Lersivirine 1000 mg QD	Etravirine 200 mg BID
N	31	32	34
n (%)	15 (48.4)	14 (43.8)	23 (67.6)
Difference (%)[a]	-21.6	-23.7	NA
SE difference (%)[a]	11.2	11.1	NA
80% CI for difference, (%)	-37.5, -5.7	-39.4, -8.0	NA

The denominator (N) used for the percentage calculation included all the subjects in ITT.
BID = twice daily; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; HIV = human immunodeficiency virus; ITT = intent-to-treat; MSDF = (missing/switch/discontinuation = failure); N = number of subjects in the ITT population; n = number of subjects with HIV-1 RNA <50 copies/mL at Week 24; NA = not applicable; PI = protease inhibitor; QD = once daily; RNA = ribonucleic acid; SE = standard error.
[a] Cochran-Mantel-Haenszel estimates adjusted for randomization stratification variables of screening HIV-1 RNA level (<100,000 versus ≥100,000 copies/mL) and PI experience status. Difference was the percentage difference between a lersivirine dose and etravirine.

Secondary Efficacy Endpoint:

Percentage of Subjects With HIV-1 RNA <50 Copies/mL at Weeks 48 and 96: The percentage of subjects with HIV-1 RNA <50 copies/mL at Week 48 and 96 are presented in Table 7. The percentage of subjects with HIV-1 RNA <50 copies/mL at Week 48 (snapshot, MSDF; ITT) was 41.9%, 31.3% and 61.8% for the lersivirine 750 mg QD, lersivirine 1000 mg QD and etravirine 200 mg BID groups, respectively. The percentage of subjects with HIV-1 RNA <50 copies/mL at Week 96 (snapshot, MSDF) was 25.0% (7/28), 14.3% (4/28) and 37.0% (10/27) for lersivirine 750 mg QD, lersivirine 1000 mg QD and etravirine

200 mg BID, respectively, for ITT but excluding those who were terminated early due to the study termination decision prior to Week 96.

Table 7. Statistical Analysis (CMH) of Difference in the Percentage of Subjects With HIV-1 RNA <50 Copies/mL at Week 48 and Week 96

	Lersivirine 750 mg QD	Lersivirine 1000 mg QD	Etravirine 200 mg BID
Snapshot MSDF ITT Main Analysis			
Week 48			
N	31	32	34
n (%)	13 (41.9)	10 (31.3)	21 (61.8)
Difference (%)[a]	-21.8	-29.9	NA
SE difference (%)[a]	11.3	11.1	NA
80% CI for difference, (%)	-37.9, -5.6	-45.7, -14.1	NA
Week 96[b]			
N	28	28	27
n (%)	7 (25)	4 (14.3)	10 (37)

The denominator (N) used for the percentage calculation included subjects in ITT excluding the subjects who discontinued early due to termination of the study for the visits post the termination.
BID = twice daily; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; HIV = human immunodeficiency virus; ITT = intent-to-treat; MSDF = (missing/switch/discontinuation = failure); n = number of subjects with HIV-1 RNA <50 copies/mL; NA = not applicable; PI = protease inhibitor; PPS = per-protocol analysis set; QD = once daily; RNA = ribonucleic acid; SE = standard error.
a. Cochran-Mantel-Haenszel estimates adjusted for randomization stratification variables of screening HIV-1 RNA level (<100,000 versus ≥100,000 copies/mL) and PI experience status. Difference was the percentage difference between a lersivirine dose and etravirine.
b. Statistical analysis was not performed for Week 96 due to early termination of the study.

Percentage of Subjects With HIV-1 RNA <400 Copies/mL at Week 24, 48 and 96 weeks:

The percentage of subjects with HIV-1 RNA <400 copies/mL at Week 24, 48, and 96 (snapshot, MSDF, ITT) are presented in Table 8.

Table 8. Statistical Analysis (CMH) of Difference in the Percentage of Subjects With HIV-1 RNA <400 Copies/mL at Week 24, 48, and 96 - MSDF- ITT

	Lersivirine 750 mg QD	Lersivirine 1000 mg QD	Etravirine 200 mg BID
Week 24			
N	31	32	34
n (%)	17 (54.8)	16 (50.0)	28 (82.4)
Difference (%)[a]	-27.4	-32.0	NA
SE Difference (%)[a]	10.7	10.2	NA
80% CI for difference, (%)	-42.7, -12.0	-46.7, -17.3	NA
Week 48			
N	31	32	34
n (%)	13 (41.9%)	11 (34.4%)	24 (70.6%)
Difference (%)[a]	-29.7	-35.6	NA
SE Difference (%)[a]	11.2	11.0	NA
80% CI for difference, (%)	-45.7, -13.7	-51.3, -19.9	NA
Week 96[b]			
N	28	28	27
n (%)	7 (25)	4 (14.3)	10 (37)

The denominator (N) used for the percentage calculation included all the subjects in ITT.
BID = twice daily; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; HIV = human immunodeficiency virus; ITT = intent-to-treat; MSDF = (missing/switch/discontinuation = failure); N = number of subjects in the ITT population; n = number of subjects with HIV-1 RNA <400 copies/mL at Week 24; NA = not applicable; PI = protease inhibitor; QD = once daily; RNA = ribonucleic acid; SE = standard error.

a. Cochran-Mantel-Haenszel estimates adjusted for randomization stratification variables of screening HIV-1 RNA level (<100,000 versus ≥100,000 copies/mL) and PI experience status. Difference was the percentage difference between a lersivirine dose and etravirine.

b. Statistical analysis was not performed for Week 96 due to early termination of the study.

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

Change from Baseline in log_{10} transformed HIV-1 RNA levels at Week 24 and 48 are presented in Table 9, and at Week 96 is presented in Table 10.

Table 9. Statistical Analysis of Change From Baseline Log_{10} Transformed Plasma HIV-1 RNA (Log_{10} Copies/mL) at Week 24 and 48 - Missing Data Method 1 - ITT

	Lersivirine 750 mg QD	Lersivirine 1000 mg QD	Etravirine 200 mg BID
Week 24			
N	31	32	34
LSM (SE)	-1.65 (0.25)	-1.74 (0.26)	-2.28 (0.24)
LSM difference (SE difference)	0.62 (0.35)	0.54 (0.34)	NA
80% CI	0.2, 1.1	0.1, 1.0	NA
Week 48			
N	31	32	34
LSM (SE)	-1.42 (0.27)	-0.95 (0.28)	-2.02 (0.26)
LSM difference (SE difference)	0.60 (0.37)	1.06 (0.36)	NA
80% CI	0.1, 1.1	0.6, 1.5	NA

Baseline log_{10} HIV-1 RNA level was calculated as the average of log_{10} transformed HIV-1 RNA values obtained prior to and including Day 1 predose.
Screening HIV-1 RNA (<100,000 and ≥100,000 copies/mL), Screening PI resistance (PI naïve and absence of PI resistance mutations versus PI experienced or presence of PI resistance mutations) and Baseline log_{10} HIV-1 RNA (continuous) were included as covariates.
Missing Data Method 1: a Baseline observation carried forward approach was used post-subject discontinuation, as well as for the last time point for subjects who completed the study but for whom the last viral load assessment was missing; last observation carried forward was used for subjects who completed the study but had a missing value at an intermediate time point of interest. If a subject had a missing Baseline viral load assessment, log_{10} changes from Baseline for all time points were considered to be 0.
BID = twice daily; CI = confidence interval; HIV = human immunodeficiency virus; ITT = intent-to-treat; LSM = least squares mean; N = number of subjects in the ITT population; NA = not applicable; PI = protease inhibitor; QD = once daily; RNA = ribonucleic acid; SE = standard error.

Table 10. Descriptive Statistics of Change From Baseline Log_{10} Plasma HIV-1 RNA (Log_{10} Copies/mL) at Week 96 - Missing Data Method 1 - ITT

	Lersivirine 750 mg QD	Lersivirine 1000 mg QD	Etravirine 200 mg BID
N	31	32	34
Mean (SD)	-0.69 (1.39)	-0.36 (1)	-0.96 (1.49)

Baseline log_{10} HIV-1 RNA level was calculated as the average of log_{10} transformed HIV-1 RNA values obtained prior to and including Day 1 predose.
Missing Data Method 1: a Baseline observation carried forward approach was used post-subject discontinuation, as well as for the last time point for subjects who completed the study but for whom the last viral load assessment was missing; last observation carried forward was used for subjects who completed the study but had a missing value at an intermediate time point of interest. If a subject had a missing Baseline viral load assessment, log_{10} changes from Baseline for all time points were considered to be 0.
BID = twice daily; HIV = human immunodeficiency virus; ITT = intent-to-treat; N = number of subjects in the ITT population; QD = once daily; RNA = ribonucleic acid; SD = standard deviation.

Time-Averaged Difference in Log_{10} Transformed HIV-1 RNA Levels at Week 24 and 48: Time-averaged difference in log_{10} transformed HIV-1 RNA levels at Week 24 and 48 is presented in Table 11.

Table 11. Statistical Analysis of TAD in Log_{10} Plasma HIV-1 RNA (Log_{10} Copies/mL) at Week 24 and 48 - ITT

	Lersivirine 750 mg QD	Lersivirine 1000 mg QD	Etravirine 200 mg BID
Week 24			
N	31	32	34
LSM (SE)	-1.54 (0.18)	-1.57 (0.19)	-2.04 (0.17)
LSM difference (SE difference)	0.50 (0.25)	0.47 (0.25)	NA
80% CI	0.2, 0.8	0.1, 0.8	NA
Week 48			
N	31	32	34
LSM (SE)	-1.39 (0.24)	-1.12 (0.25)	-1.89 (0.23)
LSM difference (SE difference)	0.50 (0.33)	0.76 (0.33)	NA
80% CI	0.1, 0.9	0.3, 1.2	NA

Screening HIV-1 RNA (<100,000 and ≥100,000 copies/mL), prior PI experience (yes and no) and Baseline log10 HIV-1 RNA (continuous) were included as covariates.
PI naïve and absence of PI resistance mutations versus PI experienced or presence of PI resistance mutations.
BID = twice daily; CI = confidence interval; HIV = human immunodeficiency virus; ITT = intent-to-treat; LSM = least squares mean; N = number of subjects in the ITT population; NA = not applicable; QD = once daily; RNA = ribonucleic acid; SE = standard error; TAD = time-averaged difference.

Percentage of Subjects With TLOVR Responders at Week 24 and 48: The percentage of TLOVR50 responders at Week 24 and 48 are presented in Table 12.

Table 12. Statistical Analysis (CMH) of Difference in Percentage of TLOVR50 Responders at Week 24 and 48 - MSDF - ITT

	Lersivirine 750 mg QD	Lersivirine 1000 mg QD	Etravirine 200 mg BID
Week 24			
N	31	32	34
n (%)	15 (48.4)	14 (43.8)	23 (67.6)
Difference (%)[a]	-21.6	-23.7	NA
SE difference (%)[a]	11.2	11.1	NA
80% CI for difference, (%)	-37.5, -5.7	-39.4, -8.0	NA
Week 48			
N	31	32	34
n (%)	13 (41.9)	9 (28.1)	19 (55.9)
Difference (%)[a]	-16.7	-27.3	NA
SE difference (%)[a]	11.4	11.0	NA
80% CI for difference, (%)	-32.9, -0.5	-42.9, -11.6	NA

The denominator (N) used for the percentage calculation included all the subjects in ITT.
BID = twice daily; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; HIV = human immunodeficiency virus; ITT = intent-to-treat; MSDF = missing/switch/discontinuation = failure; N = number of subjects in the ITT population; n = number of TLOVR50 responders; NA = not applicable; PI = protease inhibitor; QD = once daily; RNA = ribonucleic acid; SE = standard error; TLOVR = time to loss of virologic response.
a. Cochran-Mantel-Haenszel estimates adjusted for randomization stratification variables of screening HIV-1 RNA level (<100,000 versus ≥100,000 copies/mL) and PI experience status.

Change From Baseline in CD4+ (Absolute and Percentage) at Weeks 24 and 48:

CD4+ Cell Count (Absolute): Change from Baseline in CD4+ (absolute) at Weeks 24 and 48 are presented in Table 13.

Table 13. Statistical Analysis of Change From Baseline Absolute CD4+ Cell Count (cells/µL) at Week 24 and 48 - LOCF - ITT

	Lersivirine 750 mg QD	Lersivirine 1000 mg QD	Etravirine 200 mg BID
Week 24			
N	31	32	34
LSM (SE)	103 (22.2)	71 (21.5)	115 (21.0)
LSM difference (SE difference)	-11.6 (29.9)	-43.8 (29.7)	NA
80% CI	-50.3, 27.0	-82.1, -5.5	NA
Week 48			
N	31	32	34
LSM (SE)	128 (24.8)	80 (24.0)	132 (23.4)
LSM difference (SE difference)	-3.7 (33.4)	-52.2 (33.1)	NA
80% CI	-46.8, 39.4	-95.0, -9.4	NA

Baseline absolute CD4+ cell count was calculated as mean of all predose measurements.
Screening HIV-1 RNA level (<100,000 and ≥100,000 copies/mL), Screening PI resistance (PI naive and absence of PI resistance mutations versus PI experienced or presence of PI resistance mutations) and Baseline absolute CD4+ cell count (continuous) were included as covariates.
LOCF: If an observation at a visit was missing then the last non-missing observation was imputed.
BID = twice daily; CD4 = cluster of differentiation 4; CI = confidence interval; ITT = intent-to-treat; LOCF = last observation carried forward; LSM = least square mean; N = number of subjects in the ITT population; NA = not applicable; PI = protease inhibitor; QD = once daily; SE = standard error.

CD4+ Cell Count (Percentage): Change from Baseline in CD4+ (Percentage) at Weeks 24 and 48 are presented in Table 14.

Table 14. Statistical Analysis of Change From Baseline CD4+ Cell Count (Percentage) at Week 24 and 48 - LOCF - ITT

	Lersivirine 750 mg QD	Lersivirine 1000 mg QD	Etravirine 200 mg BID
N	31	32	34
LSM (SE), %	3.2 (0.66)	3.9 (0.64)	3.9 (0.62)
LSM difference (SE difference)	-0.7 (0.9)	0.1 (0.9)	NA
80% CI	-1.8, 0.5	-1.1, 1.2	NA
N	31	32	34
LSM (SE), %	4.7 (0.82)	4.2 (0.79)	4.6 (0.77)
LSM difference (SE difference)	0.1 (1.1)	-0.4 (1.1)	NA
80% CI	-1.3, 1.5	-1.8, 1.0	NA

Baseline percentage CD4+ cell count was calculated as mean of all predose measurements.
Screening HIV-1 RNA (<100,000 and ≥100,000 copies/mL), Screening PI resistance (PI naive and absence of PI resistance mutations versus PI experienced or presence of PI resistance mutations) and Baseline percentage CD4+ cell count (continuous) were included as covariates.
LOCF: If an observation at a visit was missing then the last non-missing observation was imputed.
BID = twice daily; CD4 = cluster of differentiation 4; CI = confidence interval; ITT = intent-to-treat; LOCF = last observation carried forward; LSM = least square mean; N = number of subjects in the ITT population; NA = not applicable; PI = protease inhibitor; QD = once daily; SE = standard error.

Virologic Sub-Populations, Outcomes and Data Availability: A summary of the outcomes according to the TLOVR algorithm, based on an HIV-1 RNA cut-off set at 50 copies/mL (TLOVR50), is shown in Table 15.

Table 15. Subject Accountability for the Virology Analysis Population Through Weeks 24 and 48

Analysis Population	Week 24			Week 48		
	Lersivirine 750 mg QD (N=31)	Lersivirine 1000 mg QD (N=32)	Etravirine 200 mg BID (N=34)	Lersivirine 750 mg QD (N=31)	Lersivirine 1000 mg QD (N=32)	Etravirine 200 mg BID (N=34)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total population (ITT-treated)	31 (100)	32 (100)	34 (100)	31 (100)	32 (100)	34 (100)
TLOVR50 responders	15 (48.4)	14 (43.8)	23 (67.6)	13 (41.9)	9 (28.1)	19 (55.9)
TLOVR50 failures	16 (51.6)	18 (56.3)	11 (32.4)	18 (58.1)	23 (71.9)	15 (44.1)
TLOVR50 non-virologic failures	6 (19.4)	5 (15.6)	3 (8.8)	6 (19.4)	7 (21.9)	7 (20.6)
TLOVR50 virologic failures	10 (32.3)	13 (40.6)	8 (23.5)	12 (38.7)	16 (50.0)	8 (23.5)
Failure analysis population[a]	10 (32.3)	11 (34.4)	3 (8.8)	12 (38.7)	16 (50.0)	4 (11.8)

BID = Twice daily; ITT = intent-to-treat; N = total number of subjects; n = number of evaluable subjects; QD = once daily; TLOVR = time to loss of virologic response.
a. The failure analysis population represents the sub-population of TLOVR50 failures (both virologic and non-virologic) where valid paired Baseline and on-treatment results (both phenotypic and genotypic) had been obtained using samples with HIV-1 RNA ≥500 copies/mL.

At Week 24, failure analysis population consisted of a total of 24 of 45 TLOVR50 failure subjects (lersivirine 750 mg QD: n=10/16, lersivirine 1000 mg QD: n=11/18; etravirine 200 mg BID: n=3/11). The main reason for reduced numbers evaluated was insufficient HIV-1 RNA data to perform tests.

At Week 48, a total of 32 of 56 TLOVR50 failure subjects were included in the failure analysis population (lersivirine 750 mg QD: n=12/18, lersivirine 1000 mg QD: n=16/23; etravirine 200 mg BID: n=4/15) at Week 48. The reasons for exclusion from the failure analysis population were plasma HIV-1 RNA <500 copies/mL (lersivirine 750 mg QD n=4, lersivirine 1000 mg QD n=4, etravirine n=8) or the unavailability of appropriate samples (lersivirine 750 mg QD n=2, lersivirine 1000 mg QD n=3, etravirine n=3).

Genotypic and phenotypic resistance to lersivirine, etravirine, darunavir and NRTIs at the time of treatment failure:

Table 16 summarizes the genotypes and phenotypes of viruses from subjects with emergent NNRTI resistance on-treatment. There was a clear association between the emergence of phenotypic resistance and genotypic changes in instances where treatment-emergent NNRTI

mutations were observed in the lersivirine-treated subjects. The results obtained at the Week 24 analysis are not presented as the results in Table 16 are cumulative throughout the study.

Virus from only 1 subject (in the etravirine treatment group) was found at Baseline with a lersivirine-specific mutation (H221Y) using population sequencing and all but 1 virus had NNRTI RAMs present pretreatment. Most subjects did not have virus with NRTI RAMs present before starting therapy (n=9/12, 75.0%; 7/16, 43.8% and 4/4, 100% subjects treated with lersivirine 750 mg QD, lersivirine 1000 mg QD and etravirine 200 mg BID, respectively).

The emergence of RAMs on-treatment was infrequent in the failure analysis population. In the lersivirine 750 mg QD treatment group, there were 4 subjects who experienced emergence of a single NNRTI RAM during treatment. In the lersivirine 1000 mg treatment group, 2 lersivirine RAMs (F227L and V108I) and 1 NNRTI RAM (P225H) were selected during treatment.

One subject in the lersivirine 750 mg QD treatment group developed phenotypic resistance to efavirenz, delavirdine and nevirapine without any emergent NNRTI RAMs being detected. This subject's virus did however carry the K103N and P225H mutations pretreatment.

Table 16. Pretreatment and Treatment Emergent NNRTI RAMs and Fold-Change of Drug Susceptibility in the Failure Analysis Population With Emergent Genotypic or Phenotypic Resistance Through Week 48 and Beyond

Treatment Group	Subject	On-Treatment Genotype	IC50 FC Baseline/On-Treatment[a]				
			Lersivirine	Efavirenz	Delavirdine	Etravirine	Nevirapine
Lersivirine 750 mg	1	A98A/G[b] K103K/N[b] V106V/I[b,c] V108V/I	4.79/5.28	29/35	54/37	1.37/0.99	226/≥max
Lersivirine 750 mg	2	V90V/I K103N[b] V106V/I[d]	4.51/3.97	30/23	138/115	1.80/1.48	126/143
Lersivirine 750 mg	3	V106V/I V108V/I[e] V179D[b]	1.38/4.19	0.95/2.28	1.63/4.95	0.71/0.97	0.76/1.64
Lersivirine 750 mg	4	K103N[b] Y188L	6.43/≥max	31/≥max	≥max/≥max	1.10/36	≥max/≥max
Lersivirine 750 mg	5	K103K/N[b] P225P/H[d]	1.00/1.00	1.31/3.16	1.79/8.32	0.79/0.80	1.20/5.91
Lersivirine 1000 mg	6	P225H[b] F227F/L	0.95/3.59	0.75/0.57	0.69/0.05	0.64/0.09	1.45/1.30
Lersivirine 1000 mg	7	K103S[b] M184V[b] T215T/N/S/Y[b] V108V/I	1.68/6.17	3.35/7.68	3.27/6.19	0.28/0.32	11/35
Lersivirine 1000 mg	8	K103K/N[b] P225P/H	1.55/1.15	3.48/1.38	8.38/1.65	0.83/0.80	7.26/1.60
Etravirine	9	K103N[d] E138G	1.67/0.98	12/1.00	17/3.38	0.33/1.80	74/3.64

Emergent resistance-associated mutations and IC50 FC indicating phenotypic resistance are shown in bold fonts. Mutations shown in normal font were present either both pretreatment and on-treatment or pretreatment only (see footnotes b and d below).
Where several evaluable on-treatment samples were available, the closest to treatment failure is given.
FC = fold change; IC50 = inhibitory concentration (at 50% inhibition); max = maximum; NNRTI = non-nucleoside reverse transcriptase inhibitor; RAM = resistance-associated mutation.

a. Only subjects with virus with emergent NNRTI RAMs or phenotypic resistance are reported.
b. Represents variant also present pretreatment.
c. Pretreatment variant observed on-treatment but not in the prespecified on-treatment assessment.
d. Mutation observed only pretreatment.
e. In another analysis of the failure sample, K101E was observed as an emergent mutation without V106I or V108I.

Safety Results:

Adverse Events:

Overall, 87.1%, 81.3% and 94.1% subjects in the lersivirine 750 mg QD, lersivirine 1000 mg QD and etravirine 200 mg BID groups, respectively reported at least 1 AE.
Treatment-emergent adverse events (TEAEs) (all causality) reported for ≥5% of subjects in any treatment group are presented in Table 17. The majority of TEAEs were considered by the investigator to be of mild (Grade 1) or moderate (Grade 2) severity. The most frequently reported TEAEs were nausea, diarrhea, and vomiting.

Table 17. Treatment-Emergent Adverse Events (All Causality) Reported for ≥5% of Subjects in any Treatment Group

System Organ Class MedDRA Preferred Term	Lersivirine 750 mg QD (N=31) n (%)	Lersivirine 1000 mg QD (N=32) n (%)	Etravirine 200 mg BID (N=34) n (%)
Number of subjects with adverse event	27 (87.1)	26 (81.3)	32 (94.1)
Blood and lymphatic system disorders			
Lymphadenopathy	0	0	2 (5.9)
Ear and labyrinth disorders			
Ear pain	0	2 (6.3)	0
Gastrointestinal disorders			
Abdominal pain upper	1 (3.2)	3 (9.4)	3 (8.8)
Diarrhoea	8 (25.8)	7 (21.9)	6 (17.6)
Dyspepsia	1 (3.2)	2 (6.3)	1 (2.9)
Nausea	8 (25.8)	14 (43.8)	4 (11.8)
Vomiting	6 (19.4)	3 (9.4)	3 (8.8)
General disorders and administration site conditions			
Fatigue	0	2 (6.3)	0
Infections and infestations			
Body tinea	2 (6.5)	1 (3.1)	0
Bronchitis	2 (6.5)	1 (3.1)	1 (2.9)
Cystitis	0	0	2 (5.9)
Gastroenteritis	0	1 (3.1)	2 (5.9)
Herpes zoster	0	0	5 (14.7)
Influenza	4 (12.9)	0	4 (11.8)
Lower respiratory tract infection	0	0	2 (5.9)
Nasopharyngitis	2 (6.5)	2 (6.3)	0
Rhinitis	0	0	2 (5.9)
Sinusitis	2 (6.5)	2 (6.3)	0
Tooth abscess	0	0	2 (5.9)
Upper respiratory tract infection	3 (9.7)	3 (9.4)	5 (14.7)
Urinary tract infection	0	3 (9.4)	3 (8.8)
Vulvovaginal candidiasis	2 (6.5)	0	0
Investigations			
Blood glucose increased	1 (3.2)	1 (3.1)	2 (5.9)
Metabolism and nutrition disorders			
Dyslipidaemia	1 (3.2)	0	2 (5.9)
Musculoskeletal and connective tissue disorders			
Arthralgia	2 (6.5)	1 (3.1)	1 (2.9)
Back pain	2 (6.5)	0	5 (14.7)
Muscle spasms	0	2 (6.3)	0

Table 17. Treatment-Emergent Adverse Events (All Causality) Reported for ≥5% of Subjects in any Treatment Group

System Organ Class MedDRA Preferred Term	Lersivirine 750 mg QD (N=31) n (%)	Lersivirine 1000 mg QD (N=32) n (%)	Etravirine 200 mg BID (N=34) n (%)
Myalgia	0	0	2 (5.9)
Pain in extremity	0	0	3 (8.8)
Nervous system disorders			
Dizziness	2 (6.5)	2 (6.3)	1 (2.9)
Headache	2 (6.5)	2 (6.3)	4 (11.8)
Psychiatric disorders			
Depression	0	0	3 (8.8)
Insomnia	2 (6.5)	0	1 (2.9)
Respiratory, thoracic and mediastinal disorders			
Cough	2 (6.5)	0	0
Skin and subcutaneous tissue disorders			
Eczema	0	2 (6.3)	0
Pruritus	2 (6.5)	2 (6.3)	1 (2.9)
Rash	0	0	5 (14.7)
Seborrhoeic dermatitis	2 (6.5)	1 (3.1)	0
Skin lesion	0	2 (6.3)	1 (2.9)

Subjects were only counted once per treatment for each row.
MedDRA (Version 15.1) coding dictionary applied.
BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects in the evaluable population; n = number of subjects with adverse events; QD = once daily.

Treatment-emergent treatment related AEs are presented in Table 18. Most of the gastrointestinal events in all 3 groups were treatment-related.

Table 18. Treatment-Emergent Adverse Events (Treatment Related)

System Organ Class MedDRA Preferred Term	Lersivirine 750 mg QD (N=31) n (%)	Lersivirine 1000 mg QD (N=32) n (%)	Etravirine 200 mg BID (N=34) n (%)
Gastrointestinal disorder			
Diarrhoea	7 (22.6)	6 (18.8)	4 (11.8)
Dry mouth	1 (3.2)	0	0
Nausea	8 (25.8)	11 (34.4)	4 (11.8)
Vomiting	4 (12.9)	3 (9.4)	1 (2.9)
Abdominal distension	0	1 (3.1)	0
Abdominal pain upper	0	3 (9.4)	2 (5.9)
Dyspepsia	0	2 (6.3)	0
Flatulence	0	1 (3.1)	0
Gastritis	0	1 (3.1)	0
Gastrooesophageal reflux disease	0	1 (3.1)	1 (2.9)
Oesophagitis	0	1 (3.1)	0
Salivary hypersecretion	0	1 (3.1)	0
Abdominal pain	0	0	1 (2.9)
Nervous system disorder			
Dizziness	2 (6.5)	2 (6.3)	1 (2.9)
Headache	1 (3.2)	2 (6.3)	1 (2.9)
Hypogeusia	0	1 (3.1)	0
Respiratory, thoracic and mediastinal disorders			
Cough	1 (3.2)	0	0
Bronchospasm	0	0	1 (2.9)
Skin and subcutaneous tissue disorder			
Lipodystrophy acquired	1 (3.2)	0	0
Pruritus	1 (3.2)	1 (3.1)	1 (2.9)
Dermatitis allergic	0	1 (3.1)	0
Rash maculo-papular		1 (3.1)	
Rash	0	0	4 (11.8)
Vascular disorders			
Hypotension	1 (3.2)	0	0
Endocrine disorders			
Hypothyroidism	0	1 (3.1)	0
General disorders and administration site conditions			
Pain	0	1 (3.1)	0
Musculoskeletal and connective tissue disorders			
Joint swelling	0	1 (3.1)	0
Hepatobiliary			
Hepatitis toxic	0	0	1 (2.9)
Metabolism and nutrition disorders			
Diabetes mellitus	0	0	1 (2.9)
Glucose tolerance impaired	0	0	1 (2.9)
Hypertriglyceridaemia	0	0	1 (2.9)
Vitamin D deficiency	0	0	1 (2.9)
Psychiatric disorders			
Depression	0	0	1 (2.9)

AEs and SAEs were not separated out.
MedDRA (Version 15.1) coding dictionary applied.
AE = adverse event; BID = twice daily; MedDRA = MEDICAL Dictionary for Regulatory Activities; N = total number of subjects in the evaluable population; n = number of subjects with adverse events; QD = once daily.

Serious Adverse Events:

A total of 6 subjects reported 9 SAEs: 1 (3.2%), 4 (12.5%) and 1 (2.9%) in the lersivirine 750 mg QD, lersivirine 1000 mg QD and etravirine 200 mg BID groups, respectively.

Table 19. Treatment-Emergent Serious Adverse Events by Special Organ Class and Preferred Term (All Causalities)

System Organ Class MedDRA Preferred Term	Lersivirine 750 mg QD (N=31), n (%)	Lersivirine 1000 mg QD (N=32), n (%)	Etravirine 200 mg BID (N=34), n (%)
Number of subjects with SAE	1 (3.2)	4 (12.5)	1 (2.9)
Cardiac disorders			
Coronary artery disease	0	1 (3.1)	0
Infections and infestations			
Pneumocystis jiroveci pneumonia	0	0	1 (2.9)
Pneumonia	0	0	1 (2.9)
Pulmonary tuberculosis	0	2 (6.3)	0
Injury, poisoning and procedural complications			
Head injury	0	1 (3.1)	0
Vascular disorders			
Hypertension	1 (3.2)	0	0

Subjects were only counted once per treatment for each row.
MedDRA (Version 15.1) coding dictionary applied.
BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects in the evaluable population; n = number of subjects with adverse events; QD = once daily; SAE = serious adverse events.

Two SAEs (alanine aminotransferase increased and aspartate aminotransferase increased) in the lersivirine 1000 mg QD group were considered by the investigator to be treatment-related.

Discontinuations due to Adverse Events: A total of 6 subjects permanently discontinued the study due to AEs: 2 subjects in the lersivirine 1000 mg QD group and 4 subjects in the etravirine 200 mg BID group (Table 20).

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

Serial Number	MedDRA PT (Severity)	Start Day[a]	Stop Day[a]	Causality	Outcome
Lersivirine 1000 mg QD					
1[b]	Abdominal distension (Grade 2)	2	407	Treatment-related	Resolved
2	Pulmonary tuberculosis (Grade 3)	37	>43	Treatment-unrelated	Still present
Etravirine 200 mg BID					
3[b]	Hepatitis toxic (Grade 3)	505	>549	Treatment-related	Still present
4	Diarrhoea[c] (Grade 2)	2	12	Treatment-unrelated	Resolved
5	Rash (Grade 2)	8	43	Treatment-related	Resolved
6	Hepatitis B (Grade 1)	197	421	Treatment-unrelated	Resolved

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 15.1).
ARV = antiretroviral; BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; QD = once daily.

a. Start day and stop day were the start and stop of the AE relative to the start of the treatment (Day 1).
b. Subjects discontinued due to adverse events post-Week 48.
c. Considered by investigator to be related to the background ARV darunavir/ritonavir.

Dose Reductions or Temporary Discontinuations due to TEAEs: The number of subjects who temporarily discontinued the study or had dose reductions due to TEAEs was comparable across the treatment groups: 2, 2 and 1 subjects in the lersivirine 750 mg QD, lersivirine 1000 mg QD and etravirine 200 mg BID groups, respectively (Table 21).

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

Serial Number	MedDRA PT (Severity)	Start Day[a]	Stop Day[a]	Causality	Outcome
Lersivirine 750 mg QD					
1	Diarrhoea (Grade 1)	89	101	Treatment-related	Resolved
	Nausea (Grade 1)	89	101	Treatment-related	Resolved
	Vomiting (Grade 1)	89	101	Treatment-unrelated[b]	Resolved
	Dizziness (Grade 2)	89	89	Treatment-related	Resolved
2	Influenza (Grade 1)	156	160	Treatment-unrelated	Resolved
Lersivirine 1000 mg QD					
3	Gastritis (Grade 2)	50	52	Treatment-related[c]	Resolved
4	Diarrhoea (Grade 2)	1	18	Treatment-related[c]	Resolved
	Nausea (Grade 2)	1	>84	Treatment-related[c]	Still present
	Vomiting (Grade 2)	1	246	Treatment-related[c]	Resolved
Etravirine 200 mg BID					
5	Herpes zoster (Grade 2)	203	212	Treatment-unrelated	Resolved with sequelae
	VIIth nerve paralysis (Grade 1)	217	238	Treatment-unrelated	Resolved

AE=adverse event; ARV=antiretroviral; BID=twice daily; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; QD=once daily.
AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 15.1).
a. Start day and stop day were the start and stop of the AE relative to the start of the treatment (Day 1).
b. Considered by investigator to be related to the background ARV darunavir/ritonavir.
c. Considered by investigator to be related to the study drug and/or background ARV darunavir/ritonavir.

Deaths: There were no deaths among subjects who participated in this study.

Laboratory Results: At Week 24, the incidence of laboratory abnormalities was higher in the lersivirine 1000 mg QD group (30 subjects; 96.8%) and the etravirine 200 mg BID group (31 subjects; 91.2%) as compared to the lersivirine 750 mg QD group (23 subjects; 79.3%).

At Week 48, the incidence of laboratory abnormalities was comparable across treatment groups.

- Incidence of Grade 3 and Grade 4 Laboratory Abnormalities: Overall, the incidence of subjects with Grades 3 or 4 laboratory abnormalities was higher in the etravirine group than in the lersivirine groups.

Table 22. Overall Summary of Laboratory Results - DAIDS Grades 3 and 4

	Week 24			Week 48		
	Lersivirine 750 mg QD (N=31)	Lersivirine 1000 mg QD (N=32)	Etravirine 200 mg BID (N=34)	Lersivirine 750 mg QD (N=31)	Lersivirine 1000 mg QD (N=32)	Etravirine 200 mg BID (N=34)
Number of subjects evaluable	29	31	34	29	31	34
Number of laboratory abnormalities	5	6	13	7	6	12
Number (%) of subjects with laboratory abnormalities	3 (10.3)	3 (9.7)	6 (17.6)	4 (13.8)	3 (9.7)	7 (20.6)

Abnormal refers to a DAIDS grade of 3 or greater.
For number of laboratory abnormalities, subjects with multiple occurrences of the same laboratory parameter were counted only once.
BID=twice daily; DAIDS=division of acquired immunodeficiency syndrome; N=total number of subjects; QD=once daily.

Physical Examination: At Weeks 24, 48 and 96, there was no notable mean change from Baseline in any of the anthropometric measurements.

Vital Signs: At Weeks 24, 48 and 96, there were no notable median 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 etravirine group. There were no notable median postural changes in any of the vital signs parameters in any of the treatment groups at any time point in the study.

Electrocardiogram: At Weeks 24, 48 and 96, there were no clinically relevant differences in mean Baseline ECG values or mean change from Baseline ECG values between the treatment groups in all parameters analyzed (RR interval, heart rate, PR interval, QRS complex, QT interval, QTc interval, QTcB interval [Bazett's correction], QTcF interval [Fridericia's correction]) at any time point in the study.

CONCLUSIONS:

Conclusions (Up-to 24-Week Analysis):

The efficacy conclusions are as follows:

- For the primary endpoint analysis, the percentage of subjects with HIV-1 RNA <50 copies/mL (MSDF; ITT) at Week 24 in the lersivirine groups was lower than that of the etravirine group. The percentage of subjects with HIV-1 RNA <50 copies/mL at Week 24 (MSDF) in the ITT population was 48.4%, 43.8% and 67.6% for the lersivirine 750 mg QD, lersivirine 1000 mg QD and etravirine 200 mg BID groups, respectively.

- The percentage of subjects with HIV-1 RNA <400 copies/mL (MSDF; ITT) at Week 24 in the lersivirine groups was lower than that in the etravirine group.

- The decrease from Baseline in log_{10} transformed HIV-1 RNA at Week 24 in ITT in the lersivirine groups was lower than that of the etravirine group ($p<0.2$; LSM: -1.65, -1.74, and -2.28 log_{10} copies/mL in the lersivirine 750 mg QD, lersivirine 1000 mg QD, and etravirine 200 mg BID groups, respectively).

- The decrease from Baseline in TAD log_{10} transformed HIV-1 RNA level at Week 24 in the ITT in the lersivirine groups was lower than that of the etravirine group ($p<0.2$; LSM: -1.54, -1.57, and -2.04 log_{10} copies/mL in the lersivirine 750 mg QD, lersivirine 1000 mg QD, and etravirine 200 mg BID groups, respectively).

- The mean increase from Baseline in absolute CD4+ cell count at Week 24 (ITT; last observation carried forward [LOCF]) was comparable between the lersivirine 750 mg QD group and etravirine 200 mg BID group, but was lower in the lersivirine 1000 mg QD group in comparison to the etravirine 200 mg BID group ($p<0.2$; LSM: 103, 71, and 115 cells/μL in the lersivirine 750 mg QD, lersivirine 1000 mg QD and etravirine 200 mg BID groups, respectively). Mean increase from Baseline in percentage CD4+ cell count (ITT; LOCF) at Week 24 was comparable across the treatment groups.

Conclusions (Up-to 96-Week Analysis):

The efficacy conclusions are as follows:

- The percentage of subjects with HIV-1 RNA <50 copies/mL (MSDF; ITT) at Week 48 in the lersivirine groups was lower than that of the etravirine group. The percentage of subjects with HIV-1 RNA <50 copies/mL at Week 48 (MSDF) in the ITT population was 41.9%, 31.3% and 61.8% for the lersivirine 750 mg QD, lersivirine 1000 mg QD and etravirine 200 mg BID groups, respectively.

- The percentage of subjects with HIV-1 RNA <50 copies/mL (MSDF) at Week 96 in the lersivirine groups was lower than that in the etravirine group.

- The percentage of subjects with HIV-1 RNA <400 copies/mL (MSDF; ITT) at Week 48 in the lersivirine groups was lower than that in the etravirine group.

- The decrease from Baseline in log_{10} transformed HIV-1 RNA level (ITT; Missing Data Method 1) at Week 48 in the lersivirine groups was lower than that of the etravirine group (LSM: -1.42, -0.95, and -2.02 log_{10} copies/mL in the lersivirine 750 mg QD, lersivirine 1000 mg QD, and etravirine 200 mg BID groups, respectively).

- The decrease from Baseline in TAD log_{10} transformed HIV-1 RNA level at Week 48 in the ITT in the lersivirine groups was lower than that of the etravirine group (LSM: -1.39, -1.12, and -1.89 log_{10} copies/mL in the lersivirine 750 mg QD, lersivirine 1000 mg QD, and etravirine 200 mg BID groups, respectively).

- Mean increase from Baseline in absolute CD4+ cell count at Week 48 (ITT; LOCF) was comparable between the lersivirine 750 mg QD group and etravirine 200 mg BID group, but was lower in the lersivirine 1000 mg QD group in comparison to the etravirine 200 mg BID group (LSM: 128, 80, and 132 cells/μL in the lersivirine 750 mg QD, lersivirine 1000 mg QD and etravirine 200 mg BID groups, respectively). Mean increase from Baseline in percentage CD4+ cell count (ITT; LOCF) at Week 48 was comparable across the treatment groups.

- The percentage of subjects categorized as TLOVR50 responders at Week 48 (ITT) in the lersivirine groups was lower than that of the etravirine group.

The virology conclusions are as follows:

- There was a total of 56 subjects who experienced failure through Week 48 according to the TLOVR50 algorithm. Of these, 32 subjects had valid paired Baseline and on-treatment evaluation (failure analysis population: lersivirine 750 mg QD group: n=12; lersivirine 1000 mg QD group: n=16; etravirine 200 mg BID group: n=4).

- In the failure analysis population, virus from all but 1 subject had 1 or more NNRTI mutation(s) present pretreatment, although only 5 subjects in all had any major PI RAMs. An absence of NRTI RAMs was observed pretreatment in virus from 9/12, 7/16 and 4/4 subjects treated with lersivirine 750 mg QD, lersivirine 1000 mg QD, and etravirine 200 mg BID groups, respectively.

- The emergence of RAMs was infrequent. Virus from 7 of 28 lersivirine-treated subjects were found with emergent NNRTI or lersivirine RAMs on-treatment. One of 4 etravirine-treated subjects had an emergent etravirine RAM.

- Reduced phenotypic susceptibility to delavirdine, nevirapine and efavirenz (first generation NNRTIs) was frequent pretreatment (50 to 75%). One subject whose pretreatment virus carried the K103N and P225H RAMs developed phenotypic resistance to first generation NNRTIs during lersivirine treatment.

- Genotypic changes correlated with the change of phenotypic susceptibility to lersivirine. Cross resistance was not observed to any of the other NNRTIs when the lersivirine-specific mutation, F227L, was selected.

- The presence of minority species variants associated with resistance to lersivirine was not predictive of virologic outcome or emergence of resistance.

The safety conclusions are as follows:

- There were no deaths in this study.

- Overall, lersivirine was generally well tolerated. There was a higher incidence of nausea reported in both the lersivirine groups as compared with the etravirine group. The

majority of these cases were mild (Grade 1) in severity and none resulted in discontinuation from the study. No subject experienced Grade 3 or Grade 4 nausea.

- The incidence of Grade 2, 3 or 4 AEs was higher in the etravirine 200 mg BID group (67.6%) as compared to the lersivirine groups (41.9% in the lersivirine 750 mg QD group and 37.5% in the lersivirine 1000 mg QD group).

- There were few Grade 3 or 4 AEs and only 6 subjects experienced SAEs (1 of which resulted in permanent discontinuation). A small number of subjects (6 subjects) discontinued the study due to AEs.

- There were 3 Category C events reported in 3 subjects (2 subjects in the lersivirine 1000 mg QD group and 1 subject in the etravirine 200 mg BID group) in the study, which were considered as unrelated to study treatment. Five of the 8 incidences of rash were considered related to study treatment with etravirine.

- A total of 6 subjects discontinued the study due to AEs: 0 subjects in the lersivirine 750 mg QD group, 2 (6.3%) subjects in the lersivirine 1000 mg QD group and 4 (11.8%) subjects in the etravirine 200 mg BID group.

- The incidence of Grade 3 or 4 laboratory abnormalities was lower in the lersivirine groups than in the etravirine group (7 abnormalities in 4 subjects and 6 abnormalities in 3 subjects in the lersivirine 750 mg QD and 1000 mg QD, respectively; 12 abnormalities in 7 subjects in the etravirine 200 mg BID group).