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

PROTOCOL NO.: A5271010

PROTOCOL TITLE: A Randomized, Double Blind, Placebo-Controlled, Multicentre Study in Asymptomatic HIV Infected Patients to Investigate Pharmacodynamics, Pharmacokinetics, Safety and Toleration of UK-453,061

Study Centers: Three (3) centers in Germany took part in the study and randomized subjects.

Study Initiation and Final Completion Dates: 14 February 2006 to 19 February 2007

Phase of Development: Phase 2

Study Objectives: To investigate the effects of 7-day monotherapy of UK-453,061 (lersivirine) on viral load response in asymptomatic human immunodeficiency virus (HIV) infected subjects and to assess the dose-response relationship; and to assess the pharmacokinetics (PK), safety and tolerability of lersivirine in asymptomatic HIV infected subjects.

METHODS

Study Design: This was a randomized, double-blind, placebo-controlled, parallel group multicenter study to investigate the effects of short-term monotherapy with lersivirine on viral load response in HIV infected subjects. Subjects were not blinded to whether they were receiving once daily (QD) or twice daily (BID) dosing, but were blinded with respect to the dose received. In Stage 1, 3 subjects were randomized to placebo BID, 1 subject to placebo QD, 6 subjects each to lersivirine 10 mg BID, 30 mg BID, 100 mg BID and 500 mg QD. In Stage 2, 1 subject each was randomized to placebo BID and placebo QD and 6 subjects each to lersivirine 100 mg QD, 500 mg BID and 750 mg QD. Subjects attended the unit for a screening visit, a randomization visit, visits at specified times throughout the study period and a follow-up visit. Blood samples were collected at protocol-specified times throughout the study. Screening in Stage 1 ensured that at least 28 subjects completed baseline and Day 8 predose assessments of viral load. Subjects who withdrew from the study before Day 8 were replaced but could still be included in the safety analysis and in the final PK/pharmacodynamic (PD) analyses, if appropriate. Stage 2 screening ensured that 20 subjects completed baseline and Day 8 predose assessments of viral load.

A formal decision rule was used to decide whether to proceed to Stage 2. If the probability of a 100 mg BID dose yielding >1 $\log_{10}$ copies/mL decrease in HIV viral load was >0.1, the study was to continue to Stage 2. Table 1 shows the schedule of activities.

Table 1. Schedule of Activities

Protocol Activity	Study Day															
	S	R	1	2	3	4	5	6	7	8	9	11	14	20	28	40 Follow-Up
Breath alcohol			X[a]							X[a]						
Drugs of abuse	X	X	X[a]							X[a]						
Physical examination	X		X[a]							X[a]						X
12-lead electrocardiogram	X		X[b]							X[b]						X
BP and PR[c]	X		X[b]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[b]						X
Viral load	X	X	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X	X	X	X	X	X
CD4 count	X															
Viral genotyping	X		X[a]							X[a]						X
Virus isolation			X[a]							X[a]						X
Laboratory safety	X	X	X[a]		X[a]		X[a]			X[a]	X		X			X
Urinalysis	X	X	X[a]		X[a]		X[a]			X[a]	X		X			X
Lersivirine or placebo			X	X	X	X	X	X	X	X[d]						
Pharmacokinetic samples			X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[e]	X[f]					
Subject genotype sample			X[a]													
HCV RNA			X[g]							X[g]						X[g]

BP = blood pressure; CD4 = cluster of differentiation 4; HCV = hepatitis C virus; PR = pulse rate; R = randomization; RNA = ribonucleic acid; S = screening.

a. Pre-morning dose.
b. –0.5, 1 and 2 hours (post-morning dose).
c. BP and PR: supine and standing.
d. Morning dose only.
e. 0, 1, 2, 3, 4, 6 and 12 hours postdose.
f. 24 hours post-last dose.
g. If screening HCV serology was positive.

Number of Subjects (Planned and Analyzed): It was planned to screen sufficient subjects in Stage 1 to ensure that at least 28 subjects completed the baseline and Day 8 predose assessments of viral load. Stage 2 was to enroll no more subjects than were enrolled into Stage 1. Eighty one subjects were screened and 49 were assigned to study treatment. One subject withdrew consent after randomization and prior to receiving the first dose. Forty eight subjects were treated and completed the study.

Diagnosis and Main Criteria for Inclusion: Asymptomatic HIV-1 infected males aged 18 to 55 years; with virus not containing nonnucleoside reverse transcriptase inhibitor resistant mutations as determined by the VircoGEN virtual phenotyping assay. The main exclusion criteria were: cluster of differentiation (CD) 4 count <250 cells/mm^3; viral load <5000 copies/mL using reverse transcriptase-polymerase chain reaction (Roche Amplicor version 1.5); HIV infection diagnosed <3 months prior to screening, or evidence of recent seroconversion.

Study Treatment: Lersivirine and placebo was provided as a bulk powder for preparation of an oral suspension at the Unit, which was pre-weighed and suspended predose in Avicel 1.5% (Stage 1) and provided in Stage 2 as 50 and 250-mg tablets and matching placebo.

Pharmacokinetic, Pharmacodynamic, and Safety Endpoints:

Primary Endpoint: The change in log_{10} transformed HIV viral load from Baseline to Day 8.

Secondary Endpoints: Lersivirine steady state PK, safety endpoints including adverse events (AEs), vital signs, electrocardiogram (ECGs) and laboratory data.

No efficacy evaluations were performed for this study.

Safety Evaluations: Safety evaluations included safety laboratory tests, measurements of blood pressure and pulse rate, 12-lead ECG, and physical examination at protocol-specified times, and monitoring of AEs throughout the study. In addition urine drug screen, CD4 count, hepatitis B surface antigen and hepatitis B core antibody, antihepatitis C virus serology, hepatitis C virus (HCV) ribonucleic acid (RNA) (if subject was HCV positive) were performed.

Statistical Methods:

Analysis Sets:

Intention-to-Treat (ITT) Analysis Set: The ITT analysis set was defined as those subjects who were randomized and received at least 1 dose of study medication (lersivirine or placebo).

Per Protocol (PP) Analysis Sets: There were 3 PP analysis sets:

- Per Protocol Pharmacokinetic Analysis Set: The PP pharmacokinetic analysis set was defined as those subjects in the ITT analysis set who had at least 1 postdose PK

concentration. By definition this excluded subjects on placebo. This analysis set was used for the summary of PK data and was referred to as the PK population.

- Per Protocol Pharmacodynamic Analysis Set: The PP pharmacodynamic analysis set was defined as those subjects in the ITT analysis set who had at least 1 postdose viral load measurement. This analysis set was used for the summary of PD data and was referred to as the PD population.

- Per Protocol Pharmacodynamic Modelling Analysis Set: The PP pharmacodynamic modelling analysis set was defined as those subjects in the ITT analysis set who had viral load measurements available for baseline and Day 8 and had not significantly deviated from the protocol. This was the primary analysis set and was used for the analysis of the primary endpoint, change from Baseline to Day 8 in $\log_{10}$ transformed HIV viral load. This analysis set was referred to as the Pharmacodynamic modeling population.

Safety Analysis Set: This analysis set was comprised of subjects who were randomized and received at least 1 dose of study medication (lersivirine or placebo). This analysis set was the same as the ITT population and was referred to as the Safety population.

The primary endpoint was the change in $\log_{10}$ transformed HIV viral load from Baseline to Day 8. Prior to analysis, the HIV viral load data were $\log_{10}$ transformed. Baseline $\log_{10}$ viral load values were calculated as the arithmetic mean of the 3 predose $\log_{10}$ values (screening, randomization and the pre-first dose). The HIV viral load data were summarized descriptively. Non-linear maximum drug effect relationship (E_{max}) models were investigated but the results were not presented.

The PK and safety data were summarized descriptively.

RESULTS

Subject Disposition and Demography: A total of 81 subjects were screened of which 48 subjects were treated and completed the study. One subject withdrew consent after randomization to the 100 mg BID group and prior to receiving the first dose. No discontinuations were reported in the study post the first dose. All the subjects were analyzed for safety and PD, and the subjects who received lersivirine were analyzed for PK. Details of subject evaluation groups are provided in Table 2.

Table 2. Subject Evaluation Groups

Number of Subjects	Lersivirine							Placebo
	10 mg BID	30 mg BID	100 mg BID	500 mg QD	750 mg QD	500 mg BID	100 mg QD	
Assigned to study treatment	49							
Treated	6	6	6	6	6	6	6	6
Completed	6	6	6	6	6	6	6	6
Discontinued	0	0	0	0	0	0	0	0
Randomized not treated	0	0	1	0	0	0	0	0
Analyzed for pharmacokinetics:								
PK population[a]	6	6	6	6	6	6	6	0
Analyzed for pharmacodynamics								
PDM population[b]	6	6	6	6	6	6	6	6
PD population[c]	6	6	6	6	6	6	6	6
Analyzed for safety:								
Adverse events	6	6	6	6	6	6	6	6
Laboratory data	6	6	6	6	6	6	6	6
ITT population	6	6	6	6	6	6	6	6

BID = twice daily; ITT = intent-to-treat; PD = pharmacodynamic; PDM = pharmacodynamic modeling; PK = pharmacokinetic; QD: once daily.

a. Subjects who had at least 1 postdose PK concentration.

b. Subjects who had viral load measurements available for baseline and Day 8 and had not significantly deviated from the protocol.

c. Subjects who had at least 1 postdose viral load measurement.

All the subjects were males and the majority (n=45) of subjects were White. The overall demographic and baseline characteristics are given in Table 3.

Table 3. Overall Demographic and Baseline Characteristics

Number of Subjects	Lersivirine							Placebo (N=6)
	10 mg BID (N=6)	30 mg BID (N=6)	100 mg BID (N=6)	500 mg QD (N=6)	750 mg QD (N=6)	500 mg BID (N=6)	100 mg QD (N=6)	
Age (years):								
Mean (SD)	38.8 (8.4)	38.2 (8.6)	33.5 (8.6)	41.7 (4.1)	29.2 (7.9)	40.3 (7.5)	37.0 (8.5)	33.8 (8.0)
Range	25.0-46.0	24.0-48.0	24.0-44.0	36.0-48.0	21.0-40.0	32.0-52.0	29.0-49.0	22.0-44.0
Weight (kg):								
Mean (SD)	73.6 (10.0)	80.1 (11.9)	70.3 (9.0)	82.3 (9.8)	76.4 (10.2)	70.5 (8.5)	74.9 (6.4)	68.6 (7.1)
Range	62.0-92.0	66.4-97.0	60.0-85.0	68.5-95.0	63.5-92.0	62.0-85.0	68.0-85.0	63.0-80.0
Body mass index (kg/m^2):								
Mean (SD)	23.4 (3.2)	24.2 (3.6)	22.6 (3.1)	25.2 (3.3)	23.5 (2.5)	21.1 (1.3)	22.7 (1.9)	22.4 (2.0)
Range	21.6-29.7	21.1-29.0	18.9-27.8	19.6-28.7	20.0-27.5	18.5-21.9	21.2-26.2	19.4-25.0
Viral load (log10 copies/mL)								
Mean[a] (SD)	4.57 (0.33)	4.39 (0.48)	4.41 (0.27)	4.38 (0.17)	4.65 (0.46)	4.55 (0.45)	4.70 (0.33)	4.57 (0.49)

Body mass index was calculated as weight/(height in centimeter x .01)^2.

BID = twice daily; QD = once daily; SD = standard deviation.

a. Arithmetic mean, baseline was the mean of screening, randomization and Day 1 predose log_{10} viral load measurements.

Pharmacodynamic and Pharmacokinetic Results:

Pharmacodynamic Results: The changes from Baseline in log_{10} HIV viral loads on Day 8 are summarized by dose and regimen (QD or BID) in Table 4. The results showed that there was a dose dependent decrease in log_{10} HIV viral load on Day 8 from Baseline. The mean

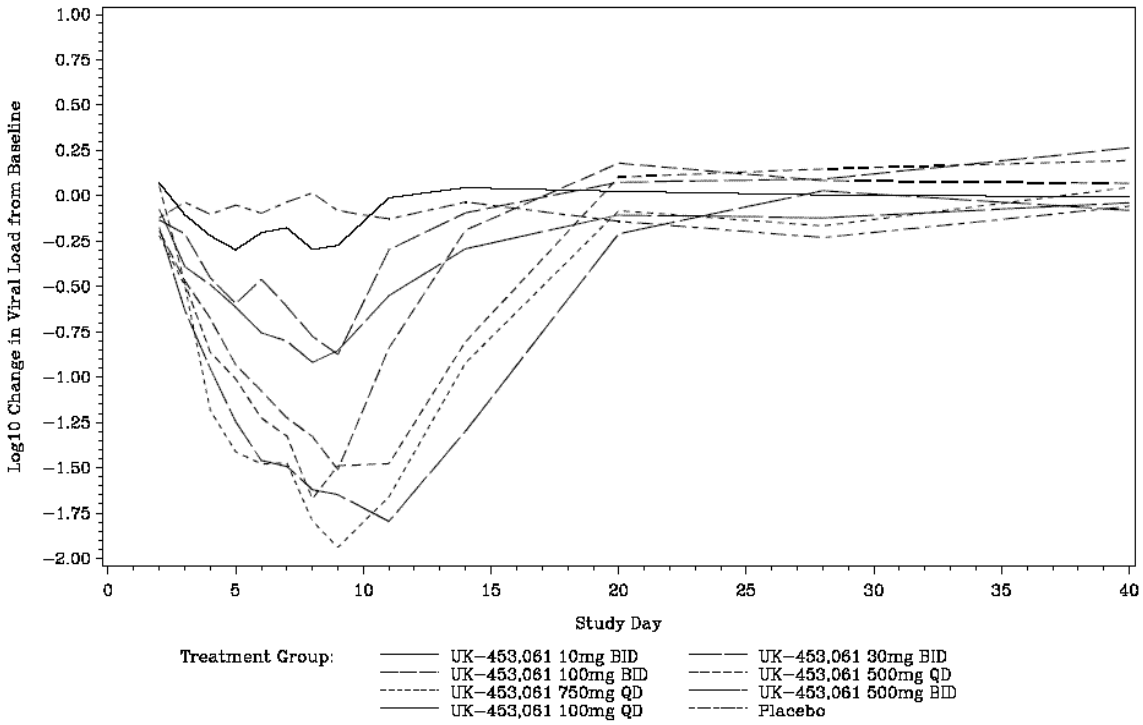
changes from Baseline in log_{10} HIV viral loads through Day 40 by treatment groups are plotted in Figure 1.

Table 4. Summary of Changes From Baseline in Log_{10} HIV Viral Load (copies/mL) on Day 8 - Pharmacodynamic Population

Parameter	Lersivirine							Placebo
	10 mg BID	30 mg BID	100 mg BID	500 mg QD	750 mg QD	500 mg BID	100 mg QD	
N	6	6	6	6	6	6	6	6
Log_{10} baseline[a]	4.57	4.39	4.41	4.38	4.65	4.55	4.70	4.57
Log_{10} Day 8[a]	4.28	3.61	3.09	2.71	2.86	2.93	3.78	4.58
Log_{10} change from baseline (SD)[a]	-0.30 (0.20)	-0.78 (0.45)	-1.33 (0.38)	-1.67 (0.19)	-1.79 (0.32)	-1.62 (0.22)	-0.92 (0.38)	0.01 (0.16)
Day 8 range (max/min)	-0.05/-0.52	-0.13/-1.14	-0.72/-1.77	-1.32/-1.85	-1.53/-2.26	-1.39/-1.99	-0.50/-1.31	0.29/-0.19

Change in viral load from Baseline (log_{10} copies/mL) = log_{10} (Day 8) - log_{10} (baseline).
Baseline was the mean of the screening, randomization and Day 1 predose log_{10} measurements.
Values below the lower limit of quantification of 50 copies/mL were set to 50 copies/mL.
BID = twice daily; HIV = human immunodeficiency virus; max = maximum; min = minimum; QD = once daily; SD = standard deviation.
a. Arithmetic mean was calculated.

Figure 1. Mean Changes From Baseline in Log_{10} HIV Viral Load Versus Day - Pharmacodynamic Population



BID = twice daily; HIV = human immunodeficiency virus; QD = once daily.

Time to rebound of HIV viral load (viral load >baseline) tended to be earlier with the lower doses and placebo (Table 5 and Figure 1). The most common day for rebound was 13 days after the last dose, but there were 13 subjects (27%) whose viral load didn't exceed their baseline value, across the doses.

Table 5. Summary of Time to Rebound of HIV Viral Load - Pharmacodynamic Population

Treatment Group	Number of Subjects Time to Rebound (Days)						
	2	4	7	13	21	Follow-Up	None
Lersivirine 10 mg BID	0	2	2	1	0	1	0
Lersivirine 30 mg BID	1	1	1	2	0	0	1
Lersivirine 100 mg BID	0	0	1	4	0	0	1
Lersivirine 500 mg QD	0	0	0	3	1	1	1
Lersivirine 750 mg QD	0	0	0	3	0	1	2
Lersivirine 500 mg BID	0	0	0	1	1	1	3
Lersivirine 1000 mg QD	0	1	0	0	1	1	3
Placebo	2	0	1	0	0	1	2

The time to rebound of viral load was calculated as the time from the last dose (Day 8) to the time of the first occasion at which the viral load was greater than the baseline value.
Baseline is the mean of the screening, randomization and Day 1 predose measurements.
Follow-up comprises of readings taken on Days 31-33 post-last dose.
BID = twice daily; HIV = human immunodeficiency virus; QD = once daily.

Stage 2 of the study was conducted as the probability of lersivirine 100 mg BID yielding a 1 $\log_{10}$ decrease in HIV viral load was >0.1 from the modeling of the Stage 1 data.

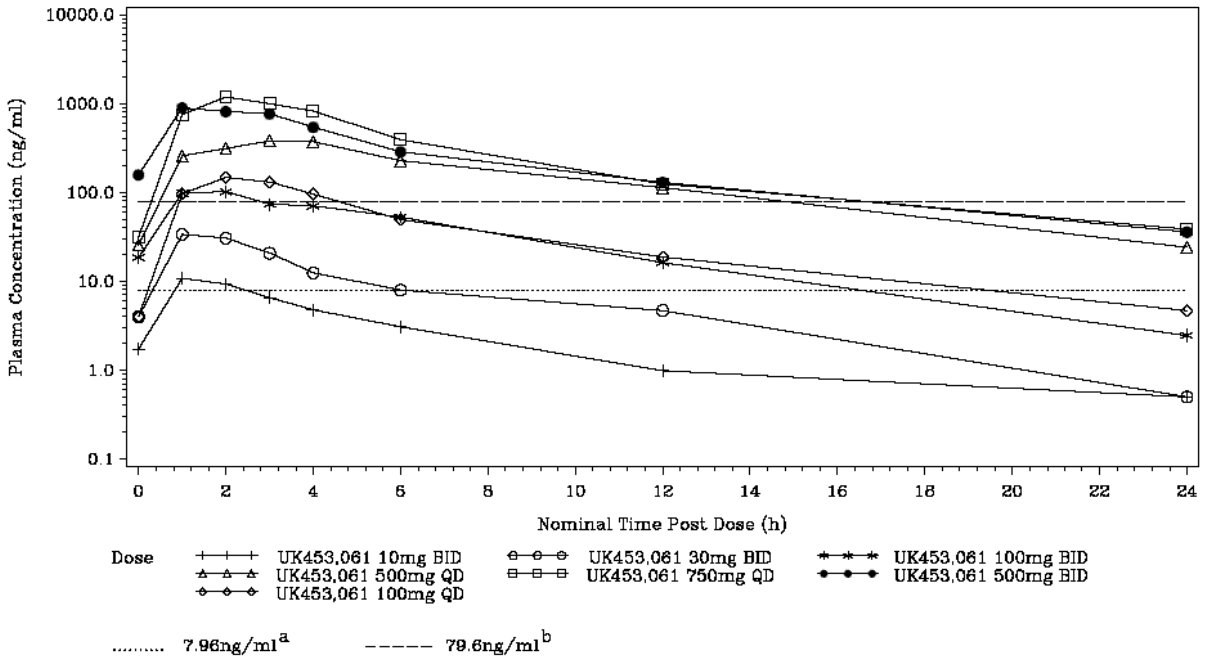
Pharmacokinetic Results: Within the BID and QD dosing regimens mean maximum observed plasma concentration (C_{max}) increased in line with dose. The increase in mean area under the plasma concentration-time curve from 0 over the dosing interval (AUC_{tau}) was more than proportional over the dose range with the suspension formulation, but in line with dose with the tablet formulation. Median time till first occurrence of C_{max} ranged between 1 to 3 hours independent of formulation type. The steady state PKs of lersivirine following QD and BID dosing are summarized in Table 6 and Figure 2. Median plasma concentrations at steady state were sustained for at least 12 hours above the in vitro concentration of drug needed to reduce HIV replication in cell culture by 90% (IC_{90}) (7.96 ng/mL) for BID and QD doses ≥100 mg and for at least 24 hours for BID and QD doses ≥500 mg. Median plasma concentrations at steady state were sustained for at least 12 hours above 10 times the in vitro IC_{90} (79.6 ng/mL) for BID and QD doses >500 mg. The steady state was reached by Day 8 with both the BID and QD dosing regimens.

Table 6. Summary of PK Parameters - Pharmacokinetic Population

Lersivirine					
Dose	**Regimen**	**Formulation**	**PK Parameter**		
			C_{max} (ng/mL)[a]	**T_{max} (h)[b]**	**AUC_{tau} (ng•h/mL)[a]**
Stage 1 (N=6/Group)					
10 mg	BID	Suspension	14.6	1.0	47.2
30 mg	BID	Suspension	42.6	1.0	150.0
100 mg	BID	Suspension	146.6	2.0	686.7
500 mg	QD	Suspension	490.2	3.0	3543.5
Stage 2 (N=6/Group)					
100 mg	QD	Tablet	172.4	2.0	863.1
500 mg	BID	Tablet	979.1	1.5	4719.4
750 mg	QD	Tablet	1245.3	2.0	6530.1

AUC_{tau} was AUC_{12} and AUC_{24} for BID and QD dosing, respectively.
AUC_{tau} = area under concentration-time curve for a dosing interval; AUC_{12} = area under concentration-time curve for 12 hours; AUC_{24} = area under concentration-time curve for 24 hours; BID = twice daily; C_{max} = maximum observed concentration; N = number of subjects; PK = pharmacokinetic; QD = once daily; T_{max} = time till first occurrence of C_{max}.
a. Geometric mean.
b. Median.

Figure 2. Log-Linear Plot of Median Lersivirine Plasma Concentrations on Day 8 Versus Time Postdose - Pharmacokinetic Population



[a] The reference line above shows the plasma concentration equivalent to the in vitro IC_{90} (7.96 ng/mL).
[b] The reference line above shows the plasma concentration equivalent to the in vitro 10 times IC_{90} (79.6 ng/mL).
BID = twice daily; HIV = human immunodeficiency virus; IC_{90} = in vitro concentration of drug needed to reduce HIV replication in cell culture by 90%; QD = once daily.

Safety Results:

The most frequently reported treatment-emergent AEs (all causalities) were gastrointestinal and nervous system disorders. The incidences of treatment-emergent AEs reported in ≥5% subjects are summarized in Table 7.

Table 7. Treatment-Emergent Non-Serious Adverse Events Occurring in ≥5% Subjects (All Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v10.0) Preferred Term	Lersivirine							
	10 mg BID	30 mg BID	100 mg BID	500 mg QD	750 mg QD	500 mg BID	100 mg QD	Placebo
Number (%) of subjects: Evaluable For Adverse Events	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**
With Adverse Events	**3 (50.0)**	**5 (83.3)**	**5 (83.3)**	**5 (83.3)**	**6 (100.0)**	**6 (100.0)**	**3 (50.0)**	**4 (66.7)**
Blood and lymphatic system disorders	0	0	0	0	0	1 (16.7)	0	0
Thrombocytopenia	0	0	0	0	0	1 (16.7)	0	0
Cardiac disorders	0	0	0	0	1 (16.7)	0	0	0
Tachycardia	0	0	0	0	1 (16.7)	0	0	0
Ear and labyrinth disorders	1 (16.7)	2 (33.3)	0	0	0	0	0	1 (16.7)
Ear pain	1 (16.7)	1 (16.7)	0	0	0	0	0	0
Vertigo	0	1 (16.7)	0	0	0	0	0	1 (16.7)
Eye disorders	0	0	0	1 (16.7)	0	0	0	0
Chloropsia	0	0	0	1 (16.7)	0	0	0	0
Gastrointestinal disorders	2 (33.3)	2 (33.3)	3 (50.0)	1 (16.7)	6 (100.0)	3 (50.0)	1 (16.7)	0
Abdominal discomfort	0	0	0	0	0	1 (16.7)	0	0
Abdominal distension	0	0	0	0	0	1 (16.7)	1 (16.7)	0
Abdominal pain upper	1 (16.7)	1 (16.7)	0	0	0	0	0	0
Abnormal faeces	0	0	0	0	2 (33.3)	0	0	0
Aphthous stomatitis	1 (16.7)	0	0	0	0	0	0	0
Constipation	0	1 (16.7)	0	0	0	0	0	0
Diarrhoea	0	1 (16.7)	1 (16.7)	0	1 (16.7)	0	1 (16.7)	0
Dyspepsia	0	0	0	1 (16.7)	0	1 (16.7)	0	0
Flatulence	1 (16.7)	1 (16.7)	2 (33.3)	0	1 (16.7)	0	0	0
Lip dry	0	1 (16.7)	0	0	0	0	0	0
Nausea	0	0	0	0	3 (50.0)	2 (33.3)	0	0
Toothache	0	0	1 (16.7)	0	0	0	0	0
Vomiting	0	0	0	0	0	1 (16.7)	0	0
General disorders and administration site conditions	0	2 (33.3)	1 (16.7)	2 (33.3)	0	1 (16.7)	0	1 (16.7)
Fatigue	0	1 (16.7)	1 (16.7)	2 (33.3)	0	1 (16.7)	0	1 (16.7)
Feeling cold	0	1 (16.7)	0	0	0	0	0	0
Malaise	0	1 (16.7)	0	0	0	0	0	0
Hepatobiliary disorders	0	1 (16.7)	0	0	0	0	0	0
Hepatic cyst	0	1 (16.7)	0	0	0	0	0	0
Infections and infestations	1 (16.7)	3 (50.0)	2 (33.3)	0	1 (16.7)	3 (50.0)	1 (16.7)	1 (16.7)
Anal chlamydia infection	0	0	0	0	0	0	0	1 (16.7)
Anogenital warts	0	0	0	0	0	0	0	1 (16.7)
Cystitis	0	0	0	0	0	0	0	1 (16.7)
Herpes simplex	1 (16.7)	0	0	0	0	0	0	0
Herpes zoster	0	1 (16.7)	0	0	0	0	0	0
Influenza	0	0	1 (16.7)	0	0	0	0	0
Nasopharyngitis	0	3 (50.0)	0	0	0	2 (33.3)	0	0
Oral herpes	0	0	0	0	0	1 (16.7)	0	0
Pharyngitis	0	0	0	0	1 (16.7)	0	0	0
Tonsillitis	0	0	1 (16.7)	0	0	0	1 (16.7)	0
Urethritis	0	0	0	0	0	0	0	1 (16.7)
Investigations	0	0	1 (16.7)	0	0	0	0	0
Hepatic enzyme increased	0	0	1 (16.7)	0	0	0	0	0
Protein total increased	0	0	1 (16.7)	0	0	0	0	0

Table 7. Treatment-Emergent Non-Serious Adverse Events Occurring in ≥5% Subjects (All Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v10.0) Preferred Term	Lersivirine							
	10 mg BID	30 mg BID	100 mg BID	500 mg QD	750 mg QD	500 mg BID	100 mg QD	Placebo
Metabolism and nutrition disorders	0	0	0	0	0	1 (16.7)	0	0
Anorexia	0	0	0	0	0	1 (16.7)	0	0
Musculoskeletal and connective tissue disorders	0	0	0	0	0	0	1 (16.7)	0
Osteoarthritis	0	0	0	0	0	0	1 (16.7)	0
Nervous system disorders	1 (16.7)	3 (50.0)	0	4 (66.7)	3 (50.0)	2 (33.3)	0	1 (16.7)
Balance disorder	1 (16.7)	0	0	0	0	0	0	0
Dizziness postural	0	0	0	0	0	0	0	1 (16.7)
Headache	1 (16.7)	2 (33.3)	0	2 (33	3 (50.0)	1 (16.7)	0	0
Motor dysfunction	1 (16.7)	0	0	0	0	0	0	0
Paraesthesia	0	0	0	1 (16.7)	0	0	0	0
Sciatica	0	0	0	0	0	1 (16.7)	0	0
Sensory disturbance	0	0	0	1 (16.7)	0	0	0	0
Syncope	0	1 (16.7)	0	0	0	0	0	0
Psychiatric disorders	0	1 (16.7)	0	0	0	1 (16.7)	0	0
Agitation	0	0	0	0	0	1 (16.7)	0	0
Disorientation	0	1 (16.7)	0	0	0	0	0	0
Renal and urinary disorders	1 (16.7)	0	0	0	0	2 (33.3)	1 (16.7)	0
Haematuria	0	0	0	0	0	0	1 (16.7)	0
Ketonuria	0	0	0	0	0	2 (33.3)	0	0
Pollakiuria	1 (16.7)	0	0	0	0	0	0	0
Reproductive system and breast disorders	0	0	0	0	0	0	0	1 (16.7)
Prostatitis	0	0	0	0	0	0	0	1 (16.7)
Respiratory, thoracic and mediastinal disorders	0	0	0	0	1 (16.7)	0	0	0
Epistaxis	0	0	0	0	1 (16.7)	0	0	0
Skin and subcutaneous tissue disorders	0	1 (16.7)	0	1 (16.7)	0	0	1 (16.7)	2 (33.3)
Hyperhidrosis	0	1 (16.7)	0	0	0	0	0	0
Night sweats	0	0	0	0	0	0	0	2 (33.3)
Rash	0	0	0	1 (16.7)	0	0	1 (16.7)	0
Xeroderma	0	0	0	0	0	0	1 (16.7)	0
Vascular disorders	1 (16.7)	2 (33.3)	0	0	1 (16.7)	1 (16.7)	0	0
Aortic arteriosclerosis	0	1 (16.7)	0	0	0	0	0	0
Hot flush	0	0	0	0	0	1 (16.7)	0	0
Hypertension	1 (16.7)	0	0	0	1 (16.7)	0	0	0
Hypotension	0	1 (16.7)	0	0	0	0	0	0
Phlebolith	0	1 (16.7)	0	0	0	0	0	0

Subjects were counted only once per treatment in each row.
Includes data up to 7 days after last dose of study drug.
MedDRA (v10.0) coding dictionary applied.
BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; QD = once daily; v = version.

The most frequently reported treatment-related AEs were also gastrointestinal and nervous system disorders. The incidences of treatment-related AEs are summarized in Table 8.

Table 8. Incidence and Severity of Treatment-Emergent Adverse Events (Treatment-Related)

Number (%) of Subjects Evaluable for Adverse Events by System Organ Class and MedDRA (v10.0) Preferred Term	Lersivirine							
	10 mg BID N=6	30 mg BID N=6	100 mg BID N=6	500 mg QD N=6	750 mg QD N=6	500 mg BID N=6	100 mg QD N=6	Placebo N=6
Cardiac disorders	0	0	0	0	1	0	0	0
Tachycardia	0	0	0	0	1	0	0	0
Ear and labyrinth disorders	0	0	0	0	0	0	0	1
Vertigo	0	0	0	0	0	0	0	1
Eye disorders	0	0	0	1	0	0	0	0
Chloropsia	0	0	0	1	0	0	0	0
Gastrointestinal disorders	1	2	2	1	6	2	1	0
Abdominal discomfort	0	0	0	0	0	1	0	0
Abdominal distension	0	0	0	0	0	1	1	0
Abdominal pain upper	1	1	0	0	0	0	0	0
Abnormal faeces	0	0	0	0	2	0	0	0
Diarrhoea	0	0	1	0	1	0	1	0
Dyspepsia	0	0	0	1	0	1	0	0
Flatulence	1	0	1	0	1	0	0	0
Lip dry	0	1	0	0	0	0	0	0
Nausea	0	0	0	0	3	2	0	0
General disorders and administration site conditions	0	1	1	2	0	1	0	1
Fatigue	0	1	1	2	0	1	0	1
Investigations	0	0	1	0	0	0	0	0
Hepatic enzyme increased	0	0	1	0	0	0	0	0
Protein total increased	0	0	1	0	0	0	0	0
Metabolism and nutrition disorders	0	0	0	0	0	1	0	0
Anorexia	0	0	0	0	0	1	0	0
Nervous system disorders	1	1	0	4	3	1	0	1
Balance disorder	1	0	0	0	0	0	0	0
Dizziness postural	0	0	0	0	0	0	0	1
Headache	1	1	0	2	3	1	0	0
Motor dysfunction	1	0	0	0	0	0	0	0
Paraesthesia	0	0	0	1	0	0	0	0
Sensory disturbance	0	0	0	1	0	0	0	0
Psychiatric disorders	0	0	0	0	0	1	0	0
Agitation	0	0	0	0	0	1	0	0
Renal and urinary disorders	1	0	0	0	0	1	0	0
Ketonuria	0	0	0	0	0	1	0	0
Pollakiuria	1	0	0	0	0	0	0	0
Skin and subcutaneous tissue disorders	0	0	0	0	0	0	1	1
Night sweats	0	0	0	0	0	0	0	1
Rash	0	0	0	0	0	0	1	0
Xeroderma	0	0	0	0	0	0	1	0
Vascular disorders	1	0	0	0	1	1	0	0
Hot flush	0	0	0	0	0	1	0	0
Hypertension	1	0	0	0	1	0	0	0

Subjects were counted only once per treatment in each row.
Includes data up to 7 days after last dose of study drug.
MedDRA (v10.0) coding dictionary applied.
BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; QD = once daily.

Serious Adverse Events (SAEs): One subject in the lersivirine 30 mg BID group had an SAE of left-sided nephrolithiasis. This SAE was not considered as treatment-related.

Discontinuations due to Adverse Events: There were no permanent discontinuations, dose reductions or temporary discontinuations due to AEs reported in the study.

Deaths: There were no deaths reported in the study.

Laboratory Evaluations: One subject in the lersivirine 100 mg BID group had 2 laboratory abnormalities reported as AEs. The subject exhibited a 7- to 8-fold increase in aspartate aminotransferase on Days 5 and 40, and a 2- to 4-fold elevation in alanine aminotransferase, as compared to Day 1 predose baseline values. The most frequently reported laboratory abnormality was increase in basophil count. Increased urine protein was reported in 4 subjects on active treatment, but all of these were at the 2 lowest doses (10 and 30 mg), and reported in 1 subject on placebo. None of the laboratory abnormalities were considered as clinically significant.

Other Safety Related Findings: Mean changes from baseline on Day 8 for vital sign and ECG measurements were small and no subject experienced an AE associated with either their vital signs or ECG. One subject, on placebo BID had absolute corrected QT interval by Fridericia (QTcF) values ≥450 msec; predose on Day 1 and 1 hour postdose on Day 8. There were no clinically significant changes in vital signs, ECG, or in physical examination findings.

CONCLUSIONS:

- There was a dose dependent decrease in $\log_{10}$ HIV viral load from Baseline after 7 days of dosing with lersivirine. The mean changes from Baseline in $\log_{10}$ HIV viral load (copies/mL) with the 500 mg BID and 750 mg QD regimens were -1.8 and -1.6, respectively.

- Within the BID and QD dosing regimens, mean C_{max} increased in line with dose. The increase in mean AUC_{tau} was more than proportional over the dose range with the suspension formulation, but in line with dose with the tablet formulation.

- Lersivirine appeared to be well-tolerated in this subject population.