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

PROTOCOL NO.: A5271037

PROTOCOL TITLE:

A Long-Term Open-Label Extension Study of Lersivirine for the Treatment of HIV-1 Infection

Study Centers:

The study was conducted in 23 study centers in Australia, Canada, Italy, Mexico, Poland, South Africa, Switzerland, and the United Kingdom.

Study Initiation Date and Final Completion Date:

22 February 2011 and 05 June 2012

The study was terminated prematurely on 29 January 2013, due to the decision of the Sponsor to discontinue development of lersivirine (LRV). The decision to terminate the study was not based on any safety or efficacy concerns.

Phase of Development:

Phase 2b

Study Objective:

The primary objective of this study was to assess the long-term safety and efficacy of LRV in subjects who had completed treatment with LRV in the parent study (Study A5271015).

METHODS

Study Design:

This was a Phase 2b open-label, multi-center extension study to assess the long term safety and efficacy of LRV in subjects who had completed 96 weeks of treatment with LRV (or comparator, where required by local regulation) in the parent study.

All subjects were to be followed up every 16 weeks until the End of the Study. End of Study was defined as the time point at which LRV was either commercially available for the parent study indication in each respective country or development of LRV was discontinued. If development of LRV was discontinued, the study was terminated and appropriate follow-up for all subjects was communicated by the Sponsor. Study design and plan and scheduled study procedures are presented in Figure 1 and Table 1.

Figure 1. Study Design and Plan

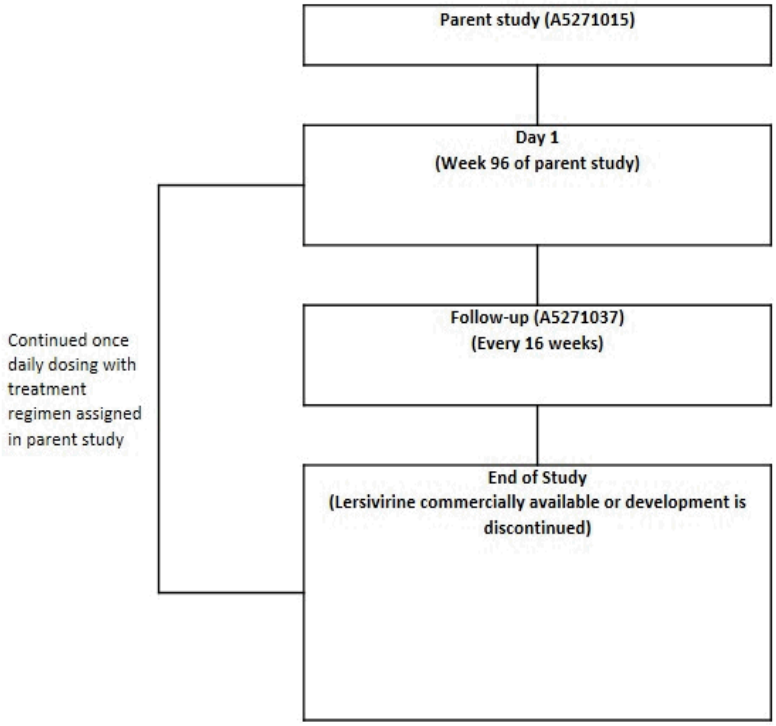

Table 1. Flowchart of Scheduled Study Procedures

Procedures	Day 1[a]	Every 16 Weeks[b]	Early Termination/End of Study
Informed consent	X		
Review inclusion/exclusion criteria	X		
Physical exam/vital signs	X		X
Targeted physical exam/vital signs		X[c]	
Waist/hip lipodystrophy measurements	X	X	X
Assessment of signs, symptoms and AEs	X	X	X
Concomitant medications	X	X	X
Serum chemistry	X	X	X
Hematology	X	X	X
CD4+ (absolute and percentage)	X	X	X
Plasma HIV-1 RNA	X[h]	X[h]	X
Fasting metabolic assessment	X	X	X
Free T4, TSH	X	X[i]	X
Plasma and PBMC samples			X[g]
Virus susceptibility		X[e]	X[f]
Urinalysis	X	X	X
Pregnancy test[d]	X	X	X
Assess dosing compliance		X	X
Dispense/prescribe study medication	X	X	

AE = adverse event; CD = cluster of differentiation; HIV = human immunodeficiency virus; RNA = ribonucleic acid; T4 = thyroxine 4; TSH = thyroid-stimulating hormone; PBMC = peripheral blood mononuclear cells.

a. The Day 1 visit in this study could occur at the same visit as the Week 96 visit in the Study A5271015. These assessments (excluding informed consent, inclusion/exclusion and drug dispensation) were to be taken from the Week 96 visit in the Study A5271015 and used as the Day 1 assessments in this study. These results were not required to be recorded. However, AEs that were ongoing as of Week 96 of the Study A5271015 were required to be transcribed to the AE for this study.

b. All scheduled visits had to occur within ±2 days.

c. Head and neck, heart, lung, abdominal, brief neurologic, skin and vital signs.

d. For women of childbearing potential. Urine tests at all visits. A positive urine test confirmed with a serum test.

e. Only for subjects who required a second measurement of HIV-1 RNA to confirm treatment failure. Sample was to be drawn at the time of collection of second HIV-1 RNA sample.

f. At the Early Termination visit only, for subjects discontinuing due to treatment failure. A sample for virus susceptibility was not collected if already collected at the time of confirmation of treatment failure (ie, when the second HIV-1 RNA sample was drawn).

g. At the Early Termination visit only, for subjects discontinuing due to treatment failure. Two (2) whole blood samples for plasma aliquots and peripheral blood mononuclear cells preparation; samples were stored for future analysis.

h. If the subject met the treatment failure criteria, a confirmatory HIV-1 RNA sample was drawn within 14 days of the first measurement.

i. Performed at the first visit and then at every other visit, eg, every 32 weeks.

Number of Subjects (Planned and Analyzed):

There was no pre-determined number of subjects. Subjects from the parent study were eligible for enrolment provided they met the inclusion/exclusion criteria. A total of 108 subjects enrolled to LRV 500 (47 subjects), LRV 750 (43 subjects), and efavirenz (EFV) 600 (18 subjects) groups.

Diagnosis and Main Criteria for Inclusion and Exclusion:

- Adult subjects who had completed of 96 weeks of treatment with LRV (or comparator where required by local regulation) in 1 of the parent studies (Studies A5271015 and A5271022).

- Subjects with a viral load <50 copies/mL at Week 84 of the Study A5271015.

- Negative urine pregnancy test for women of childbearing potential at the Day 1 visit, prior to receiving study medication.

Main Exclusion Criteria:

- Subjects with any Grade 4 Division of acquired immunodeficiency syndrome toxicity (except for lipids and asymptomatic glucose elevations and those discussed and agreed by the Investigator and the Sponsor's medical monitor prior to enrollment).

Study Treatment:

Subjects continued on the treatment regimen to which they were assigned in the parent study. Study medication was taken orally once daily (QD).

In the parent study, subjects were randomized to receive 1 of the following treatments:

- LRV 500 mg tablet QD.

- LRV 750 mg tablet QD.

- EFV 600 mg tablet QD.

LRV and EFV was taken without food at bedtime.

Efficacy and Safety Endpoints:

Primary Endpoints:

- Safety and tolerability of LRV as measured by adverse events (AEs) reports and safety laboratory tests.

- The percentage of subjects with human immunodeficiency virus (HIV) 1 ribonucleic acid (RNA) level <50 copies/mL at 48 weeks (ie, 144 weeks from Day 1 of the parent study).

    - All subjects had antiviral activity assessed by plasma HIV-1 RNA level.

    - Blood samples were collected at all visits. If a subject met the treatment failure criteria or the criterion for discontinuation from the study potentially, a confirmatory HIV-1 RNA level was to be obtained within 14 days of the first measurement with the following exception in South Africa. Subjects in South Africa with HIV-1 RNA >1000 copies/mL was to be confirmed by a second consecutive measurement taken

≤3 months after the first HIV-1 RNA measurement that is >1000 copies/mL with regard to the discontinuation from study criterion.

- Blood samples were collected at all visits. If a subject met the treatment failure criteria, a confirmatory HIV-1 RNA level was to be obtained within 14 days of the first measurement.

Secondary Endpoints:

- Change from Baseline in cluster of differentiation (CD) 4+ lymphocyte counts (absolute and percentage) at 48 weeks (ie, 144 weeks from Day 1 of the parent study).
- Outcomes of treatment (snapshot – based on HIV-1 RNA level and subject summary) at Week 144.
- Genotypic and phenotypic susceptibility at the time of study defined treatment failure.

Safety Evaluations:

Safety was assessed in all subjects by AE reports, physical examinations and laboratory test results. Safety assessments were performed at specified study visits and included complete or symptom directed physical examination, vital signs, waist/hip lipodystrophy measurements and laboratory tests. All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product were reported.

Statistical Methods:

Analysis Sets: All subjects enrolled in this study constituted the analysis population associated with Study A5271015 and were used in all analyses. Additional demographic summaries were produced using the full analysis set (FAS) of the parent study, which consisted of all randomized subjects who had received at least 1 dose of study medication from Day 1 of the parent study.

Virology Analysis Set: Only subjects with evaluable samples were included in the Virology Analysis Set. Evaluable for the purpose of virology analyses denoted a subject with a valid on-treatment genotypic or phenotypic susceptibility testing result and with HIV-1 RNA level >500 copies/mL at a time point associated with failure.

Primary Efficacy Endpoint: Descriptive summaries for the primary efficacy endpoint (percentage of subjects with HIV-1 RNA level <50 copies/mL at 144 weeks) were performed (a category for missing data was included where applicable).

Secondary Endpoint (Change From Baseline in Absolute CD4+ Cell Count at Week 144): For the endpoints - change from Baseline absolute CD4+ cell count (cells/μL), descriptive summaries were performed.

RESULTS

Subject Disposition and Demography:

Of the108 subjects were screened in the parent Study A5271015, 47, 43, and 18 subjects from the LRV 500, LRV 750, and EFV 600 groups, respectively were enrolled in the study. A total of 5 (10.6%), 2 (4.7%), and 2 (11.1%) subjects in the LRV 500, LRV 750, and EFV 600 groups, respectively, discontinued the study post Week 96 through Week 144 (Table 2). The main reasons for discontinuation were insufficient clinical response, and no longer willing to participate in the study.

Table 2. Subject Disposition

	LRV 500 mg (N=47)	LRV 750 mg (N=43)	EFV 600 mg (N=18)
Screened (N=108)			
Enrolled	47	43	18
Number (%) of subjects discontinued post Week 96 through Week 144	5 (10.6)	2 (4.7)	2 (11.1)
Reasons for discontinuation			
Subject died	0	1	0
Insufficient clinical response	3	0	0
Lost to follow-up	1	0	0
No longer willing to participate in study	2	1	1
Withdrawn due to pregnancy	0	0	1
Adverse event (related to study drug)	1		

The summary table includes subject discontinuations post Week 96 through Week 144.
EFV = efavirenz; LRV = lersivirine; N = total number of subjects.

Mean age of the subjects was 36.6, 35.8, and 38.5 years in the LRV 500, LRV 750, and EFV 600 groups, respectively. The majority of subjects were male (Table 3).

Table 3. Demographic and Baseline Characteristics

	LRV 500 mg (N=47)	LRV 750 mg (N=43)	EFV 600 mg (N=18)
Gender (n)			
Male	37	32	10
Female	10	11	8
Age (years)			
18-44	41	37	14
45-64	6	6	4
Mean	36.6	35.8	38.5
SD	8.4	8.7	7.8
Range	24-61	22-62	24-54
Race (n)			
White	30	26	3
Black	12	13	15
Asian	4	0	0
Other	1	4	0
Exposure category (n)			
Heterosexual	16	12	15
Male to male sexual contact	31	29	2
Other	0	2	1
Body mass index (kg/m^2)			
Mean	25.0	24.9	27.0
SD	5.5	4.0	6.1
Range	18.6-45.2	19.0-38.1	20.5-44.5

LRV = lersivirine; EFV = efavirenz; N = total number of subjects; n = number of subject for specified category; SD = standard deviation.

Efficacy Results:

Primary Endpoint - Percentage of Subjects with HIV-1 RNA Level <50 copies/mL at Week 144: The primary efficacy endpoint was the percentage of subjects with HIV-1 RNA level <50 copies/mL at 48 weeks (ie, 144 weeks from Day 1 of the parent study). In the primary analysis (all subjects) at Week 144, 40 (85.1%), 40 (93.0%), and 16 (88.9%) subjects in the LRV 500, LRV 750, and EFV 600 groups, respectively, had HIV-1 RNA levels of <50 copies/mL (Table 4).

Table 4. Percentage of Subjects With HIV-1 RNA Level <50 Copies/mL by Visit - Non-completer = Failure - All Subjects - Primary Analysis at Week 144

Visit	Treatment Group	N	n	%	80% CI - Lower	80% CI - Upper
Week 128	LRV 500 mg	47	41	87.2	79.9	94.5
	LRV 750 mg	43	40	93.0	86.9	99.2
	EFV 600 mg	18	16	88.9	76.6	100.0
Week 144	LRV 500 mg	47	40	85.1	77.4	92.8
	LRV 750 mg	43	40	93.0	86.9	99.2
	EFV 600 mg	18	16	88.9	76.6	100.0

Imputation P1: Subjects who had been discontinued from the study, had been lost to follow-up, or had missing HIV-1 RNA level data at a visit were considered to have HIV-1 RNA levels ≥50 copies/mL. This was also referred to as (non-completer = failure). The denominator (N) used for the percentage calculation included all the subjects. Week 112 visit for 17 subjects fall outside the upper limit of the Week 112 visit window for reporting purposes. As a consequence, the values for these subjects at Week 112 were missing and interpretation of the Week 112 summary data was questionable. The Week 112 data were therefore excluded in this summary.
CI = confidence interval; EFV = efavirenz; HIV = human immunodeficiency virus; LRV = lersivirine; N = total number of subjects ; n=number of subjects for specified category ; RNA = ribonucleic acid.

Secondary Endpoint – Changes From Baseline in CD4+ Cell Counts (Absolute and Percentage) at Week 144: Mean (SD [standard deviation]) changes from Baseline in CD4+ cell counts (absolute) at Week 144 in the last observation carried forward (LOCF) analysis (all subjects) were 293 (206), 302 (163), and 303 (163) cells/µL for subjects in the LRV 500, LRV 750, and EFV 600 groups, respectively (Table 5).

Table 5. Descriptive Statistics of Change From Baseline (Absolute) CD4+ Cell Count (cells/µL) by Visit - LOCF - All Subjects

Visit	Treatment Group	N	Mean	SD	CV (%)	Min	Q1	Median	Q3	Max
Week 112	LRV 500 mg	47	249	178	71	-183	137	234	354	707
	LRV 750 mg	43	267	159	60	-93	141	278	384	556
	EFV 600 mg	18	264	161	61	2	187	217	375	586
Week 128	LRV 500 mg	47	282	153	54	3	168	256	374	694
	LRV 750 mg	43	307	207	67	-42	156	309	393	995
	EFV 600 mg	18	260	158	61	10	107	250	380	531
Week 144	LRV 500 mg	47	293	206	70	-64	152	253	423	812
	LRV 750 mg	43	302	163	54	-163	206	307	421	633
	EFV 600 mg	18	303	163	54	8	213	274	394	659

Baseline was calculated as mean of all pre-dose measurements in parent study.
CV = coefficient of variation; EFV = efavirenz; LRV = lersivirine; LOCF = last observation carried forward; Min = minimum; Max = maximum; N = total number of subjects; SD = standard deviation; Q = quartile.

Mean (SD) changes from Baseline in CD4+ cell count (percentage) at Week 144 in the LOCF analysis (all subjects) were 13 (6), 13 (5), and 13 (6) percent in the LRV 500, LRV 750, and EFV 600 groups, respectively.

In the primary analysis (all subjects, non-completer/missing as failure) at Week 144, 40 (85.1%), 40 (93.0%), and 16 (88.9%) subjects in the LRV 500, LRV 750, and EFV 600 groups, respectively, had HIV-1 RNA levels of <50 copies/mL.

- Outcomes of Treatment at Week 144: For outcomes of treatment (snapshot – based on HIV-1 RNA level and subject summary) at Week 144, subjects were categorized based on HIV-1 RNA level and the status recorded at Week 144. A total of 43 (91.5%), 42 (97.9%), and 16 (88.9%) subjects in the LRV 500, LRV 750, and EFV 600 groups, respectively, completed the Week 144 visit. A total of 4 (8.5%), 1 (2.3%), and 2 (11.1%) subjects in the LRV 500, LRV 750, and EFV 600 groups, respectively, discontinued prematurely before the Week 144 visit. Two (2) subjects were designated as "other": 1 was a subject (in the LRV 500 mg group) who was lost to follow-up on Day 1016, and the other was a subject (in the LRV 750 mg group) who died on Day 1020, with their HIV-1 RNA missing in the Week 144 visit window. A total of 2 (4.3%), 1 (2.3%), and 0 (0.0%) subjects in the LRV 500, LRV 750, and EFV 600 groups, respectively, met study defined treatment failure criteria, ie, had an increase in HIV1-RNA to ≥50 copies/mL on 2 consecutive measurements (Table 6).

Table 6. Outcomes of Treatment (Snapshot - Based on HIV-1 RNA Level and Subject Summary) at Week 144 - Non-completer = Failure - All Subjects

Outcome	LRV 500 mg (N=47)		LRV 750 mg (N=43)		EFV 600 mg (N=18)	
	n	%	n	%	n	%
Subjects who completed the Week 144 visit	43	91.5	42	97.7	16	88.9
HIV-1 RNA level <50 copies/mL at Week 144	40	85.1	40	93.0	16	88.9
HIV-1 RNA level ≥50 copies/mL at Week 144	2	4.3	1	2.3	0	0
Other[a]	1	2.1	1	2.3	0	0
Subjects who died or discontinued prematurely before Week 144	4	8.5	1	2.3	2	11.1
Death	0	0	0	0	0	0
Due to insufficient clinical response	2	4.3	0	0	0	0
Due to adverse events	1	2.1	0	0	0	0
Due to other reasons	1	2.1	1	2.3	2	11.1
Study defined treatment failure criteria						
Increase in HIV1-RNA to ≥50 copies/mL on 2 consecutive measurements	2	4.3	1	2.3	0	0

If multiple reasons for discontinuation, the following order of preference was used: Death> AE>Other. If a subject had HIV-1 RNA level <50 copies/mL but discontinued or died within the window of week 144, the death/discontinuation prevailed. Each subject was counted once in each row.
EFV = efavirenz; HIV = human immunodeficiency virus; LRV = lersivirine; N = total number of subjects ; n = number of subject for specified category; RNA = ribonucleic acid.
a. Other denotes 2 subjects (1 subject in the LRV 500 mg group who lost to follow-up on Day 1016 and another subject in the LRV 750 mg group who died on Day 1020), who had missing HIV-1 RNA level, within the Week 144 visit window.

- Genotypic and Phenotypic Susceptibility: A total of 15 subjects were identified as having experienced Time to Loss of Virologic Response 50 (TLOVR50) failure through Week 144 (Table 7).

Table 7. Virology Analysis Subject Accountability

Failure Criterion	LRV 500 mg	LRV 750 mg	EFV 600 mg
TLOVR50 failure	10	3	2
TLOVR50 virologic failure	6	1	0
Study-defined treatment failure	6	1	0
Evaluable TLOVR50 virologic failure[a]	1	0	0
Other TLOVR50 failures with attempted analysis	5	2	1
Virologic failure	3	1	0
Other failure	2	1	1
TLOVR50 responders with attempted analysis	1	2	0

EFV = efavirenz; LRV = lersivirine; TLOVR = Time to Loss of Virologic Response.
a. This represents the Virology Analysis Set.

- Only 1 subject qualified as an evaluable TLOVR50 virologic failure to be included in the visual analog score (VAS). However, on-treatment plasma samples from a further 11 subjects were submitted for testing (LRV 500 mg n=6; LRV 750 mg n=4; EFV n=1). These included 4 TLOVR50 virologic failures (LRV 500 mg: n=3; LRV 750 mg: n=1), 4 other failures (LRV 500 mg: n=2; LRV 750 mg: n=1; EFV: n=1) and 3 TLOVR50 responders (LRV 500 mg: n=1; LRV 750 mg: n=2). Six (6) other subjects with TLOVR50 failure did not have suitable samples available for testing (LRV 500 mg n=4: 2 subjects experienced viral rebound at or prior to Week 96, but virus resupressed from then through Week 144 (plasma HIV-1 RNA <40 copies/mL); 2 subjects withdrew consent for trial participation prior to the first Post-Week 96 sample being taken; LRV 750 mg n =1: subject died with plasma HIV-1 RNA <40 copies/mL within the same window; EFV n =1: subject withdrew consent for trial participation prior to the first sample being taken). Due to low plasma HIV-1 RNA, only 5 of the failure sample analyses were successful.

- Overall, successful analyses were obtained from the failure samples of 5 subjects (LRV 500 mg: n=4; LRV 750 mg: n=1; efavirenz: n=0). There were no instances of the emergence of any nucleoside reverse transcriptase inhibitor (NRTI), non-nucleoside reverse transcriptase inhibitor (NNRTI) or LRV resistance-associated mutations. This was supported by drug susceptibility determinations, where significant increases of fold change were not observed.

- Only 1 subject had a valid on-treatment virology assessment at failure confirmation and was therefore included in the VAS. Day-1 (pre-dose) and last on-treatment time point samples were taken for evaluation of HIV-1 genotypic and phenotypic susceptibility to NRTIs and NNRTIs, including LRV. This subject had plasma HIV-1 RNA 78933 copies/mL at Baseline and fully suppressed plasma HIV-1 RNA (<40 copies/mL) from Week 12, but experienced viral rebound at Day 687 (Week 96). However, a further sample was taken at Day 799 (Week 112) when plasma HIV-1 RNA was 37996 copies/mL (-0.32 log copies/mL change from Baseline) and treatment was discontinued. There was no significant change of reverse transcriptase genotype or NRTI, NNRTI or LRV phenotype relative to findings at Baseline or at the Week 96 visit window.

Four (4) subjects who discontinued therapy early for non-virologic reasons, were tested at the Investigator's request (LRV 500 mg n=2: 1 subject discontinued for 'other reasons' (insufficient clinical response despite showing full virologic suppression) and another discontinued due to an AE; LRV 750 mg n=1: subject withdrew consent for study participation; EFV n=1: subject discontinued due to pregnancy). Each of these samples had a plasma HIV-1 RNA <40 copies/mL and returned a non-reportable result.

- Samples from 3 subjects who responded to therapy through Week 144 were also submitted for analysis at the Investigator's request (LRV 500 mg n=1; LRV 750 mg n=2). All of these samples had plasma HIV-1 RNA <40 copies/mL and returned non-reportable results.

In summary, TLOVR50 virologic failure was uncommon between Week 96 and Week 144 and no emergence of NRTI, NNRTI or LRV associated resistance-associated mutations (RAMS) or phenotypic resistance to regimen components was observed in any of the subjects with successful on-treatment assessments.

Among the failure subjects defined by the snapshot algorithm, numbers of subjects in each of the outcome categories were small and there was no apparent trend at Week 144.

Regarding genotypic and phenotypic susceptibility, virologic failure was uncommon between Week 96 and Week 144 and no emergence of NRTI, NNRTI or LRV associated RAMS or phenotypic resistance to regimen components was observed in any of the subjects with successful on-treatment assessments (5 subjects).

Safety Results:

Serious Adverse Events: A total of 7 subjects reported serious AEs; 5 subject in LRV 500 group (gastroenteritis and syphilis (1 subject), condition aggravated and chronic sinusitis (1 subject), biliary colic and cholecystectomy (1 subject), , paranoia (1 subject), hepatitis C (1 subject) and 2 subjects in the LRV 750 group experienced a road traffic accident (1 subject) and adenoma (1 subject), respectively. All these events were considered unrelated to the study drug. Summary of AEs (All Causality) Reported in this study (without the parent study) is presented in Table 8.

Table 8. Summary of Adverse Events (All Causality) Reported in A5271037 (Without Parent Study)

	LRV 500 mg (N=47)		LRV 750 mg (N=43)		EFV 600 mg (N=18)	
	n	%	n	%	n	%
Number of AEs	80	-	94	-	22	-
Subjects with AEs	28	(59.6)	33	(76.7)	12	(66.7)
Subjects with SAEs[a]	5	(10.6)	3	(7.0)	0	(0.0)
Subjects with grade 3 or 4 AEs	4	(8.5)	3	(7.0)	1	(5.6)
Subjects discontinued due to AEs	1	(2.1)	0[b]	(0.0)	0	(0.0)

Except for the number of AEs subjects are counted only once per treatment in each row. MedDRA (version 15.1) coding dictionary applied.
SAE and non SAE are not separated out.
AEs = adverse events; EFV = efavirenz; LRV = lersivirine; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; n = number of subject for specified categrory; SAE = serious adverse event.
a. Serious Adverse Events - according to the Investigator's assessment. Source of SAEs was OC (Oracle Clinical) and ARGUS databases.
b. One (1) subject (LRV 750 mg) died. Subject was incorrectly checked as "subject withdrawn from study". Due to this reason the subject was counted incorrectly as "subject discontinued due to AEs"

Adverse Events: AEs are summarized in Table 9. A total of 23/108 subjects had AEs of special interest (or pregnancy) (without the parent study). The most frequently reported event was insomnia.

Table 9. Treatment Emergent Adverse Events by Preferred Term with a Frequency >1 in Any Treatment Group (All Causality, without Parent Study)

Preferred Term	LRV 500 mg (N =47)		LRV 750 mg (N =43)		EFV 600 mg (N =18)	
	n	%	n	%	n	%
Abdominal pain	0	(0.0)	2	(4.7)	0	(0.0)
Dyspepsia	0	(0.0)	2	(4.7)	0	(0.0)
Nausea	0	(0.0)	2	(4.7)	0	(0.0)
Chest pain	0	(0.0)	2	(4.7)	0	(0.0)
Fatigue	0	(0.0)	2	(4.7)	0	(0.0)
Bronchitis	0	(0.0)	2	(4.7)	0	(0.0)
Gastroenteritis	1	(2.1)	2	(4.7)	1	(5.6)
Influenza	0	(0.0)	2	(4.7)	0	(0.0)
Oral herpes	1	(2.1)	0	(0.0)	0	(0.0)
Pharyngitis	0	(0.0)	1	(2.3)	1	(5.6)
Sinusitis	2	(4.3)	0	(0.0)	0	(0.0)
Syphilis	2	(4.3)	0	(0.0)	0	(0.0)
Upper respiratory tract infection	2	(4.3)	3	(7.0)	3	(16.7)
Arthralgia	1	(2.1)	2	(4.7)	0	(0.0)
Back pain	6	(12.8)	2	(4.7)	1	(5.6)
Areflexia	0	(0.0)	1	(2.3)	2	(11.1)
Headache	2	(4.3)	3	(7.0)	1	(5.6)
Depression	0	(0.0)	1	(2.3)	0	(0.0)
Insomnia	2	(4.3)	1	(2.3)	0	(0.0)
Haematuria	2	(4.3)	0	(0.0)	0	(0.0)
Eczema	0	(0.0)	3	(7.0)	0	(0.0)
Rash	2	(4.3)	1	(2.3)	1	(5.6)

Any AEs (preferred term) that occurred with a frequency >1 in any treatment group are summarized. The summary table includes new treatment emergent AEs in A5271037 and AEs that were ongoing at the time of enrollment in A5271037 with worsening grading from A5271015 to A5271037. MedDRA (v15.1) coding dictionary applied.
AE = adverse event; EFV = efavirenz; LRV = lersivirine; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; n = number of subject for specified category.

Discontinuation due Adverse Events: One (1) of 108 subjects discontinued the study due to a non-serious AE of renal impairment. The event was considered related to the study drug.

Deaths: One (1) subject in the LRV 750 group died due to possible gastrointestinal haemorrhage and neoplasm malignant, both events were considered unrelated to the study drug.

Laboratory Tests: In general, there were no clinically relevant observations regarding the results of clinical laboratory evaluations, physical examination and vital signs, fasting metabolic assessments, and anthropometric measurements in this study.

CONCLUSIONS:

- Long-term treatment (up to 144 weeks) with LRV had a sustained effect on suppression of HIV-1 RNA levels and increasing CD4+ cell counts.

- Long-term treatment (up to 144 weeks) with LRV was safe and well tolerated.