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

PROTOCOL NO.: A5271038

PROTOCOL TITLE: A Phase 2b/3 Open-Label Rollover Study for Subjects Discontinuing From the UK-453,061 Protocols for the Treatment of HIV-1 Infected Subjects

Study Centers: Twenty six (26) centers in Brazil, Malaysia, Portugal, Puerto Rico, South Africa, Ukraine, Poland, Italy, Argentina, Switzerland, the United Kingdom, and the United States took part in the study and enrolled subjects.

Study Initiation Date and Final Completion Date: 17 July 2009 to 15 July 2013

The study was terminated prematurely on 29 January 2013.

Phase of Development: Phase 2b

Study Objective: To assess long-term safety for subjects who were enrolled in the lersivirine (LRV) studies for treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infection.

METHODS

Study Design: This was an open-label, rollover study to assess long-term safety for HIV-1 infected subjects who were enrolled in a LRV parent study from all treatment groups. Subjects from 2 parent studies (1: A Phase 2b Multicenter, Randomized, Double-Blind, Comparative Trial of UK-453,061, in Combination With Tenofovir Df and Emtricitabine Versus Efavirenz in Combination With Tenofovir Df and Emtricitabine for the Treatment of Antiretroviral-Naive HIV-1 Infected Subjects [NCT00824421] and 2: A Phase 2b Multicenter, Randomized, Comparative Trial of UK-453,061 Versus Etravirine in Combination With Darunavir/Ritonavir and a Nucleos(t)ide Reverse Transcriptase Inhibitor for the Treatment of Antiretroviral Experienced HIV-1 Infected Subjects With Evidence of Non-Nucleoside Reverse Transcriptase Inhibitor [NNRTI] Resistant HIV-1 [NCT00823979]) were included if they discontinued treatment (in those studies) for any reason. Subjects were treated with an open-label antiretroviral (ARV) regimen that was selected by the Investigator, and did not include LRV. The final analysis was conducted when all the enrolled subjects had completed the End of Study Visit or Early Termination Visit.

On 10 December 2012, the Sponsor decided to discontinue further development of LRV, as it was determined that the compound would not provide an improvement over existing medicines in the NNRTI class.

The schedule of activities is presented in the Table 1.

Table 1. Schedule of Activities

Protocol Activity	Baseline[a]	Day 1[b]	Every 6 Months[c, d]	Early Termination End of Study
Informed consent	X			
Assign single subject identifier	X			
Plasma HIV-1 RNA level (viral load)	X[e]		X[f, g]	X[f, g]
Virus susceptibility (genotype, phenotype)	X[e]		X[f, h]	X[f, h]
CD4+ lymphocyte count (absolute and percentage)	X[e]		X[f,g]	X[f, g]
Adverse events	X		X	X
Select treatment regimen[i]	X			
Record treatment regimen	X		X	X
Record concomitant medications	X		X	X
Confirm treatment regimen and start dates		X		

CD4+ = cluster of differentiation 4+; HIV-1 RNA = Human Immunodeficiency Virus Type 1 Ribonucleic Acid.

a. The Baseline visit occurred at the Early Termination/Week 96 visit or within 42 days of the Early Termination/Week 96 visit from the parent study.
b. The Day 1 visit was to be conducted by telephone within 7 days of the Baseline Visit.
c. Occurred ±7 days.
d. For subjects who entered due to discontinuation from a parent-study for any reason: visits occurred ±7 days at 6 month intervals following Day 1 for a total duration of 1 year.
e. Data collected at the Early Termination/Week 96 visit under the parent studies was to be used as the Baseline assessments for this study. These results were directly transferred from the parent study database and did not need to be recorded on the Case Report Forms of this study.
f. Results of HIV-1 RNA level, virus susceptibility (genotype, phenotype) and CD4+ lymphocyte counts (absolute and percentage) were performed between visits.
g. Blood samples for measurement of HIV-1 RNA level and CD4+ lymphocyte counts (absolute and percentage) were collected in the clinic (within 7 days of the scheduled visit) only if these tests had not already been performed locally within 3 months of the visit.
h. Virus susceptibility testing (genotype, phenotype) was only performed for subjects with HIV-1 RNA level ≥1000 copies/mL at each 6 month visit (within 14 days of the HIV-1 RNA level results).
i. Individual treatment regimen was selected by the Investigator on the basis of susceptibility testing, treatment history and safety considerations.

Number of Subjects (Planned and Analyzed): Number of subjects was not estimated for this study. All subjects from the parent study meeting the eligibility criteria were enrolled in the study. A total of 52 subjects were enrolled (12 from parent study 1 and 40 from parent study 2).

Diagnosis and Main Criteria for Inclusion: Male and female subjects aged 18 years and older who had previously participated in 1 of the 2 parent studies with LRV (or comparator where required by local regulation) within the previous 42 days and with a viral load <50 copies/mL at Week 84 (or at the Early Termination Visit) of the parent study were eligible to be enrolled in the study. Females of child bearing potential required a negative urine pregnancy test at the Day 1 visit.

Exclusion Criteria: Subjects with any Grade 4 division of acquired immunodeficiency syndrome toxicity (except for lipids and asymptomatic glucose elevations) or those being treated with another investigational product or in another clinical trial (except the LRV parent studies) were excluded from the study.

Study Treatment: In parent study 1, subjects were randomized to receive 1 of the following treatments: LRV 500 mg once a day (QD), LRV 750 mg QD, or efavirenz (EFV) 600 mg QD. In parent study 2, subjects received LRV 750 mg QD, LRV 1000 mg QD, or etravirine (ETR) 200 mg BID. In the present study subjects did not receive any investigational drug (LRV) but received open-label ARV regimen selected by the Investigator. Subjects who were assigned to ETR 200 mg BID in the parent study were allowed to continue taking ETR.

Efficacy and Safety Endpoints:

Primary Endpoint: Safety assessed by adverse events (AEs).

Secondary Endpoints:

- Percentage of subjects with HIV-1 Ribonucleic acid (RNA) level <50 copies/mL.
- Cluster of differentiation 4+ (CD4+) lymphocyte count (absolute and percentage).

Safety Evaluations: Safety was assessed by new onset AEs under this study and laboratory test results.

Statistical Methods:

The full analysis set included all subjects who were enrolled in the study.

All analyses were descriptive in nature; no inferential statistics were provided and no imputation was applied to missing data; only available data was summarized.

The number and percentage of subjects with HIV-1 RNA level <50 copies/mL plasma were provided by visit and treatment. The lower limit of quantification (LLOQ) of the HIV-1 RNA assays ranged from 20 to 70 copies/mL. Due to this variability in the assay LLOQ, an additional endpoint was defined as the number and percentage of subjects with HIV-1 RNA <50 copies/mL or below LLOQ.

Descriptive statistics (total number of subjects [N], mean, standard deviation [SD], median, minimum, first quartile, third quartile and maximum) were used to summarize CD4+ lymphocyte count by visit.

RESULTS

Subject Disposition and Demography: A total of 12 subjects from parent study 1 and 40 from parent study 2 were enrolled in this study. Subject disposition is presented in Table 2 and Table 3.

Table 2. Subject Disposition (Subjects Enrolled From Parent Study 1)

	Treatment Group in Parent Study 1		
	LRV 500 mg QD	LRV 750 mg QD	EFV 600 mg QD
Screened (N=12)			
Assigned to study	5	4	3
Completed/study terminated by Sponsor	4 (80.0)	4 (100.0)	2 (66.7)
Number (%) of subjects discontinued	1 (20.0)	0	1 (33.3)
Reasons for discontinuation			
Relation to study drug not defined	1 (20.0)	0	1 (33.3)
No longer willing to participate in study	1 (20.0)	0	1 (33.3)

EFV = efavirenz; LRV = lersivirine; N = number of subjects; QD = once a day.

Table 3. Subject Disposition (Subjects Enrolled From Parent Study 2)

	Treatment Group in Parent Study 2		
	LRV 750 mg QD	LRV 1000 mg QD	ETR 200 mg BID
Screened (N=40)			
Assigned to study	11	12	17
Completed/study terminated by Sponsor	9	11	16
Number of subjects discontinued	2	1	1
Reasons for discontinuation			
Relation to study drug not defined	2	1	1
Lost to follow-up	0	1	0
No longer willing to participate in study	2	0	1

Subject discontinuations excluded those who were terminated due to Sponsor's study termination decision.
BID = twice per day; ETR = etravirine; LRV = lersivirine; N = total number of subjects; QD = once a day.

A summary of demographic characteristics are presented in Table 4 and Table 5.

Table 4. Demographic Characteristics (Subjects Enrolled From Parent Study 1)

	Treatment Group in Parent Study 1			
	LRV 500 mg QD N=5	LRV 750 mg QD N=4	EFV 600 mg QD N=3	Total N=12
Sex, n (%)				
Male	3 (60.0)	2 (50.0)	2 (66.7)	7 (58.3)
Female	2 (40.0)	2 (50.0)	1 (33.3)	5 (41.7)
Age (years)				
18-44	5	4	3	12
Mean	33.8	31.5	38.3	34.2
SD	6.1	1.7	3.2	4.8
Range	24-40	29-33	36-42	24-42

Data in this table are the demographic and screening/baseline data from the first parent study.
EFV = efavirenz; LRV = lersivirine; n = number of subjects with measurements; N = total number of subjects in group; QD = once a day; SD = standard deviation.

Table 5. Demographic Characteristics (Subjects Enrolled From Parent Study 2)

	Treatment Group in Parent Study 2			
	LRV 750 mg QD N=11	LRV 1000 mg QD N=12	ETR 200 mg BID N=17	Total N=40
Gender, n				
Male	6	5	6	17
Female	5	7	11	23
Age (years), n (%)				
18-44	8 (72.7)	9 (75.0)	12 (70.6)	29 (72.5)
45-64	3 (27.3)	3 (25.0)	4 (23.5)	10 (25.0)
≥65	0	0	1 (5.9)	1 (2.5)
Mean	42.7	39.1	41.6	41.2
SD	9.1	9.0	9.4	9.1
Range	32-62	21-50	24-66	21-66

Data in this table are the demographic and screening/baseline data from the second parent study.
BID = twice per day; ETR = etravirine; LRV = lersivirine; n = number of subjects with measurements; N = total number of subjects in group; QD = once a day; SD = standard deviation.

Efficacy Results:

The number and percentage of subjects enrolled from parent study 1 with an HIV-1 RNA level of <50 copies/mL by visit is provided in Table 6 and with an HIV-1 RNA level of <50 copies/mL or below LLOQ by visit in Table 7.

Table 6. Percentage of Subjects With HIV-1 RNA Level < 50 Copies/mL by Visit (Subjects Enrolled From Parent Study 1)

Visits	Treatment Group	N	n	%	80% CI-Lower	80% CI-Upper
Baseline	LRV 500 mg QD	5	2	40.0	1.9	78.1
	LRV 750 mg QD	4	3	75.0	34.8	100.0
	EFV 600 mg QD	3	0	0.0	0	16.7
Month 6	LRV 500 mg QD	3	2	66.7	15.1	100.0
	LRV 750 mg QD	2	2	100.0	75	100.0
	EFV 600 mg QD	3	2	66.7	15.1	100.0
Month 12	LRV 500 mg QD	3	2	66.7	15.1	100.0
	LRV 750 mg QD	3	3	100.0	83.3	100.0
	EFV 600 mg QD	1	0	0.0	0	50.0
Last visit	LRV 500 mg QD	4	3	75.0	34.8	100.0
	LRV 750 mg QD	3	3	100.0	83.3	100.0
	EFV 600 mg QD	3	1	33.3	0	84.9

Early Termination Visit under the parent study was used as the Baseline Visit assessments.
The Baseline Visit could have occurred at the Early Termination Visit or within 42 days of the Early Termination Visit from the parent study.
Last visit uses the last available visit of each enrolled subject.
Subjects where the HIV-RNA level was measured on an assay with a lower limit of quantification >50 are not included in the analysis at the visit of interest.
The last non-missing record was used in analysis, while multiple records within the same visit.
CI = confidence interval; EFV = efavirenz; HIV-1 = Human Immunodeficiency Virus Type 1;
LRV = lersivirine; n = number of subjects with an HIV-1 RNA level of <50 copies/mL; N = total number of subjects in group; QD = once a day; RNA = ribonucleic acid.

Table 7. Percentage of Subjects With HIV-1 RNA Level <50 Copies/mL or Below LLOQ by Visit (Subjects Enrolled From Parent Study 1)

Visits	Treatment Group	N	n	%	80% CI-Lower	80% CI-Upper
Baseline	LRV 500 mg QD	5	2	40.0	1.9	78.1
	LRV 750 mg QD	4	3	75.0	34.8	100.0
	EFV 600 mg QD	3	0	0.0	0.0	16.7
Month 6	LRV 500 mg QD	4	3	75.0	34.8	100.0
	LRV 750 mg QD	4	4	100.0	87.5	100.0
	EFV 600 mg QD	3	2	66.7	15.1	100.0
Month 12	LRV 500 mg QD	4	3	75.0	34.8	100.0
	LRV 750 mg QD	4	4	100.0	87.5	100.0
	EFV 600 mg QD	1	0	0.0	0.0	50.0
Last visit	LRV 500 mg QD	5	4	80.0	47.1	100.0
	LRV 750 mg QD	4	4	100.0	87.5	100.0
	EFV 600 mg QD	3	1	33.3	0.0	84.9

Early Termination Visit during the parent study was used as the Baseline Visit assessments. The Baseline Visit could have occurred at the Early Termination Visit or within 42 days of the Early Termination Visit from the parent study. Last visit uses the last available visit of each enrolled subject. The last non-missing record was used in analysis, while multiple records within the same visit.
CI = confidence interval; EFV = efavirenz; HIV-1 = Human Immunodeficiency Virus Type 1; LLOQ = lower limit of quantification; LRV = lersivirine; n = number of subjects with an HIV-1 RNA level of <50 copies/mL or below LLOQ; N = total number of subjects in group; QD = once a day; RNA = ribonucleic acid.

The number and percentage of subjects enrolled from parent study 2 with an HIV-1 RNA level of <50 copies/mL by visit is provided in Table 8 and with an HIV-1 RNA level of <50 copies/mL or below LLOQ by visit in Table 9.

Table 8. Percentage of Subjects With HIV-1 RNA Level < 50 Copies/mL by Visit (Subjects Enrolled From Parent Study 2)

Visits	Treatment Group	N	n	%	80% CI-Lower	80% CI-Upper
Baseline	LRV 750 mg QD	11	9	81.8	62.4	100.0
	LRV 1000 mg QD	12	7	58.3	35.9	80.7
	ETR 200 mg BID	17	15	88.2	75.3	100.0
Month 6	LRV 750 mg QD	8	5	62.5	34.3	90.7
	LRV 1000 mg QD	11	5	45.5	21.7	69.2
	ETR 200 mg BID	15	12	80.0	63.4	96.6
Month 12	LRV 750 mg QD	2	2	100.0	75.0	100.0
	LRV 1000 mg QD	5	4	80.0	47.1	100.0
	ETR 200 mg BID	7	5	71.4	42.4	100.0
Last visit	LRV 750 mg QD	11	7	63.6	40.5	86.8
	LRV 1000 mg QD	12	7	58.3	35.9	80.7
	ETR 200 mg BID	17	14	82.4	67.6	97.1

Early Termination Visit under the parent study was used as the Baseline Visit assessments.
The Baseline Visit could have occurred at the Early Termination Visit or within 42 days of the Early Termination Visit from the parent study. Last visit uses the last available visit of each enrolled subject.
Subjects where the HIV-RNA level was measured on an assay with a lower limit of quantification >50 were not included in the analysis at the visit of interest.
The last non-missing record was used in analysis, while multiple records within the same visit.
BID = twice per day; CI = confidence interval; ETR = etravirine; HIV-1 = Human Immunodeficiency Virus Type 1; LRV = lersivirine; n = number of subjects with an HIV-1 RNA level of <50 copies/mL; N = total number of subjects in group; QD = once daily; RNA = ribonucleic acid.

Table 9. Percentage of Subjects With HIV-1 RNA Level <50 Copies/mL or Below LLOQ by Visit (Subjects Enrolled From Parent Study 2)

Visits	Treatment Group	N	n	%	80% CI-Lower	80% CI-Upper
Baseline	LRV 750 mg QD	11	9	81.1	62.4	100.0
	LRV 1000 mg QD	12	7	58.3	35.9	80.7
	ETR 200 mg BID	17	15	88.2	75.3	100.0
Month 6	LRV 750 mg QD	8	5	62.5	34.3	90.7
	LRV 1000 mg QD	11	5	45.5	21.7	69.2
	ETR 200 mg BID	15	12	80.0	63.4	96.6
Month 12	LRV 750 mg QD	2	2	100.0	75.0	100.0
	LRV 1000 mg QD	5	4	80.0	47.1	100.0
	ETR 200 mg BID	7	5	71.4	42.4	100.0
Last visit	LRV 750 mg QD	11	7	63.6	40.5	86.8
	LRV 1000 mg QD	12	7	58.3	35.9	80.7
	ETR 200 mg BID	17	14	82.4	67.6	97.1

Early Termination Visit during the parent study was used as the Baseline Visit assessments. The Baseline Visit could have occurred at the Early Termination Visit or within 42 days of the Early Termination Visit from the parent study. Last visit uses the last available visit of each enrolled subject. The last non-missing record was used in analysis, while multiple records within the same visit.
BID = twice per day; CI = confidence interval; ETR = etravirine; HIV-1 = human Immunodeficiency Virus Type 1; LLOQ = lower limit of quantification; LRV = lersivirine; n = number of subjects with an HIV-1 RNA level of <50 copies/mL or below LLOQ; N = total number of subjects in group; QD = once per day; RNA = ribonucleic acid.

At Month 12, the mean (SD) absolute CD4+ cell counts were 618 (285) cells/µL, 607 (326) cells/µL, and 556 (65) cells/µL from the LRV 500 mg QD, LRV 750 mg QD, and EFV 600 mg QD treatment groups, respectively (subjects enrolled from parent study 1) (Table 10).

Table 10. Descriptive Statistics of Absolute CD4+ Cell Count (Cells/µL) by Visit - Available Data (Subjects Enrolled From Parent Study 1)

Visit	Treatment Group	N	Mean	SD	Min	Q1	Median	Q3	Max
Baseline	LRV 500 mg	4	285	97	152	214	311	357	368
	LRV 750 mg	4	574	274	317	371	519	778	942
	EFV 600 mg	3	564	121	425	425	619	647	647
Month 6	LRV 500 mg	4	456	175	325	352	393	560	714
	LRV 750 mg	4	514	195	309	365	493	663	760
	EFV 600 mg	2[a]	606	120	521	521	606	691	691
Month 12	LRV 500 mg	4	618	285	389	440	525	796	1032
	LRV 750 mg	4	607	326	373	378	492	836	1070
	EFV 600 mg	2[a]	556	65	510	510	556	602	602

Early Termination Visit under the parent protocols was used as the Baseline visit assessments.
The Baseline Visit could have occurred at the Early Termination Visit or within 42 days of the Early Termination Visit from the parent protocol.
CD4+ = cluster differentiation 4+; EFV = efavirenz; LRV = lersivirine; Max = maximum; Min = minimum; N = number of subjects with measurements; Q1 = first quartile; Q3 = third quartile; SD = standard deviation.
a. One subject from treatment group EFV 600 mg had unusually high CD4+ values of 567000 cells/µL for Month 6 and 585000 cells/µL for Month 12 due to an error in the units reported. As these values are erroneous, they have been excluded from this table.

Descriptive statistics of CD4+ cell count (percentage) (subjects enrolled from parent study 1) is presented in Table 11.

Table 11. Descriptive Statistics of CD4+ Cell Count (Percentage) by Visit - Available Data (Subjects Enrolled From Parent Study 1)

Visit	Treatment Group	N	Mean	SD	CV%	Min	Q1	Median	Q3	Max
Baseline	LRV 500 mg QD	4	21	10	49	7	14	23	29	31
	LRV 750 mg QD	4	29	9	32	21	21	27	36	40
	EFV 600 mg QD	3	26	2	8	24	24	27	28	28
Month 6	LRV 500 mg QD	4	36	14	39	15	28	41	44	46
	LRV 750 mg QD	4	31	12	38	16	22	32	40	43
	EFV 600 mg QD	3	26	1	4	25	25	27	27	27
Month 12	LRV 500 mg QD	4	38	14	37	18	29	43	47	49
	LRV 750 mg QD	4	30	10	32	20	22	29	38	40
	EFV 600 mg QD	3	27	7	25	21	21	25	34	34

Early Termination visit under the parent protocols was used as the Baseline visit assessments.
The Baseline visit could have occurred at the Early Termination visit or within 42 days of the Early Termination visit from the parent protocol.
CD4+ = cluster of differentiation; CV = coefficient of variation; EFV = efavirenz; LRV = lersivirine; max = maximum; min = minimum; N = number of subjects with measurements; Q1 = first quartile; Q3 = third quartile; QD = once a day; SD = standard deviation.

At Month 6, the mean (SD) absolute CD4+ cell counts were 615 (248), 413 (266) and 451 (221) cells/µL for LRV 750 mg QD, LRV 100 mg QD and ETR 200 mg BID treatment groups, respectively (subjects enrolled from parent study 2) (Table 12).

Table 12. Descriptive Statistics of Absolute CD4+ Cell Count (cells/uL) by Visit - Available Data (Subjects Enrolled From Parent Study 2)

Visit	Treatment Group	N	Mean	SD	Min	Q1	Median	Q3	Max
Baseline	LRV 750 mg QD	11	473	191	198	302	416	636	798
	LRV 1000 mg QD	12	411	259	61	158	476	564	849
	ETR 200 mg BID	17	455	212	183	300	396	564	907
Month 6	LRV 750 mg QD	8	615	248	275	475	540	807	999
	LRV 1000 mg QD	11	413	266	80	190	387	635	912
	ETR 200 mg BID	15	451	221	215	286	391	538	971
Month 12	LRV 750 mg QD	3	378	57	333	333	360	442	442
	LRV 1000 mg QD	6	361	309	94	157	227	563	895
	ETR 200 mg BID	7	452	247	184	253	301	686	783

Early Termination Visit under the parent protocols will be used as the Baseline Visit assessments. The Baseline Visit can occur at the Early Termination Visit or within 42 days of the Early Termination Visit from the parent protocol.
BID = twice per day; CD4+ = cluster differentiation 4; ETR = etravirine; LRV = lersivirine; Max = maximum; Min = minimum; N = number of subjects with measurements; Q1 = first quartile; Q3 = third quartile; QD = once per day; SD = standard deviation.

Descriptive statistics of CD4+ cell count (percentage) (subjects enrolled from parent study 2) is presented in the Table 13.

Table 13. Descriptive Statistics of CD4+ Cell Count (Percentage) by Visit - Available Data (Subjects Enrolled From Parent Study 2)

Visit	Treatment Group	N	Mean	SD	CV%	Min	Q1	Median	Q3	Max
Baseline	LRV 750 mg QD	11	26	10	39	11	19	25	33	50
	LRV 1000 mg QD	12	21	12	56	4	10	24	32	34
	ETR 200 mg BID	17	23	8	36	6	19	23	28	36
Month 6	LRV 750 mg QD	8	28	12	44	16	18	23	38	48
	LRV 1000 mg QD	11	22	11	49	4	14	21	33	38
	ETR 200 mg BID	14	23	6	28	9	19	25	27	31
Month 12	LRV 750 mg QD	3	26	11	42	17	17	22	38	38
	LRV 1000 mg QD	6	19	10	54	7	12	17	27	35
	ETR 200 mg BID	6	18	7	42	4	15	21	23	23

Early Termination visit under the parent protocols was used as the Baseline visit assessments.
The Baseline visit could have occurred at the Early Termination visit or within 42 days of the Early Termination visit from the parent protocol.
BID = twice per day; CD4+ = cluster differentiation 4; CV = coefficient of variation; ETR = etravirine; LRV = lersivirine; Max = maximum; Min = minimum; N = number of subjects with measurements; Q1 = first quartile; Q3 = third quartile; QD = once per day; SD = standard deviation.

Safety Results: The treatment-emergent adverse events (TEAEs) in subjects enrolled in this study from parent study 1 are presented in Table 14. TEAEs were defined as starting after initiation of ARV regimen in this study or ongoing AEs from the parent study with a worsening severity in this study.

Table 14. Treatment-Emergent Non Serious Adverse Events (All Causalities) (Subjects Enrolled From Parent Study 1)

System Organ Class Preferred Term	LRV 500 mg QD N=5 n (%)	LRV 750 mg QD N=4 n (%)	EFV 600 mg QD N=3 n (%)
With any adverse events	3 (60.0)	4 (100.0)	2 (66.7)
Gastrointestinal disorders	1 (20.0)	3 (75.0)	2 (66.7)
Abdominal pain lower	1 (20.0)	0	0
Anal haemorrhage	0	1 (25.0)	0
Aphthous stomatitis	0	0	1 (33.3)
Diarrhoea	1 (20.0)	2 (50.0)	1 (33.3)
Haemorrhoids	0	1 (25.0)	0
General disorders and administration site conditions	0	1 (25.0)	0
Fatigue	0	1 (25.0)	0
Hepatobiliary disorders	0	0	1 (33.3)
Jaundice	0	0	1 (33.3)
Infections and infestations	0	2 (50.0)	0
Nasopharyngitis	0	1 (25.0)	0
Oral herpes	0	1 (25.0)	0
Varicella	0	1 (25.0)	0
Injury poisoning and procedural complications	1 (20.0)	0	0
Ligament sprain	1 (20.0)	0	0
Investigations	0	0	1 (33.3)
Blood creatinine increased	0	0	1 (33.3)
Musculoskeletal and connective tissue disorders	0	1 (25.0)	0
Back pain	0	1 (25.0)	0
Nervous system disorders	0	1 (25.0)	0
Carpal tunnel syndrome	0	1 (25.0)	0
Psychiatric disorders	1 (20.0)	0	0
Anxiety	1 (20.0)	0	0
Stress	1 (20.0)	0	0
Reproductive system and breast disorders	2 (40.0)	0	0
Epididymitis	1 (20.0)	0	0
Vaginal discharge	1 (20.0)	0	0
Respiratory, thoracic and mediastinal disorders	1 (20.0)	0	1 (33.3)
Cough	1 (20.0)	0	0
Oropharyngeal pain	0	0	1 (33.3)
Skin and subcutaneous tissue disorders	0	0	1 (33.3)
Rash papular	0	0	1 (33.3)

Each subject was counted once only for each row.
This table included new treatment emergent AEs in this study and AEs ongoing at the time of enrollment in this study with worsening grading from parent study 1 to this study.
MedDRA (v15.1) coding dictionary applied.
AE = adverse event; EFV = efavirenz; LRV = lersivirine; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with adverse events; N = total number of subjects; QD = once a day; v = version.

Three (3) subjects experienced 3 TEAEs considered related to ARV treatment as shown in the Table 15. No TEAEs were reported by the Investigators as related to use of parent study investigational drug (ie, LRV or EFV).

Table 15. Treatment-Related Treatment-Emergent Non Serious Adverse Events (Treatment-Related - Any Current or Parent Protocol ARV) (Subjects Enrolled from Parent Study 1)

System Organ Class Preferred Term	Total n	 %
LRV 750 mg QD (N=4)		
Subjects with any AEs	2	50
Gastrointestinal disorder	1	25
Diarrhoea	1	25
General disorders and administration site conditions	1	25
Fatigue	1	25
EFV 600 mg QD (N=3)		
Subjects with any AEs	1	33.3
Investigations	1	33.3
Blood creatinine increased	1	33.3

Each subject was counted once only for each row.
This table includes new treatment emergent AEs in this study and AEs ongoing at the time of enrollment in this study with worsening grading from first parent study to this study.
MedDRA (v15.1) coding dictionary applied.
AE = adverse event; ARV = antiretroviral; EFV = efavirenz; LRV = lersivirine; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with adverse events; N = total number of subjects; v = version.

There were no SAEs or subjects who discontinued the study due to a TEAE for subjects enrolled from parent study 1.

The TEAEs in subjects enrolled in this study from parent study 2 are presented in Table 16. TEAEs were defined as starting after initiation of ARV regimen in this study or ongoing AEs from the parent study with a worsening severity in this study.

Table 16. Treatment-Emergent Non Serious Adverse Events (Subjects Enrolled From Parent Study 2)

System Organ Class Preferred term	LRV 750 mg QD N=11 n (%)	LRV 1000 mg QD N=12 n (%)	ETR 200 mg BID N=17 n (%)
With any adverse events	6 (54.5)	7 (58.3)	11 (64.7)
Blood and lymphatic system disorders	0	1 (8.3)	1 (5.9)
Anaemia	0	0	1 (5.9)
Thrombocytopenia	0	1 (8.3)	0
Eye disorders	0	0	1 (5.9)
Conjunctivitis	0	0	1 (5.9)
Gastrointestinal disorders	2 (18.2)	2 (16.7)	1 (5.9)
Abdominal pain upper	0	0	1 (5.9)
Cheilitis	0	1 (8.3)	0
Constipation	1 (9.1)	0	0
Frequent bowel movements	0	1 (8.3)	0
Gastrointestinal disorder	0	1 (8.3)	0
Nausea	1 (9.1)	0	0
General disorders and administration site conditions	0	1 (8.3)	1 (5.9)
Chest pain	0	1 (8.3)	0
Cyst	0	0	1 (5.9)
Hepatobiliary disorders	0	0	1 (5.9)
Hepatomegaly	0	0	1 (5.9)
Immune system disorders	0	1 (8.3)	0
Seasonal allergy	0	1 (8.3)	0
Infections and infestations	3 (27.3)	2 (16.7)	3 (17.6)
Acarodermatitis	1 (9.1)	0	0
Cellulitis	0	0	1 (5.9)
Herpes zoster	0	1 (8.3)	0
Onychomycosis	0	0	1 (5.9)
Oropharyngeal candidiasis	0	1 (8.3)	0
Salpingo-oophoritis	1 (9.1)	0	0
Upper respiratory tract infection	1 (9.1)	0	1 (5.9)
Investigations	2 (18.2)	0	3 (17.6)
Blood glucose increased	1 (9.1)	0	1 (5.9)
Blood pressure increased	0	0	1 (5.9)
Blood thyroid stimulating hormone increased	1 (9.1)	0	0
Blood triglycerides increased	0	0	1 (5.9)
Gamma-glutamyltransferase increased	0	0	1 (5.9)
Low density lipoprotein increased	0	0	1 (5.9)
Weight decreased	0	0	1 (5.9)
Metabolism and nutrition disorders	1 (9.1)	3 (25.0)	3 (17.6)
Decreased appetite	0	2 (16.7)	0
Dyslipidaemia	1 (9.1)	0	2 (11.8)
Hypophosphataemia	0	1 (8.3)	0
Type 2 diabetes mellitus	0	0	1 (5.9)
Musculoskeletal and connective tissue disorders	0	1 (8.3)	1 (5.9)
Back pain	0	0	1 (5.9)
Flank pain	0	1 (8.3)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (8.3)	0
Uterine leiomyoma	0	1 (8.3)	0

Table 16. Treatment-Emergent Non Serious Adverse Events (Subjects Enrolled From Parent Study 2)

System Organ Class Preferred term	LRV 750 mg QD N=11 n (%)	LRV 1000 mg QD N=12 n (%)	ETR 200 mg BID N=17 n (%)
Nervous system disorders	0	2 (16.7)	1 (5.9)
Dizziness	0	0	1 (5.9)
Nerve compression	0	1 (8.3)	0
Somnolence	0	1 (8.3)	1 (5.9)
Psychiatric disorders	0	1 (8.3)	0
Depression	0	1 (8.3)	0
Renal and urinary disorders	0	0	1 (5.9)
Renal impairment	0	0	1 (5.9)
Reproductive system and breast disorders	0	0	1 (5.9)
Breast mass	0	0	1 (5.9)
Skin and subcutaneous tissue disorders	0	1 (8.3)	2 (11.8)
Lichen planus	0	0	1 (5.9)
Pruritus	0	1 (8.3)	0
Rash papular	0	0	1 (5.9)
Vascular disorders	1 (9.1)	1 (8.3)	0
Hypertension	1 (9.1)	1 (8.3)	0

Subjects were only counted once per treatment for each row.
This table includes new treatment emergent AEs in this study and AEs ongoing at the time of enrollment in this study with worsening grading from parent study 2 to this study.
MedDRA (v15.1) coding dictionary applied.
AE = adverse event; BID = twice per day; ETR = etravirine; LRV = lersivirine; MedDRA = Medical Dictionary for Regulatory Activities; n = subjects with adverse events; N = total number of subjects; v = version.

Four TEAEs, considered related to current ARV treatment, were reported in 2 (11.8%) subjects in the ETR 200 mg group (Table 17).

Table 17. Treatment-Related Treatment-Emergent Adverse Events (Treatment-Related - Any Current or Parent Protocol ARV) (Subjects Enrolled from Parent Study 2)

System Organ Class Preferred Term	ETR 200 mg BID (N=17)	
	n	%
Subjects with any AEs	2	11.8
Gastrointestinal disorders	1	5.9
Abdominal pain upper	1	5.9
Hepatobiliary disorders	1	5.9
Hepatomegaly	1	5.9
Nervous system disorders	1	5.9
Dizziness	1	5.9
Somnolence	1	5.9

Each subject was counted once only for each row.
This table includes new treatment emergent AEs in this study and AEs ongoing at the time of enrollment in this study with worsening grading from first parent study to this study.
MedDRA (v15.1) coding dictionary applied.
AE = adverse event; ARV = antiretroviral; BID = twice per day; ETR = etravirine; MedDRA = Medical Dictionary for Regulatory Activities; n = subjects with adverse events; N = total number of subjects; v = version.

One (1) subject was reported to have had the dose of 1 or more components of their assigned ARV regimen reduced, due to the event of upper abdominal pain. No other subjects had dose reductions or were temporarily discontinued treatment due to an AE.

There were no SAEs or subjects who discontinued the study due to a TEAE for subjects enrolled from parent study 2.

No deaths were reported in this study.

CONCLUSIONS:

- HIV-1 RNA and CD4+ cell count data from this small rollover long-term (12-months) safety study suggested that subjects who previously received LRV, ETR or EFV-based treatment in either parent study and were discontinued for various reasons were able to maintain or regain virologic and immunologic response on subsequent ARV regimens selected by Investigators in the study.

- The majority of TEAEs were mild in severity, and there were no SAEs, deaths, or study discontinuations due to TEAEs.

- There were no TEAEs reported by the Investigators as related to the use of the parent study investigational drug (ie, LRV or EFV or ETR).