



# Elvucitabine vs Lamivudine with Tenofovir and Efavirenz in Antiretroviral-Treatment-Naïve HIV-1 Infected Patients: 96 Week Final Results

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## ABSTRACT

**Background:** Elvucitabine (ACH123,446)(ELV) is a L-cytosine NRTI analog with a half-life of ~100 hours that has an in-vitro EC50 value of 1.1 ng/mL, 3-4 times more potent than lamivudine (LAM). The trough minimum plasma concentration levels of elvucitabine at 10 mg/day exceeded the in vitro 50% and 90% inhibition concentration values for wild type HIV-1 isolates.

**Methods:** A Phase II, prospective, randomized (1:1), double-blind, multi-center, 96-week comparison of ELV 10 mg versus lamivudine 300 mg both administered daily in combination with efavirenz (EFV) 600 mg and tenofovir DF (TDF) 300 mg in HIV-1-infected, treatment-naïve subjects. CD4 count was between 200 and 500 cells/mL. Endpoints included the proportion of subjects with HIV-RNA levels < 50 copies/mL at Weeks 12, 24, 48, and 96.

**Results:** 77 subjects were randomized and 76 subjects (39 ELV; 37 LAM) were treated. Baseline characteristics were similar between treatment groups. 48 subjects (21 ELV; 27 LAM) completed 96 weeks of treatment. Discontinuations were due to lost to follow-up (n=7), voluntary withdrawal (n=7), physician decision (n=6), sponsor decision (n=4), adverse event (n=4), and death (n=1).

The proportion of subjects at week 96 with HIV-1 levels < 50 copies/mL in the ITT patient population was 54% (20/37) in the ELV treatment group and 68% (25/37) in the LAM treatment group [95% CI (-36%, 9%)]. The proportion of subjects in the as-treated patient population was 95% (20/21) for ELV subjects and 93% (25/27) for LAM subjects [95% CI (-11%, 16%)].

At week 96, the ELV treatment group experienced a mean (SD) change in percent CD4 of +11 (7) versus +12 (8) with LAM. None of the SAEs reported during the trial were study-drug related. The same number of subjects (8%, n=3) in each of the treatment groups reported study-drug related adverse events that were graded severe by the investigator. The incidence, type, and severity of adverse events were similar between treatment groups. Virologic failure (VF) (protocol defined: > 50 copies/mL after wk 12) occurred in one subject between weeks 12 and 48, and in 8 subjects between weeks 48 and 96. However, only 2 subjects discontinued protocol treatment for VF and only one PI mutation was identified. No NRTI or NNRTI mutations emerged between weeks 12 and 96 in either treatment group among subjects tested.

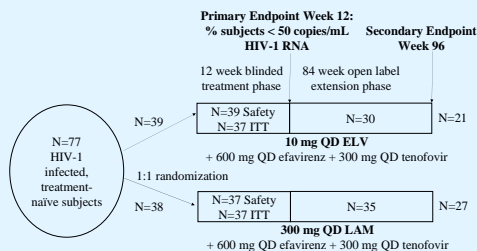
**Conclusions:** ELV administered in combination with tenofovir and efavirenz demonstrated comparable safety and efficacy to LAM, with sustained virologic suppression at 96 weeks.

## METHODS

A Phase II, randomized, double-blind trial at 16 sites in the United States and 3 sites in India. Subjects started dosing May 31, 2006 and the last randomized subject enrolled May 15, 2007. Primary endpoint: proportion of subjects with HIV-1 RNA levels < 50 copies/mL at Week 12. Secondary endpoints at Weeks 12, 24, 48 and 96 included:

- Change in HIV-1 RNA level from Baseline
- Proportion of subjects with HIV-1 RNA levels < 400 copies/mL
- Proportion of subjects with HIV-1 RNA levels < 50 copies/mL (Weeks 24, 48, 96)
- Time to occurrence of less than 400 copies/mL and less than 50 copies/mL
- Change in CD4 count from Baseline

Periodic assessments of clinical, metabolic, immunologic status, and plasma viral load were performed every 2 weeks through Week 16 and every 4 weeks thereafter. PK assessments occurred at Baseline, and Weeks 4, 6, 8, 12, 16 and 24, 48, 72 and 96.



## RESULTS

### Subject Disposition

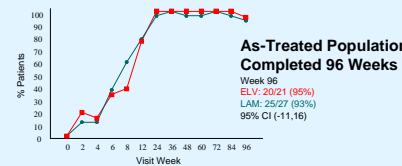
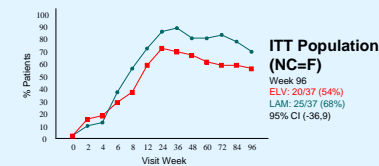
	Elvucitabine N=39			Lamivudine N=38		
	Weeks < 12	12 to < 48	48 to < 96	< 12	12 to < 48	48 to < 96
Completed	30	25	21	35	30	27
Discontinued	9	5	4	3	5	3
Adverse event	1 <sup>a</sup>	2 <sup>b</sup>		1 <sup>c</sup>		
Lost to follow-up	2 <sup>d</sup>	2	1		2	
Subject died	1 <sup>e</sup>					
Voluntarily withdrew	3	1	1 <sup>f</sup>	1	1	
Physician/sponsor decision	2	1	2	2	3	

<sup>a</sup> Castleman's disease, unrelated to study drug  
<sup>b</sup> (1) Post operative complications after appendicitis and deemed unrelated to drug; and (2) severe neutropenia starting at Week 24 and deemed probably related to drug  
<sup>c</sup> severe neutropenia starting at Week 32 and deemed unrelated to drug  
<sup>d</sup> one patient did not have follow-up data and is not included in the ITT population  
<sup>e</sup> Suicide, deemed unrelated to study drug  
<sup>f</sup> one patient did not receive treatment and is not included in either the safety or ITT population.

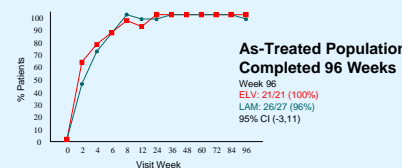
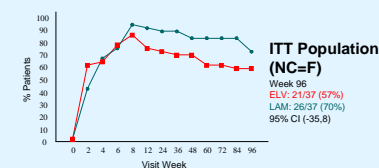
**Discontinuations from Week 48 through 96 unrelated to study drug**

### Efficacy

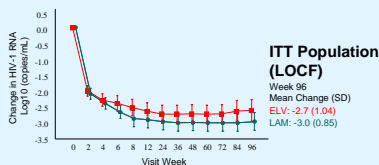
#### % Patients with HIV-1 RNA < 50 copies/mL



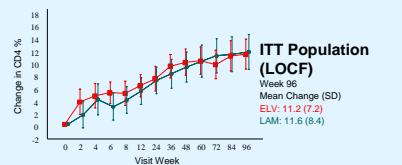
#### % Patients with HIV-1 RNA < 400 copies/mL



#### Mean Change (95% CI) From Baseline HIV-1 RNA Log10



#### Mean Change (95% CI) From Baseline CD4 %



## Safety

### Serious Adverse Events

- None of the SAEs were considered related to study drug.
- 25 SAEs (13 ELV; 12 LAM) reported by 15 patients (10 ELV; 5 LAM).
- All SAEs (other than Castleman's disease and the suicide) resolved, with subjects continuing study treatment.

### Grade 3/4 Laboratory Abnormalities Number (% of Patients)

Laboratory Parameter (unit)	ELV N=39 (%)	LAM N=37 (%)
Absolute neutrophils (x10 <sup>9</sup> /L)	2 (5)	1 (3)
Hemoglobin (g/dL)	1 (3)	1 (3)
Platelets (x10 <sup>9</sup> /L)	1 (3)	
White blood cells (x10 <sup>9</sup> /L)	1 (3)	
Alkaline phosphatase (U/L)	1 (3)	
ALT (U/L)	2 (5)	1 (3)
AST (U/L)	1 (3)	2 (5)
Bicarbonate (mEq/L)	1 (3)	
Calcium (mg/dL)	1 (3)	
Cholesterol (Total) (mg/dL)	1 (3)	3 (8)
CK (U/L)	4 (11)	3 (8)
Creatinine (mg/dL)	1 (3)	
Glucose (Serum, Random) (mg/dL)	2 (5)	3 (8)
LDL-cholesterol (Calc) (mg/dL)		3 (8)
Lipase (U/L)	1 (3)	1 (3)
Phosphate (mg/dL)	1 (3)	1 (3)
Sodium (mEq/L)	2 (5)	1 (3)
Triglycerides (mg/dL)		3 (8)

### Adverse Events Number (% of Patients)

	ELV N=39 (%)	LAM N=37 (%)
# Patients reporting any AE	37 (95)	35 (95)
# AEs reported	366	430

# Patients reporting a drug-related AE	16 (41)	20 (54)
# Drug-related AEs reported	56	73

### Drug Related Adverse Events in ≥ 2 Patients

Nausea	6 (15)	4 (11)
Headache	4 (1)	5 (14)
Dizziness	5 (13)	2 (5)
Diarrhea	2 (5)	5 (14)
Vomiting	2 (5)	2 (5)
Fatigue	3 (8)	1 (3)
Hyperlipidaemia	1 (3)	3 (8)
Dyspepsia	2 (5)	1 (3)
Abnormal dreams	3 (8)	
Rash	3 (8)	
Asthenia	2 (5)	1 (3)
Anorexia	1 (3)	2 (5)
Insomnia	1 (3)	1 (3)
Back Pain	1 (3)	1 (3)
Palpitations	2 (5)	
Peripheral neuropathy		2 (5)
Increased lipase	1 (3)	1 (3)
Increased cholesterol	1 (3)	1 (3)
Increased LDL	1 (3)	1 (3)
Somnolence	1 (3)	1 (3)

### Virologic Failure and Emergence of Mutations

	ELV N=37	LAM N=37
<b>Baseline to Week 12: VL &gt;400 and VL change from baseline &lt; 2 logs</b>	2	1
Discontinuations	2 <sup>a</sup>	1
Paired BL and VF genotypes	1	1
IAS-USA NRTI/NNRTI mutations	K103N	K103N, M184V, P225H
<b>Weeks 24 to 96 confirmed &gt; 50</b>		
<b>Weeks &gt;24 to 48</b>		
VF Discontinuations	1 <sup>a</sup>	
Paired BL and VF genotypes	---	
IAS-USA NRTI/NNRTI mutations		
<b>Weeks &gt;48 to 96</b>		
VF Discontinuations	1	---
Paired BL and VF genotypes	1	1 <sup>b</sup>
IAS-USA NRTI/NNRTI mutations	---	---

<sup>a</sup> Genotyping not done for one subject  
<sup>b</sup> Genotyping from one subject who completed the study.

## CONCLUSIONS

**The use of ELV 10 mg + EFV + TDF QD in treatment-naïve patients for 96 weeks:**

- Resulted in excellent virologic and immunologic responses
- Was well tolerated, with a favorable safety profile
- No resistance to ELV was documented at 96 weeks

**In comparison to LAM 300mg + EFV + TDF QD in treatment-naïve patients, both treatment groups:**

- Resulted in comparable substantial and sustained viral suppression
- Demonstrated increasing CD4 cell counts
  - At Week 96, the ELV group had a mean (SD) of 512 (202) cells/uL vs the LAM group of 597 (202) cells/uL
- Demonstrated similar safety profile
- No differences between frequency, type, or severity of AEs