



## CLINICAL STUDY REPORT

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**Study Title:** An Open-label Study of a Once-daily Dose of Emtricitabine in Combination with Other Antiretroviral Agents in HIV-infected Pediatric Subjects

**Name of Test Drug:** Emtricitabine (FTC, Emtriva<sup>®</sup>)

**Sponsor:** Gilead Sciences, Inc.  
4 University Place  
4611 University Drive  
Durham, NC 27707, USA

**Study No.:** FTC-211

**Phase:** 2

**Study Start Date:** 19 November 2002 (First Subject Enrolled)

**Study End Date:** 21 July 2004 (Last Subject Completed Through 48 Weeks)

**Gilead Medical Signatory:** Name: Franck Rousseau, MD

**Report Date:** 18 November 2004 (FINAL)

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### CONFIDENTIAL AND PROPRIETARY INFORMATION

This study was performed in compliance with the guidelines of Good Clinical Practice (GCP) and all essential documents are being archived.

## 2. STUDY SYNOPSIS

**Gilead Sciences, Inc.  
4 University Place  
4611 University Drive  
Durham, NC 27707**

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<b>Name of Sponsor:</b> Gilead Sciences, Inc.	<b>Individual Study Table Referring to Part of the Dossier:</b>	<i>(For National Authority Use Only)</i>
<b>Name of Finished Product:</b> Emtriva® (emtricitabine, FTC)	<b>Volume:</b> <b>Page:</b>	
<b>Name of Active Ingredient:</b> 5-fluoro-1-[(2R, 5S)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine		
<b>Title of Study:</b>	An Open-label Study of a Once-daily Dose of Emtricitabine in Combination with Other Antiretroviral Agents in HIV-infected Pediatric Subjects	
<b>Investigators:</b>	Adrian Streinu-Cercel, MD Institutul de Boli Infectioase Prof. Dr. Matei Bals Str. Dr. Grozovici Nr. 1 Sector 2 Bucuresti, Romania  Petre Iacob Calistru, MD Spitalul de Boli Infectioase Victor Babes Sos. Mihai Bravu Nr. 281-283 Sector 3 Bucuresti, Romania	
<b>Study Centers:</b>	Two study centers in Bucharest, Romania	
<b>Publications:</b>	None	

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## STUDY SYNOPSIS (CONTINUED)

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- Study Period:** 19 November 2002 (First subject enrolled)  
01 August 2003 (Last subject enrolled before enrollment stopped)  
21 July 2004 (Last subject completed through 48 weeks)
- Phase of Development:** 2
- Objectives:** The objectives of this study were as follows:
- To obtain safety experience for antiretroviral regimens containing emtricitabine in HIV-1 infected pediatric subjects.
  - To determine the steady-state emtricitabine concentrations in HIV-1 infected pediatric subjects and, if necessary, to refine the dose of emtricitabine to achieve plasma concentrations comparable to those in adults given 200 mg emtricitabine once daily.
  - To obtain antiretroviral activity data for antiretroviral regimens containing emtricitabine in HIV-1 infected pediatric subjects.
- Methodology:** This was an open-label, non-randomized clinical study designed to evaluate the safety, pharmacokinetics, and activity of antiretroviral therapy (ART) regimens containing a once-daily dose of emtricitabine in ART-naïve or ART-experienced, HIV-1 infected pediatric subjects. Depending on their age, 30 to 50 eligible HIV-1 infected pediatric subjects < 18 years of age were to receive one of two emtricitabine-containing treatment options (see below).
- Number of Subjects (Planned and Analyzed):** Enrollment of 30 to 50 subjects was planned, with a minimum of 10 subjects to be recruited into each of the following three age groups:
- Age Group 1: from 3 to 24 months,  
Age Group 2: from 7 to 12 years, and  
Age Group 3: from 13 to 17 years.
- Because of slower than expected enrollment, enrollment into this study was stopped before the targeted minimum of 30 subjects was reached. A total of 16 subjects were actually enrolled in this study, 1 in Age Group 2 and 15 in Age Group 3.

## STUDY SYNOPSIS (CONTINUED)

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**Diagnosis and Main  
Criteria for Inclusion:**

Male and female pediatric subjects with documented HIV-1 infection were eligible to participate in this study if they were from 3 to 24 months of age (and ART-naïve) or from 7 to 17 years of age (either ART-naïve or ART-experienced).

ART-naïve was defined as having no prior exposure to any ART (with the exception of  $\leq 56$  days of perinatal prophylaxis for the prevention of maternal-to-child transmission or  $\leq 6$  weeks of cumulative postnatal treatment with zidovudine [Retrovir<sup>®</sup>, ZDV] monotherapy) and having a plasma HIV-1 RNA level of  $\geq 5,000$  copies/mL at Screening. Children  $\geq 7$  years of age (i.e., Age Groups 2 and 3) also had to have a Screening plasma HIV-1 RNA level of  $\leq 600,000$  copies/mL.

ART-experienced was defined as having previously been treated with an ART regimen(s) that did not include either lamivudine (3TC) and/or a non-nucleoside reverse transcriptase inhibitor (NNRTI) and having a Screening plasma HIV-1 RNA level of  $\leq 600,000$  copies/mL.

**Duration of Treatment:**

Subjects were to be treated for up to 48 weeks. At the end of the 48 weeks, Gilead continued to make emtricitabine available to any subject whose plasma HIV-1 RNA level was  $\leq 400$  copies/mL through an expanded access program. The study is complete and all subjects have now rolled over into the expanded access program.

**Test Product, Dose,  
Mode of Administration,  
and Batch No.:**

Subjects in Age Group 1 (ART-naïve) were to receive Treatment 1, a combination of emtricitabine, stavudine, and lopinavir/ritonavir. No subjects were actually enrolled into Age Group 1 or received Treatment 1.

**Treatment 1:**

Emtricitabine (6 mg/kg QD) plus stavudine (Zerit<sup>®</sup>, d4T; 1 mg/kg BID if  $< 30$  kg) plus lopinavir/ritonavir (Kaletra<sup>®</sup>, LPV/r; 12/3 mg/kg BID if  $\geq 7$  to  $< 15$  kg; 10/2.5 mg/kg BID if  $\geq 15$  to  $\leq 40$  kg).

Subjects in Age Groups 2 and 3 (ART-naïve and ART-experienced) received Treatment 2, a combination of emtricitabine, didanosine, and efavirenz.

**Treatment 2:**

Emtricitabine (6 mg/kg QD, up to a maximum of 200 mg QD using the capsule formulation or up to 240 mg QD using the oral solution formulation) plus didanosine (Videx<sup>®</sup> or Videx<sup>®</sup>EC, ddI; 240 mg/m<sup>2</sup> QD, up to a maximum of 400 mg QD) plus efavirenz (Stocrin<sup>®</sup>, EFV; based on body weight, up to a maximum of 600 mg QD using the capsule formulation or up to 720 mg QD using the oral solution formulation).

## STUDY SYNOPSIS (CONTINUED)

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<b>Test Product, Dose, Mode of Administration, and Batch No. (Cont.):</b>	<p>Subjects received emtricitabine as one 200 mg gelatin capsule QD or as a flavored, sweetened oral solution (10 mg/mL) to be taken QD in combination with didanosine and efavirenz. Gilead lot numbers were TP-0006-02017 and TP-0006-01030 for emtricitabine 200 mg capsules and TP-0006-00216 for the oral solution.</p> <p>Subjects received didanosine as delayed-release capsules containing enteric-coated (EC) beadlets (125 and 200 mg) or as pediatric powder for oral solution (4 g of ddI in 8 oz glass bottles). Manufacturer lot numbers were MJE12 and A014 for the 125 mg capsules, MGE05 and A017 for the 200 mg capsules, and MKM32 for the powder for oral solution.</p> <p>Subjects received efavirenz as an oral solution (30 mg/mL) or capsules (50, 100, and 200 mg). Efavirenz was purchased by the contract research organization (CRO) in Romania from a drug warehouse facility and shipped directly to the drug depot. Manufacturer lot numbers are not available.</p> <p>In this study, drugs were administered at different time of the day; subjects did not receive a fully QD regimen as suggested per the protocol.</p>
<b>Reference Therapy, Dose, Mode of Administration, and Batch No.:</b>	Not applicable
<b>Criteria for Evaluation:</b>	Plasma HIV-1 RNA levels were determined at Screening, Baseline (i.e., immediately prior to administration of the first dose of study medication on Day 1), and at every scheduled clinic visit thereafter.
<b>Efficacy:</b>	Viral genotyping was to have been performed for all subjects at virological failure if applicable. CD4+ cell count (i.e., absolute and percent) was measured at Screening, Baseline, and every 12 weeks thereafter.
<b>Pharmacokinetics:</b>	<p>Full-profile blood sampling for plasma concentrations of emtricitabine was to be performed at Week 2 for up to 10 subjects per age group. If the full-profile sampling could not be performed at Week 2, the Investigator could perform it as late as Week 4, after receiving approval from the sponsor. Full-profile sampling for emtricitabine concentrations could be repeated on these same subjects between Weeks 8 and 24, inclusive, if an emtricitabine dose adjustment was required, based on the results from the Week 2 sampling.</p> <p>Trough blood samples for plasma concentrations of emtricitabine were collected from all subjects at Weeks 8, 16, 24, and 36.</p>

## STUDY SYNOPSIS (CONTINUED)

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**Pharmacokinetics  
(Cont.):**

Random (population) blood samples for plasma concentrations of emtricitabine were collected from all subjects at Weeks 4, 12, 20, and 32 for the purpose of potential adherence monitoring and population pharmacokinetic evaluations, if possible or necessary.

**Safety:**

Safety was evaluated by collection of adverse events (AEs) and HIV-1-related events, clinical laboratory testing (including hematology, clinical chemistry and urinalysis), pregnancy testing for females of childbearing potential, physical examination, and vital signs measurements. AEs and HIV-1-related events were reviewed at every clinic visit. Clinical laboratory evaluations were performed at Screening, Baseline, Week 2 (chemistry only), every 4 weeks from Weeks 4 to 24, and then every 8 weeks from Weeks 24 to 48. Pregnancy testing was performed at Screening, Baseline, and every 12 weeks and/or as needed in females of childbearing potential. Physical examinations were performed at Screening, Baseline, at Week 4 and then every 8 weeks from Weeks 4 to 48. Vital signs were measured at every clinic visit.

**HIV/HBV Substudy:**

A substudy was planned to determine the response of chronic HBV infection to emtricitabine therapy in a pediatric population co-infected with HIV-1 virus. All HIV/HBV co-infected subjects enrolled in the FTC-211 study were eligible to participate in the HIV/HBV substudy.

Surplus serum from the blood samples collected at each visit (with the exception of the Week 28, 36, and 44 visits) for scheduled chemistry assessments was aliquoted and stored to provide serum samples for HBV DNA quantification, serological testing, and possible HBV genotyping. At Weeks 28, 36 and 44, the scheduled hematology or chemistry blood draw was replaced with a separate blood draw (9 mL) to obtain serum for storage.

Samples were analyzed but the sub-study data was not tabulated and statistically analyzed due to small number of HIV-HBV co-infected subjects (n=3).

## STUDY SYNOPSIS (CONTINUED)

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**Statistical Methods:**

**Efficacy:**

The primary efficacy endpoint was defined as the suppression of plasma HIV-1 RNA levels below 50 copies/mL at Week 48. The number and percentage of patients that met this endpoint were to be summarized, as well as, the 95% confidence interval for the percentage. Any patient that was missing an HIV-1 RNA value at Week 48 was to be considered a failure, unless the missing data point was preceded (at Week 44) and followed (at Week 52) by a value that was less than 50 copies/mL. In this case, the missing data points were to be censored.

Secondary efficacy endpoints included: FDA Defined Time to Loss-of-Virologic-Response (TLOVR), plasma HIV-1 RNA change from baseline were to be summarized at Week 48; the proportion of patients with plasma HIV-1 RNA levels below 400 copies/mL were to be summarized at Week 48, as well as, the 95% confidence interval for the percentage; CD4 change from baseline was to be summarized by study visit; the proportion of virologic failures that occurred during the study.

Virological response parameters that were continuous data (e.g.,  $\log_{10}$  HIV-1 RNA) are summarized by the mean, standard error, median, minimum, and maximum. Categorical data (e.g., proportion of subjects with plasma HIV-1 RNA below the assay lower limit of quantification, proportion of subjects who were effectiveness failures) were summarized by the number and percent of subjects belonging to a specific classification.

Subjects were considered virological failures if they had either a lack of virological response or a loss of virological response. Subjects were classified as having a lack of virological response if they never had a plasma HIV-1 RNA level of  $\leq 400$  copies/mL by Week 24. Subjects were classified as having a loss of virological response if they had either 1) a  $> 1 \log_{10}$  increase from nadir on 2 consecutive plasma HIV-1 RNA measurements, preferably within 1 month of each other, or 2) plasma HIV-1 RNA measurements  $> 400$  copies/mL on 3 consecutive visits over approximately 2 months while on study drug(s) after having had at least 2 consecutive plasma HIV-1 RNA measurements at  $\leq 400$  copies/mL.

One subject experienced a protocol-defined virological failure in this study.

Effectiveness failure was defined as having any of the following: tolerability failure (defined under Safety below), virological failure, clinical disease progression, or loss to follow up.

One subject experienced a protocol-defined effectiveness failure in this study.

## STUDY SYNOPSIS (CONTINUED)

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- Pharmacokinetics:** PK parameters calculated for emtricitabine from plasma concentration-time data included the following:
- steady-state daily (0–24 hour) plasma AUC of emtricitabine performed at Week 2 and between Weeks 8 to 24, inclusive, if dose adjustment(s) was/were required;
  - emtricitabine plasma trough concentration at steady-state, and
  - population pharmacokinetic evaluation(s) of emtricitabine, if possible or necessary.
- Safety:** The primary safety endpoint was tolerability failure. A subject was classified as a tolerability failure if (s)he had any AE or laboratory toxicity that was severe enough to warrant the permanent discontinuation of emtricitabine.
- The incidences of AEs, laboratory toxicities, and treatment discontinuations were summarized.
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## SUMMARY – RESULTS:

**Subject Disposition:** Of the 16 subjects in the ITT Population, 15 (93.8%) subjects completed the study through Week 48. One subject decided to withdraw from the study on the first day of dosing.

**Demographic/Baseline Characteristics:** All subjects were Caucasian and half (50%) were female. Mean age was 14.1 years (range: 12.8 to 15.2 years). Median baseline plasma HIV-1 RNA was 4.88 log<sub>10</sub> copies/mL (range: 4.03 to 5.75 log<sub>10</sub> copies/mL) and median absolute and percent CD4+ cell counts were 372 cells/mm<sup>3</sup> (range: 266.0 to 1100 cells/mm<sup>3</sup>) and 23% (range: 16 to 38%), respectively. All but one subject was ART-naïve.

### Efficacy Results:

**Suppression of Plasma HIV-1 RNA below LLOQ:** Using a non-completer = failure analysis at Week 48, 75% of the ITT Population achieved complete suppression of plasma HIV-1 RNA to ≤ 50 copies/mL. All but one subject achieved suppression of plasma HIV-1 RNA to ≤ 400 copies/mL, approximately 94% at Week 48.

Based on the TLOVR algorithm through Week 48, 69% of the subjects achieved and maintained suppression of plasma HIV-1 RNA to ≤ 400 copies/mL; 56% of the subjects achieved and maintained suppression of plasma HIV-1 RNA to ≤ 50 copies/mL.

**Change in HIV-1 RNA Viral Load from Baseline:** An overall decrease in HIV-1 RNA viral load suppression was achieved through Week 48 with a median value of -3.03 log<sub>10</sub> copies/mL (range: -4.05, -2.30).

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## STUDY SYNOPSIS (CONTINUED)

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### SUMMARY – RESULTS (Continued):

**Virologic Failure:** One subject met the protocol defined virologic failure but did not discontinue the study.

Per the TLOVR algorithm, 5 subjects were defined as virologic failure using the 400 copies/mL, threshold, including 4 subjects due to HIV-1 RNA rebound and 1 subject who withdrew consent.

**CD4+ Cell Counts:** The overall median (range) change in absolute CD4+ and percent CD4+ cell count was +201 (-107 to +366) cells/mm<sup>3</sup> and +8 (+3 to +29)%, respectively.

### **Safety Results:**

The safety analyses are based on data collected from all 16 subjects in the ITT Population through Week 48. Overall the median time on study treatment was 337 days (range: 1 to 337); one subject being on the study for one day.

**Tolerability Failure:** No subjects discontinued the study for adverse events.

**Deaths and Other Serious Adverse Events:** No subject died during the study. Overall, one (6.3%) subject (15-year-old ART naïve subject) experienced an SAE through Week 48. The subject experienced an episode of mumps/orchitis that was assessed as not related to study drug by the Investigator.

**Overall Adverse Events:** Ten (62.5%) subjects experienced at least one adverse event during the study. The most frequently reported adverse events were: pharyngitis (n=4, 25%), rash (n=3, 18.8%), conjunctivitis (n=2, 12.5%), interstitial pneumonia (n=2, 12.5%), accidental injury (n=2, 12.5%), pain (n=2, 12.5%) and hypertension (n=2, 12.5%).

**Drug-Related Adverse Events:** Two subjects had an adverse event assessed by the Investigator as possibly or probably drug related. The drug-related adverse events were leukopenia (n=1) and rash (n=1).

**Adverse Events of Grade 3 or 4 Severity:** Overall, one subject had one adverse event of grade 3 severity (leukopenia). No grade 4 adverse events were reported.

**Laboratory Abnormalities:** Almost all (15/16, 93.8%) subjects had at least one treatment-emergent laboratory abnormality (Grade 1 to 4). Treatment-emergent Grade 3 or 4 laboratory abnormalities were reported in 6 subjects. The Grade 3 or 4 abnormalities were Grade 3 neutropenia in 1 subject, Grade 3 serum amylase increase in 3 subjects, Grade 4 serum amylase increase in 1 subject and Grade 4 neutropenia in 1 subject. No subjects discontinued the study for treatment-emergent laboratory abnormality.

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## STUDY SYNOPSIS (CONTINUED)

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### Pharmacokinetics Results:

Week 2 pharmacokinetic evaluations are available for 15 of the 16 children entered in the study (1/1 subject in Age Group 2, and 14/15 subjects in Age Group 3. All subjects received the 200 mg capsule formulation with the exception of one subject in Age Group 3. The principal pharmacokinetic parameters for the subjects receiving the capsule formulation (n=14) are summarized below.

Age Group	N		C <sub>max</sub> (µg/mL)	C <sub>min</sub> (µg/mL)	t <sub>max</sub> , (hr)	AUC <sub>τ</sub> (hr·µg/mL)	t <sub>1/2</sub> (hr)	CL/F (mL/min)	Vd/F (L)
2	1	Mean	3.84	0.046	1.0	14.83	10.59	180	165
		CV%	-	-	-	-	-	-	-
3	13	Mean	2.92	0.035	1.31	10.61	7.30	330	214
		CV%	23	53	65	23	30	23	50

The emtricitabine dosage regimen for pediatric subjects in this study was expected to achieve a target daily AUC of at least 6 hr\*µg/mL (the 10<sup>th</sup> percentile of the adult AUC given 200 mg once daily). All subjects in this study achieved this minimum target exposure level (range 7.16 to 16.24 hr\*µg/mL).

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### CONCLUSION:

In HIV-infected pediatric subjects, once-daily treatment of emtricitabine in combination with didanosine and efavirenz was effective in the suppression of HIV-1 RNA levels to below detectable limits: 12 of the 16 (75%) subjects achieved less than 50 copies/mL at week 48 (ITT, NC=F analysis). One subject met the protocol defined virologic failure criteria but did not discontinue the study.

Three major factors could have contributed to the differences in efficacy noted when using the TLOVR algorithm: the small sample size, the difference in the virological failure definition (3 consecutive values above the LLOQ per the protocol definition versus 2 per the TLOVR algorithm) the fluctuation of the viral load reflecting possibly an adherence issue and more importantly the administration of the three drugs on a different schedules and not as an entirely QD regimen.

Treatment-related adverse clinical or laboratory events were infrequent. One subject was observed to have two SAEs considered not related to study drug. No subjects discontinued the study for tolerability failure.

The average plasma emtricitabine AUC, achieved in 14 subjects in this study (ages 12.8 to 15.2 years) was similar to exposure achieved in adults receiving a dose of emtricitabine 200 mg QD.

In conclusion the results of this small open-label study confirm that emtricitabine in combination with didanosine and efavirenz provides an effective and well tolerated treatment in HIV-infected pediatric subjects. The findings are consistent with the demonstrated efficacy and safety of emtricitabine in clinical trials of adult naïve and experience patients.