2 SYNOPSIS

Name of Sponsor Company: Achillion Pharmaceuticals, Inc.	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Elvucitabine	Volume: Page:	
Name of Active Ingredient: Elvucitabine		

Title of Study: A 14-day, Randomized, Double-Blind, Comparative Viral Kinetic Study of Elvucitabine Versus Lamivudine Administered Once Daily to HIV-1 Infected Subjects with a Documented M184V Variant

Study centers: A total of 20 study centers located in the United States and Western Europe participated in the study; 8 centers enrolled subjects

Publication (reference): None

Phase of development: 2a

Study Period:
Date of first screening: 13 March 2006
Date of first enrollment: 06 April 2006
Date of last contact: 19 November 2007

Objectives:

- To assess the viral kinetics of 10 mg of elvucitabine administered once daily (QD) for 14 days in combination with background antiretroviral therapy in human immunodeficiency virus (HIV-1) infected subjects with a documented M184V variant.
- To demonstrate the antiviral activity of 10 mg of elvucitabine administered QD for 14 days in combination with background antiretroviral therapy as compared with lamivudine in combination with background antiretroviral therapy in HIV-1 infected subjects with a documented M184V variant.
- To assess the safety of elvucitabine therapy in HIV-1 infected subjects with a documented M184V variant.

Methodology:

HIV-1 infected subjects with a documented M184V variant were randomized to receive elvucitabine 10 mg QD or lamivudine 300 mg QD for 14 days. Subjects were required to be on a stable antiretroviral regimen (defined as no change in antiretroviral therapy for at least 4 weeks prior to randomization) that included lamivudine or emtricitabine. At 72 hours prior to randomization, only lamivudine or emtricitabine was stopped for washout; subjects continued to receive the other drugs in their prescribed regimen (background antiretroviral therapy) during the 72-hour washout period. Subjects were then randomized to receive blinded elvucitabine or lamivudine in a 1:1 ratio and continued to receive their prescribed background antiretroviral therapy for 14 days on an outpatient basis. Pharmacokinetic (PK) sampling was performed on Days 1, 7, and 14 before elvucitabine or lamivudine was administered following a strict overnight fast (starting at 12 AM the night before the visit, water ad lib allowed). No food was to be consumed for 2 hours after study dose administration. Additional PK samples were obtained on Days 21 ± 1 and 28 ± 1 for subjects who did not enroll in the extension study (ACH443-018). On Days 2 to 6 and on Days 8 to 13, the elvucitabine/lamivudine was administered either at least

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30 minutes prior to or at least 2 hours following a meal. Subjects were followed for an additional 14 days posttreatment for safety. If subjects were enrolled into the ACH443-018 extension study, treatment and safety assessments continued.

Number of subjects (planned and analyzed):

Planned: 20 (10 per treatment group)

Randomized: 18

Analyzed: Safety: 18; Efficacy: 16; Pharmacokinetics: 8

Diagnosis and main criteria for inclusion:

HIV-1 infected subjects who at the time of enrollment were failing an antiretroviral therapy regimen containing lamivudine or emtricitabine, genotypically demonstrated a MI84V variant and < 2 TAMs, and had an HIV ribonucleic acid (RNA) plasma level ≥ 2,000 and ≤ 150,000 copies/mL.

Test product, dose and mode of administration, lot number:

Elvucitabine, 10 mg QD, administered orally. Lot #B05371A1, B06233A1, B06233A2, and B06233A3.

Reference therapy, dose and mode of administration, lot number:

Lamivudine, 300 mg QD, administered orally. Lot #B147005

Duration of treatment: 14 days

Criteria for evaluation:

Efficacy: The antiviral activity of elvucitabine was measured by the change in plasma HIV-1 RNA between baseline (average of Day -3 and Day 1) and Day 14.

Pharmacokinetics: Predose plasma concentrations of elvucitabine were measured on Day 1, Day 7, and Day 14. Additional samples were taken on Days 21 ± 1 and 28 ± 1 for those subjects who did not participate in the extension study ACH443-018.

Safety: Safety was determined by clinical and laboratory adverse events (AEs) occurring during the treatment period and up to 2 weeks after the last dose, as well as genotypic changes over the treatment period.

Statistical Methods:

Efficacy: The primary efficacy endpoint was defined as a ≥ 0.5 log fall in HIV-1 RNA levels between baseline (average of Day -3 and Day 1) and Day 14.

HIV-1 RNA levels expressed as $\log_{10}$ ratios to baseline (log fall) were summarized for Days 14, 21, and 28. Treatment mean differences with 95% 2-sided confidence intervals and statistical significance based on 2-group t-tests were reported for the treatment comparisons of each evaluation interval.

Proportions of subjects in each treatment group with ≥ 0.5 log fall in HIV-1 RNA levels at Days 14, 21,

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and 28 were summarized and the statistical significance of Fisher's exact test for the 2-sided comparison between treatment groups was reported.

Pharmacokinetics: Plasma concentrations of elvucitabine were summarized by treatment and study days using descriptive statistics. Selected PK parameters of elvucitabine were calculated from the concentration-time data by a standard non-compartmental analysis.

Safety: Safety data were summarized using descriptive statistics.

Results:

Efficacy Results:

Changes in HIV-1 RNA levels and CD4 counts were comparable between treatment groups. Treatment response was comparable between treatment groups. Clinical evaluation of the Day 21 and Day 28 assessments was limited by the decreased sample size on those days as the majority of subjects enrolled into the extension protocol; subjects who continued in the extension study did not have assessments of HIV-1 RNA levels collected on Day 21 or Day 28. Differences between treatment groups on the efficacy endpoints were either not statistically significant or not clinically meaningful.

PK Results:

Of the 9 subjects who received 10 mg of elvucitabine on Day 1, 1 subject had no detectable levels at any time and a second subject had a single detectable concentration at 24 hours postdose. The PK of elvucitabine was moderately variable on both Days 1 and 14, with the coefficient of variation (%CV) ranging from 36% to 72%. For both Days 1 and 14, the half-life of elvucitabine could not be determined due to the lack of a clearly defined terminal phase in the concentration-time profiles. The steady-state clearance of elvucitabine on Day 14 was estimated to be 39 L/h. Based on AUC_{0-t} for Days 1 and 14, there was a 1.9-fold accumulation in elvucitabine exposure following multiple daily dosing of 10 mg for 14 days. Accumulation in terms of peak concentrations from Day 1 to Day 14 was less than the observed overall exposure.

Safety Results:

No deaths or AEs that led to study discontinuation were reported in either treatment group. One SAE was reported during the study for a subject receiving elvucitabine that was assessed by the investigator as not related to study drug treatment. Treatment-emergent AEs were generally low in frequency and mild in severity. No clinically significant genotypic changes were apparent over the treatment period. No clinically significant trends within or between treatment groups for changes in hematologic and hepatic laboratory parameters occurred during this study. Although individual subjects had reports of sporadic laboratory findings outside the normal range, no patterns of clinical significance were apparent in the number or type of abnormal laboratory findings. No clinically significant trends were seen within or between treatment groups in vital signs, physical examination findings, or ECG data.

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Conclusions:

Based on the data in this report, the following conclusions can be made:

- Differences between treatment groups on the efficacy endpoints were either not statistically significant or not clinically meaningful.
- Based on AUC_{0-t} for Days 1 and 14, there was a 1.9-fold increase in elvucitabine exposure after multiple dosing.
- The study drug was well tolerated in this subject population.

Date of Report: 27 October 2008