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 Enteric Coated Tablet	Volume: Page:	
Name of Active Ingredient: Elvucitabine		

Title of study: An Open-Label, 48-Week Extension Study of Elvucitabine Administered in Combination With Background Antiretroviral Agents in Subjects Who Have Completed 14 Days of Treatment in Protocol ACH443-014A

Study centers: A total of 13 study centers located in the United States, Caribbean, and Western Europe participated in the study; 6 centers enrolled subjects

Publication (reference): None

Phase of development: 2a

Study period:
Date of first enrollment: 29 November 2006
Date of last contact: 29 November 2008

Objectives:

- To assess the safety of 48 weeks of 10 mg (2 x 5 mg) once daily (QD) of elvucitabine therapy with background antiretroviral therapy in human immunodeficiency virus (HIV-1)-infected subjects who have completed 14 days of treatment in Protocol ACH443-014A
- To describe the antiviral activity as measured by plasma HIV-1 ribonucleic acid (RNA) levels of 10 mg QD of elvucitabine, plus background antiretroviral therapy over 48 weeks in HIV-1-infected subjects who have completed 14 days of treatment in Protocol ACH443-014A

Methodology:

This study was an open-label extension study for subjects who were enrolled into and had completed 14 days of study treatment as part of Achillion Protocol ACH443-014A. On Study Day 15 of ACH443-014A (Day 1 of Protocol ACH443-018), subjects were offered open-label elvucitabine 10 mg enteric coated (EC) tablet QD to be used in combination with the background antiretroviral therapy chosen by the investigator. Subjects were assessed for safety every 2 weeks for 8 weeks, then every 4 weeks thereafter. Levels of HIV-1 RNA (copies/mL) and counts of lymphocytes with the CD4 marker (CD4) (cells/µL) were obtained every 4 weeks. Subjects were permitted to receive elvucitabine up to 48 weeks after study start. Study drug therapy may have been discontinued earlier by the investigator based on safety concerns, if no increase in the CD4 cell count of at least 25 cells/µL above the 014A baseline occurred over a 1-year period, HIV-RNA levels returned to the 014A baseline following an initial decrease in levels, the occurrence or recurrence of HIV-related events after Week 12, or if the subject developed any drug-related Grade 3 or Grade 4 adverse event (AE) or drug-related Grade 3 or Grade 4 laboratory abnormality (except an asymptomatic Grade 3 or 4 cholesterol or triglyceride increase) as confirmed by repeat testing, unless in the opinion of the investigator, immediate discontinuation was indicated. Toxicities were graded as defined by the National Institute of Health's Division of AIDS (DAIDS) Toxicity Table for Grading Severe Adult and Pediatric Adverse Events.

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Subjects had a follow-up visit at 4 weeks (± 4 days) after discontinuation of elvucitabine therapy.

An interim summary of safety was prepared after half of all eligible subjects had completed 24 weeks of therapy.

Number of subjects (planned and analyzed):

Planned: 18

Analyzed: 14

Diagnosis and main criteria for inclusion:

M184V-positive, HIV-1 infected subjects who had completed the ACH443 014A study and had consented to participate in Protocol ACH443-018.

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

Elvucitabine enteric coated tablets, 10 mg (2 x 5 mg) QD, administered orally. Lot numbers: B06246A, B06311A, B06351A

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

Not applicable

Duration of treatment: 48 weeks until completion of the study or if no increase in the CD4 cell count of at least 25 cells/µL above the 014A baseline occurred over a 1-year period, HIV-RNA levels returned to the 014A baseline following an initial decrease in levels, the occurrence or recurrence of HIV-related events after Week 12, until development of any drug-related Grade 3 or Grade 4 AEs or drug related Grade 3 or Grade 4 laboratory abnormality (except asymptomatic Grade 3 or 4 cholesterol or triglyceride increases) as confirmed by repeat testing, unless in the opinion of the investigator, immediate discontinuation was indicated.

Criteria for evaluation:

Safety was determined by clinical and laboratory AEs occurring during the extension study. Antiviral activity was measured by plasma HIV-1 RNA levels and CD4 cell counts over 48 weeks.

Statistical methods:

Safety variables were listed individually for each subject for clinical review.

All AEs that were reported during the study through 30 days after the date of last dose were tabulated by system organ class and preferred term. Additional tables summarized AEs by severity and relationship to the investigational product. Adverse events leading to withdrawal from the study, serious AEs (SAEs), and deaths were presented in separate listings.

Extent of exposure was presented in a listing and summary table.

All laboratory results and vital sign measurements were summarized using appropriate descriptive

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statistics.

Due to the availability of laboratory measurements on Day 14 and not Day 15 of ACH443-014A, for all tables and listings presenting laboratory data, Day 1 of this study was Day 14 of the base study (ACH443 014A).

HIV-1 RNA levels and CD4 counts at baseline through end of study were summarized using appropriate descriptive statistics.

Results:

The objective of the study was to demonstrate the safety and antiviral activity of 10 mg of elvucitabine administered QD for an extended duration (up to 48 weeks) in combination with background antiretroviral treatments (ART) in subjects with a documented M184V variant. There were no clinically significant trends observed for treatment-emergent AEs (TEAEs), physical examination assessments, or vital signs. A decrease in the group mean $\log_{10}$ copies/mL in HIV-1 RNA levels was observed between baseline and all but 1 time point when these levels were measured. The sample size decreased as well between baseline and the subsequent assessments. This result is consistent with observations from other trials utilizing elvucitabine in combination with other ART.

Of the 14 subjects who completed 14 days of treatment in protocol ACH443-014A and enrolled in the extension protocol ACH443-018, 7 subjects experienced antiviral activity as measured by a decline in HIV-1 RNA by study completion or discontinuation. Six of these subjects had less than 400 copies/mL at multiple time points (> 1) during the study. Each subject received a ritonavir boosted protease inhibitor regimen during therapy which in combination with elvucitabine was able to provide adequate and sustained viral suppression (< 400 copies/mL) through to study completion or discontinuation. Five of the 6 subjects completed 48 weeks of treatment on ACH443-018, which included elvucitabine with sustained viral suppression (< 400 copies/mL) starting at Week 8. One subject, the sixth, completed 36 weeks of treatment on ACH443-018 and achieved viral suppression (< 400 copies/mL) by Week 8 with 2 episodes of virologic breakthrough due to nonadherence to the protocol.

Changes in CD4 counts (cells/µL) were observed between baseline and various time points during the study. The mean and median CD4 count increased from the baseline assessment at Weeks 24 and 48.

Five subjects discontinued due to virological failure or immunological and virological failure. Among subjects who had paired samples suitable for the analysis, there were few new emergent mutations. The genotypic changes that were observed largely represented expected mutations from the non-elvucitabine ART medications being used as optimized background treatment in these subjects. These included the M461 mutation that can confer resistance to atazanavir and the K103N mutation that confers resistance to nevirapine and efavirenz. The earliest observation occurred at Week 20, and the remaining observations were made by Week 24. Each of the subjects who had paired samples and who had specific new mutations observed also had received lamivudine in the 14-day lead-in study, ACH443-014A.

No deaths occurred during the study, but 1 subject was discontinued due to an SAE of neutropenia. The event was assessed as probably related to study drug treatment and resolved without sequelae. An additional event of Grade 3 neutropenia was considered not related to study drug in one other subject. The

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absolute neutrophil count returned to the subject's baseline range without change to elvucitabine treatment with optimized background ART for the completion of 48 weeks.

Treatment-emergent AEs were generally low in frequency and mild in severity. The most frequently reported TEAE was pyrexia, with 4 subjects (4/14, 29%) experiencing the event. All 4 events were assessed as mild or moderate in severity and all events resolved without sequelae.

No clinically significant trends for changes in hematologic, pancreatic, 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 numbers or types of abnormal laboratory findings.

No clinically significant trends were seen in vital signs and physical examination findings.

Conclusions:

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

- The study drug was well tolerated in this subject population.
- A decrease in the group mean $\log_{10}$ copies/mL in HIV-1 RNA levels was observed between baseline and all but 1 time point when these levels were measured.
- Of the 14 subjects who completed 14 days of treatment in protocol ACH443-014A and enrolled in the extension protocol ACH443-018, 7 subjects experienced antiviral activity as measured by a decline in HIV-1 RNA by study completion or discontinuation.
- Six of these subjects had less than 400 copies/mL at multiple time points (> 1) during the study. Each subject received a ritonavir boosted protease inhibitor regimen during therapy which in combination with elvucitabine was able to provide adequate and sustained viral suppression (< 400 copies/mL) through to study completion or discontinuation.
- Five of the 6 subjects completed 48 weeks of treatment on ACH443-018, which included elvucitabine with sustained viral suppression (< 400 copies/mL) starting at Week 8.
- The mean and median CD4 count increased from the baseline assessment at Weeks 24 and 48.
- The genotypic changes that were observed largely represented expected mutations from the non-elvucitabine ART medications being used as optimized background treatment in these subjects.

Date of report: Final 18 December 2009