PHARMASSET, INC.

CLINICAL STUDY REPORT

Study Title:	A Multi-center, Randomized, Double-Blind, Active-Control, 96 Week, Phase III Trial of the Efficacy and Safety of Clevudine Compared with Adefovir at Weeks 48 and 96 in Nucleoside Treatment-Naïve Patients with HBeAg Positive Chronic Hepatitis due to Hepatitis B Virus
Name of Test Drug:	clevudine
Sponsor:	Pharmasset, Inc. 303-A College Road East Princeton, NJ 08540
Study No.:	CI-PSI-5268-06-305
Phase:	Phase III
First Patient Randomized:	08 November 2007
Last Patient Observation (on Treatment):	9 June 2009
Voluntary Study Termination Date:	20 April 2009
Company Medical Signatory:	Name: M. Michelle Berrey, MD, MPH Title: Chief Medical Officer
Report Date:	01 February 2010 (Final)
Previous Report Date(s):	Not applicable

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.

This abbreviated clinical study report (CSR) presents results for the dosing phase, which refers to the time period when patients were on study treatment prior to the withdrawal visit. Another abbreviated CSR will be issued for the follow-up phase, which refers to the period of time when patients were off study treatment.

2. STUDY SYNOPSIS

Pharmasset, Inc.
303-A College Road East
Princeton, NJ 08540

Name of Sponsor: Pharmasset, Inc. **Name of Finished Product:** Clevudine **Name of Active Ingredient:** [1-(2-deoxy-2-fluoro-β-L-arabinofuranosyl) thymine]	**Individual Study Table Referring to Part of the Dossier:** **Volume:** **Page:**	***(For National Authority Use Only)***

Title of Study: A Multi-center, Randomized, Double-Blind, Active-Control, 96 Week, Phase III Trial of the Efficacy and Safety of Clevudine Compared with Adefovir at Weeks 48 and 96 in Nucleoside Treatment-Naïve Patients with HBeAg Positive Chronic Hepatitis due to Hepatitis B Virus

Investigators: Multicenter

Study Centers: The study was conducted in 110 study sites in North America (Canada, United States); South America (Brazil, Argentina); Europe (Romania, Greece, United Kingdom, Spain, Czech Republic, and Turkey); Asia (Thailand, Singapore, Taiwan, and Hong Kong); Australia; and New Zealand.

Publications: None

Study Period:	8 November 2007 (First patient randomized) 20 April 2009 (date of early termination of study) 09 June 2009 (Last patient observation on treatment)

Phase of Development: Phase III

STUDY SYNOPSIS (CONTINUED)

Objectives:

As described under Changes in the Conduct of the Study, this study was terminated early. The planned objectives are described below.

The primary objective of this study was as follows:

- To compare, in nucleoside treatment-naïve patients with chronic HBeAg+ HBV infection, the efficacy of clevudine 30 mg once daily and adefovir 10 mg once daily, each as monotherapy, by assessing the proportion of patients with serum HBV DNA levels <300 copies/mL and alanine aminotransferase (ALT) normalization at 48 weeks.

The secondary objectives of this study characterized other aspects of the patients' responses to treatment. Comparisons were to be made between the clevudine 30 mg once daily and adefovir 10 mg once daily treatment groups. These secondary objectives were as follows:

- To provide supportive efficacy characterization of the primary objective through the use of histological, virological, and biochemical responses at different times throughout the study;

- To assess the safety and tolerability of the study treatments; and

- To investigate the pharmacokinetics of clevudine.

The primary objectives of the non-responder option (established per Amendment 5 to the study protocol) were to provide an on-study treatment option for patients who had met criteria for treatment failure in spite of adherence to the requirements and procedures of the blinded portion of Study CI-PSI-5268-06-305 and to explore the safety and efficacy of clevudine used in combination with another locally approved antiviral drug with established activity against HBV. Locally approved antiviral drugs included entecavir and tenofovir. Eligible patients had experienced primary treatment failure (did not suppress on clevudine or adefovir monotherapy) or secondary treatment failure (experienced early viral rebound or remained >1000 copies/mL) in Study CI-PSI-5268-06-305.

Ethical Conduct of Study:

This study was conducted in full conformance with the principles of the "Declaration of Helsinki" (as amended in Tokyo, Venice, Hong Kong, and South Africa) or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. A comprehensive description of the ethical

STUDY SYNOPSIS (CONTINUED)

conduct of this study is provided in the study protocol in Appendix 11.1.1.

Methodology:

As described in the Changes in the Conduct of the Study section, this study was terminated early. The planned methods are described in this section.

This study was planned as a Phase III, randomized, double-blind, parallel-group, active-control, multi-center trial of 96-weeks' duration. Treatment-naïve patients with ALT >1.3 × the upper limit of normal (ULN) and compensated hepatic disease were assigned to receive either clevudine 30 mg once daily or adefovir 10 mg once daily for 72 to 96 weeks. At Week 24, patients underwent their first assessment for a potential endpoint:

- Any patient who had not achieved a >2 log decrease in HBV DNA by Week 24 was considered a primary treatment failure. At this point, the non-responder patient was eligible to receive combination therapy with open-label clevudine and a locally approved antiviral drug with activity against HBV (e.g., entecavir or tenofovir).

At Week 48, patients remaining on therapy were assessed for HBV DNA levels, serum ALT, and HBeAg seroconversion. Patients then continued to be followed based on results. The following patients were considered non-responders:

- Patients whose HBV DNA had been suppressed <300 copies/mL and rebounded at any time on or after the Week 24 visit to >1 log from nadir ("Rebounders"), which was confirmed by a second test, separated by a minimum of 7 days (secondary treatment failure). If the re-test confirmed the initial result, the patient was considered a treatment non-responder (secondary treatment failure). These patients were eligible to receive combination therapy with open-label clevudine and a locally approved antiviral drug with established activity against HBV (e.g., entecavir or tenofovir).

- Patients whose HBV DNA remained >1000 copies/mL at Week 48 were also considered secondary treatment failures and were eligible to receive combination therapy.

In vitro viral susceptibility testing shows a reduction in the potency of clevudine when the N236T mutation, which can be selected during adefovir therapy, is present. Therefore, patients meeting non-responder criteria were not permitted to switch to the alternate arm of blinded monotherapy. They discontinued their assigned blinded treatment and were eligible to receive combination therapy with open-label clevudine and a locally approved antiviral drug with established activity against HBV (e.g., entecavir or tenofovir).

Those patients who remained on blinded therapy at Week 48 were to be assessed for the following response criteria: HBV DNA, ALT normalization, and HBeAg loss/anti-

STUDY SYNOPSIS (CONTINUED)

HBeAb detection. These patients were to continue in the study under 1 of the 2 categories below:

- Patients who were complete responders were defined as the following: 1) had responded virologically (HBV DNA <300 copies/mL), 2) had a normal range serum ALT, and 3) had loss of HBeAg/detection of anti-HBeAb. These patients were to be followed through Week 72, and if they remained complete responders, they were then to discontinue therapy at their next visit. These patients did not receive placebo and were followed closely off treatment for potential flare.

- Patients who failed to achieve all 3 response criteria at 48 weeks were to remain on **blinded therapy through Week 96** or until they achieved all 3 criteria, at which time they were to continue on blinded therapy for another 24 weeks and then discontinue blinded therapy. Patients who discontinued blinded therapy did not receive placebo and were followed closely off treatment for potential flare.

For patients in the non-responder option, the total treatment duration was to be 96 weeks, including the time the patient received blinded clevudine or adefovir and open-label combination therapy. The post-treatment follow-up period for patients completing the non-responder option and discontinuing all therapy was to be 24 weeks.

All patients were to have liver biopsies performed at screening (or within 6 months prior to the Baseline visit) and at Week 48 for evaluation of histological improvement and potential treatment effect on quantitative hepatic cccDNA (covalently closed circular deoxyribonucleic acid). PPD

Patients completing 96 weeks of treatment (blinded or non-responder portion of study) were to be eligible to continue participating in a roll-over study for long-term evaluation of safety, efficacy, and durability of viral suppression on or off therapy.

Any patient withdrawing from blinded therapy for any reason was to be followed for safety and serum HBV DNA for a minimum of 6 months.

Changes in the Conduct of the Study (Including Early Study Termination):

At the time of this report, the original CI-PSI-5268-06-305 study protocol (5 December 2006) had been amended 6 times: 04 March 2007 (Amendment 1); 03 April 2007 (Amendment 2); 29 June 2007 (Amendment 3); 02 October 2007 (Amendment 4); 30 September 2008 (Amendment 5); and 21 January 2010 (Amendment 6). The first patient in this study was enrolled under Amendment 3. Amendment 4 specified that all patients were to be followed for an additional 24 weeks (through Week 96). Amendment 5 (which was instituted when 177 patients had been enrolled in the study) added the non-

STUDY SYNOPSIS (CONTINUED)

responder option of the study. In addition, a 30 April 2009 letter (described below) to the sites documented the plan for patient management after voluntary termination of the study. To satisfy regulatory requirements, this plan for patient management was formally documented in protocol Amendment 6. A copy of the original protocol and each protocol amendment, as well as an associated document describing changes from the earlier version of the protocol, is provided in Appendix 11.1.1.

On 20 April 2009, Pharmasset voluntarily terminated its Phase III QUASH studies of clevudine for the treatment of chronic hepatitis B (HBV) infection, including this study, CI-PSI-5268-06-305, as well as Study CI-PSI-5268-06-306 (see Appendix 11.4). This decision was made after consultation with the independent Data Safety Monitoring Board (DSMB), the Food and Drug Administration (FDA), and scientific advisors.

Pharmasset had recently become aware of a number of spontaneous Serious Adverse Event (SAE) reports and Events of Special Interest in patients receiving clevudine as prescribed therapy for hepatitis B in South Korea. Though only a small number of cases of mild-to-moderate myopathy, or muscle weakness, associated with creatine kinase (CK) elevations were reported in the QUASH studies, many of the patients in South Korea have had longer exposures to clevudine than patients in the QUASH studies and have reported more serious myopathy than have patients in the Pharmasset clinical trials. Given the number and severity of cases observed in South Korea, Pharmasset concluded that it was in the best interest of patients to terminate the studies at this time.

On 30 April 2009, Pharmasset issued a letter to all study sites providing continuing medical management guidance (see Appendix 11.1.2). The letter included the following instructions for discontinuing patients from study medication:

- **All patients who received clevudine as a single agent or in combination** should discontinue clevudine no later than 28 days and have an "Early Withdrawal Evaluation" as described in Table 1c of the protocols. These patients should then be followed for 6 months for ALT flare, musculoskeletal symptoms, and creatine kinase (CK) elevations.

- **All patients who received adefovir** should have an "Early Withdrawal Evaluation" within 28 days and will be terminated from the study at that point.

- **Patients receiving clevudine (as a single agent or in combination) who are experiencing any musculoskeletal symptoms should be discontinued from clevudine as soon as possible and monitored until the symptoms resolve. Also, patients with grade 3 or grade 4 CK elevations should be discontinued from clevudine as soon as possible and monitored until CK returns to screening or baseline level, whichever is higher.** If the investigator deems it appropriate, Pharmasset will provide reimbursement for an alternative commercially available

STUDY SYNOPSIS (CONTINUED)

HBV therapy for a maximum of six months.

This letter also stated that early withdrawal procedures should include the following:

- Physical exam
- Laboratory tests including: chemistry (including CK and INR), hematology, urinalysis, serology, HBV genotyping sample, HBV DNA, pregnancy test (if applicable)
- 12-lead ECG
- Adverse event and concomitant medication reporting
- Drug accountability

On 06 May 2009, Pharmasset issued an administrative letter to all sites with further information on patient management after discontinuation of study therapy (see Appendix 11.1.2). This letter stated the following:

Off-Study Visits: Following the Early Withdrawal Visit, all patients previously **treated with clevudine** will have an Off-Study Visit every 4 weeks for a total of 24 weeks. Off-Study Visits will include the following assessments/tasks:

- laboratory panel (chemistry including ALT and CK, HBV DNA)
- Brief physical exam
- Muscle assessment (if indicated)
- AE monitoring
- Off-Study CRF completion

The letter also stated that additional visits should be performed for patients experiencing ALT flares or CK elevations that require additional monitoring per the study protocol. Other information about adefovir-treated patients and administrative issues were also included in this letter.

Number of Patients (Planned and Analyzed):

Up to 376 patients were to be enrolled in a 2:1 ratio (clevudine: adefovir) resulting in at least 200 evaluable patients for clevudine and 100 evaluable patients for adefovir.

A total of 346 patients were actually enrolled and treated with clevudine (230 patients) or adefovir (116 patients) blinded treatment. Of these, 10 clevudine patients and 21 adefovir patients discontinued their randomized blinded treatment and received combination therapy with open-label clevudine and a locally approved antiviral drug with established activity against HBV (e.g., entecavir or tenofovir).

STUDY SYNOPSIS (CONTINUED)

Diagnosis and Main Criteria for Inclusion:

Patients eligible for this study were nucleoside treatment-naïve, of either gender (females had to be non-pregnant and non-lactating), aged 16 years or older (or the legal age of majority as allowed by local regulations), and had compensated hepatic function despite a diagnosis of chronic HBeAg+ hepatitis B infection (i.e., based on serological, virological, and histological markers). Patients had to have current liver biopsy (or an historical biopsy obtained within 6 months prior to baseline) with evidence of chronic hepatic inflammatory injury at screening (equivalent to a Knodell HAI Grade ≥4 and modified Ishak fibrosis score ≤5). If applicable, patients had to cease previous treatment with any form of alpha interferon 12 months prior to baseline. Patients participating in a clinical trial or receiving an investigational agent for any reason within 60 days of baseline were excluded. Patients with clinically significant concomitant diseases were excluded. Patients were not to be in the acute phase of HBV infection, as documented by the presence of HBsAg+ ≥6 months prior to Baseline.

Patients had to have a screening ALT value ≥1.3 × and ≤10 × ULN and at least 1 additional documented ALT value within this range during the previous 6 months. In addition, patients had to meet the laboratory criteria for total bilirubin, prothrombin time, serum albumin, platelet count, absolute neutrophil count, and antinuclear antibody (ANA) titer and have an estimated creatinine clearance of ≥50 mL/min.

Duration of Treatment:

Patients were to receive in a double-blind, double-dummy fashion either clevudine 30 mg once daily or adefovir 10 mg once daily in the morning for 72 to 96 weeks.

For patients in the non-responder option, the total treatment duration was to be 96 weeks, including the time the patient received blinded clevudine or adefovir and open-label combination therapy.

Test Product, Dose, Mode of Administration, and Batch No.: Clevudine was supplied as a 30-mg capsule. Batch numbers for clevudine and clevudine matching placebo capsules are on file.

Reference Therapy, Dose, Mode of Administration, and Batch No.: Adefovir was supplied as a 10 mg capsule. Batch numbers for adefovir and adefovir matching placebo capsules are on file.

Criteria for Evaluation:

Efficacy: Patients were evaluated at designated time points after initiation of therapy. The primary efficacy endpoint was to be a composite endpoint of the proportion of

STUDY SYNOPSIS (CONTINUED)

patients with undetectable serum HBV DNA (<300 copies/mL) and normalized ALT at Week 48. The most important secondary histology endpoint was an assessment of histologic improvement (≥2 point decrease from baseline in the Knodell necroinflammatory grade with no worsening of the Knodell fibrosis stage) at Week 48.

Viral dynamics in patients receiving clevudine versus adefovir were to be characterized.

Pharmacokinetics: Clevudine's pharmacokinetics were to be characterized by a population pharmacokinetic approach through the first 48 weeks of treatment.

Safety: All AEs spontaneously reported, elicited, or observed by the investigators were recorded. Definitions of AE and serious AE (SAE) are provided in the study protocol (Appendix 11.1.1). Laboratory test abnormalities were also recorded. Vital signs, 12-lead ECGs, and physical examination results were recorded and reviewed throughout the duration of the study.

Statistical Methods:

General Considerations: Because this study (and the program of which it was a part) was terminated early, the planned analyses were not performed. The analyses reported here were performed in the interest of patient safety.

This abbreviated clinical study report (CSR) presents results for the dosing phase, which refers to the time period when patients were on study treatment prior to the withdrawal visit. Events reported prior to or at the withdrawal visit were attributed to the dosing phase. Data are summarized for 5 groups of patients, according to treatments received: blinded clevudine; blinded adefovir; combination therapy with clevudine after discontinuing blinded clevudine treatment; combination therapy with clevudine after discontinuing blinded adefovir treatment; and total clevudine (blinded and combination treatment combined).

Another abbreviated CSR was issued for the follow-up phase of the study and is provided in Appendix 11.6. The follow-up phase report presents results for the 24-week period of time when patients were off study treatment. Only clevudine-treated patients were followed during the follow-up phase.

Analysis Populations: Only safety data were summarized for this abbreviated CSR. The safety population consisted of all patients who received any study treatment.

Patient Disposition: All patients in the safety population were listed according to the reason for treatment discontinuation and study withdrawal, treatment start date, and treatment stop date. Inclusion and exclusion criteria were listed for the safety population.

STUDY SYNOPSIS (CONTINUED)

Baseline Demographic and Disease Characteristics: Baseline demographic characteristics (age, race/ethnicity, height, weight, and body mass index [BMI]) and log-transformed HBV DNA levels were summarized by treatment group in the safety population. Medical history is listed for the safety population.

Study Medication and Concomitant Therapies: Study drug exposure was summarized in the safety population for the 5 treatment groups described above. Because this study was terminated early, prior and concomitant medication data are not summarized or listed for this abbreviated CSR.

Efficacy: Because this study was terminated early, efficacy data were not summarized for this abbreviated CSR. Log-transformed HBV DNA values were listed for the safety population.

Pharmacokinetics: Because this study was terminated early, pharmacokinetic data were not summarized or listed for this abbreviated CSR.

Safety: Only SAE/AE data were summarized for this abbreviated clinical study report, as described below. Other safety data were listed, as described below. All safety summaries and listings used the safety population.

AE summaries were performed using the preferred terms and body systems assigned by the Medical Dictionary for Regulatory Activities (MedDRA).

AEs were summarized by the 5 treatment groups described above (blinded clevudine, blinded adefovir, combination therapy from clevudine, combination therapy from adefovir, and total clevudine) overall and by relationship to study drug and severity. AEs assessed by the investigators as possibly or probably related to treatment were categorized as "drug related." Grade 3 and 4 AEs were also summarized by treatment group. In addition, the most common (≥5%) AEs were summarized by treatment group and severity, as were AEs of special interest. AEs of special interest were to include the following: pancreatitis; QT prolongation; blood dyscrasias, including neutropenia ($<500/mm^3$) or thrombocytopenia ($<90{,}000/mm^3$); anaphylaxis; seizure or syncope; rash with fever; rash with hyperbilirubinemia; exacerbation of hepatitis or flare (ALT value at least twice baseline value and >10 × the ULN); muscle weakness; myopathy; and neuropathy.

SAEs and AEs leading to discontinuation were summarized by treatment group.

Full details for all AEs were listed. Other safety data listed were individual muscular assessments for patients identified as having myopathy; laboratory data (clinical chemistry and haematology) for patients with a Grade 3 or 4 abnormality; patients with ALT flares; and patients with a Grade 3 or 4 CK elevation.

STUDY SYNOPSIS (CONTINUED)

SUMMARY – RESULTS:

During double-blind therapy, the overall incidence of SAEs was 4.3% and 1.7% in the clevudine and adefovir groups, respectively. Two patients, both in the clevudine group, had a drug-related SAE (ALT increased or transaminases increased). None of the SAEs were fatal. Among the 40 patients who discontinued for reasons other than study termination, 3 (1.3%) patients in the blinded clevudine group discontinued the study because of an AE. No patients in the blinded adefovir group discontinued the study because of an AE. The patients in the blinded clevudine group discontinued due to muscular weakness (n=1) or myositis (n=2).

Of the 5 pregnancies reported during the dosing period, 3 occurred in female patients and 2 occurred in the partners of male patients. All 3 female patients electively terminated their pregnancies; no complications were reported. Information on the outcomes of the 2 pregnancies in the partners of male patients is not available.

During double-blind therapy, the overall incidence of AEs of special interest was 6.1% and 1.7% in the clevudine and adefovir groups, respectively. In the blinded clevudine group, the most frequent AE of special interest was ALT increased (n=6, 2.6% clevudine vs. n=1, 0.9% adefovir); transaminases increased was also reported (n=3, 1.3% clevudine vs. n=1, 0.9% adefovir).

Elevated serum creatine kinase (CK) levels and clinical myopathy were observed in 3 patients randomized to receive clevudine in CI-PSI-5268-06-305. These cases were also reported as events of special interest. Of note, there were no myopathy events noted in patients randomized to receive adefovir. A review of these myopathy cases, in addition to those reported in CI-PSI-5268-06-306 and in post-marketing surveys in Korea, led to the decision to terminate the development of clevudine.

A total of 108 (43.0%) clevudine-treated patients reported a least one AE during treatment. In clevudine-treated patients, the most frequent AEs were headache (7.6%), nasopharyngitis (6.0%), upper respiratory tract infection (5.6%), and influenza (5.2%); for all of these AEs, incidences were generally comparable between the blinded clevudine and blinded adefovir treatment groups. Most of the AEs were mild or moderate in intensity. Less than 5% of clevudine-treated patients had a Grade 3 AE, and none had a Grade 4 event.

CONCLUSION:

Elevated creatine kinase levels and clinical myopathy were noted in 3 patients randomized to receive clevudine in CI-PSI-5268-06-305. None of the analyses of safety data revealed unexpected findings other than the previously discussed myopathy cases.