This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

2. SYNOPSIS

SPONSOR COMPANY NAME: Cubist Pharmaceuticals, Inc. **NAME OF FINISHED PRODUCT:** HepeX-B™ **NAME OF ACTIVE INGREDIENT:** HepeX-B™	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER:** **VOLUME:** **PAGE:**	**(FOR NATIONAL AUTHORITY USE ONLY)**

TITLE OF STUDY:

A Phase II, Multicenter, Randomized, Open-Label, Dose-Ranging, Parallel Group Study to Compare the Anti-Viral Effects, Pharmacokinetics and Safety of HepeX-B™, a Mixture of Two Monoclonal Antibodies, as Compared to Hepatitis B Immune Globulin in Patients who have Received Hepatic Allografts for Treatment of End-Stage Liver Disease due to Hepatitis B Virus Infection

INVESTIGATORS AND STUDY CENTERS:

This was a multicenter study conducted in Europe, Israel, New Zealand, and the US. Nineteen study sites were initiated for the study and patients were enrolled at 17 sites prior to the end of enrollment. A complete list of Investigators and participating study centers is provided in Appendix 16.1.4.

PUBLICATION (REFERENCE):

None.

STUDIED PERIOD:

Initiation Date (first patient enrolled): 06 November 2003
Completion Date (last patient completed): 30 August 2005

PHASE OF DEVELOPMENT:

Phase 2

STUDY OBJECTIVES:

The primary objective of this study was to compare the anti-viral effects of HepeX-B to Hepatitis B Immune Globulin (HBIg) as measured by serum concentrations of hepatitis B virus (HBV) deoxyribonucleic acid (DNA) and hepatitis B surface antigen (HBsAg), in patients who have received hepatic allografts for treatment of HBV infection.

Secondary objectives were to compare the trough concentrations of antibodies to hepatitic B surface antigen (anti-HBs) and to describe the safety of the reference and test agents.

METHODOLOGY:

The study was designed to evaluate the anti-viral effects, pharmacokinetics and safety of HepeX-B as compared to standard HBIg maintenance therapy in patients who had received hepatic allografts for treatment of end-stage liver disease due to HBV infection and who were currently receiving HBIg and concomitant treatment with an inhibitor of HBV polymerase. Eligible patients were randomized on a 1:1:1 basis to 1 of 3 treatment groups: 20 mg intravenous (IV) HepeX-B, 40 mg IV HepeX-B, or 5,000 IU IV HBIg. Patients were to receive an infusion of study medication every 4 weeks for 20 weeks (6 infusions) in the core trial, with the option of an additional 52 weeks of treatment (dosed every 4 weeks) in the extension phase of the trial. Patients were observed at 2 and 4 weeks after completion of each monthly treatment.

Periodic blood samples were collected for determination of serum concentrations of anti-HBs, HBsAg and HBV DNA. Virologic breakthrough and safety were monitored by an independent Data and Safety Monitoring Board (DSMB) who were blinded to treatment assignment.

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NUMBER OF PATIENTS (PLANNED AND ANALYZED):

Up to 75 patients were to have been enrolled in order to achieve at least 45 evaluable patients (15 patients per treatment group). To be considered evaluable, patients must either have received 6 infusions of study medication and completed the 4-week follow-up visit, or must have met the study protocol criteria for treatment failure. Patients who terminated the core phase of the study prematurely for reasons other than treatment failure were to be replaced.

The Sponsor terminated the study early on 22 July 2005 due to product-related issues (precipitates noted in the product). At that time a total of 62 patients had been enrolled in the trial; 51 of these patients received at least one dose of study treatment: 15 received HepeX-B 20 mg, 18 received HepeX-B 40 mg, and 18 received HBIg.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Patients who were at least 6 months post first orthotopic liver transplantation for treatment of end-stage liver disease due to HBV infection, who had received HBIg from the time of transplant through the time of entry into the study, who had received an inhibitor of HBV polymerase for at least the 3 months immediately prior to entry into the study, and who had undetectable serum concentrations of HBsAg and HBV DNA on 2 consecutive tests within the 45-day screening period, were eligible for the study.

Patients who were co-infected with hepatitis delta virus (HDV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV), or who had received other organ transplants requiring immunosuppression were ineligible to participate.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, LOT NUMBER(S):

Patients received HepeX-B 20 or 40 mg (based on random assignment), which is a mixture of two monoclonal antibodies: libivirumab and exbivirumab, diluted in 100 to 250 mL of normal saline solution (NSS) and infused intravenously over 2 hours every 4 weeks.

Lot number(s): libivirumab: [redacted] exbivirumab: [redacted]

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, LOT NUMBER(S):

Patients randomized to HBIg received 5,000 IU diluted in 100 to 250 mL of NSS and infused intravenously over 2 hours every 4 weeks.

Lot number(s): [redacted]

DURATION OF TREATMENT:

Duration of treatment was 20 weeks for all patients enrolled in the core trial, with the possibility of an additional 52 weeks for all patients enrolled in the extension phase.

CRITERIA FOR EVALUATION:

ANTI-VIRAL ASSESSMENTS:

HBV DNA and HBsAg serum concentrations were determined prior to and 2 weeks following each infusion. Positive results were to be confirmed by repeat testing at least 1 week later.

PHARMACOKINETICS:

Anti-HBs antibody serum concentrations were determined immediately prior to and at the end of each infusion and at 2 weeks after each infusion.

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SAFETY:

Safety was evaluated by periodic physical examinations, vital signs assessments, routine clinical laboratory tests (including a complete blood count, coagulation studies, serum chemistry and urinalysis), and reported and observed adverse events (AEs). Emergence of viral replication (as indicated by detectable concentrations of HBsAg and HBV DNA in serum) also was reviewed as a safety measure. Selected safety measures, including virologic status, were reviewed periodically by an independent DSMB. Criteria were prospectively established to terminate one or both of the experimental arms in the event of unacceptable risk to study participants.

STATISTICAL METHODS:

The primary endpoint was the proportion of patients in each treatment regimen without virologic breakthrough, where virologic breakthrough was defined as the persistent recurrence of detectable serum concentrations of HBsAg and HBV DNA measured on 2 consecutive assessments between 7 and 10 days apart. To test the null hypothesis, the lower bound of the two-sided 90% confidence interval (CI) of the difference between the proportions of response in HepeX-B and the active comparator was compared to the pre-set threshold (-15% difference, HepeX-B minus the active comparator). The use of the two-sided 90% CI allowed for the evaluation of an effective one-sided 95% CI (as specified in the sample size justification) in order to evaluate whether the criteria for non-inferiority was met.

Secondary endpoints included comparison of trough concentrations of anti-HBs antibodies, including the proportion of patients in each arm of the study with trough concentrations of anti-HBs <200 IU/L.

Tabulations of safety data, including AEs, laboratory results, vital signs, and concomitant medications, were descriptive only.

Because of early study termination, all efficacy and safety data available up to the termination date were analyzed together, regardless of the treatment phase (core and extension).

SUMMARY AND CONCLUSIONS:

SUMMARY OF DEMOGRAPHICS AND BASELINE CHARACTERISTICS:

Overall, the treatment groups were well balanced in demographic and baseline characteristics. The majority of patients in the study were male, including 85% of patients in the HepeX-B groups and 83% of patients in the HBIg group. Patients ranged in age from 21 to 70 years; the median age was 52 years for patients treated with HepeX-B and 54 years for those treated with HBIg. Patients were predominantly Caucasian, including 55% of patients treated with HepeX-B and 78% of patients treated with HBIg.

The median time from hepatitis B diagnosis to liver transplantation was 5 years and 3 years in the HepeX-B groups and the HBIg group, respectively. The median time from liver transplantation to first study medication infusion was 2 years and 3 years in the HepeX-B groups and the HBIg group, respectively.

Patients were stratified by the type of HBV polymerase inhibitor that they were using at the time of enrollment. Lamivudine was the most frequently used HBV polymerase inhibitor at study enrollment (80% of all patients). In the HBIg group, 3 patients stratified to lamivudine actually received a different HBV polymerase inhibitor; therefore, the proportion of patients taking lamivudine in the HBIg group (67%) was lower than that in the HepeX-B 20 mg group (93%) and the HepeX-B 40 mg group (83%).

SUMMARY OF ANTI-VIRAL ACTIVITY:

All treated patients were included in the analysis of efficacy even if they received just 1 dose. All patients in both the HepeX-B groups and the HBIg group achieved the primary efficacy endpoint of no virologic breakthrough during the study. No patient in any treatment group had simultaneous positive results for HBsAg

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and HBV DNA persisting on 2 consecutive tests between 7 and 10 days apart.

No patient in either HepeX-B dose group had a positive HbsAg or HBV DNA value at any time during the study. One patient in the HBIg group had one positive HBsAg and HBV DNA result at Week 21 and Week 23, respectively. This patient also had a trough anti-HBs concentration <200 IU/L at Week 21. This patient did not meet the protocol criteria for virologic breakthrough because the positive results for HBsAg and HBV DNA were not simultaneous or persistent on 2 consecutive tests between 7 and 10 days apart, however, the patient was discontinued by the Investigator secondary to a concurrent illness.

SUMMARY OF PHARMACOKINETICS:

Increases from baseline in serum anti-HBs concentration appeared to be greater in the HepeX-B groups compared with the HBIg group, with the greatest increases observed in the HepeX-B 40 mg group. At the end of the core phase (Week 25), the median change from baseline in trough (pre-infusion) serum anti-HBs concentration was 3144 IU/L in the HepeX-B 40 mg group, compared with 1478 IU/L in the HepeX-B 20 mg group and 353 IU/L in the HBIg group.

SUMMARY OF SAFETY:

No serious adverse events related to study medication or discontinuations due to drug-related adverse events were reported. The majority of all reported adverse events were assessed by the Investigator as mild or moderate in severity and unrelated to study medication. An overview of adverse events is provided in the table below.

Summary of Treatment-Emergent Adverse Events (Safety Population)

Category	HepeX-B 20 mg (N=15) N (%)	HepeX-B 40 mg (N=18) N (%)	HBIg (N=18) N (%)	Total (N=51) N (%)
At least one AE	14 (93.3)	12 (66.7)	16 (88.9)	42 (82.4)
At least one SAE	1 (6.7)	1 (5.6)	7 (38.9)	9 (17.6)
At least one severe AE	1 (6.7)	1 (5.6)	4 (22.2)	6 (11.8)
At least one drug-related AE	5 (33.3)	7 (38.9)	5 (27.8)	17 (33.3)
Discontinued due to AE	0	0	2 (11.1)	2 (3.9)

At least 1 adverse event was reported by 14 (93%) patients in the HepeX-B 20 mg group, 12 (67%) patients in the HepeX-B 40 mg group, and 16 (89%) patients in the HBIg group. The most commonly reported adverse events across all patients were headache (11 patients, 22%), cough (10 patients, 20%), and arthralgia (9 patients, 18%). The most commonly reported drug-related adverse events overall were headache (7 patients, 14%), nausea (3 patients, 6%), and arthralgia (3 patients, 6%). No individual adverse event was reported as severe for more than one patient. Only one severe drug-related adverse event was reported (nephrolithiasis in the HBIg group).

Seven (39%) patients in the HBIg group compared with 1 (7% and 6%, respectively) patient each in the HepeX-B 20 mg and 40 mg groups experienced at least one serious adverse event unrelated to study medication. Two (11%) patients in the HBIg group discontinued from the study because of adverse events, compared with no patients in either HepeX-B dose group.

No safety concerns were raised from clinical laboratory results or vital signs evaluations. Median changes in laboratory values and vital signs during the study were generally small in all treatment groups. No clinically

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meaningful differences were apparent among treatment groups for changes in any laboratory or vital signs parameter.

The most commonly reported abnormality reported as an adverse event was proteinuria, reported in 1 (7%) patient in the HepeX-B 20 mg group, 2 (11%) patients in the HepeX-B 40 mg group, and 1 (6%) patient in the HBIg group; proteinuria was judged by the Investigator to be related to study medication for the 1 patient in the HepeX-B 20 mg group and 1 of the 2 patients in the HepeX-B 40 mg group with this event. Elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were the only other laboratory abnormalities that were reported as adverse events for more than one patient; each of these abnormalities was reported in 2 (11%) patients in the HBIg group; ALT and AST increased was judged by the Investigator to be related to study medication for 1 of the 2 patients with these events.

Pyrexia was the most commonly reported adverse event related to vital signs abnormalities; this event occurred in 3 (17%) patients in the HBIg group compared with 1 patient each (7% and 6%, respectively) in the HepeX-B 20 mg and 40 mg groups. All of the adverse events related to vital signs abnormalities were mild or moderate in severity and none of the events were judged by the Investigator to be related to study medication.

CONCLUSIONS:

Although this study was terminated early for product-related issues, results show that HepeX-B, at both the 20 mg and 40 mg doses, was as effective as HBIg in suppressing virologic breakthrough in patients following hepatic allografts for end-stage liver disease due to hepatitis B virus infection. The highest serum anti-HBs concentrations were observed at the 40 mg dose of HepeX-B. Furthermore, HepeX-B was well-tolerated at doses of 20 mg and 40 mg administered every 4 weeks for up to 18 doses in this study and the percentage of patients who had adverse events including serious adverse events was similar between the two doses.

DATE OF THE REPORT: 15 June 2006