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JUN 13 2006

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Director
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Blood Research and Review
c/o Documents Control Center (HFM-348)
Woodmont Office Center, Suite 200N
1401 Rockville Pike
Rockville, Maryland 20852-1448

**Attention: Don Jehn, Executive Secretary, BPAC**

**Re: U.S. License No. 1687**
**BLA STN 125073**
**Hepatitis B Immune Globulin (Human), Intravenous**
**Nabi-HB IV**
**Correspondence: July 13, 2006 BPAC Meeting Package**

Dear Dr. Epstein:

Please refer to Nabi Biopharmaceuticals (Nabi) Biologic License Application (BLA) STN 125073 submitted on November 26, 2002, for Hepatitis B Immune Globulin (Human), Intravenous, Nabi-HB IV, manufactured at Nabi's Boca Raton, Florida fractionation facility under U.S. License No. 1687.

Nabi is seeking the Blood Products Advisory Committee's (BPAC) advice concerning BLA 125073, for the indication of "prevention of hepatitis B clinical disease in HBsAg-positive liver transplant recipients." We appreciate your consent to take this matter before the BPAC. This submission contains the briefing document to be provided to the committee.

Background

Prior to licensure of hepatitis B immune globulin (HBIG), patients with end-stage liver disease (ESLD) due to hepatitis B could not have liver transplants without a high risk of Hepatitis B Virus (HBV) reinfection of the transplanted liver (80-90% reinfection rate). In addition, due to the immunosuppressive treatment necessary to prevent organ rejection, the clinical course of HBV reinfection was most often very severe, with rapid progression to fulminant liver disease of the transplanted liver. For that reason, patients with hepatitis B were not candidates for liver transplant in most transplant centers,

leaving patients with ESLD due to HBV with no therapeutic options. This grim prognosis changed with the advent of HBIG. Several studies, including the landmark paper by McGory et al. (Transplantation 1996; 61[9]: 1358-1364), demonstrated that high doses of HBIG dramatically reduce the rate of reinfection from 80-90% to 30-40%. This changed the treatment paradigm and suddenly made liver transplants in these patients a therapeutic option. The prognosis further improved when antiviral drugs against HBV were introduced and studies demonstrated that concomitant treatment with HBIG and antivirals could further reduce the reinfection rate to somewhere between 0 and 11%. These early studies also led to an unbridled enthusiasm for antivirals, which some physicians thought could be used alone to prevent reinfection of HBV. However, with longer follow-up, it has become apparent that resistance to antivirals develops. The two-year historical recurrence rate for lamivudine monotherapy is calculated to be around 45%. As the meta-analysis that demonstrated this figure contained a number of older studies, and as the resistance rate to lamivudine has increased, a 2-year recurrence rate of 45% is probably an under-estimate.

HBIG efficacy as monotherapy, as well as in combination with antivirals, is very well documented in literature. Alone, or more recently in combination with antiviral drugs, HBIG has become the standard of care for prevention of recurrence of HBV post-liver transplant in the US for more than 15 years, and is approved for the liver transplant indication in the EU, as well as in most other parts of the world. The US is the only major area in the developed world where HBIG is not approved for liver transplants. The development of HBIG in the US has been complicated by a number of different factors. Most significantly, combination therapy with HBIG and antiviral drugs has been the standard of care for the last 10 years, which makes a placebo-controlled efficacy study unethical and any controlled randomized study difficult. Additionally, the size of the clinical trials that could be performed is limited. This is a life-threatening disease for a very small patient population - 200 Hepatitis B positive liver transplants are performed in the US annually in approximately 125 transplant sites. Due to these difficulties, the criteria for approval were not clear until the March 2004 BPAC meeting.

An intramuscular (IM) version of Nabi-HB IV is currently licensed and marketed in the US under the tradename Nabi-HB®. The IM product is provided in 2 mL and 6 mL vials with a potency of > 312 IU/mL, and is intended for use as a prophylaxis following acute exposure to HBV. Nabi-HB has been used widely off-label for prevention of recurrent hepatitis B-related clinical disease in liver transplant recipients in the US since its approval in 1999. However, the lack of guidance in the US label for intravenous use has resulted in numerous examples documenting recurrence of HBV infection after premature discontinuation of Nabi-HB IV (Dickson et al. 2006; Hayashi et al. 2006). These recurrences have resulted in several deaths and indicate that the lack of guidance poses a significant risk to patients.

Biologics License Application for Nabi-HB IV

Nabi's Hepatitis B Immune Globulin for intravenous administration (Nabi-HB IV) is a sterile, non-pyrogenic solution of 5 ± 1% (w/v) human immune globulins containing antibodies to the hepatitis B surface antigen. The product is formulated in glycine and sodium chloride, and stabilized with Polysorbate 80. It can be stored at 2 – 8°C for up to 39 months. Nabi-HB IV is provided in a 30 mL vial containing > 5000 IU (> 208 IU/ml). In November 2002, Nabi submitted a Biologics License Application (BLA) to the US FDA for Nabi-HB IV for the prevention of hepatitis B clinical disease in HBsAg-positive liver transplant recipients. A series of meetings and responses to Complete Response Letters ensued for the next two years, during which Nabi and the FDA struggled to determine what the basis of approval should be for this type of product. The regulatory requirements for approval were finally clarified at the March 2004 meeting of the BPAC. (Refer to Attachment 1 for the Regulatory Chronology/History).

In May 2004, FDA sent Nabi a letter outlining the BPAC requirements from the March 2004 meeting. Nabi followed the BPAC recommendations by collecting extended follow-up data on 62 new transplant subjects administered Nabi-HB IV/lamivudine combination therapy. These data were submitted to FDA in December 2004. Nabi believes that the information provided to the FDA and BPAC provides substantial evidence of efficacy and safety supporting the approval of Nabi-HB IV. Attachment 2 describes how the data for Nabi-HB IV meet the BPAC criteria described at the March 2004 meeting. Nabi also provides as Attachment 3 a Clinical Efficacy and Safety Summary that further demonstrates our data meet the requirements for approval. The draft package insert is provided as Attachment 4.

Nabi subsequently met with FDA in December 2005 and April 2006 to discuss the database supporting approval. As stated in the FDA minutes from the April 2006 meeting, included as Attachment 5, FDA did not agree with the details of our meta-analysis of the calculated historical recurrence rate for lamivudine monotherapy, nor on the inclusion criteria used to analyze the efficacy database. The Agency also expressed reservations as to the size of the database. However, Dr. Epstein indicated that he is interested in seeing a hepatitis B immune globulin approved and offered to seek advice from the BPAC.

In Attachment 6, we specifically address the concerns summarized in the April 2006 FDA meeting minutes. Additionally, Nabi provides a copy of our proposed Phase IV protocol as Attachment 7 and selected references as Attachment 8.

We look forward to meeting with BPAC on July 13, 2006. The issues and an overall history of Nabi–HB IV will be presented to the BPAC by Dr. Henrik Rasmussen, Sr. Vice President of Regulatory, Clinical and Medical Affairs. Should you have any questions or comments regarding this meeting package, please contact Mr. Michael Harlow at 301 255-6897 or me at 301 255-6896.

Sincerely,

Lewis Pollack

Lewis Pollack, Ph.D.
Vice President, Regulatory Affairs

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
FOOD AND DRUG ADMINISTRATION

# APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

*(Title 21, Code of Federal Regulations, Parts 314 & 601)*

*Form Approved: OMB No. 0910-0338*
*Expiration Date: September 30, 2008*
*See OMB Statement on page 2.*

**FOR FDA USE ONLY**

APPLICATION NUMBER

**APPLICANT INFORMATION**

| | |
|---|---|
| NAME OF APPLICANT<br>Nabi Biopharmaceuticals | DATE OF SUBMISSION JUN 13 2006 |
| TELEPHONE NO. *(Include Area Code)*<br>301-255-6896 | FACSIMILE *(FAX)* Number *(Include Area Code)*<br>301-255-6823 |
| APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*<br>5800 Park of Commerce Blvd. NW<br>Boca Raton, FL 33487<br>US License No. 1687 | AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE |

**PRODUCT DESCRIPTION**

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)*

| | |
|---|---|
| ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*<br>Hepatitis B Immune Globulin (Human), Intravenous | PROPRIETARY NAME *(trade name)* IF ANY<br>Nabi-HB Intravenous |

| | |
|---|---|
| CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* | CODE NAME *(If any)* |

| | | |
|---|---|---|
| DOSAGE FORM:<br>Injectable | STRENGTHS:<br>208 IU/mL | ROUTE OF ADMINISTRATION:<br>Intravenous |

(PROPOSED) INDICATION(S) FOR USE:
Prevention of hepatitis B clinical disease in HbsAg-positive liver transplant recipients

**APPLICATION DESCRIPTION**

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☒ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Correspondence: July 13, 2006 BPAC Meeting Package

PROPOSED MARKETING STATUS *(check one)* ☐ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

**ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)**
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Nabi-HB Manufacturing/Testing Nabi – Boca Raton 5800 Park of Commerce Blvd.Boca Raton, FL 33487Reg. No. (CFN): 1059191,
Nabi-HB Testing Nabi – Boca Raton 5900 Park of Commerce Blvd.Boca Raton, FL 33487Reg. No. (CFN): 1059191,
Authorized Official: Lewis Pollack, Ph.D. V.P., RAPH: (301) 255-6896FAX: (301) 255-6823. Both Sites Ready for Inspection

**Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)**

U.S. License No. 1687
DMFs 1034, 501, 10095, 4258, 9543, 13014, and 5125
IND's 7998, 7409, and 8452

**FORM FDA 356h (10/05)**

This application contains the following items: *(Check all that apply)*

| | |
|---|---|
| ☒ | 1. Index |
| ☐ | 2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling |
| ☐ | 3. Summary (21 CFR 314.50 (c)) |
| ☐ | 4. Chemistry section |
| ☐ | A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2) |
| ☐ | B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request) |
| ☐ | C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2) |
| ☐ | 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2) |
| ☐ | 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2) |
| ☐ | 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4)) |
| ☐ | 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2) |
| ☐ | 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2) |
| ☐ | 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2) |
| ☐ | 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2) |
| ☐ | 12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2) |
| ☐ | 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c)) |
| ☐ | 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A)) |
| ☐ | 15. Establishment description (21 CFR Part 600, if applicable) |
| ☐ | 16. Debarment certification (FD&C Act 306 (k)(1)) |
| ☐ | 17. Field copy certification (21 CFR 314.50 (l)(3)) |
| ☐ | 18. User Fee Cover Sheet (Form FDA 3397) |
| ☐ | 19. Financial Information (21 CFR Part 54) |
| ☒ | 20. OTHER *(Specify)* Correspondence: July 13, 2006 BPAC Meeting Package |

**CERTIFICATION**

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
**Warning:** A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

| SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT | TYPED NAME AND TITLE | DATE |
|---|---|---|
| Lewis Pollack | Lewis Pollack, Ph.D., Vice President, RA | JUN 13 2006 |

| ADDRESS *(Street, City, State, and ZIP Code)* | Telephone Number |
|---|---|
| 12280 Wilkins Ave., Rockville, MD 20852 | ( 301 ) 255-6896 |

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**FORM FDA 356h (10/05)**

**Attachment 1**

**Regulatory Chronology/History**

## Regulatory Chronology

### Key Events

| Date | Key Event |
|---|---|
| 1994 | IND BB 5665 for Hepatitis B Immune Globulin IV Submission |
| 1995 | Orphan Drug Designation |
| 1997 | Telecons: FDA accepts HBIG as efficacious in the perioperative period of OLT. Due to Abbott's H-BIG not being virally inactivated and containing thimerosal, a proposal is accepted to compare pK data between Nabi-HB IV against the McGory paper (Abbott H-BIG) for the liver transplant indication. |
| 1999 | Discussions continued between Nabi and the FDA on the proposed pK study. FDA confirms the McGory data is acceptable for pivotal efficacy as long as it is auditable. The BLA for the IM formulation for Hepatitis B post exposure prophylaxis indication is approved. |
| 2000 | FDA letter indicates trough levels are not sufficient. The pK study requires statistical analysis and hypothesis testing. In December, a meeting was held between FDA and Nabi to determine an appropriate analysis plan for a pK study. At the meeting, FDA agrees that the statistical analysis will not be the basis for approval. The FDA asks Nabi to submit a pre-BLA meeting request for the liver transplant indication once all efficacy data have been analyzed. |
| 2001 | FDA approves the BLA for the IM formulation manufactured in Boca Raton, Florida. |
| 2002 | In March, Nabi requested a Pre-BLA Meeting for the IV formulation and liver transplant indication. This meeting was denied. In November, a BLA for the liver transplant indication was filed. |
| 2003 | FDA Telecon: FDA communicates that the McGory data now are not acceptable as a pivotal efficacy trial. No explanation was provided for this change in position. |
| 2004 | March: A BPAC meeting discussed requirements for development of immunoglobulins for prevention of hepatitis B in hepatitis B positive liver transplant recipients. For the first time, firm guidelines for the development of such agents were laid out, including a need for 24-month follow-up data for patients receiving HBIG in combination with antivirals.<br>December: Complete Response (CR) Amendment addresses the BPAC recommendations from the March meeting. |
| 2005 | FDA June CR letter cites calculation of historical recurrence rate for lamivudine monotherapy and Nabi HB IV database as being insufficient. Nabi resubmits for a December discussion. CBER upper management agrees to work with Nabi to characterize the database and historical recurrence rates. Proposal for BPAC is considered. |
| 2006 | Telecon: April discussion of recalculated recurrence rates and database; consensus not reached. FDA agrees to recommend BLA 125073 for July 13 BPAC Meeting. |

## 1.0 Summary of Regulatory History

### 1.1 HBIG

During the 1990's, physicians, in the practice of medicine, began treating orthotopic liver transplant (OLT) patients off-label with hepatitis B immune globulin (HBIG) intravenously, either alone or in combination with an antiviral drug (typically lamivudine). Prior to introduction of HBIG, liver transplantation in hepatitis B positive patients was contra-indicated due to rapid recurrence of hepatitis B in the transplanted liver with rapid development of fulminant hepatitis often the consequence. However, introduction of HBIG treatment markedly lowered the rates of re-infection from the hepatitis virus in the newly transplanted livers.

Hepatitis B immune globulin is licensed only for intramuscular use and post-exposure prophylaxis to the hepatitis B virus (HBV). The post-exposure could be sexual exposure, needle stick, accidental transfusion or mucosal splash. Therefore, the use of HBIG, which is the well-established standard of care in hepatitis B positive liver transplant recipients, has been off-label in the US since the early nineties. HBIG is licensed for the liver transplant indication in Europe as well as the rest of the developed world.

### 1.2 Nabi-HB IV

In October 1996, Nabi began discussions with FDA CBER OBRR (Division of Hematology) on the appropriate approach for approval of the off label use indication. Nabi proposed performing a clinical trial to compare the licensed Abbott H-BIG with a Nabi manufactured Hepatitis B Immune Globulin. This proposal was rejected based on safety concerns pertaining to the lack of viral inactivation and the use of thimerosal in the Abbott product (although HBIG was routinely used off-label for this indication). As an alternative proposal, FDA proposed that Nabi request licensure based on data from the McGory paper (for safety and efficacy) and perform an intravenous pharmacokinetics study, in which the Nabi manufactured Hepatitis B Immune Globulin would be characterized.

In February 1997, Nabi submitted a meeting request to discuss a new study design based on that suggested by FDA for the OLT indication (IND 5665, Serial number 10). In October 1997, CBER called Nabi and stated that FDA accepted that Abbott H-BIG was efficacious in peri- as well as post-operative OLT.

In June 1999, an IND for the OLT indication (IND 8452) with product manufactured at Boca Raton, Florida was submitted and a meeting (August 1999) was requested to review the clinical plan.

During the August 1999 meeting, FDA re-affirmed that the McGory data could be used as the pivotal data, provided the data was auditable; subsequent audit by Nabi demonstrated that the data were auditable. It was Nabi's understanding that the additional pharmacokinetic trial, designed to demonstrate that Nabi manufactured product could maintain trough levels at greater than 500 IU/L, was also acceptable (minutes submitted October 1997 to IND 5665).

Following the August 1999 meeting, FDA sent a letter requesting that the protocol include a formal hypothesis testing for the pK study. FDA was concerned enough about this issue that they called several months later to advise that study Nabi-4203 was not to be analyzed until there was agreement on an analysis plan. Several proposals for analysis were submitted and rejected. Nabi determined that a meeting (December 2000) would be required to come to an agreement.

During the December 2000 meeting, CBER agreed that the requested statistical analyses, as well as the alternatives proposed by Nabi, were all essentially unworkable given the nature of disparate databases from the clinical trials. FDA suggested that Nabi compile all efficacy data and request a pre-BLA meeting.

The BLA was submitted on November 26, 2002, without a pre-BLA meeting. Subsequent discussions with FDA followed through the next two years regarding the basis of approval; e.g., the use HBsAg as a surrogate; however, the basis for approval remained unclear.

In March 2004, a BPAC Meeting was held that, for the first time, outlined criteria for approval; 1) pivotal study should be from time of transplantation; 2) a historical control could be used for the pivotal trial; 3) pK data should be captured that can be used to guide therapeutic dosing; and 4) two-year follow-up is required for subjects receiving concomitant lamivudine. Upon discussion with CBER, this information was compiled and submitted in December 2004. In a Complete Response letter from CBER (June 2005), CBER commented that the retrospective databases were too small and too incomplete for supporting monotherapy and the results of Nabi-HB IV plus lamivudine do not support the conclusion that Nabi-HB IV contributed to the treatment response.

Nabi disagreed with this assessment and requested a meeting with CBER OBRR upper management, which was held in December 2005. Nabi stressed that underdosing of patients contributed to re-infection and the medical community needed guidelines. As an outcome of the meeting, CBER restated the two points that were preventing approval of the BLA, but indicated that FDA would work with Nabi to put together a consensus database on the available data submitted and a historical recurrence rate. In addition, FDA would consider seeking advice from BPAC.

In order to come to a consensus on the database, Nabi submitted detailed patient summaries on Nabi-4204 and Nabi-4409, (which had been conducted in new transplant patients), as well as patient listings and lab values. A meta-analysis for calculating the historical recurrence rate for lamivudine monotherapy was also submitted that was based on criteria proposed by BPAC at the March 2004 meeting. A telecon was held on April 5, 2006. Although some agreements were made, CBER generally maintained its position regarding the patient database and calculated historical recurrence rate of 45% for lamivudine monotherapy, in that they did not believe the calculated rate satisfied the most conservative scenario. However, FDA agreed to place the BLA before the BPAC advisory committee scheduled on July 13, 2006 for the indication of "for the prevention of hepatitis B clinical disease in HBsAg-positive liver transplant recipients."

**Attachment 2**

**BPAC Recommendations From the March 2004 Meeting**

**BPAC Recommendations From the March 2004 Meeting**

## 1.0 Introduction

A summary of the BPAC recommendations from the March 2004 meeting according to the FDA's Complete Response letter to Nabi on May 25, 2004 follows. Nabi has responded to each of BPAC's recommendations and believes we have fully met these guidelines.

1) The pivotal study should start dosing from the time of transplantation, and should not be solely based on data from the "maintenance phase," i.e., six months or more after transplantation.

2) PK data should be captured that can be used to guide therapeutic dosing

3) In choosing an historical control form the medical literature, consideration should be given to baseline risk factors to ensure comparability between study arms.

4) In the case of HBV antiviral use, a minimum of 2 years of follow-up time will be necessary for subjects receiving concomitant lamivudine. This is required in order to capture the additional clinical benefit that may be conferred by HBIGIV.

## 2.0 BPAC Criterion

### 2.1 Pivotal Study Should be From Time of Transplantation

The pivotal data are from two studies in 62 new transplant recipients (Nabi-4204 and Nabi 4409). These data are supported by 4 studies (Nabi-2906, Nabi-4203, Nabi-4406 and Nabi-4409), in a total of 173 maintenance phase patients. Thus, the database consists of 235 patients. However, nineteen patients participated in more than one of the aforementioned studies, accounting for a total of 29 repeats in patient count. Therefore, there were a total of 206 unique patients among the five studies included in this submission. Based on BPAC criteria, 6 patients in Nabi-4204 and 15 patients in Nabi-4409 were excluded from the 235 patient count for the efficacy assessments (resulting in 214 evaluable patients in total).

### 2.2 Pharmacokinetics Data Should be Captured That Can be Used to Guide Therapeutic Dosing

The dosing regime of this agent is critically important, as minimum trough levels of antibodies need to be maintained to ensure that the patient remains HBsAg seronegative. Nabi-HB IV pharmacokinetic data in both new transplant and maintenance patients support the proposed dosing recommendations, which correspond roughly to the EMEA guidelines.[20]

Target trough levels were achieved in new transplant patients in Nabi-4204 (Dickson study); i.e., 300 IU/ml in weeks 1-7, 200 IU/mL for weeks 8-12, and 100 IU/mL thereafter. These levels prevented seroconversion and were similar to those shown to be efficacious in the McGory study, which FDA had accepted as demonstrating efficacy. Pharmacokinetic comparisons to the McGory study show that co-administration with lamivudine does not interfere with Nabi-HB IV kinetics and provides additional support. Target trough levels were also observed in maintenance phase individuals in several studies.

### 2.3 Historical Control Should Ensure Comparability Between Study Arms in Terms of Baseline Risk Factors

Nabi used a very conservative estimate for lamivudine efficacy (45%, based on meta-analysis). The results of the meta-analysis are consistent with other reports from the literature (refer to Attachment 3, Table 1-1). Additionally, the literature provides no evidence that baseline risk factors have changed. Nabi is therefore confident that the baseline risk factors among transplant patients in the reported literature and patients evaluated in studies Nabi-4409 and Nabi-4204 are comparable. Furthermore, the estimate of 45% is a conservative estimate of recurrence rate due to lamivudine monotherapy for analyses. Additionally, the increased use of lamivudine prior to liver transplantation, may, if anything, increase the recurrence rate due to increased development of viral resistance, which is currently as high as 67% when administered post transplant.

### 2.4 Two-Year Follow-Up Required for Patients Receiving Concomitant Lamivudine

The pivotal efficacy data are from Nabi-4204 and Nabi-4409 in 62 new transplant recipients. Follow-up data well exceed the 2-year recommendation (mean follow-up of 3.5 yrs).

For the combined Nabi-4204 and Nabi-4409 databases, there was 1 recurrence among the 41 patients who either had clinical follow-up for at least 2 years or died at least 30 days post transplantation. The observed recurrence rate of 2.4% (1 of 41) was significantly less than the 45% with lamivudine monotherapy (relative efficacy of 94.6%). Similarly, there was 1 recurrence among the 29 patients who either had serology follow-up for at least 2 years or died at least 30 days post transplantation. The observed recurrence rate of 3.4% (1 of 29) was statistically significantly less than the 45% with lamivudine monotherapy (relative efficacy 92.3%).

**Attachment 3**

**Clinical Efficacy and Safety Summaries**

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## 1.0 Introduction

### 1.1 Clinical History

The hepatitis B surface antigen (HBsAg) is a protein expressed on the outer surface of the virion. It consists primarily of two major polypeptides, one with a molecular weight of 24,000 and its glycosylated counterpart with a molecular weight of 28,000. HBsAg is required for, and facilitates infection by the virus.[1] Circulating HBsAg precedes elevations of serum aminotransferase activity and clinical symptoms and remains detectable during the symptomatic phase of the infection and beyond. In typical cases of acute hepatitis B (HBV) disease, HBsAg becomes undetectable 1-2 months following the onset of jaundice.[1] Disappearance correlates with an increase in antibodies to HBsAg (anti-HBs) in serum, and anti-HBs remains detectable indefinitely thereafter.[1]

HBsAg is a very well established surrogate marker for clinical disease in hepatitis B, and is used in most studies to assess recurrence post-transplantation in patients undergoing orthotopic liver transplant (OLT) due to hepatitis B-induced end-stage liver disease. For three decades, regulatory approval of immune globulins and vaccines for prevention of HBV disease have been based on, in part, the use of HBsAg as a surrogate marker for efficacy. A literature review follows.

Table 1-1 summarizes the relevant literature for HBsAg recurrence rates in patients undergoing OLT for end-stage-liver disease caused by HBV. Included are studies of treatment with none or short-term HBIG treatment, treatment with long-term (> 6 months) HBIG treatment, treatment with lamivudine alone, and combinations of lamivudine and HBIG.

**Table 1-1: Recurrence Rate of HBsAg Positivity in Patients Undergoing Orthotopic Liver Transplant for End-Stage-Liver Disease Caused by HBV**

| Author | Non or Short- Term HBIG (<3 months) | Long – Term HBIG (> 6 months) | Lamivudine Only | HBIG plus Lamivudine |
|---|---|---|---|---|
| Samuel[28] | 74% (111/150) | 36% (75/209) | --- | --- |
| Samuel[2] | --- | 23% (25/110) | --- | --- |
| O'Grady[14] | 83% (24/29) | --- | --- | --- |
| Ottobreli[29] | 81% (22/27) | --- | --- | --- |
| Todo[3] | 82% (37/45) | --- | --- | --- |
| Nauman[4] | --- | 45%(31/69) | --- | --- |
| Bain[23] | --- | --- | 50% (2/3) | --- |
| Mutimer[25] | --- | --- | 42% (5/12) | --- |
| Perrillo[26] | --- | --- | 41% (16/39) | --- |
| Chan[24] | --- | --- | 30% (6/20) | --- |
| Ben-Ari[30] | --- | --- | --- | 11% (1/9) |
| Anselmo[22] | 82% (24/29) | 48% (13/28) | 65% (13/20) | 11% (10/89) |
| Terrault[8] | 76% (21/28) | 19% (4/24) | --- | --- |
| Muller[5] | 100% (11/11) | 26% (6/23) | --- | --- |
| McGory[16] | --- | 7% (2/27) | --- | --- |
| Sawyer[31] | --- | 23% (9/40) | --- | --- |
| Chu[18] | 75% (15/20) | 19% (4/21) | | |
| Al-Hemsi[19] | | 9% (3/32) | | |
| Nymann[7] | 100% (4/4) | 21% (3/14) | --- | --- |
| Grazi[32] | 80% (8/10) | 16% (4/25) | --- | --- |
| Markowitz[33] | --- | --- | --- | 0% (0/14) |
| Marzano[6] | --- | --- | --- | 4% (1/25) |
| Starkel[34] | --- | --- | --- | 0% (0/8) |

Samuel et al.[2] evaluated 110 HBsAg positive patients, who underwent OLT, and received long-term (>6 month) treatment with HBIG. Twenty-five (25) of 110 patients (22.7%) had recurrence of HBsAg, whereas the remaining 85 remained HBsAg negative. Twenty-one (21) of the 25 HBsAg positive patients and 60/85 HBsAg negative patients were followed with repeated liver biopsies, allowing the authors to assess the correlation between HBsAg and liver pathology. Twenty (20) out of 21 patients (95%), who became HBsAg positive had abnormal liver pathology as compared to only 12/72 (17%) of the patients who remained HBsAg negative. The liver pathology associated with HBsAg reappearance was not trivial, as 43% of the patients demonstrated histological signs of chronic hepatitis, 19% acute hepatitis, 14% cirrhosis and 14% fulminant liver failure[2].

Todo et al.[3] evaluated the livers histologically of 35 out of 37 patients, who developed reappearance of HBsAg more than 60 days after OLT. All 35 patients had significantly

abnormal liver pathology with the majority demonstrating histologic signs of chronic active hepatitis or liver cirrhosis.

Naumann et al.[4] transplanted a total of 69 patients with HBV-induced end-stage liver disease; all received therapy with hepatitis B immune globulin (HBIG). HBsAg reappeared in 31/69 patients (45%); in all cases (100%), reappearance of HBsAg was associated with histologically proven hepatitis (acute as well as chronic active) in the graft. Thirty-eight (38) of 69 patients (55%) remained HBsAg free; only 2/38 (5%) of these patients showed histological signs of hepatitis, which in both cases were classified as mild. Fifteen (15) patients died, all in the HBsAg recurrence group, 11/15 (73%) as a direct result of HBV or liver damage, 3/15 (20%) due to recurrence of hepatocellular carcinoma and 1/15 (7%) due to unrelated causes. In addition, graft failure occurred in 13/31 (42%) patients in the HBsAg recurrence group, in all cases caused by severe acute or chronic graft hepatitis due to HBV recurrence. None of the patients who did not become HBsAg positive died or developed graft failure during the 2 year follow-up, providing perhaps the strongest evidence of the prognostic significance of reappearance of HBsAg post-transplantation.

Muller et al.[5] evaluated long-term passive immunization with hepatitis B immune globulin in 23 patients compared with 11 patients who received no treatment or short-term HBIG therapy. All 11 (100%) with no treatment or short-term HBIG showed recurrent infection within 15 months of transplant, where as 26% showed HBV recurrences in the long-term group. In 13 patient who underwent liver biopsy after transplantation, none of the 5 HBsAg negative patients developed hepatitis or other significant liver pathologies. In contrast, all 8 HBsAg positive patients demonstrated significant histological abnormalities, with two patients developed cirrhosis, another 5 patients showed histologic evidence of chronic aggressive or persistent hepatitis and the last patient showed evidence of acute hepatitis.

Nymann et al.[7] compared 4 patients who did not receive high HBIG with 14 patients who did. All four patients (100%) who did not receive HBIG developed HBsAg recurrence, as compared to 3/14 patients (21%) who received HBIG. All 7 patients who became HBsAg-positive, compared to 0/11 patients who remained HBsAg-negative, demonstrated histologic evidence of hepatitis.

Marzano et al.[6] treated a total of 25 patients with a combination of high-dose HBIG and lamivudine. In 24 of 25 patients, this regimen prevented reappearance of HBsAg; these 24 patients had normal liver histology as compared to the one patient who sero-converted and became HBsAg positive. That individual developed histologic changes consistent with chronic hepatitis.

HBsAg negativity confers a good prognosis, even in the continuous presence of HBV DNA detected by polymerase chain reaction (PCR). Terrault, et al.[8] found that HBV DNA was detectable in the sera in 67% of patients, in the lymphocytes in 50% of the patients and in the liver in 57% of the patients. However, in the HBsAg-negative patients, presence of HBV DNA was not associated with clinical, biochemical or histological signs of hepatitis. Marzano, et al.[6] reported similar findings, as 64% of patients who remained HBsAg-negative

were sporadically positive for HBV DNA. As in Terrault's study, detection of HBV DNA in HBsAg-negative patients was not associated with clinical or histological signs of hepatitis.

Liver transplantation currently represents the definitive therapy for end-stage liver disease (ESLD), including ESLD caused by chronic HBV infection, which worldwide is still one of the major causes of ESLD.[9] However, prior to the introduction of HBIG, the presence of virus in extrahepatic sites resulted in a very high probability (in excess of 80%) of re-infection of the grafted liver among patients transplanted due to HBV-related hepatic failure.[12] Furthermore, the clinical and pathological course of re-infection is typically significantly more aggressive than the original infection, in most cases leading to graft rejection and failure of the transplanted liver within the initial year following transplantation. This very poor prognosis in patients with hepatitis B-induced ESLD precluded them from being transplant candidates in most major centers.

Early efforts using moderate doses and stopping HBIG administration a few days to a few months after transplantation were disappointing[13-15] (see Table 1-1). Increased doses of HBIG and chronic administration (essentially indefinitely), typically decreased the rate of HBV infection of the grafted tissue to 36% or less.[16-19] It is now well accepted by the liver transplant community that therapeutic levels of anti-HBs will prevent hepatitis B infection, and anti-HBs are, in fact, the basis for demonstration of protection following vaccination against hepatitis B.[1, 9] Furthermore, anti-HBs have been accepted as a surrogate for efficacy in licensure of recombinant hepatitis B vaccines. By co-administration of reverse transcriptase inhibitors, such as lamivudine and HBIG, it is possible to further reduce the incidence of recurrent disease, to somewhere between 0 and 11%. That combination is now the standard of care in the United States and Europe, and has revolutionized the prognosis of patients with hepatitis B-induced end-stage liver disease. Although FDA did not accept maintenance of trough anti-HBs levels as a basis for regulatory approval, BPAC agreed it could be supportive data.

Clinical experience by numerous investigators demonstrate that in the first several weeks following transplantation, anti-HBs levels are quite variable due to variances in HBV load and liver function. As a result, frequent monitoring of anti-HBs levels and HBsAg serology during this time is important to assure adequate therapy. In contrast, several months after transplantation, as long as the patient is clinically stable on a constant maintenance dose of HBIG, there is less dependence on anti-HBs levels and HBsAg serology.

HBIG dosage regimens have varied widely. They have included various regimens, such as a fixed dose (e.g., 10,000 IU) given at fixed intervals, and either fixed or varying doses given at varying intervals. The idea behind all of these regimens was to achieve or exceed target minimum trough anti-HBs levels. Given the extraordinary effort and cost involved in the transplant procedure, and the significant morbidity and mortality associated with HBV recurrence, transplant physicians and the transplant recipients have been hesitant to discontinue maintenance HBIG administration to patients who have successfully remained HBsAg-seronegative. Several recent papers have demonstrated that those concerns have been well founded in that they described a very significant risk of recurrence of hepatitis B post-liver transplant after discontinuation of HBIG in the chronic phase, both in patients who

were replicators (Dickson et al. Liver Transplantation 2006[27]) as well as in non-replicators (Hayashi et al. Liver Transplantation 2006); in press[21]).

### 1.2 European Guidelines

Due to the overwhelming evidence supporting the administration of high doses of HBIG to prevent recurrence of HBV-related disease in liver transplant recipients, the Committee on Proprietary Medicinal Products (CPMP) recently issued guidelines for the treatment of patients undergoing liver transplantation due to hepatitis B. The EMEA guideline is titled, "Core SPC for Human Plasma Derived Hepatitis-B Immunoglobulin for Intravenous use" (CPMP/BPWG/4027/02). [20] The guideline specifies the following schedule for administration of HBIG:

- 2,000-10,000 IU on the day of transplantation, and daily through day 7 post transplantation to maintain trough levels of 100-150 IU/L for HBV DNA-negative and 500 IU/L for HBV DNA-positive patients.
- After day 7, dose as necessary to achieve trough level >100-150 IU/L for HBV DNA-negative patients
- After day 7, dose as necessary to achieve trough level >500 IU/L for HBV DNA-positive patients

The dosing recommendations for Nabi-HB IV in the US correspond roughly to those issued by the EMEA.

### 1.3 Current US Regulatory Status

There are currently no FDA guidelines for the use of HBIG for prevention of recurrence in liver transplant patients. HBIG efficacy is well documented in the literature, has been the standard of care for prevention of recurrence of hepatitis B post-liver transplant in the US for more than 15 years, and is approved for the liver transplant indication in the EU as well as elsewhere throughout the developed world. However, in the US the development of HBIG for liver transplantation was impeded by a number of different factors. Most significantly, HBIG in combination with antivirals had been standard of care for the last 10 years, which made a placebo controlled efficacy study unethical and any randomized controlled study very difficult. Additionally, the size of the clinical trials that could be performed is limited due to the very small number of patients. There are only approximately 200 Hepatitis B positive liver transplants performed in the US annually in approximately 125 transplant sites. Finally, there is also no approved comparator. Due to these difficulties, there was no guidelines for development of drugs in this indication, which complicated regulatory development and, indeed, the criterion for approval did not become clear until the March 2004 BPAC meeting.

BPAC recommended that the following criteria should be used for regulatory approval of a hepatitis B immune globulin for prevention of recurrence of hepatitis B in liver transplant patients with hepatitis B induced ESLD.

1) A historical control can be used for comparison in the pivotal study;

2) Pharmacokinetics data should be captured that can be used to guide therapeutic dosing;

3) The pivotal study should start dosing from the time of transplantation, and should not be solely based on data from the "maintenance phase," (i.e., six months or more after transplantation); and

4) For HBIG/lamivudine combination therapy, two years of follow-up time will be necessary.

### 1.4 Nabi-HB IV

Nabi's Hepatitis B Immune Globulin for intravenous administration (Nabi-HB IV) is a sterile, non-pyrogenic solution of 5 ± 1% (w/v) human immune globulins containing antibodies to the hepatitis B surface antigen. The product is formulated in glycine and sodium chloride, and stabilized with Polysorbate 80. It can be stored at 2 – 8°C for up to 39 months. Nabi-HB IV is provided in a 30 mL vial containing > 5000 IU (> 208 IU/ml).

An intramuscular (IM) version of Nabi-HB IV is currently licensed and marketed in the US under the tradename Nabi-HB®. The IM product is provided in 2 mL and 6 mL vials with a potency of > 312 IU/mL, and is intended for use following acute exposure to HBV.

In November 2002, Nabi submitted a Biologics License Application (BLA) to the FDA for Nabi-HB® to be indicated for intravenous (IV) administration to HBsAg-positive liver transplant recipients for the prevention of hepatitis B clinical disease in HBsAg-positive liver transplant recipients.

## 2.0 Description of Clinical Studies

Four Nabi-sponsored clinical trials, Nabi-2906, Nabi-4406, Nabi-4203, and Nabi-4409, and an investigator-based trial sponsored in part by the US National Institutes of Health (NIH), Nabi-4204, provide evidence for the efficacy of Nabi-HB. Each study was a multi-center, uncontrolled, open-label, prospective trial. In addition, another investigator-based study sponsored by McGory and other investigators at the University of Virginia (UVA) is included. This landmark study is included because it established the efficacy of high-dose, long-term administration of HBIG in preventing recurrence of HBV-related disease in HBsAg-positive liver transplant recipients. Each patient in all studies had chronic hepatitis B-related liver failure prior to transplantation.

The pivotal data are from two studies in 62 new transplant recipients in studies Nabi-4204 and Nabi-4409. The efficacy and safety of Nabi-HB IV are supported by 4 maintenance phase studies. Nabi-HB IV was administered to 52 patients in Nabi-2906, Nabi-4203, and Nabi-4406, and to 121 patients in Nabi-4409, for a combined database of 173 maintenance phase patients. Thus, the database consists of 235 patients. However, nineteen patients participated in more than one of the aforementioned studies, accounting for a total of 29 repeats in patient count. Therefore, there were a total of 206 unique patients among the five studies included in this submission. Based on BPAC criteria, 6 patients in Nabi-4204 and 15 patients in Nabi-4409 were excluded from the 235 patient count for the efficacy assessments (resulting in 214 evaluable patients in total).

## 2.1 Table of Studies

Table 2-1 summarizes studies that demonstrate safety, pharmacokinetics and efficacy of Nabi-HB IV to prevent recurrence of HBV-related disease in transplant recipients. A summary of each individual study follows in Section 2.2.

**Table 2-1: Summary of Studies**

| Study No. | Start Date<br>Status | Dose and Dose Regimen | Objective(s) of the Study | Design | Measurements | Patients | Age Range (yr.) | M/F B/W/O |
|---|---|---|---|---|---|---|---|---|
| Nabi-2906<br>Multicenter Trial;<br>6 centers | 4-Aug-97<br>Complete | 180 IU/kg; intravenous infusion over at least 1 hour once every 28 days for 3 months | To evaluate pharmacokinetic parameters of Nabi-HB and to evaluate the safety of IV administration | Open-label; uncontrolled | $C_{max}$; $AUC_{0-28}$<br>Anti-HBs levels<br>HBsAg presence<br>Anti-HCV presence<br>Adverse events<br>Laboratory tests | 21 patients >6 months post liver transplant | 35-71 | 19/2<br>0/17/4 |
| Nabi-4203<br>Multicenter Trial<br>5 centers | 8-Nov-99<br>Complete | 10,000 IU in 250 ml; intravenous infusion over at least 1 hour once every 28 days for 3 months | To evaluate pharmacokinetic parameters of Nabi-HB and to evaluate the safety of IV administration | Open-label; uncontrolled | $C_{max}$; $AUC_{0-28}$<br>Anti-HBs levels<br>HBsAg presence<br>Anti-HCV presence<br>Adverse events<br>Laboratory tests | 21 patients >6 months post liver transplant | 29-68 | 19/2<br>2/18/1 |
| Nabi-4406<br>Multicenter Trial;<br>3 centers | 4-May-98<br>Complete | Dose and dose regimen were determined by the standard practice of the individual investigator | To assess the safety of Nabi-HB and provide investigational product at patients request | Open-label; uncontrolled | Adverse events<br>HBsAg presence<br>Laboratory tests | 10 liver transplant patients who completed Nabi 2906 | 35-71 | 8/2<br>0/10/0 |
| Nabi-4409<br>Multicenter Trial;<br>26 centers | 24-Nov-98<br>Complete | Dose and dose regimen were determined by the standard practice of the individual investigator | Provide investigational product during shortage of commercial product, also to evaluate safety and efficacy | Expanded Access Open-label; uncontrolled | Limited adverse events<br>HBsAg presence<br>Anti-HB levels; HBV DNA presence<br>HBeAg presence | 153 liver transplant patients;<br>32 new transplant;<br>121 maintenance | 19-69 | 125/28<br>11/88/54 |
| Nabi-4204<br>Multicenter<br>11 centers | Jun-99<br>Complete | 20,000 IU day of Surgery; 10,000 IU daily days 1-7; 10,000 IU once weeks 4 and 8; 5,000 IU monthly from weeks 12 to 36 | To evaluate pharmacokinetic parameters of Nabi-HB in combination with Lamivudine, also to evaluate safety and efficacy | Open-label; Uncontrolled | $C_{max}$; $AUC_{0-28}$<br>Anti-HBs levels<br>HBsAg presence<br>Anti-HCV presence<br>Adverse events<br>Laboratory tests<br>Clinical Status | 30 new liver transplant patients | 31-71 | 27/3<br>2/15/13 |
| McGory<br>Single-center Trial | Dec-90<br>Complete | 10,000 IU during the anhepatic phase; 10,000 IU for 6 days; subsequently 10,000 IU given as needed to maintain <500 IU/L | To evaluate pharmacokinetic parameters and efficacy of 16.5% HBIG | Open-label; uncontrolled | Cl, Vd, $T_{1/2}$,<br>Anti-HBs levels<br>HBsAg presence<br>Anti-HCV presence<br>Clinical Status | 27 new liver transplant patients | 31-63 | 27/3<br>1/23/5 |

## 2.2 Summary of Studies

### 2.2.1 Nabi-2906

This was the first clinical evaluation of Nabi-HB IV (manufactured under contract) conducted in liver transplant patients. Twenty-one (21) maintenance-phase liver transplant recipients were evaluated for safety and pharmacokinetics of the product. The study demonstrated that intravenous administration of 10,000 IU of the product was safe, well-tolerated, and maintained clinically meaningful trough anti-HBs levels.

### 2.2.2 Nabi-4203

This was the first evaluation of Nabi-HB IV (manufactured at the Boca Raton facility) conducted in liver transplant patients. Twenty-one (21) maintenance-phase transplant recipients were evaluated for safety and pharmacokinetics of Nabi-HB IV. Subsequently, the pharmacokinetics of intravenous administration of Nabi-HB derived from this study was compared to those from the patients enrolled in Nabi-2906. The study demonstrated that intravenous administration of 10,000 IU of the product was safe and well tolerated. Similar to the levels measured in Nabi-2906, in this study, patients maintained clinically meaningful trough anti-HBs levels. Furthermore, comparison of the pharmacokinetics demonstrated that the product from both facilities were equivalent, thus confirming the previous demonstration of bioequivalence of intramuscular administration of the two products, which was used for regulatory approval of Nabi-HB manufactured in Boca Raton, Florida.

### 2.2.3 Nabi-4406

This was a compassionate use extension study of 10 patients who previously participated in Nabi-2906. The intent was to provide Nabi-HB IV to patients who requested to be included in a study to continue treatment.

### 2.2.4 Nabi-4409

This was an expanded access study, which due to a market shortage of licensed hepatitis B immune globulin, was approved by the FDA to provide Nabi-HB IV to transplant recipients (newly transplanted, and maintenance-phase transplant recipients) while the FDA reviewed the BLA for the post-exposure prophylaxis indication. A total of 32 new transplant recipients and 121 maintenance-phase transplant recipients were evaluated. In the original study, there was no recurrence of HBV-related disease among the maintenance-phase patients, and only 1 recurrence among the newly transplanted patients. A follow-up study (Nabi-4409EXT) was designed to collect extended follow-up information.

### 2.2.5 Nabi-4204

This was an investigator-based, NIH-funded study designed to evaluate the safety, efficacy and pharmacokinetics of concomitant Nabi-HB IV and lamivudine in 30 newly transplanted liver transplant recipients. Concomitant administration of Nabi-HB IV and lamivudine was well tolerated, with no unexpected adverse events. This study was extended to provide follow-up data for at least 2 years.

### 2.2.6 McGory Study

This was a pharmacokinetics and efficacy study of 16.5% HBIG (Abbott H-BIG) conducted in newly transplanted recipients by investigators at UVA.

Nabi audited source data at UVA pertaining to 27 HBsAg-positive transplant recipients from UVA. The audited data were collected retrospectively onto case report forms and subsequently entered into a clinical database, and analyzed. These data and the subsequent analyses confirmed the UVA findings published by McGory.[16] McGory's work is a seminal contribution to the field of liver transplantation of HBV-infected patients in the US and together with data from Samuel et al.[28] set the medical standard for treatment of such patients. McGory's study observed that larger doses and more frequent dosing with HBIG was highly effective in preventing recurrence of HBV-related disease in transplant patients, particularly during the initial week following transplantation. Therefore, aggressive passive immunization with HBIG was shown to minimize the risk of HBV-related liver disease.

## 3.0 Pharmacokinetics and Pharmacodynamics

Pharmacokinetic data are available for studies Nabi-2906, Nabi-4203 and Nabi-4204. Anti-HBs levels achieved were shown to be efficacious by McGory et al.[16] (see paper, Figure 4) and substantiate the dosing recommendations that Nabi is proposing. The suggested dose and dose-schedule for Nabi-HB IV administration to maintain the target minimum trough levels is shown in Table 3-1.

**Table 3-1: Dosing Recommendations for Nabi-HB IV**

| Weeks Post Transplant | Minimum Trough anti-HBs Level | Usual Dose Necessary |
|---|---|---|
| 0-2 | 500 IU/L | 10,000 IU anhepatically and then daily |
| 2-12 | 250 IU/L | 10,000 IU weekly or every 2 weeks* |
| >12 | 100 IU/L | 10,000 IU monthly** |

*Depending on measured anti-HBs titer
**After one year some patients may achieve minimum trough levels with longer dosing intervals

## 3.1 Summary Results of Individual Studies (pK)

### 3.1.1 Nabi-2906

Nabi-2906 was an open-label pharmacokinetics and safety study of 21 maintenance-phase liver transplant recipients administered intravenous infusions of HBIG. The first three infusions (180 IU/kg body weight) were analyzed using non-compartmental and compartmental calculations.

The mean $t_{max}$ was 0.1 day and the geometric mean $C_{max}$ and AUC were 5,889 IU/L, and 78,151 days•IU/L, respectively.

Minimum levels of anti-HBs were greater than 500 IU/L for the 28 days between infusions of HBIG. Further, the pharmacokinetics of multiple infusions of Nabi-HB in maintenance-phase liver transplant recipients was comparable to that described in the literature for most immune globulins.[1]

### 3.1.2 Nabi-4203

Nabi-4203 was an open-label pharmacokinetics and safety study of 21 maintenance-phase liver transplant recipients administered intravenous infusions of Nabi-HB (Boca). Pharmacokinetics analysis was based on data from the first three infusions and included compartmental and non-compartmental analyses.

For the population as a whole, the first, second, and third infusions had similar pharmacokinetics. The overall geometric mean $C_{max}$ and $AUC_{0-28}$ were 4,012 IU/L and 46,074 IU•day/L, respectively.

A non-compartmental estimate of clearance was obtained as the sum of the three administered infusions divided by the sum of the AUCs resulting from each of the three infusions. This estimate yielded a geometric mean of 0.215 L/day, and median of 0.190 L/day (range, 0.127-0.518 L/day). As was the case for patients in Nabi-2906, patients in Nabi-4203 had mean trough levels of anti-HBs above 500 IU/L for the 28 days between infusions of Nabi-HB IV.

All patients were HBsAg-negative at enrollment, and remained seronegative throughout the 3 months of study, providing evidence that Nabi-HB IV successfully suppresses HBV in transplant recipients.

The infusions were well tolerated even though the infusion times were between one and two hours (rather than four to six typical with 16.5% protein HBIG) for all but two patients.

### 3.1.3 Nabi-4204

For the purpose of analysis, a replicator was defined as either HBV DNA ≥ 5 pg/mL or presence of HBeAg and a positive qualitative HBV DNA result. A non-replicator was defined as a serum HBV DNA < 5 pg/mL. The patients were divided into 3 groups based on the HBV replication status at the time of lamivudine initiation and the time of liver transplantation. The Nn Group consisted of patients who were non-replicators at the time of lamivudine initiation and at the time of liver transplantation; the Rn Group consisted of patients who were replicators at the time of lamivudine initiation but non-replicators at the time of, or within two weeks prior to, transplantation; and the Rr Group consisted of patients who were replicators at both evaluations.

All data from the population were analyzed using the nonlinear mixed effects modeling program NONMEM version V, level 1.1. A one-compartment model with first-order elimination and intermittent infusion input was specified and used to determine the half-life (T½), volume of distribution (Vd) and clearance (CL) for each patient during specified time periods. For each group (Rr, Rn, and Nn), the Vd, T½, and CL were determined for four periods following transplantation; days 1-2, days 3-7, days 8-30, and for the period beyond 30 days. The Vd did not change significantly over time and there were no significant differences between the different groups based on replicator status. In contrast, the CL decreased and the T½ increased with time after transplantation for all patient groups. At all time points during the trial, the CL was greater, and the T½ was shorter among patients with measurable virus replication at the time of transplantation (See Table 3-2).

**Table 3-2: Comparison of pK Parameters by HBV Replication Status**

| pK Parameter | Period (Days) | Geometric Mean (GM) | | |
|---|---|---|---|---|
| | | Nn | Rn | Rr |
| Clearance (CL) (L/hr) | 1-2 | 0.070 | 0.134 | 3.260 |
| | 3-7 | 0.046 | 0.064 | 0.450 |
| | 8-30 | 0.014 | 0.014 | 0.024 |
| | >30 | 0.007 | 0.007 | 0.013 |
| Half-life (T½) (hr) | 1-2 | 59.1 | 27.3 | 0.7 |
| | 3-7 | 83.6 | 57.4 | 5.1 |
| | 8-30 | 266.2 | 270.2 | 123.4 |
| | >30 | 445.7 | 544.6 | 204.4 |
| Volume of Distribution (Vd) (L) | 1-2 | 5.99 | 5.29 | 3.31 |
| | 3-7 | 5.55 | 5.29 | 3.31 |
| | 8-30 | 5.55 | 5.29 | 4.23 |
| | >30 | 4.59 | 5.29 | 3.69 |

Pharmacodynamics were evaluated by analyzing paired serum HBsAg and anti-HBs titer samples to determine the lowest anti-HBs titers at which HBsAg was not detected for three different time intervals. During week one, HBsAg was present in 9/11 (82%) with anti-HBs < 300 IU/L vs. 1/44 (2%) with anti-HBs > 300 IU/L. In weeks two through twelve, HBsAg was present in 4/7 (57%) with anti-HBs < 200 IU/L. vs. 2/112 (2%) with levels > 200 IU/L ($p < 0.001$ for both comparisons). In weeks twelve through thirty-six HBsAg was not detected in 131 samples despite 4 titers < 100 IU/L and 16 titers < 300 IU/L. Based on these data, threshold trough titers of 300, 200 and 100 IU/L for each respective time period were used for further analysis.

In the first twelve weeks following transplantation, there was a significant difference between HBV replicative groups and the percentage of patients and titers less than the threshold titers outlined in Table 3-3. The difference remained significant between the Rr vs. (combined Rn + Nn) groups at all time points within the first twelve weeks. During the first four days post transplantation there was a trend towards a greater percentage of Rn compared to Nn patients to have titers below the threshold level. After Day 6, there were no patient from either group (Rr + Nn) who had any titers below the designated threshold levels. After week twelve, 1 of the 4 Rr patients had a single titer less than the threshold level. There were no significant differences in percentages of patients in any of the three groups with anti-HBs titers less than the threshold level.

**Table 3-3: Nabi-HB Pharmacokinetics with Concomitant Lamivudine**
**Number of Patients Below Specified Anti-HBs Levels [1]**

| Study Period | Anti HBs (IU/L) | Nn[2] Patients | Rn[3] Patients | Rr[4] Patients | HBsAg Recurrence |
|---|---|---|---|---|---|
| Day 1-2 | < 300 | 5/10 (50%) | 8/11 (73%) | 6/6 (100%) | 0 |
| Day 3-4 | < 300 | 1/9 (11%) | 3/11 (27%) | 6/6 (100%) | 0 |
| Day 5 | < 300 | 0/9 (0%) | 1/11 (9%) | 1/5 (20%) | 0 |
| Day 6-7 | < 300 | 0/9 (0%) | 0/11 (0%) | 2/6 (33%) | 0 |
| Day 8-30 | < 200 | 0/9 (0%) | 0/11 (0%) | 2/5 (40%) | 0 |
| Day 31-Week 12 | < 200 | 0/8 (0%) | 0/11 (0%) | 2/4 (50%) | 0 |
| Weeks 13-24 | < 100 | 0/7 (0%) | 0/10 (0%) | 1/4 (25%) | 0 |
| Weeks 25-36 | < 100 | 0/7 (0%) | 0/10 (0%) | 1/4 (25%) | 0 |

[1]Dickson RC, et al, Liver Transplantation 12:124-133, 2006
[2]Nn = Native non-replicators
[3]Rn = Native Replicators, who became non-replicators as a result of treatment
[4]Rr = Native Replicators, who remained replicators despite treatment

Anti-HBs trough values varied markedly between patients within the different replicator groups at the different time periods. The GM trough levels for the non-replicator groups were similar starting in week two (Table 3-4 and Figure 3-1). The Rr group GM trough anti-HBs levels were always less than those for the other two groups, and were significantly less during the first twelve weeks.

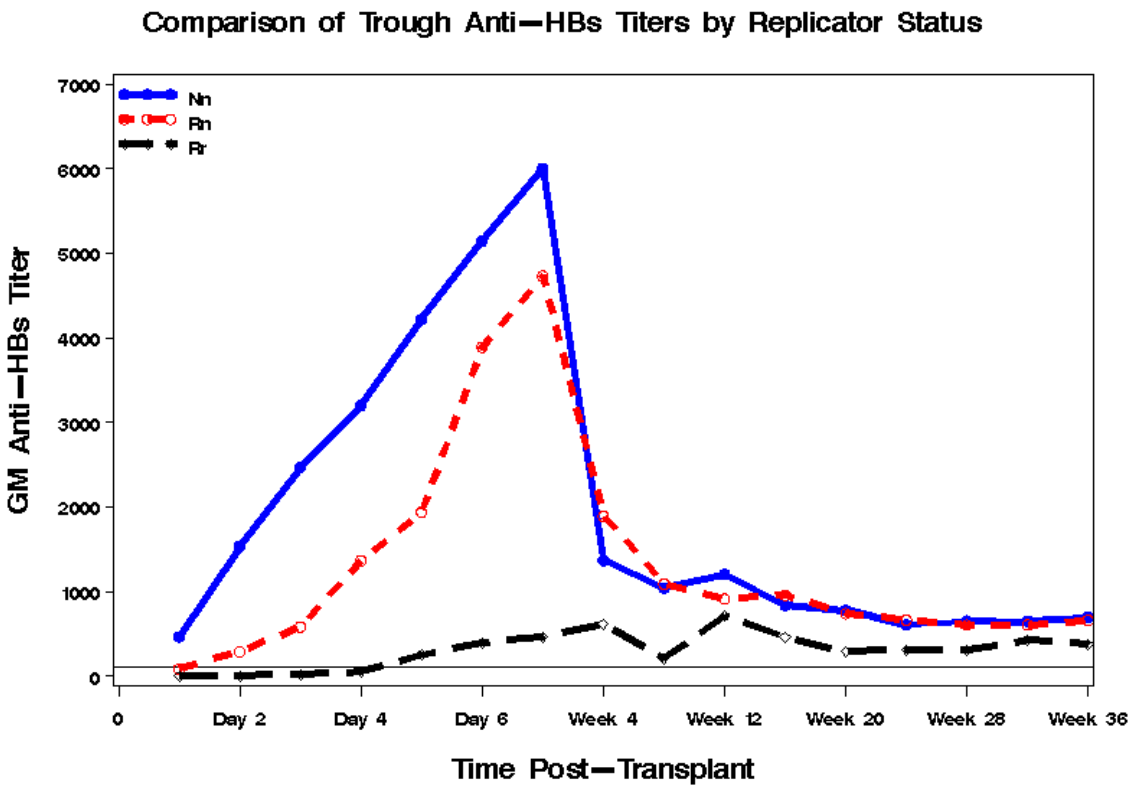
These data are consistent with observations by others showing an increased anti-HBs requirement when there is a large virus load and the need to carefully adjust the dose of HBIG to the patient's requirements.

**Table 3-4: Nabi-HB Pharmacokinetics with Concomitant Lamivudine**
**Comparison of Trough Anti-HBs Titers by Replicator Status[1]**

| | Number of Patients | | | GM Anti-HBs Titer | | |
|---|---|---|---|---|---|---|
| **Week 36** | **Nn[2]** | **Rn[3]** | **Rr[4]** | **Nn** | **Rn** | **Rr** |
| Day 1 | 10 | 11 | 6 | 467 | 89 | 4 |
| Day 2 | 10 | 11 | 5 | 1540 | 292 | 9 |
| Day 3 | 9 | 11 | 5 | 2417 | 586 | 20 |
| Day 4 | 9 | 11 | 6 | 3206 | 1370 | 51 |
| Day 5 | 9 | 11 | 5 | 4223 | 1943 | 253 |
| Day 6 | 9 | 11 | 5 | 5148 | 3895 | 394 |
| Day 7 | 8 | 11 | 6 | 6007 | 4734 | 469 |
| Week 4 | 9 | 11 | 5 | 1371 | 1896 | 615 |
| Week 8 | 8 | 11 | 4 | 1044 | 1093 | 213 |
| Week 12 | 7 | 10 | 4 | 1208 | 915 | 711 |
| Week 16 | 7 | 10 | 3 | 838 | 961 | 464 |
| Week 20 | 7 | 10 | 4 | 784 | 743 | 293 |
| Week 24 | 7 | 9 | 4 | 610 | 666 | 314 |
| Week 28 | 8 | 10 | 4 | 658 | 607 | 309 |
| Week 32 | 6 | 9 | 4 | 656 | 609 | 429 |
| Week 36 | 5 | 10 | 4 | 703 | 664 | 373 |

[1]Dickson RC, et al, Liver Transplantation 12:124-133, 2006
[2]Nn = Native non-replicators
[3]Rn = Native Replicators, who became non-replicators as a result of treatment
[4]Rr = Native Replicators, who remained replicators despite treatment

**Figure 3-1: Nabi-HB Pharmacokinetics with Concomitant Lamivudine**




Sample Sizes: Nn = 10, Rn = 11, Rr = 6

**Nn = Native Non-replicators**

**Rr = Native Replicators, who remained replicators despite treatment**

**Rn = Native Replicators, who became non-replicators as a result of treatment**

## 3.2 Comparison and Analyses of Results

### 3.2.1 Population pK Effect of Lamivudine on HBIG Clearance and Volume of Distribution

The pharmacokinetics of HBIG was studied by comparing Nabi protocols 4404 and 4204. The McGory study (Nabi-4404) evaluated intravenous HBIG as monotherapy, while in Nabi-4204, Nabi-HB IV and lamivudine was co-administered. Examination of the anti-HB titers obtained in these two studies provides a mechanism to evaluate the effect of lamivudine on HBIG pharmacokinetic parameters. A standard one-compartment pharmacokinetic model parameterized in terms of clearance and volume of distribution was used for the analysis

The analysis showed no significant effect from lamivudine on either clearance or volume of distribution parameters

### 3.2.2 Pharmacokinetic Comparison of Nabi-HB IV to 16.5% HBIG

A pharmacokinetics comparison of Nabi-4203 with McGory was also undertaken, as this study provided the initial rationale for the use of large and frequent doses of HBIG in transplant patients. Since these two studies were quite different in their designs, Nabi chose to demonstrate that there was no evidence of a difference between the two formulations. Using one- and two-compartment pharmacokinetics models, we defined, tested, and demonstrated that Nabi-HB IV and the 16.5% HBIG used in the McGory study were comparable by three key pharmacokinetics parameters, namely clearance (Cl), volume of distribution (Vd), and half-life ($T_{1/2}$) (see Table 3-5).

**Table 3-5: Nabi-4203 and The McGory Study**
**Comparison of Three Pharmacokinetics Parameters**

| | **Nabi-4203 mean ± std. dev.** | **McGory Study Mean ± std. dev.** | **p-value of t-test** |
|---|---|---|---|
| Nabi-4203: 2-compartment model; McGory Study: 1-compartment model | | | |
| Clearance | 0.220 ± 0.109 | 0.202 ± 0.295 | 0.79 |
| Volume | 4.99 ± 1.98 | 5.23 ± 8.09 | 0.90 |
| $T_{1/2}$ | 18.6 ± 5.85 | 15.9 ± 7.26 | 0.21 |
| Nabi- 4203: 1-compartment model; McGory Study: 1-compartment model | | | |
| Clearance | 0.226 ± 0.106 | 0.202 ± 0.295 | 0.72 |
| Volume | 4.30 ± 1.50 | 5.23 ± 8.09 | 0.61 |
| $T_{1/2}$ | 14.1 ± 3.2 | 15.9 ± 7.26 | 0.33 |

### 3.3 Summary of Pharmacokinetics

To summarize, Nabi-HB IV pharmacokinetic data in both new transplant and maintenance patients support the proposed dosing recommendations (McGory et al.[16] see figure 4 from paper). The comparison to the McGory study, which FDA had accepted as demonstrating efficacy, provides additional support.

## 4.0 Clinical Efficacy Studies

HBsAg has been accepted by the transplant community, by BPAC at the March 2004 meeting, and by FDA as the appropriate surrogate for recurrence of HBV-related liver disease in transplant patients. However, as there is an excellent correlation between HBsAg and clinical liver symptomatology, many transplant teams do not routinely measure HBsAg as long as the patient is clinically stable without symptoms of liver disease. Therefore, in our efficacy studies, we have typically longer clinical follow-up data than we have serology, for the simple reason that in many cases, if the patient was clinically well, HBsAg was not determined. As a result, we compiled databases for calculations of efficacy based on serology and on clinical status at last known clinical observation.

Two studies comprise the Nabi-HB IV database for new transplant patients, Nabi-4204 and Nabi-4409. Nabi-4204 was a prospective, well-conducted, NIH-funded, multi-center trial of HBV prophylaxis in patients undergoing OLT. Nabi-HB IV in combination with lamivudine was administered to determine anti-HBs titers required to neutralize HBsAg, to determine whether suppression of HBV replication by lamivudine prior to OLT affects Nabi-HB pharmacokinetics, and to evaluate the efficacy of lower dose Nabi-HB from 12 to 36 weeks post-transplantation. Dr. Rolland Dickson conducted the study under an investigator sponsored IND.[27]

All patients included in Nabi-4204 received Nabi-HB manufactured in Boca Raton, Florida. Most patients enrolled in Nabi-4204 continued indefinitely to receive both Nabi-HB (generally 5,000 IU monthly) and lamivudine.

Nabi-4409 was an open-label, expanded access study of Nabi-HB administered intravenously or intramuscularly to 153 liver transplant recipients. Twenty-six centers participated in the study. A total of 32 patients were newly transplanted, and 121 were maintenance-phase patients.

A listing of all HBsAg serology by patient is contained in Appendix 1, and a summary assessment pertaining to evaluability can be found in Appendix 2.

The demographic characteristics for the patients enrolled in the studies are displayed in Table 4-1 and Table 4-2. The patients were young adult to elderly, with mean age of 52 and 47 years in studies Nabi-4202 and Nabi-4409, respectively. The majority of the patients were male (85%) and Caucasian (54.7%).

**Table 4-1: Demographic Characteristics – Nabi-4204**

| **Nabi-HB Plus Lamivudine ([1]N=30)** | |
|---|---|
| **Age** | |
| Mean | 52 |
| STD | 8 |
| Max | 71 |
| Median | 51 |
| Min | 31 |
| **Height (cm)** | |
| Mean | 173 |
| STD | 10 |
| Max | 196 |
| Median | 173 |
| Min | 152 |
| **Weight (kg) Day 0** | |
| Mean | 81 |
| STD | 15 |
| Max | 123 |
| Median | 80 |
| Min | 56 |
| **Race** | |
| American Indian or Alaskan Native | 0(0.0) |
| Asian or Pacific Islander | 10(33.3) |
| Black, Not of Hispanic Origin | 2(6.7) |
| Hispanic | 1(3.3) |
| Caucasian, Not of Hispanic Origin | 15(50.0) |
| Other | 2(6.7) |
| **Sex** | |
| Female | 3(10.0) |
| Male | 27(90.0) |

[1] N (%)- Percent based on total number of patients within treatment group.

**Table 4-2: Demographic Characteristics – Nabi-4409**

| **Nabi-HB ([1]N=32)** | |
|---|---|
| **Age** | |
| Mean | 47 |
| STD | 10 |
| Max | 59 |
| Median | 50 |
| Min | 19 |
| **Height (cm)** | |
| Mean | 174 |
| STD | 9 |
| Max | 188 |
| Median | 174 |
| Min | 157 |
| **Weight (kg) Day 0** | |
| Mean | 75 |
| STD | 17 |
| Max | 123 |
| Median | 72 |
| Min | 49 |
| **Race** | |
| American Indian or Alaskan Native | 0(0.0) |
| Asian or Pacific Islander | 10(31.3) |
| Black, Not of Hispanic Origin | 2(6.3) |
| Hispanic | 1(3.1) |
| Caucasian, Not of Hispanic Origin | 15(59.4) |
| Missing | 4 |
| **Sex** | |
| Female | 6(18.8) |
| Male | 26(81.3) |

[1] N (%)- Percent based on total number of patients within treatment group.

The populations used in the statistical analyses consisted of the following:

1) The All Patients population, which included all patients who have been enrolled and were HBsAg negative after OLT.

2) The Modified All Patients population, which was a subset of patients from the All Patients population with a minimum of at least two year follow-up data on serology. This population was created in line with the recommendation from the March 2004 BPAC Meeting.

3) Clinically evaluable population, since the standard of care for patients who are shown to be HBsAg negative by several observations is to follow them clinically and obtain serology only when clinically indicated.

### 4.1 Counts of Patients with Recurrence –Evaluable Population

These analyses concern whether or not a recurrence occurred, but do not use the timing of recurrence or the duration of follow-up for those with no recurrence. Thus, the outcome is binary {event occurred: yes/no} and the analyses are by tables of counts. The chances of recurrence are the number of patients with this recurrence divided by the number of at-risk patients. These data yield an estimate of Nabi-HB IV efficacy, which is 100 times one minus the Nabi-HB IV-to-lamivudine ratio of the chances of recurrence. An overall efficacy estimate is based on simply pooling the data from the two studies.

The database for Nabi-4204, which began with 30 enrolled patients, is comprised of 24 evaluable patients. The table below (Table 4-3) summarizes the patients that were considered not evaluable, reducing our database from 30 patients to 24 patients. More information on the database is available in Appendices 1 and 2.

**Table 4-3: Database of Evaluable Patients for Nabi-4204**

| Database Began with 30 Patients | | |
|---|---|---|
| **Patient ID** | **Reason Subtracted from Total** | **New Total** |
| 4204-002006<br>4204-004002 | Patients died within 30 days after transplant | 28 |
| 4204-015001 | Nabi-HB was discontinued at 252 days for economic reasons | 27 |
| 4204-002005 | Nabi-HB was discontinued at 249 days for economic reasons | 26 |
| 4204-015004 | Patient has less than 2-years follow-up (lost to follow-up at 254 days) | 25 |
| 4204-002004 | Patient has less than 2-years follow-up (withdrew consent at 43 days) | 24 |
| **Therefore, the database for Nabi-4204 is Comprised of 24 Evaluable Patients** | | |

As shown in Appendices 1 and 2, twenty-four (24) of the 28 patients with an evaluable clinical endpoint were followed clinically for ≥ 2 years (mean 3.2 years). The 0% recurrence is less than 45%, the literature rate for recipients of lamivudine monotherapy (relative efficacy = 100%, two-sided p value <0.0001 for a one-sample binomial comparison to lamivudine recurrence rate of 0.45). (See Table 4-5).

The database for Nabi-4409, which began with 32 enrolled patients, is comprised of 17 evaluable patients. The table following (Table 4-4) summarizes the patients that were considered not evaluable, reducing our database from 32 patients to 17 patients. More information on the database is available in Appendices 1 and 2.

**Table 4-4: Database of Evaluable Patients for Nabi-4409**

| Database Began with 32 Patients | | |
|---|---|---|
| **Patient ID** | **Reason Subtracted from Total** | **New Total** |
| 4409-002001<br>4409-028005<br>4409-020002 | Patients died within 30 days after transplant | 29 |
| 4409-003013<br>4409-028004 | Patient was discovered on the day of transplantation to have been HBsAg-negative pre-transplant | 27 |
| 4409-010005<br>4409-010007 | Patient received a HBV-positive donor liver, but was not infected with HBV pre-transplantation | 25 |
| 4409-005007 | Patient received only 10 doses with the last dose given within 2 weeks after transplant: thereafter the patient was given lamivudine monotherapy | 24 |
| 4409-011001<br>4409-016005<br>4409-016015<br>4409-079001<br>4409-218001<br>4409-219008<br>4409-221001 | Patients had less than 2 years follow-up data available | 17 |
| **Therefore, the database for Nabi-4409 is Comprised of 17 Evaluable Patients** | | |

Ten of the 32 new transplant patients in Nabi-4409 received concomitant lamivudine therapy, and the remaining 22 received Nabi-HB IV monotherapy. Twenty-nine (29) patients (10 who received concomitant lamivudine therapy and 19 who received Nabi-HB IV monotherapy) survived 30 days post transplantation. Rather than comparing some of the patients in Nabi-4409 who received Nabi-HB monotherapy to an historical control recurrence rate of 80% (prior to use of HBIG monotherapy), all patients were assumed to have received Nabi-HB and concomitant lamivudine. This represents the most conservative scenario. Therefore, similar to what was done for the analysis of Nabi-4204, we compared efficacy for patients in Nabi-4409, having ≥ 2 years of follow-up, to the 45% recurrence rate of lamivudine monotherapy, rather than the 80% recurrence rate on no therapy. This conservative assumption raised the statistical threshold for this analysis.

There was 1 clinical recurrence among the 17 patients (5.9%), which is less than 45% for patients treated with lamivudine monotherapy (relative efficacy = 86.9%, two-sided p value = 0.0012 for a one-sample binomial comparison to the 45% recurrence rate of lamivudine monotherapy). (See Table 4-5).

For the combined Nabi-4204 and Nabi-4409 databases, there was 1 recurrence among the 41 patients who had clinical follow-up for at least 2 years post-transplantation. The

recurrence rate of 2.4% (1 of 41) was less than the 45% with lamivudine monotherapy (relative efficacy of 94.6%, p-value < 0.0001 for an exact, one-sample, two-sided test) (See Table 4-5).

**Table 4-5: Efficacy of Nabi-HB with Lamivudine Compared to Lamivudine Monotherapy for Evaluable Population[1]**

| Study | Recurrences (Relative Efficacy[2]) | p-value[3] |
|---|---|---|
| Nabi-4204 | 0/24 (100%) | < 0.0001 |
| Nabi-4409 | 1/17 (86.9%) | 0.0012 |
| Pooled | 1/41 (94.6%) | < 0.0001 |

[1]New OLT Patients with ≥ 2 Years of Clinical Follow-up
[2] Relative efficacy assuming lamivudine recurrent rate = 0.45 (details of lamivudine recurrence rate of 0.45 is provided in Section 5.3.2) .
[3]P-value is based on one-sample comparison of recurrent rate to Lamivudine recurrent rate of 0.45.

## 4.2 Counts of Patients with Recurrence – Modified All Patients Population

There were 18 patients remaining on the Nabi-4204 with at least two years of follow-up serology data. There were no recurrences. Again, the 0% recurrence rate is significantly less than 45% (relative efficacy = 100%, two-sided p value <0.0001 for a one-sample binomial comparison to a recurrent rate of 0.45 for lamivudine alone) (Table 4-6). The 18 patients were followed for a mean of 2.8 years.

Based on these data, it is clear that Nabi-HB in combination with lamivudine is superior to lamivudine monotherapy among new transplant recipients followed for at least 2 years. The superior efficacy is demonstrated independent of whether HBsAg seroconversion or clinical assessments are used as primary endpoints.

There were 11 patients remaining on the Nabi-4409 with at least two years of follow-up serology data. A listing of all HBsAg serology by patient, and a summary containing an assessment pertaining to evaluability outcome can be found in Appendices 1 and 2.

There was 1 recurrence among the 11 patients (9.0%), and this rate is less than 45%, (relative efficacy = 79.8%, two-sided p value = 0.028 for a one-sample binomial comparison to a recurrent rate of 0.45 for lamivudine alone) (Table 4-6).

For the pooled studies, there was 1 recurrence among the 29 patients who had serology follow-up for at least 2 years The observed recurrence rate of 3.4% (1 of 29) was statistically significantly less than the 45% with lamivudine monotherapy (relative efficacy 92.3%, p-value < 0.0001 by an exact, one-sample, two-sided test) (Table 4-6).

The data from the two studies indicate low recurrence of HBV (3.4%), which is comparable to the 7.4% recurrent rate reported by McGory, in patients treated with 10,000 IU of 16.5% HBIG for periods of 2 to 55 months. Adding maintenance-phase patients (see Table 4-7) to the denominator of patients who received Nabi-HB IV; the overall recurrence rate is 0.5%.

**Table 4-6: Efficacy of Nabi-HB with Lamivudine Compared to Lamivudine Monotherapy for Modified All Patients Population[1]**

| Study | Recurrences (Relative Efficacy[2]) | p-value[3] |
|---|---|---|
| Nabi-4204 | 0/18 (100%) | < 0.0001 |
| Nabi-4409 | 1/11 (79.8%) | 0.028 |
| Pooled | 1/29 (92.3%) | < 0.0001 |

[1]New OLT Patients with HBsAg Serology ≥ 2 years.
[2] Relative efficacy assuming lamivudine recurrent rate = 0.45 (details of lamivudine recurrence rate of 0.45 is provided in Section 5.3.2).
[3]P-value is based on one-sample comparison of recurrent rate to lamivudine recurrent rate of 0.45.

**Table 4-7: Seroconversion Results from Maintenance-Phase Studies**

| Study | Number of Patients | Type of Study | Recurrence(%) |
|---|---|---|---|
| Nabi-4203 | 21 | Maintenance-Phase | 0 (0) |
| Nabi-2906 | 21 | Maintenance-Phase | 0 (0) |
| Nabi-4406 | 10 | Maintenance-Phase | 0 (0) |
| Nabi-4409 | 121 | Maintenance-Phase | 0 (0) |

## 4.5 Summary

Due to the evidence that supports the efficacy of lamivudine, this antiviral is now included as standard of care in most transplant centers. Therefore, it is no longer possible to conduct monotherapy studies to evaluate efficacy of new drugs in patients with chronic HBV-related ESLD undergoing liver transplantation. However, with a baseline lamivudine monotherapy recurrence probability of 45%, as shown by the meta-analysis of the literature, it is feasible to evaluate a drug or therapy expected to provide a clinically meaningful (e.g. > 20%) decrement in that probability relative to lamivudine monotherapy.

In Nabi-4204, there was no recurrence (assessed by serology or clinical follow-up) among the patient populations utilized in the analysis for new liver transplant recipients who received Nabi-HB and concomitant lamivudine. In Nabi-4409, there was one recurrence among the patient populations utilized in the analysis for new transplant patients. Compared to lamivudine monotherapy, each study independently, and combined in a meta-analysis, using either HBsAg serology or clinical assessments for well beyond 2 years (as recommended by BPAC at the March 2004 meeting) provides an adequate database to demonstrate the statistically significant efficacy of Nabi-HB IV**.** The table below (Table 4-8) shows that the Nabi-HB IV database exceeds that needed to show efficacy, based on the historical recurrences rates described in the next section. These data are supported by the data in maintenance patients as well as the extensive off-label use of Nabi-HB (described in Section 6.0). Among newly transplanted and maintenance-phase transplant recipients, the overall efficacy was 92-98%.

**Table 4-8: Number of Patients Required to Statistically Compare Nabi-HB to no Therapy or to Lamivudine Monotherapy (Sample Size Calculations)**

| **Nabi-HB IV Monotherapy: One-Year Recurrence Probabilities** | | | | | |
|---|---|---|---|---|---|
| **No Therapy** | 0.30 | 0.20 | 0.20 | 0.05 | 0.03 |
| 0.80 | 9 | 6 | 4 | 3 | 3 |
| **Nabi HB IV: Two-Year Recurrence Probabilities** | | | | | |
| **lamivudine** | 0.30 | 0.20 | 0.20 | 0.05 | 0.03 |
| 0.60 | 22 | 13 | 7 | 6 | 4 |
| 0.50 | 50 | 20 | 12 | 9 | 6 |
| 0.45 | 70 | 32 | 15 | 10 | 8 |
| 0.40 | 191 | 44 | 18 | 12 | 11 |
| 0.30 | -- | 151 | 36 | 21 | 17 |

Single-group sample size needed to compare a proportion to a standard. Tests are two-sided, with type I error 5% and power 80%.

## 5.0 Historical Control Calculation

### 5.1 Criteria

A literature search for articles on treatment of hepatitis B in liver transplantation from 1980 to 2005 resulted in 36 potential articles that were then reviewed for potential inclusion in this meta-analysis. Articles were selected based on 1) being an original study of patients transplanted due to end-stage hepatitis B-related liver disease, 2) containing data on relevant disease markers (principally HBsAg), 3) patients receiving lamivudine monotherapy, and 4) patients having at least 2 years of follow-up. Five articles (Anselmo, et al. [22], Bain, et al. [23], Chan, et al. [24], Mutimer, et al. [25] and Perrillo, et al. [26]) qualified for the meta-analysis.

We determined the proportion of patients who were HBsAg-positive at ≥104 weeks (two years) in the articles. Patients failure counts refer to patients who:

- had an OLT, and
- died >30 days post x-plant, or
- were HBsAg negative after OLT and then seroconverted

A brief summary including the baseline demographics (age, ethnicity, and replicative status), duration of follow-up, HBsAg serology, and outcomes for each of five original studies that reported lamivudine monotherapy of OLT is provided in Section 5.2. The meta-analysis of the 2-year HBV-liver disease recurrence with lamivudine monotherapy from the studies is presented in Table 5-1.

## 5.2 Narratives of the Five Articles Used for Inclusion in the Meta-Analysis

### 5.2.1 Anselmo, Ghobrial, *et al.* [2002] [22]

This was a retrospective review of 166 (136 male, 30 female) OLT recipients transplanted for HBV-related end-stage liver disease at UCLA over a 17-year period (1984-2001). The median age was 49 years (range 12-73 years). The median follow-up time was 29 months (range 4-204 months). Patients were categorized according to post-transplant treatment. Prior to OLT, all patients were HBsAg-positive, 43 were HbeAg positive, and 23 of 89 patients tested by dot-blot hybridization were HBV DNA-positive. In total, 55 of 142 patients tested, (24 of the 166 patients were not included because the data on markers of pre-transplant viral replication status was not available), showed evidence of active viral replication prior to OLT. Lamivudine monotherapy was given to 20/166 patients (12%). The two-year Kaplan-Meier estimate of the recurrence rate in Figure 1 shows approximately 65%. Among the 20 lamivudine monotherapy patients with two-year follow up, there was 65% recurrence.

### 5.2.2 Bain, Kneteman, *et al.* [1996] [23]

A total of 5 patients were enrolled in this prospective study at one transplant center in Canada from 1994-1995. Pre-OLT, all patients were HBsAg-positive, HBV DNA-positive, and HCV-negative. One patient (patient #2) did not have an OLT. Of the four OLT recipients, patient # 1, a 43 year old Asian male, was HBsAg-negative at 26 months; patient #3, a 55 year old Asian male, seroconverted to HBsAg-positive at 12 months; patient #4, a 40 year old Caucasian female, remained HBsAg-positive through 14 months; and patient #5, a 66 year old Caucasian male, was HBsAg-negative at 3 months. Thus, for the 3 patients with 24-month data, there were 2/3 (67%) recurrences by 24 months.

### 5.2.3 Chan, Chui, *et al.* [2004] [24]

Twenty-three (23) consecutive patients scheduled for transplantation at Prince of Wales Hospital, Hong Kong were enrolled in the study. Pre-OLT, all patients were HBsAg-

positive, and one was HCV-positive. Three patients died within the first 4 weeks after transplantation and are excluded. Twenty (20) OLT recipients (17 male, 3 female), were followed over the 3-year study period, (1999-2002). The median follow-up time was 94 weeks. The median age at OLT was 50.5 years (range 33-61 years). Pre-transplant, 10 of 20 patients were HBeAg positive, and 7 of the 15 tested were HBV DNA-positive. All 20 patients received 100 mg lamivudine daily before and after transplantation. HBsAg and HBV DNA were regularly monitored. Six patients developed YMDD mutants (lamivudine resistant HBV mutants at the YMDD motif of the polymerase genome) and seroconverted. The authors state that 6/20 had recurrence at two years [by YMDD].

### 5.2.4 Mutimer, Dusheiko, *et al*. [2000] [25]

Twenty-three (23) candidates for OLT were enrolled in this prospective study conducted from 1994-1998 at 2 transplant centers in England. All patients had chronic HBV, and were HCV, HDV, and HIV-negative. A total of 13/23 patients were HBV DNA-positive. Seventeen patients, (16 male and 1 female), received OLT. The median age pre-OLT was 49 (range 29-62) years. All were HBsAg-positive, 11/17 were HBeAg-positive, and 9/17 were HBV DNA-positive. Of these, 4 died without evidence of recurrence. One patient withdrew consent at week 36, but had no evidence of recurrence at the time he/she was dropped from the study. Two of the remaining 12 patients died (at 19 and 23 months post OLT) and both had recurrence. Of the remaining 10, the median duration of follow-up was 37 months. Two patients developed recurrence at 9 and 15 months post OLT, and one became HBsAg positive (but did not have evidence of the YMDD mutant). Thus, there was recurrence in 5/12 (42%).

### 5.2.5 Perrillo, Wright, *et al*. [2001] [26]

A total of 77 transplant candidates were enrolled in this prospective study conducted from 1995-2000 in 10 transplant centers in the United States and Canada. Thirty (30) patients were not transplanted. Of the 47 patients, (39 male, 8 female), who were transplanted, the median age was 49 years, (range 30-67 years). Pre-transplant, all patients were HBsAg-positive, 26 were HBV DNA-negative, and 24 were HBeAg positive. Ten subjects did not complete 1-year follow-up (6 deaths and 4 lost to follow-up). Including the 10 patients who died or were loss to follow-up, there was recurrence in 16/39=41% at two years.

**Table 5-1: Meta-Analysis of 2-Year HBV-Liver Disease Recurrence With Lamivudine Monotherapy**

| Study | N | Recurrence |
|---|---|---|
| Anselmo | 13/20 | 65% |
| Bain | 2/3 | 67% |
| Chan | 6/20 | 30% |
| Mutimer | 5/12 | 42% |
| Perrillo | 16/39 | 41% |
| **Total** | **42/94** | **45%** |

## 5.3 Meta-Analysis for Determination of Recurrence Rate for Lamivudine Monotherapy

### 5.3.1 Technical Methods for Meta-analysis

Suppose that there are K single-arm studies, with sample size $n_i$ and estimated HBV recurrence probability $p_i$ in study i. We assume that the design of the studies is similar enough that it makes sense to pool the recurrence probability estimates across studies.

The pooled estimate of the recurrence probability is $p^* = \Sigma w_i p_i / \Sigma w_i$ summed over studies. For each study, $w_i$ is a weight that reflects the size and precision of the estimated probability of recurrence. If $v_i$ is the variance of the estimated probability in study i, then

$$\mathrm{Var}(p^*) = \Sigma w_i^2 v_i / (\Sigma w_i)^2$$

If furthermore, $w_i = 1/v_i$, so that weights are inverse to each result's variance, we have the results that

$$\mathrm{Var}(p^*) = 1 / (\Sigma(1/v_i)) = 1 / \Sigma(n_i / p_i(1-p_i))$$

and

$$p^* = (\Sigma n_i/(1-p_i)) / (\Sigma n_i/p_i(1-p_i))^2$$

The 100(1-α)% confidence interval for p* is given by

$$p^* - z_{\alpha/2}\sqrt{\mathrm{Var}(p^*)} \leq p^* \leq p^* + z_{\alpha}\sqrt{\mathrm{Var}(p^*)},$$

where $z_{\alpha/2}$ is the two-sided critical value of the standard normal distribution at significance level α.

### 5.3.2 Meta-analysis Results

The meta-analysis demonstrates a 45% (95% confidence interval of 0.35 to 0.54) rate of recurrence for HBsAg-positive OLT recipients treated with lamivudine monotherapy and followed for at least 2 years. The 45% rate of recurrence is used as the reference recurrence rate from the literature at two years. Efficacy of combination Nabi-HB IV and lamivudine therapy is calculated by comparison to the 55% (1-0.45) efficacy from the literature references above.

## 6.0 Safety

A total of 324 adverse events were reported among the 206 patients. Of the 324 adverse events, 46% (150) were considered mild, 35% (113) moderate, 18% (59) severe in intensity and 1% (2) were of unknown intensity. The most frequently reported adverse event was back pain, which occurred in 6% of patients for a total of 37 episodes (11% of all adverse events). The other most frequently occurring adverse events were nausea (5% of patients for 15 episodes), sepsis (3% of patients for 6 episodes), leg pain (2% of patients for 8 episodes), fatigue (2% of patients for 6 episodes), headache (2% of patients for 6 episodes), hepatic failure (2% of patients for 5 episodes), and abnormal liver function tests (2% of patients for 5 episodes). Among the 324 adverse events, 38 were multiple recordings of the same adverse event (e.g., SID 2906-005003 had 5 records for back pain). Discounting the repeat records, there were 285 adverse events. When adverse events were analyzed with respect to the relationship to the study product, only 22% (71/324) were considered related to the medication (including cases in which relationship to study product was “unknown”). The most frequently reported adverse events related to the study product were back pain (32 events), leg pain (7 events), and nausea (6 events). All episodes of related adverse events resolved.

A total of 46 serious adverse events were recorded during the clinical program. Only one (2%) of these events, (a case of moderate chest pain reported for a patient enrolled in Nabi-2906), was considered related to administration of study product. This event was similar in nature to the back pain experienced by the same patient during and after infusions of study product; myocardial infarction was ruled out. The most frequent serious adverse events were sepsis (six episodes), hepatic failure (three episodes), and gastrointestinal hemorrhage (three episodes).

A total of eight patients (4%) died during these clinical studies. However, all deaths in this very ill patient population were considered by the investigators to have no causal relationship to the study product. The causes of death were sepsis (four patients), acute upper gastrointestinal hemorrhage (one patient), intra-cranial hemorrhage (one patient), and hepatic failure (one patient), all of which are not unexpected in this patient population.

In general, no clinically meaningful changes in laboratory parameters or vital signs were noted upon administration of Nabi-HB.

Taken together, these safety results demonstrate that intravenous administration of Nabi-HB is safe and well tolerated in transplant recipients who had undergone transplantation due to hepatitis B-related liver failure. Moreover, the adverse event profile obtained during these clinical investigations is consistent with that reported previously for intravenous administration of human hepatitis B immune globulin. Thus, the safety results from these clinical trials provide evidence that Nabi-HB IV administered in doses of approximately 10,000 IU is safe and well tolerated in liver transplant recipients who have undergone transplantation due to hepatitis B-related liver failure.

Since Nabi-HB® for post-exposure prophylaxis (administered by intramuscular injection) received marketing approval in 1999, there have been 30 adverse events (among 16 patients) reported to Nabi. Twenty-one (21) adverse events in 13 patients were for Nabi-HB administered by intravenous infusion. To put this in context, Nabi estimates that approximately 60,000 intravenous infusions of Nabi-HB, generally 10,000 IU per administration, have been given since 1999.

Nabi believes that the occurrence of anti-HCV in a Chinese patient (58-year old Chinese female in 2002 living in Hong Kong at the time of the report - report No. 234-2002-0001) was not related to Nabi-HB. This patient had hepatocellular carcinoma and end-stage liver disease resulting in a need for liver transplantation. Unfortunately, there were no PCR tests for HCV RNA prior to transplantation, nor were there any tests on the donor organ. In addition to the seven 10,000 IU doses of Nabi-HB administered following transplantation, the patient was also administered eight units of albumin. It is not known whether any other blood products were administered. All plasma used to make Nabi-HB is determined to be HCV-negative by PCR. Given this patient's ethnic background (there is a high incidence of hepatitis C (HCV) among Chinese, and a high incidence of HCV and HBV co-infection), the history of ESLD with hepatocarcinoma, and the HCV PCR screening of all plasma used in manufacture of Nabi-HB, Nabi believes the positive HCV PCR in this patient was <u>not</u> due to the Nabi-HB.

One patient had a pulmonary embolism considered to be possibly related to Nabi-HB administration, and 1 episode each of back pain and rigors, which was considered to be probably related. The remainder of the reports includes events such as nausea, vomiting, and myalgias, adverse events consistent with those reported for other immune globulins administered intravenously. The paucity of reports among an estimated 60,000 infusions speaks to the safety profile of IV administration of Nabi-HB. The adverse event rate (without regard to whether the adverse events are truly related to Nabi-HB IV) is 0.04% (21/60,000).

In Nabi's post marketing experience no patient discontinued Nabi-HB due to anaphylaxis or an anaphylactoid reaction.

## 7.0 Risk/Benefit

### 7.1 Risk

The safety results demonstrate that intravenous administration of Nabi-HB is safe and well tolerated in transplant recipients who have undergone transplantation due to hepatitis B-related liver failure.

In the five trials of intravenous administration of the product (Nabi-2906, -4406, -4409, -4203, and -4204), 206 patients received a total of 1,320 infusions of Nabi-HB IV. The data base safety is substantial and more than adequate to establish that Nabi-HB IV is safe and well-tolerated in this population, particularly in light of the relatively small number of transplant procedures performed in hepatitis B positive patients.

Additionally, Nabi-HB has been used widely off-label for prevention of recurrent hepatitis B-related clinical disease in liver transplant recipients in the US since its approval in 1999 (estimated 60,000 infusions). Upon examination of the patient population no significant demographic trends were noted. The paucity of reports of adverse events (and lack of treatment failures) provides further support for the safety (and efficacy) of Nabi-HB IV.

### 7.2 Benefit

Nabi believes that this information provided to FDA and BPAC provides overwhelming evidence of efficacy and safety supporting the approval of Nabi-HB IV. When used concomitantly with lamivudine, efficacy was enhanced compared to historical rates and the safety profile was not affected. This is an important result as antiviral therapy is routinely used by physicians for the treatment of HBV infection and any adverse effects of this concomitant treatment would be detrimental to the acceptability and use of Nabi-HB IV.

Furthermore, since Nabi-HB is not approved for intravenous administration to liver transplant patients, Nabi has not been able to adequately guide the healthcare professional on safety issues pertaining to this route of administration and for this patient population. In this regard, we would like to bring attention to two recent publications emphasizing the importance of life-long treatment with Nabi-HB. In both papers, clinicians tried to discontinue Nabi-HB in the maintenance phase, mostly for cost and convenience reasons. The data underlying one of the papers, Dickson et al., (Nabi-4204), is discussed in detail elsewhere in this submission. The other is titled "*Importance of Continued Hepatitis B Immunoglobulin in Preventing Reinfection Following Liver Transplantation*", Hayashi MS, Cooke J, Imagawa DK: HBIG ILTS Abstract; 2006.[21] This abstract reviewed medical records of OLT for HBV-related ESLD in 20 patients who underwent liver transplantation due to hepatitis B disease from 1996 to 2001. The data demonstrate that Nabi-HB IV must be administered for life, in combination therapy, since later recurrences do occur at a very high rate. In that study, 5 patients discontinued Nabi-HB in the

maintenance phase, predominantly due to the cost of treatment. In the 4/5 patients who were evaluable for follow-up, 3/4 developed recurrent severe hepatitis B infection despite continued treatment with lamivudine. All three patients were non-replicators, which illustrates that at least for the time being, all hepatitis B positive liver transplant patients needs long-term (probably indefinite) treatment with HBIG as well as antivirals. This recent information provides strong support for our position that Nabi-HB IV should be administered with antivirals on a chronic basis, and that monotherapy with antivirals is inadequate.

Despite the small number of patients included in this submission, the data provides overwhelming support for the efficacy of Nabi-HB in preventing HBV recurrence in new and maintenance-phase liver transplant recipients. The data clearly demonstrate statistically significant and clinically relevant efficacy of Nabi-HB and concomitant lamivudine for patients followed for at least 2 years, meet or exceed recommendations from BPAC, and thus support approval of Nabi-HB for the indication of "prevention of hepatitis B clinical disease in HBsAg-positive liver transplant recipients." The Nabi-HB IV database is based on both new and maintenance phase patients and exceeds that used for regulatory approval of a number of other orphan drug indications. Recently, Genzyme's Myozyme was approved based on a single open-label study of 18 patients.

Although the risk/benefit ratio for Nabi-HB IV is very favorable, Nabi is committed to provide additional scientifically rigorous evaluation of the use of Nabi-HB in preventing HBV-related disease. Post-approval, Nabi will conduct an additional well-controlled study to corroborate efficacy data presented thus far, for use of Nabi-HB IV and concomitant antiviral therapy to prevent recurrence of HBV-related liver disease. The approximately 50 patients study will be similar in design to Nabi-4204 and will prospectively follow transplant recipients for a minimum of 2 years post-transplantation.

Finally, although the EMEA has issued guidance on how hepatitis B immune globulin should be administered, the lack of similar guidance in the US places Americans who receive transplants due to hepatitis B at continuing risk. Requiring an additional study pre-approval to replicate the results already obtained in the Dickson study would prevent Nabi from providing definitive dosing guidance to hepatitis B transplant recipients for approximately five years.

## 8.0 Appendices

Appendix 1-Patient Listings Nabi-4204 and Nabi-4409

Appendix 2-Patient Summaries Nabi-4204 and Nabi-4409

## 9.0 References

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**Appendix 1**

**Patient Listings Nabi-4204 and Nabi-4409**

| SID | Test Date | Xplant Date | Test - Xplant (Days) | HBsAg | Anti HBs | HBV DNA | Death |
|---|---|---|---|---|---|---|---|
| 4204-001001 | 19-Dec-99 | 19-Dec-99 | 0 | Positive | Positive | <5.00 | |
| 4204-001001 | 21-Dec-99 | 19-Dec-99 | 2 | Negative | | | |
| 4204-001001 | 4-Jan-00 | 19-Dec-99 | 16 | Negative | | | |
| 4204-001001 | 10-Jan-00 | 19-Dec-99 | 22 | Negative | | | |
| 4204-001001 | 17-Jan-00 | 19-Dec-99 | 29 | Negative | | | |
| 4204-001001 | 14-Feb-00 | 19-Dec-99 | 57 | Negative | | | |
| 4204-001001 | 13-Mar-00 | 19-Dec-99 | 85 | Negative | | | |
| 4204-001001 | 10-Apr-00 | 19-Dec-99 | 113 | Negative | | | |
| 4204-001001 | 5-Jun-00 | 19-Dec-99 | 169 | Negative | | | |
| 4204-001001 | 31-Jul-00 | 19-Dec-99 | 225 | Negative | | | |
| 4204-001001 | 28-Aug-00 | 19-Dec-99 | 253 | Negative | | | |
| 4204-001001 | 15-Jan-01 | 19-Dec-99 | 393 | Negative | 7124 | | |
| 4204-001001 | 12-Mar-01 | 19-Dec-99 | 449 | | 14138 | < 142 | |
| 4204-001001 | 15-May-01 | 19-Dec-99 | 513 | | 8330 | | |
| 4204-001001 | 18-Jun-01 | 19-Dec-99 | 547 | | 8275 | | |
| 4204-001001 | 19-Feb-02 | 19-Dec-99 | 793 | Negative | Positive | < 142 | |
| 4204-001001 | 25-Mar-02 | 19-Dec-99 | 827 | | 10796 | | |
| 4204-001001 | 29-Apr-02 | 19-Dec-99 | 862 | | 6095 | | |
| 4204-001001 | 10-Jun-02 | 19-Dec-99 | 904 | | 14664 | | |
| 4204-001001 | 29-Jul-02 | 19-Dec-99 | 953 | | 9100 | | |
| 4204-001001 | 16-Sep-02 | 19-Dec-99 | 1002 | | 12530 | | |
| 4204-001001 | 10-Feb-03 | 19-Dec-99 | 1149 | | 6771 | | |
| 4204-001001 | 14-Apr-03 | 19-Dec-99 | 1212 | Negative | Positive | < 141.5 | |
| 4204-001001 | 20-Mar-04 | 19-Dec-99 | 1553 | Negative | < 8303 | < 357 | |
| **4204-001001** | **20-Mar-04** | **19-Dec-99** | **1553** | **Negative** | | | |
| 4204-001002 | 30-Nov-99 | 6-Feb-00 | -68 | Positive | Negative | <5.00 | |
| 4204-001002 | 6-Feb-00 | 6-Feb-00 | 0 | | | <5.00 | |
| 4204-001002 | 13-Feb-00 | 6-Feb-00 | 7 | Negative | | | |
| 4204-001002 | 21-Feb-00 | 6-Feb-00 | 15 | Negative | | | |
| 4204-001002 | 28-Feb-00 | 6-Feb-00 | 22 | Negative | | | |
| 4204-001002 | 6-Mar-00 | 6-Feb-00 | 29 | Negative | | | |
| 4204-001002 | 3-Apr-00 | 6-Feb-00 | 57 | Negative | | | |
| 4204-001002 | 1-May-00 | 6-Feb-00 | 85 | Negative | | | |
| 4204-001002 | 29-May-00 | 6-Feb-00 | 113 | Negative | | | |
| 4204-001002 | 28-Jun-00 | 6-Feb-00 | 143 | Negative | | | |
| 4204-001002 | 24-Jul-00 | 6-Feb-00 | 169 | Negative | | | |
| 4204-001002 | 21-Aug-00 | 6-Feb-00 | 197 | Negative | | | |
| 4204-001002 | 18-Sep-00 | 6-Feb-00 | 225 | Negative | | | |
| 4204-001002 | 16-Oct-00 | 6-Feb-00 | 253 | Negative | | | |
| 4204-001002 | 5-Feb-01 | 6-Feb-00 | 365 | | 1448 | | |
| 4204-001002 | 12-Mar-01 | 6-Feb-00 | 400 | Negative | | | |
| 4204-001002 | 13-Mar-01 | 6-Feb-00 | 401 | | 77 | | |
| 4204-001002 | 9-Apr-01 | 6-Feb-00 | 428 | | | < 142 | |
| 4204-001002 | 7-May-01 | 6-Feb-00 | 456 | | 146 | | |
| 4204-001002 | 26-Feb-02 | 6-Feb-00 | 751 | Negative | 80 | < 142 | |
| 4204-001002 | 11-Mar-02 | 6-Feb-00 | 764 | | 88 | | |
| 4204-001002 | 29-Apr-02 | 6-Feb-00 | 813 | | 70 | | |
| 4204-001002 | 7-May-02 | 6-Feb-00 | 821 | | 14 | | |
| 4204-001002 | 3-Aug-02 | 6-Feb-00 | 909 | | 40 | | |
| 4204-001002 | 15-Aug-02 | 6-Feb-00 | 921 | | 107 | | |
| 4204-001002 | 5-Nov-02 | 6-Feb-00 | 1003 | | 35 | | |
| 4204-001002 | 3-Dec-02 | 6-Feb-00 | 1031 | | 21 | | |

| SID | Test Date | Xplant Date | Test - Xplant (Days) | HBsAg | Anti HBs | HBV DNA | Death |
|---|---|---|---|---|---|---|---|
| 4204-001002 | 10-Feb-03 | 6-Feb-00 | 1100 | | 31 | | |
| 4204-001002 | 28-Feb-03 | 6-Feb-00 | 1118 | Negative | | < 470 | |
| 4204-001002 | 3-Feb-04 | 6-Feb-00 | 1458 | Negative | | | |
| 4204-001002 | 6-Jul-04 | 6-Feb-00 | 1612 | | 66 | | |
| **4204-001002** | **6-Jul-04** | **6-Feb-00** | **1458** | **Negative** | **66** | | |
| 4204-001003 | 23-Jun-00 | 6-Jul-00 | -13 | Positive | Negative | 10 | |
| 4204-001003 | 6-Jul-00 | 6-Jul-00 | 0 | | | <5.00 | |
| 4204-001003 | 8-Jul-00 | 6-Jul-00 | 2 | Positive | | | |
| 4204-001003 | 13-Jul-00 | 6-Jul-00 | 7 | Negative | | | |
| 4204-001003 | 20-Jul-00 | 6-Jul-00 | 14 | Negative | | | |
| 4204-001003 | 27-Jul-00 | 6-Jul-00 | 21 | Negative | | | |
| 4204-001003 | 3-Aug-00 | 6-Jul-00 | 28 | Negative | | | |
| 4204-001003 | 31-Aug-00 | 6-Jul-00 | 56 | Negative | | | |
| 4204-001003 | 28-Sep-00 | 6-Jul-00 | 84 | Negative | | | |
| 4204-001003 | 27-Dec-00 | 6-Jul-00 | 174 | Negative | | | |
| 4204-001003 | 24-Jan-01 | 6-Jul-00 | 202 | Negative | | | |
| 4204-001003 | 21-Feb-01 | 6-Jul-00 | 230 | Negative | | | |
| 4204-001003 | 21-Mar-01 | 6-Jul-00 | 258 | Negative | | | |
| **4204-001003** | **21-Mar-01** | **6-Jul-00** | **258** | **Negative** | | | |
| 4204-001004 | 15-Dec-00 | 20-Jan-01 | -36 | Positive | | | |
| 4204-001004 | 19-Dec-00 | 20-Jan-01 | -32 | | | 142000 | |
| 4204-001004 | 21-Dec-00 | 20-Jan-01 | -30 | | Not Done | | |
| 4204-001004 | 20-Jan-01 | 20-Jan-01 | 0 | | | 142000 | |
| 4204-001004 | 22-Jan-01 | 20-Jan-01 | 2 | Negative | | | |
| 4204-001004 | 27-Jan-01 | 20-Jan-01 | 7 | Negative | | | |
| 4204-001004 | 3-Feb-01 | 20-Jan-01 | 14 | Negative | | | |
| 4204-001004 | 10-Feb-01 | 20-Jan-01 | 21 | Negative | | | |
| 4204-001004 | 16-Feb-01 | 20-Jan-01 | 27 | Negative | | | |
| 4204-001004 | 17-Mar-01 | 20-Jan-01 | 56 | | Positive | | |
| **4204-001004** | **17-Mar-01** | **20-Jan-01** | **27** | **Negative** | **Positive** | | 18-Mar-01 |
| 4204-001005 | 26-Oct-00 | 23-Jan-01 | -89 | Positive | Positive | 142000 | |
| 4204-001005 | 23-Jan-01 | 23-Jan-01 | 0 | | | 142000 | |
| 4204-001005 | 25-Jan-01 | 23-Jan-01 | 2 | Positive | | | |
| 4204-001005 | 30-Jan-01 | 23-Jan-01 | 7 | Negative | | | |
| 4204-001005 | 5-Feb-01 | 23-Jan-01 | 13 | Negative | | | |
| 4204-001005 | 12-Feb-01 | 23-Jan-01 | 20 | Negative | | | |
| 4204-001005 | 16-Feb-01 | 23-Jan-01 | 24 | Negative | | | |
| 4204-001005 | 19-Mar-01 | 23-Jan-01 | 55 | Negative | | | |
| 4204-001005 | 14-May-01 | 23-Jan-01 | 111 | Negative | | | |
| 4204-001005 | 11-Jun-01 | 23-Jan-01 | 139 | Negative | | | |
| 4204-001005 | 9-Jul-01 | 23-Jan-01 | 167 | Negative | | | |
| 4204-001005 | 6-Aug-01 | 23-Jan-01 | 195 | Negative | | | |
| 4204-001005 | 4-Sep-01 | 23-Jan-01 | 224 | Negative | | | |
| 4204-001005 | 1-Oct-01 | 23-Jan-01 | 251 | Negative | | | |
| 4204-001005 | 7-Jan-02 | 23-Jan-01 | 349 | Negative | 14 | | |
| 4204-001005 | 29-Apr-02 | 23-Jan-01 | 461 | | Positive | | |
| 4204-001005 | 14-May-02 | 23-Jan-01 | 476 | Negative | | | |
| 4204-001005 | 23-Dec-02 | 23-Jan-01 | 699 | | 5340 | | |
| **4204-001005** | **23-Dec-02** | **23-Jan-01** | **476** | **Negative** | **5340** | | |
| 4204-001006 | 13-Dec-00 | 23-Mar-01 | -100 | | Negative | 1176.3 | |
| 4204-001006 | 14-Dec-00 | 23-Mar-01 | -99 | Positive | | | |
| 4204-001006 | 23-Mar-01 | 23-Mar-01 | 0 | | | 142000 | |

| SID | Test Date | Xplant Date | Test - Xplant (Days) | HBsAg | Anti HBs | HBV DNA | Death |
|---|---|---|---|---|---|---|---|
| 4204-001006 | 25-Mar-01 | 23-Mar-01 | 2 | Negative | | | |
| 4204-001006 | 30-Mar-01 | 23-Mar-01 | 7 | Negative | | | |
| 4204-001006 | 21-May-01 | 23-Mar-01 | 59 | Negative | | | |
| 4204-001006 | 18-Jun-01 | 23-Mar-01 | 87 | Negative | | | |
| 4204-001006 | 13-Jul-01 | 23-Mar-01 | 112 | Negative | | | |
| 4204-001006 | 13-Aug-01 | 23-Mar-01 | 143 | Negative | | | |
| 4204-001006 | 10-Sep-01 | 23-Mar-01 | 171 | Negative | | | |
| 4204-001006 | 8-Oct-01 | 23-Mar-01 | 199 | Negative | | | |
| 4204-001006 | 5-Nov-01 | 23-Mar-01 | 227 | Negative | | | |
| 4204-001006 | 6-Dec-01 | 23-Mar-01 | 258 | Negative | | | |
| 4204-001006 | 15-May-02 | 23-Mar-01 | 418 | Negative | 412 | | |
| 4204-001006 | 9-Sep-03 | 23-Mar-01 | 900 | | 1022 | 4142 | |
| 4204-001006 | 12-Jul-04 | 23-Mar-01 | 1207 | Negative | 766 | < 357 | |
| **4204-001006** | **12-Jul-04** | **23-Mar-01** | **1207** | **Negative** | **766** | **< 357** | |
| 4204-001007 | 23-Jan-01 | 3-Apr-01 | -70 | Positive | | | |
| 4204-001007 | 12-Mar-01 | 3-Apr-01 | -22 | | Positive | >1700000000.00 | |
| 4204-001007 | 5-Apr-01 | 3-Apr-01 | 2 | Positive | | | |
| 4204-001007 | 10-Apr-01 | 3-Apr-01 | 7 | Positive | | | |
| 4204-001007 | 19-Apr-01 | 3-Apr-01 | 16 | Positive | | | |
| 4204-001007 | 27-Apr-01 | 3-Apr-01 | 24 | Positive | | | |
| 4204-001007 | 4-May-01 | 3-Apr-01 | 31 | Positive | | | |
| 4204-001007 | 4-Jun-01 | 3-Apr-01 | 62 | Positive | | | |
| 4204-001007 | 2-Jul-01 | 3-Apr-01 | 90 | Negative | | | |
| 4204-001007 | 27-Jul-01 | 3-Apr-01 | 115 | Negative | | | |
| 4204-001007 | 27-Aug-01 | 3-Apr-01 | 146 | Negative | | | |
| 4204-001007 | 24-Sep-01 | 3-Apr-01 | 174 | Negative | | | |
| 4204-001007 | 22-Oct-01 | 3-Apr-01 | 202 | Negative | | | |
| 4204-001007 | 19-Nov-01 | 3-Apr-01 | 230 | Negative | | | |
| 4204-001007 | 17-Dec-01 | 3-Apr-01 | 258 | Negative | | | |
| 4204-001007 | 4-Mar-02 | 3-Apr-01 | 335 | Negative | 22 | 4142 | |
| 4204-001007 | 22-Jul-02 | 3-Apr-01 | 475 | Negative | 566 | | |
| 4204-001007 | 28-Oct-02 | 3-Apr-01 | 573 | | 93 | | |
| 4204-001007 | 25-Nov-02 | 3-Apr-01 | 601 | Negative | | | |
| 4204-001007 | 23-Apr-03 | 3-Apr-01 | 750 | Negative | 60 | < 142 | |
| 4204-001007 | 18-Aug-03 | 3-Apr-01 | 867 | Negative | 146 | < 142 | |
| 4204-001007 | 13-Oct-03 | 3-Apr-01 | 923 | Negative | 81 | | |
| 4204-001007 | 22-Jan-04 | 3-Apr-01 | 1024 | Negative | | 142 | |
| 4204-001007 | 26-Apr-04 | 3-Apr-01 | 1119 | Negative | 118 | < 357 | |
| 4204-001007 | 22-Jun-04 | 3-Apr-01 | 1176 | | 67 | | |
| 4204-001007 | 22-Sep-04 | 3-Apr-01 | 1268 | Negative | 67 | < 357 | |
| **4204-001007** | **22-Sep-04** | **3-Apr-01** | **1268** | **Negative** | **67** | **< 357** | |
| 4204-002001 | 16-Jun-00 | 13-Jul-00 | -27 | Positive | Negative | <5.00 | |
| 4204-002001 | 12-Jul-00 | 13-Jul-00 | -1 | | | <5.00 | |
| 4204-002001 | 15-Jul-00 | 13-Jul-00 | 2 | Negative | | | |
| 4204-002001 | 24-Jul-00 | 13-Jul-00 | 11 | Negative | | | |
| 4204-002001 | 1-Aug-00 | 13-Jul-00 | 19 | Negative | | | |
| 4204-002001 | 8-Aug-00 | 13-Jul-00 | 26 | Negative | | | |
| 4204-002001 | 5-Sep-00 | 13-Jul-00 | 54 | Negative | | | |
| 4204-002001 | 3-Oct-00 | 13-Jul-00 | 82 | Negative | | | |
| 4204-002001 | 30-Oct-00 | 13-Jul-00 | 109 | Negative | | | |
| 4204-002001 | 24-Nov-00 | 13-Jul-00 | 134 | Negative | | | |
| 4204-002001 | 23-Dec-00 | 13-Jul-00 | 163 | Negative | | | |

| SID | Test Date | Xplant Date | Test - Xplant (Days) | HBsAg | Anti HBs | HBV DNA | Death |
|---|---|---|---|---|---|---|---|
| 4204-002001 | 22-Jan-01 | 13-Jul-00 | 193 | Negative | | | |
| 4204-002001 | 17-Feb-01 | 13-Jul-00 | 219 | Negative | | | |
| 4204-002001 | 17-Mar-01 | 13-Jul-00 | 247 | Negative | | | |
| 4204-002001 | 3-Jul-01 | 13-Jul-00 | 355 | | | < 4700000000 | |
| 4204-002001 | 29-Aug-01 | 13-Jul-00 | 412 | Negative | Positive | | |
| 4204-002001 | 16-Jul-02 | 13-Jul-00 | 733 | | | < 200 | |
| 4204-002001 | 24-Oct-02 | 13-Jul-00 | 833 | | | 200 | |
| 4204-002001 | 1-Jul-03 | 13-Jul-00 | 1083 | Negative | Positive | < 200 | |
| **4204-002001** | **1-Jul-03** | **13-Jul-00** | **1083** | **Negative** | **Positive** | **< 200** | |
| 4204-002002 | 5-Jul-00 | 20-Sep-00 | -77 | | | 0.01 | |
| 4204-002002 | 19-Sep-00 | 20-Sep-00 | -1 | Positive | Negative | 5 | |
| 4204-002002 | 22-Sep-00 | 20-Sep-00 | 2 | Negative | | | |
| 4204-002002 | 27-Sep-00 | 20-Sep-00 | 7 | Negative | | | |
| 4204-002002 | 2-Oct-00 | 20-Sep-00 | 12 | Negative | | | |
| 4204-002002 | 10-Oct-00 | 20-Sep-00 | 20 | Negative | | | |
| 4204-002002 | 17-Oct-00 | 20-Sep-00 | 27 | Negative | | | |
| 4204-002002 | 14-Nov-00 | 20-Sep-00 | 55 | Negative | | | |
| 4204-002002 | 12-Dec-00 | 20-Sep-00 | 83 | Negative | | | |
| 4204-002002 | 9-Jan-01 | 20-Sep-00 | 111 | Negative | | | |
| 4204-002002 | 2-Feb-01 | 20-Sep-00 | 135 | Negative | | | |
| 4204-002002 | 6-Mar-01 | 20-Sep-00 | 167 | Negative | | | |
| 4204-002002 | 30-Mar-01 | 20-Sep-00 | 191 | Negative | | | |
| 4204-002002 | 30-Apr-01 | 20-Sep-00 | 222 | Negative | | | |
| 4204-002002 | 25-May-01 | 20-Sep-00 | 247 | Negative | | | |
| 4204-002002 | 7-Jan-03 | 20-Sep-00 | 839 | Negative | Negative | | |
| **4204-002002** | **7-Jan-03** | **20-Sep-00** | **839** | **Negative** | **Negative** | | |
| 4204-002003 | 1-Jan-01 | 2-Feb-01 | -32 | | | <5.00 | |
| 4204-002003 | 9-Jan-01 | 2-Feb-01 | -24 | Positive | Negative | | |
| 4204-002003 | 1-Feb-01 | 2-Feb-01 | -1 | | | <5.00 | |
| 4204-002003 | 4-Feb-01 | 2-Feb-01 | 2 | Negative | | | |
| 4204-002003 | 9-Feb-01 | 2-Feb-01 | 7 | Negative | | | |
| 4204-002003 | 13-Feb-01 | 2-Feb-01 | 11 | Negative | | | |
| 4204-002003 | 20-Feb-01 | 2-Feb-01 | 18 | Negative | | | |
| 4204-002003 | 27-Feb-01 | 2-Feb-01 | 25 | Negative | | | |
| 4204-002003 | 27-Mar-01 | 2-Feb-01 | 53 | Negative | | | |
| 4204-002003 | 24-Apr-01 | 2-Feb-01 | 81 | Negative | | | |
| 4204-002003 | 22-May-01 | 2-Feb-01 | 109 | Negative | | | |
| 4204-002003 | 19-Jun-01 | 2-Feb-01 | 137 | Negative | | | |
| 4204-002003 | 13-Jul-01 | 2-Feb-01 | 161 | Negative | | | |
| 4204-002003 | 14-Aug-01 | 2-Feb-01 | 193 | Negative | | | |
| 4204-002003 | 11-Sep-01 | 2-Feb-01 | 221 | Negative | | | |
| 4204-002003 | 10-Oct-01 | 2-Feb-01 | 250 | Negative | | | |
| 4204-002003 | 12-Feb-02 | 2-Feb-01 | 375 | Positive | Positive | | |
| 4204-002003 | 8-Apr-02 | 2-Feb-01 | 430 | Negative | Positive | | |
| 4204-002003 | 19-Jul-02 | 2-Feb-01 | 532 | Negative | | | |
| 4204-002003 | 22-Jul-02 | 2-Feb-01 | 535 | | | < 0.017 | |
| **4204-002003** | **22-Jul-02** | **2-Feb-01** | **532** | **Negative** | | **< 0.017** | |
| 4204-002004 | 17-Jan-01 | 4-Feb-01 | -18 | Positive | Negative | | |
| 4204-002004 | 1-Feb-01 | 4-Feb-01 | -3 | | | <5.00 | |
| 4204-002004 | 4-Feb-01 | 4-Feb-01 | 0 | | | 5 | |
| 4204-002004 | 6-Feb-01 | 4-Feb-01 | 2 | Negative | | | |
| 4204-002004 | 11-Feb-01 | 4-Feb-01 | 7 | Negative | | | |

| SID | Test Date | Xplant Date | Test - Xplant (Days) | HBsAg | Anti HBs | HBV DNA | Death |
|---|---|---|---|---|---|---|---|
| 4204-002004 | 13-Feb-01 | 4-Feb-01 | 9 | Negative | | | |
| 4204-002004 | 20-Feb-01 | 4-Feb-01 | 16 | Negative | | | |
| 4204-002004 | 27-Feb-01 | 4-Feb-01 | 23 | Negative | | | |
| **4204-002004** | **27-Feb-01** | **4-Feb-01** | **23** | **Negative** | | | |
| 4204-002005 | 17-Feb-01 | 17-Feb-01 | 0 | Positive | Negative | <5.00 | |
| 4204-002005 | 19-Feb-01 | 17-Feb-01 | 2 | Negative | | | |
| 4204-002005 | 24-Feb-01 | 17-Feb-01 | 7 | Negative | | | |
| 4204-002005 | 27-Feb-01 | 17-Feb-01 | 10 | Negative | | | |
| 4204-002005 | 6-Mar-01 | 17-Feb-01 | 17 | Negative | | | |
| 4204-002005 | 13-Mar-01 | 17-Feb-01 | 24 | Negative | | | |
| 4204-002005 | 10-Apr-01 | 17-Feb-01 | 52 | Negative | | | |
| 4204-002005 | 8-May-01 | 17-Feb-01 | 80 | Negative | | | |
| 4204-002005 | 5-Jun-01 | 17-Feb-01 | 108 | Negative | | | |
| 4204-002005 | 6-Jul-01 | 17-Feb-01 | 139 | Negative | | | |
| 4204-002005 | 31-Jul-01 | 17-Feb-01 | 164 | Negative | | | |
| 4204-002005 | 31-Aug-01 | 17-Feb-01 | 195 | Negative | | | |
| 4204-002005 | 28-Sep-01 | 17-Feb-01 | 223 | Negative | | | |
| 4204-002005 | 24-Oct-01 | 17-Feb-01 | 249 | Negative | | | |
| 4204-002005 | 12-Aug-03 | 17-Feb-01 | 906 | Positive | | 430000000 | |
| 4204-002005 | 20-Oct-03 | 17-Feb-01 | 975 | | | 1600000 | |
| **4204-002005** | **20-Oct-03** | **17-Feb-01** | **906** | **Positive** | | **1600000** | |
| 4204-002006 | 18-Feb-01 | 22-Feb-01 | -4 | Positive | Negative | <5.00 | |
| 4204-002006 | 21-Feb-01 | 22-Feb-01 | -1 | | | <5.00 | |
| 4204-002006 | 24-Feb-01 | 22-Feb-01 | 2 | Negative | | | |
| **4204-002006** | **24-Feb-01** | **22-Feb-01** | **2** | **Negative** | | | **24-Feb-01** |
| 4204-003001 | 6-Apr-00 | 11-Apr-00 | -5 | Positive | Negative | 4700 | |
| 4204-003001 | 11-Apr-00 | 11-Apr-00 | 0 | | | 4700 | |
| 4204-003001 | 13-Apr-00 | 11-Apr-00 | 2 | Positive | | | |
| 4204-003001 | 18-Apr-00 | 11-Apr-00 | 7 | Negative | | | |
| 4204-003001 | 25-Apr-00 | 11-Apr-00 | 14 | Negative | | | |
| 4204-003001 | 2-May-00 | 11-Apr-00 | 21 | Negative | | | |
| 4204-003001 | 9-May-00 | 11-Apr-00 | 28 | Negative | | | |
| 4204-003001 | 6-Jun-00 | 11-Apr-00 | 56 | Negative | | | |
| 4204-003001 | 6-Jul-00 | 11-Apr-00 | 86 | Negative | | | |
| 4204-003001 | 1-Aug-00 | 11-Apr-00 | 112 | Negative | | | |
| 4204-003001 | 29-Aug-00 | 11-Apr-00 | 140 | Negative | | | |
| 4204-003001 | 29-Sep-00 | 11-Apr-00 | 171 | Negative | | | |
| 4204-003001 | 24-Oct-00 | 11-Apr-00 | 196 | Negative | | | |
| 4204-003001 | 20-Nov-00 | 11-Apr-00 | 223 | Negative | | | |
| 4204-003001 | 19-Dec-00 | 11-Apr-00 | 252 | Negative | | | |
| 4204-003001 | 11-Apr-01 | 11-Apr-00 | 365 | Negative | | < 4700 | |
| 4204-003001 | 20-Mar-02 | 11-Apr-00 | 708 | | Negative | 53 | |
| 4204-003001 | 13-Dec-02 | 11-Apr-00 | 976 | | | Negative | |
| 4204-003001 | 1-Apr-03 | 11-Apr-00 | 1085 | | | Negative | |
| **4204-003001** | **1-Apr-03** | **11-Apr-00** | **365** | **Negative** | | **Negative** | |
| 4204-004001 | 5-May-00 | 10-May-00 | -5 | Positive | Negative | | |
| 4204-004001 | 8-May-00 | 10-May-00 | -2 | | | 539 | |
| 4204-004001 | 1-Jun-00 | 10-May-00 | 22 | Negative | | | |
| **4204-004001** | **1-Jun-00** | **10-May-00** | **22** | **Negative** | | | **15-Jun-00** |
| 4204-004002 | 21-Jun-00 | 31-Jul-00 | -40 | Positive | Negative | 74 | |

| SID | Test Date | Xplant Date | Test - Xplant (Days) | HBsAg | Anti HBs | HBV DNA | Death |
|---|---|---|---|---|---|---|---|
| 4204-004002 | 25-Jul-00 | 31-Jul-00 | -6 | | | 0.08 | |
| 4204-004002 | 2-Aug-00 | 31-Jul-00 | 2 | Positive | | | |
| 4204-004002 | 7-Aug-00 | 31-Jul-00 | 7 | Positive | | | |
| **4204-004002** | **7-Aug-00** | **31-Jul-00** | **7** | **Positive** | | | **23-Aug-00** |
| 4204-004003 | 6-Dec-00 | 10-Jan-01 | -35 | Positive | | | |
| 4204-004003 | 9-Dec-00 | 10-Jan-01 | -32 | | | <0.01 | |
| 4204-004003 | 10-Jan-01 | 10-Jan-01 | 0 | | | Not Done | |
| 4204-004003 | 12-Jan-01 | 10-Jan-01 | 2 | Negative | | | |
| 4204-004003 | 17-Jan-01 | 10-Jan-01 | 7 | Negative | | | |
| 4204-004003 | 29-Jan-01 | 10-Jan-01 | 19 | Negative | | | |
| 4204-004003 | 1-Feb-01 | 10-Jan-01 | 22 | Negative | | | |
| 4204-004003 | 9-Mar-01 | 10-Jan-01 | 58 | Negative | | | |
| 4204-004003 | 5-Apr-01 | 10-Jan-01 | 85 | Negative | | | |
| 4204-004003 | 3-May-01 | 10-Jan-01 | 113 | Negative | | | |
| 4204-004003 | 31-May-01 | 10-Jan-01 | 141 | Negative | | | |
| 4204-004003 | 28-Jun-01 | 10-Jan-01 | 169 | Negative | | | |
| 4204-004003 | 23-Aug-01 | 10-Jan-01 | 225 | Negative | | | |
| 4204-004003 | 20-Sep-01 | 10-Jan-01 | 253 | Negative | | | |
| 4204-004003 | 28-Mar-02 | 10-Jan-01 | 442 | Negative | | | |
| 4204-004003 | 11-Apr-02 | 10-Jan-01 | 456 | Negative | | | |
| 4204-004003 | 13-Aug-02 | 10-Jan-01 | 580 | Negative | | | |
| 4204-004003 | 17-Sep-02 | 10-Jan-01 | 615 | Negative | | | |
| **4204-004003** | **17-Sep-02** | **10-Jan-01** | **615** | **Negative** | | | **29-Sep-02** |
| 4204-004004 | 14-May-01 | 14-May-01 | 0 | Positive | Negative | 39.6 | |
| 4204-004004 | 16-May-01 | 14-May-01 | 2 | Positive | | | |
| 4204-004004 | 21-May-01 | 14-May-01 | 7 | Negative | | | |
| 4204-004004 | 4-Jun-01 | 14-May-01 | 21 | Negative | | | |
| 4204-004004 | 9-Jul-01 | 14-May-01 | 56 | Negative | | | |
| 4204-004004 | 6-Aug-01 | 14-May-01 | 84 | Negative | | | |
| 4204-004004 | 4-Sep-01 | 14-May-01 | 113 | Negative | | | |
| 4204-004004 | 1-Oct-01 | 14-May-01 | 140 | Negative | | | |
| 4204-004004 | 29-Oct-01 | 14-May-01 | 168 | Negative | | | |
| 4204-004004 | 26-Nov-01 | 14-May-01 | 196 | Negative | | | |
| 4204-004004 | 24-Dec-01 | 14-May-01 | 224 | Negative | | | |
| 4204-004004 | 24-Jan-02 | 14-May-01 | 255 | Negative | | | |
| 4204-004004 | 29-May-02 | 14-May-01 | 380 | Negative | > 150 | | |
| 4204-004004 | 7-Aug-02 | 14-May-01 | 450 | Negative | > 150 | 0.017 | |
| 4204-004004 | 1-May-03 | 14-May-01 | 717 | Negative | | < 100 | |
| 4204-004004 | 1-Aug-03 | 14-May-01 | 809 | Negative | 480 | < 100 | |
| 4204-004004 | 3-Nov-03 | 14-May-01 | 903 | | > 150 | < 200 | |
| 4204-004004 | 1-Mar-04 | 14-May-01 | 1022 | Negative | | < 100 | |
| 4204-004004 | 10-May-04 | 14-May-01 | 1092 | Negative | > 150 | < 100 | |
| **4204-004004** | **10-May-04** | **14-May-01** | **1092** | **Negative** | **> 150** | **< 100** | |
| 4204-005001 | 18-May-00 | 20-May-00 | -2 | Positive | Negative | <0.50 | |
| 4204-005001 | 20-May-00 | 20-May-00 | 0 | | | <0.50 | |
| 4204-005001 | 22-May-00 | 20-May-00 | 2 | Negative | | | |
| 4204-005001 | 27-May-00 | 20-May-00 | 7 | Negative | | | |
| 4204-005001 | 2-Jun-00 | 20-May-00 | 13 | Negative | | | |

| SID | Test Date | Xplant Date | Test - Xplant (Days) | HBsAg | Anti HBs | HBV DNA | Death |
|---|---|---|---|---|---|---|---|
| 4204-005001 | 16-Jun-00 | 20-May-00 | 27 | Negative | | | |
| 4204-005001 | 14-Jul-00 | 20-May-00 | 55 | Negative | | | |
| 4204-005001 | 11-Aug-00 | 20-May-00 | 83 | Negative | | | |
| 4204-005001 | 8-Sep-00 | 20-May-00 | 111 | Negative | | | |
| 4204-005001 | 6-Oct-00 | 20-May-00 | 139 | Negative | | | |
| 4204-005001 | 3-Nov-00 | 20-May-00 | 167 | Negative | | | |
| 4204-005001 | 1-Dec-00 | 20-May-00 | 195 | Negative | | | |
| 4204-005001 | 27-Dec-00 | 20-May-00 | 221 | Negative | | | |
| 4204-005001 | 26-Jan-01 | 20-May-00 | 251 | Negative | | | |
| 4204-005001 | 20-Apr-01 | 20-May-00 | 335 | | | Negative | |
| 4204-005001 | 4-May-01 | 20-May-00 | 349 | Negative | | | |
| 4204-005001 | 29-May-01 | 20-May-00 | 374 | Negative | | | |
| 4204-005001 | 21-Aug-01 | 20-May-00 | 458 | Negative | | Negative | |
| 4204-005001 | 12-Oct-01 | 20-May-00 | 510 | Negative | | | |
| 4204-005001 | 4-Jan-02 | 20-May-00 | 594 | | | Negative | |
| 4204-005001 | 19-Apr-02 | 20-May-00 | 699 | | 476 | | |
| 4204-005001 | 31-May-02 | 20-May-00 | 741 | Negative | 146 | | |
| 4204-005001 | 21-Jun-02 | 20-May-00 | 762 | Negative | | | |
| 4204-005001 | 19-Jul-02 | 20-May-00 | 790 | Negative | 132 | Negative | |
| 4204-005001 | 10-Sep-02 | 20-May-00 | 843 | Negative | | | |
| 4204-005001 | 8-Oct-02 | 20-May-00 | 871 | | | Negative | |
| 4204-005001 | 3-Jan-03 | 20-May-00 | 958 | Negative | | | |
| 4204-005001 | 31-Jan-03 | 20-May-00 | 986 | Negative | | Negative | |
| 4204-005001 | 18-Apr-03 | 20-May-00 | 1063 | Negative | | Negative | |
| 4204-005001 | 30-May-03 | 20-May-00 | 1105 | Negative | | | |
| 4204-005001 | 20-Jun-03 | 20-May-00 | 1126 | | | Negative | |
| 4204-005001 | 8-May-04 | 20-May-00 | 1449 | Negative | | | |
| **4204-005001** | **8-May-04** | **20-May-00** | **1449** | **Negative** | | | |
| 4204-005002 | 19-Jun-00 | 23-Jun-00 | -4 | Positive | Negative | 2.7 | |
| 4204-005002 | 23-Jun-00 | 23-Jun-00 | 0 | | | 0.5 | |
| 4204-005002 | 25-Jun-00 | 23-Jun-00 | 2 | Negative | | | |
| 4204-005002 | 30-Jun-00 | 23-Jun-00 | 7 | Negative | | | |
| 4204-005002 | 7-Jul-00 | 23-Jun-00 | 14 | Negative | | | |
| 4204-005002 | 14-Jul-00 | 23-Jun-00 | 21 | Negative | | | |
| 4204-005002 | 21-Jul-00 | 23-Jun-00 | 28 | Negative | | | |
| 4204-005002 | 18-Aug-00 | 23-Jun-00 | 56 | Negative | | | |
| 4204-005002 | 15-Sep-00 | 23-Jun-00 | 84 | Negative | | | |
| 4204-005002 | 13-Oct-00 | 23-Jun-00 | 112 | Negative | | | |
| 4204-005002 | 10-Nov-00 | 23-Jun-00 | 140 | Negative | | | |
| 4204-005002 | 9-Dec-00 | 23-Jun-00 | 169 | Negative | | | |
| 4204-005002 | 5-Jan-01 | 23-Jun-00 | 196 | Negative | | | |
| 4204-005002 | 2-Feb-01 | 23-Jun-00 | 224 | Negative | | | |
| 4204-005002 | 2-Mar-01 | 23-Jun-00 | 252 | Negative | | | |
| 4204-005002 | 13-Jul-01 | 23-Jun-00 | 385 | Negative | 247 | | |
| 4204-005002 | 8-Aug-01 | 23-Jun-00 | 411 | | | < 0.5 | |
| 4204-005002 | 21-Sep-01 | 23-Jun-00 | 455 | Negative | 266 | | |
| 4204-005002 | 4-Oct-01 | 23-Jun-00 | 468 | Negative | 194 | | |
| 4204-005002 | 1-Nov-01 | 23-Jun-00 | 496 | | | Negative | |
| 4204-005002 | 29-Nov-01 | 23-Jun-00 | 524 | Negative | 150 | | |
| 4204-005002 | 2-Jan-02 | 23-Jun-00 | 558 | Negative | | | |
| 4204-005002 | 17-Jan-02 | 23-Jun-00 | 573 | | | Negative | |
| 4204-005002 | 29-Jan-02 | 23-Jun-00 | 585 | Negative | | | |

| SID | Test Date | Xplant Date | Test - Xplant (Days) | HBsAg | Anti HBs | HBV DNA | Death |
|---|---|---|---|---|---|---|---|
| 4204-005002 | 25-Jun-02 | 23-Jun-00 | 732 | Negative | | | |
| 4204-005002 | 31-Oct-02 | 23-Jun-00 | 860 | Negative | | | |
| 4204-005002 | 27-Mar-03 | 23-Jun-00 | 1007 | Negative | | | |
| 4204-005002 | 23-Sep-03 | 23-Jun-00 | 1187 | Negative | | | |
| **4204-005002** | **23-Sep-03** | **23-Jun-00** | **1187** | **Negative** | | | |
| 4204-009001 | 29-Nov-99 | 2-Jun-00 | -186 | | | 0 | |
| 4204-009001 | 1-Jun-00 | 2-Jun-00 | -1 | Positive | Negative | | |
| 4204-009001 | 2-Jun-00 | 2-Jun-00 | 0 | | | Not Done | |
| 4204-009001 | 22-Jun-00 | 2-Jun-00 | 20 | Negative | | | |
| 4204-009001 | 29-Jun-00 | 2-Jun-00 | 27 | Negative | | | |
| 4204-009001 | 27-Jul-00 | 2-Jun-00 | 55 | Negative | | | |
| 4204-009001 | 24-Aug-00 | 2-Jun-00 | 83 | Negative | | | |
| 4204-009001 | 21-Dec-00 | 2-Jun-00 | 202 | Negative | | | |
| 4204-009001 | 22-Jan-01 | 2-Jun-00 | 234 | Negative | | | |
| 4204-009001 | 16-Feb-01 | 2-Jun-00 | 259 | Negative | | | |
| 4204-009001 | 10-Jul-01 | 2-Jun-00 | 403 | | 282 | | |
| 4204-009001 | 11-Sep-01 | 2-Jun-00 | 466 | | 258 | | |
| 4204-009001 | 10-Dec-01 | 2-Jun-00 | 556 | | 350 | | |
| 4204-009001 | 11-Jun-02 | 2-Jun-00 | 739 | Negative | 477 | | |
| 4204-009001 | 24-Sep-02 | 2-Jun-00 | 844 | | 326 | | |
| 4204-009001 | 26-Nov-02 | 2-Jun-00 | 907 | | 366 | | |
| 4204-009001 | 22-Mar-03 | 2-Jun-00 | 1023 | | 275 | | |
| 4204-009001 | 28-Mar-03 | 2-Jun-00 | 1029 | | | < 2.3 | |
| 4204-009001 | 12-Jun-03 | 2-Jun-00 | 1105 | | | < 2.3 | |
| 4204-009001 | 17-Jun-03 | 2-Jun-00 | 1110 | | 139 | | |
| **4204-009001** | **17-Jun-03** | **2-Jun-00** | **739** | **Negative** | **139** | | |
| 4204-011001 | 27-Dec-00 | 5-Jan-01 | -9 | Positive | Negative | | |
| 4204-011001 | 8-Jan-01 | 5-Jan-01 | 3 | | | <5.00 | |
| 4204-011001 | 19-Jan-01 | 5-Jan-01 | 14 | Negative | | | |
| 4204-011001 | 26-Jan-01 | 5-Jan-01 | 21 | Negative | | | |
| 4204-011001 | 2-Feb-01 | 5-Jan-01 | 28 | Negative | | | |
| 4204-011001 | 2-Mar-01 | 5-Jan-01 | 56 | Negative | | | |
| 4204-011001 | 3-Apr-01 | 5-Jan-01 | 88 | Negative | | | |
| 4204-011001 | 27-Apr-01 | 5-Jan-01 | 112 | Negative | | | |
| 4204-011001 | 24-May-01 | 5-Jan-01 | 139 | Negative | | | |
| 4204-011001 | 27-Jun-01 | 5-Jan-01 | 173 | Negative | | | |
| 4204-011001 | 21-Aug-01 | 5-Jan-01 | 228 | Negative | | | |
| 4204-011001 | 18-Sep-01 | 5-Jan-01 | 256 | Negative | | | |
| 4204-011001 | 15-Jan-02 | 5-Jan-01 | 375 | Negative | | < 200 | |
| 4204-011001 | 26-Mar-02 | 5-Jan-01 | 445 | | | < 200 | |
| 4204-011001 | 30-Apr-02 | 5-Jan-01 | 480 | Negative | | | |
| 4204-011001 | 4-Jun-02 | 5-Jan-01 | 515 | Negative | | | |
| 4204-011001 | 30-Apr-03 | 5-Jan-01 | 845 | Negative | | | |
| 4204-011001 | 24-Jun-03 | 5-Jan-01 | 900 | Negative | | | |
| 4204-011001 | 23-Sep-03 | 5-Jan-01 | 991 | Negative | | < 200 | |
| 4204-011001 | 13-Jan-04 | 5-Jan-01 | 1103 | Negative | | < 160 | |
| **4204-011001** | **13-Jan-04** | **5-Jan-01** | **1103** | **Negative** | | **< 160** | |
| 4204-012001 | 30-Jan-00 | 30-Jan-00 | 0 | Positive | Negative | Not Done | |
| 4204-012001 | 21-Feb-00 | 30-Jan-00 | 22 | Positive | | | |
| 4204-012001 | 24-Mar-00 | 30-Jan-00 | 54 | Negative | | | |
| 4204-012001 | 20-Apr-00 | 30-Jan-00 | 81 | Positive | | | |
| 4204-012001 | 18-May-00 | 30-Jan-00 | 109 | Negative | | | |

| SID | Test Date | Xplant Date | Test - Xplant (Days) | HBsAg | Anti HBs | HBV DNA | Death |
|---|---|---|---|---|---|---|---|
| 4204-012001 | 15-Jun-00 | 30-Jan-00 | 137 | Negative | | | |
| 4204-012001 | 20-Jul-00 | 30-Jan-00 | 172 | Negative | | | |
| 4204-012001 | 17-Aug-00 | 30-Jan-00 | 200 | Negative | | | |
| 4204-012001 | 21-Sep-00 | 30-Jan-00 | 235 | Negative | | | |
| 4204-012001 | 16-Jan-01 | 30-Jan-00 | 352 | | 2200 | | |
| 4204-012001 | 24-Apr-01 | 30-Jan-00 | 450 | Negative | 3375 | | |
| 4204-012001 | 19-Jun-01 | 30-Jan-00 | 506 | | 2961 | | |
| 4204-012001 | 17-Jan-02 | 30-Jan-00 | 718 | | 3614 | | |
| 4204-012001 | 17-Apr-02 | 30-Jan-00 | 808 | | 3959 | | |
| 4204-012001 | 10-Jun-02 | 30-Jan-00 | 862 | Negative | 3458 | 541000 | |
| 4204-012001 | 22-Oct-02 | 30-Jan-00 | 996 | | 2297 | | |
| 4204-012001 | 27-Feb-03 | 30-Jan-00 | 1124 | | 1519 | | |
| **4204-012001** | **27-Feb-03** | **30-Jan-00** | **862** | **Negative** | **1519** | | |
| 4204-012002 | 11-May-00 | 23-May-00 | -12 | Positive | Negative | Not Done | |
| 4204-012002 | 23-May-00 | 23-May-00 | 0 | | | Not Done | |
| 4204-012002 | 25-May-00 | 23-May-00 | 2 | Negative | | | |
| 4204-012002 | 6-Jun-00 | 23-May-00 | 14 | Negative | | | |
| 4204-012002 | 20-Jun-00 | 23-May-00 | 28 | Negative | | | |
| 4204-012002 | 18-Jul-00 | 23-May-00 | 56 | Negative | | | |
| 4204-012002 | 19-Jan-01 | 23-May-00 | 241 | Negative | 365 | | |
| 4204-012002 | 21-May-03 | 23-May-00 | 1093 | Negative | 4404 | | |
| **4204-012002** | **21-May-03** | **23-May-00** | **1093** | **Negative** | **4404** | | |
| 4204-012003 | 29-Mar-01 | 17-Apr-01 | -19 | | | 4148000 | |
| 4204-012003 | 8-Apr-01 | 17-Apr-01 | -9 | Positive | Negative | | |
| 4204-012003 | 17-Apr-01 | 17-Apr-01 | 0 | | | Not Done | |
| 4204-012003 | 24-Apr-01 | 17-Apr-01 | 7 | Negative | | | |
| 4204-012003 | 4-May-01 | 17-Apr-01 | 17 | Negative | | | |
| 4204-012003 | 8-May-01 | 17-Apr-01 | 21 | Negative | | | |
| 4204-012003 | 12-Jun-01 | 17-Apr-01 | 56 | Negative | | | |
| 4204-012003 | 10-Jul-01 | 17-Apr-01 | 84 | Negative | | | |
| 4204-012003 | 6-Aug-01 | 17-Apr-01 | 111 | Negative | | | |
| 4204-012003 | 4-Sep-01 | 17-Apr-01 | 140 | Negative | | | |
| 4204-012003 | 2-Oct-01 | 17-Apr-01 | 168 | Negative | | | |
| 4204-012003 | 30-Oct-01 | 17-Apr-01 | 196 | Negative | | | |
| 4204-012003 | 26-Nov-01 | 17-Apr-01 | 223 | Negative | | | |
| 4204-012003 | 27-Dec-01 | 17-Apr-01 | 254 | Negative | | | |
| 4204-012003 | 29-Apr-02 | 17-Apr-01 | 377 | Negative | 551 | | |
| 4204-012003 | 28-Jun-02 | 17-Apr-01 | 437 | Negative | 325 | Negative | |
| 4204-012003 | 30-Sep-02 | 17-Apr-01 | 531 | Negative | 58 | | |
| 4204-012003 | 30-Apr-03 | 17-Apr-01 | 743 | | 1648 | | |
| 4204-012003 | 2-Jul-03 | 17-Apr-01 | 806 | | 384 | | |
| 4204-012003 | 6-Oct-03 | 17-Apr-01 | 902 | | 63 | | |
| 4204-012003 | 26-Jan-04 | 17-Apr-01 | 1014 | | 105 | | |
| 4204-012003 | 19-Apr-04 | 17-Apr-01 | 1098 | Negative | 85 | | |
| **4204-012003** | **19-Apr-04** | **17-Apr-01** | **1098** | **Negative** | **85** | | |
| 4204-013001 | 18-Jul-97 | 31-Aug-00 | -1140 | Positive | | <0.50 | |
| 4204-013001 | 10-Oct-97 | 31-Aug-00 | -1056 | | Negative | | |
| 4204-013001 | 31-Aug-00 | 31-Aug-00 | 0 | | | <0.50 | |
| 4204-013001 | 2-Sep-00 | 31-Aug-00 | 2 | Positive | | | |
| 4204-013001 | 7-Sep-00 | 31-Aug-00 | 7 | Negative | | | |
| 4204-013001 | 14-Sep-00 | 31-Aug-00 | 14 | Negative | | | |
| 4204-013001 | 28-Sep-00 | 31-Aug-00 | 28 | Negative | | | |

| SID | Test Date | Xplant Date | Test - Xplant (Days) | HBsAg | Anti HBs | HBV DNA | Death |
|---|---|---|---|---|---|---|---|
| 4204-013001 | 26-Oct-00 | 31-Aug-00 | 56 | Negative | | | |
| 4204-013001 | 21-Nov-00 | 31-Aug-00 | 82 | Negative | | | |
| 4204-013001 | 21-Dec-00 | 31-Aug-00 | 112 | Negative | | | |
| 4204-013001 | 18-Jan-01 | 31-Aug-00 | 140 | Negative | | | |
| 4204-013001 | 15-Feb-01 | 31-Aug-00 | 168 | Negative | | | |
| 4204-013001 | 15-Mar-01 | 31-Aug-00 | 196 | Negative | | | |
| 4204-013001 | 12-Apr-01 | 31-Aug-00 | 224 | Negative | | | |
| 4204-013001 | 10-May-01 | 31-Aug-00 | 252 | Negative | | | |
| 4204-013001 | 6-Aug-01 | 31-Aug-00 | 340 | Negative | 2587 | Negative | |
| 4204-013001 | 29-Nov-01 | 31-Aug-00 | 455 | | > 150 | | |
| 4204-013001 | 18-Mar-02 | 31-Aug-00 | 564 | | 29.9 | | |
| 4204-013001 | 4-Apr-02 | 31-Aug-00 | 581 | Negative | | Negative | |
| 4204-013001 | 16-Aug-02 | 31-Aug-00 | 715 | | > 150 | | |
| 4204-013001 | 2-Dec-02 | 31-Aug-00 | 823 | | | Negative | |
| 4204-013001 | 2-Jan-03 | 31-Aug-00 | 854 | | 19 | | |
| 4204-013001 | 29-Jan-03 | 31-Aug-00 | 881 | | | 0.019 | |
| 4204-013001 | 28-Mar-03 | 31-Aug-00 | 939 | | > 150 | | |
| 4204-013001 | 30-Jun-03 | 31-Aug-00 | 1033 | | 147 | Negative | |
| 4204-013001 | 8-Oct-03 | 31-Aug-00 | 1133 | Negative | 59 | Negative | |
| 4204-013001 | 27-May-04 | 31-Aug-00 | 1365 | Negative | 40 | Negative | |
| 4204-013001 | 23-Sep-04 | 31-Aug-00 | 1484 | | 221 | Negative | |
| 4204-013001 | 8-Dec-04 | 31-Aug-00 | 1560 | | 61 | | |
| **4204-013001** | **8-Dec-04** | **31-Aug-00** | **1365** | **Negative** | **61** | | |
| 4204-015001 | 25-Jun-00 | 23-Aug-00 | -59 | Positive | Negative | | |
| 4204-015001 | 6-Jul-00 | 23-Aug-00 | -48 | | | 0.5 | |
| 4204-015001 | 23-Aug-00 | 23-Aug-00 | 0 | | | 0.5 | |
| 4204-015001 | 25-Aug-00 | 23-Aug-00 | 2 | Negative | | | |
| 4204-015001 | 30-Aug-00 | 23-Aug-00 | 7 | Positive | | | |
| 4204-015001 | 6-Sep-00 | 23-Aug-00 | 14 | Negative | | | |
| 4204-015001 | 11-Sep-00 | 23-Aug-00 | 19 | Negative | | | |
| 4204-015001 | 20-Sep-00 | 23-Aug-00 | 28 | Negative | | | |
| 4204-015001 | 18-Oct-00 | 23-Aug-00 | 56 | Negative | | | |
| 4204-015001 | 15-Nov-00 | 23-Aug-00 | 84 | Negative | | | |
| 4204-015001 | 13-Dec-00 | 23-Aug-00 | 112 | Negative | | | |
| 4204-015001 | 10-Jan-01 | 23-Aug-00 | 140 | Negative | | | |
| 4204-015001 | 7-Feb-01 | 23-Aug-00 | 168 | Negative | | | |
| 4204-015001 | 21-Feb-01 | 23-Aug-00 | 182 | | | < 0.5 | |
| 4204-015001 | 7-Mar-01 | 23-Aug-00 | 196 | Negative | | | |
| 4204-015001 | 4-Apr-01 | 23-Aug-00 | 224 | Negative | | | |
| 4204-015001 | 2-May-01 | 23-Aug-00 | 252 | Negative | | | |
| 4204-015001 | 20-May-02 | 23-Aug-00 | 635 | Positive | Negative | | |
| 4204-015001 | 5-Nov-03 | 23-Aug-00 | 1169 | | | < 0.5 | |
| **4204-015001** | **5-Nov-03** | **23-Aug-00** | **635** | **Positive** | | **< 0.5** | |
| 4204-015002 | 24-Jul-00 | 26-Oct-00 | -94 | Positive | Positive | <0.50 | |
| 4204-015002 | 26-Oct-00 | 26-Oct-00 | 0 | | | <0.50 | |
| 4204-015002 | 28-Oct-00 | 26-Oct-00 | 2 | Negative | | | |
| 4204-015002 | 2-Nov-00 | 26-Oct-00 | 7 | Negative | | | |
| 4204-015002 | 8-Nov-00 | 26-Oct-00 | 13 | Negative | | | |
| 4204-015002 | 15-Nov-00 | 26-Oct-00 | 20 | Negative | | | |
| 4204-015002 | 22-Nov-00 | 26-Oct-00 | 27 | Negative | | | |
| 4204-015002 | 22-Dec-00 | 26-Oct-00 | 57 | Negative | | | |
| 4204-015002 | 19-Jan-01 | 26-Oct-00 | 85 | Negative | | | |

| SID | Test Date | Xplant Date | Test - Xplant (Days) | HBsAg | Anti HBs | HBV DNA | Death |
|---|---|---|---|---|---|---|---|
| 4204-015002 | 16-Feb-01 | 26-Oct-00 | 113 | Negative | | | |
| 4204-015002 | 15-Mar-01 | 26-Oct-00 | 140 | Negative | | | |
| 4204-015002 | 13-Apr-01 | 26-Oct-00 | 169 | Negative | | | |
| 4204-015002 | 11-May-01 | 26-Oct-00 | 197 | Negative | | | |
| 4204-015002 | 8-Jun-01 | 26-Oct-00 | 225 | Negative | | | |
| 4204-015002 | 5-Jul-01 | 26-Oct-00 | 252 | Negative | | | |
| 4204-015002 | 27-Jul-01 | 26-Oct-00 | 274 | | | 0.5 | |
| 4204-015002 | 11-Apr-02 | 26-Oct-00 | 532 | Negative | | | |
| 4204-015002 | 16-Jul-02 | 26-Oct-00 | 628 | | | < 100 | |
| 4204-015002 | 14-Aug-02 | 26-Oct-00 | 657 | | | < 100 | |
| 4204-015002 | 6-Jan-03 | 26-Oct-00 | 802 | | | < 100 | |
| 4204-015002 | 4-Apr-03 | 26-Oct-00 | 890 | | | < 100 | |
| 4204-015002 | 5-May-03 | 26-Oct-00 | 921 | | | < 100 | |
| 4204-015002 | 19-May-03 | 26-Oct-00 | 935 | | | < 100 | |
| **4204-015002** | **19-May-03** | **26-Oct-00** | **532** | **Negative** | | **< 100** | |
| 4204-015003 | 20-Jun-00 | 26-Oct-00 | -128 | Positive | Negative | | |
| 4204-015003 | 26-Oct-00 | 26-Oct-00 | 0 | | | <0.50 | |
| 4204-015003 | 28-Oct-00 | 26-Oct-00 | 2 | Negative | | | |
| 4204-015003 | 2-Nov-00 | 26-Oct-00 | 7 | Negative | | | |
| 4204-015003 | 8-Nov-00 | 26-Oct-00 | 13 | Negative | | | |
| 4204-015003 | 15-Nov-00 | 26-Oct-00 | 20 | Negative | | | |
| 4204-015003 | 22-Nov-00 | 26-Oct-00 | 27 | Negative | | | |
| 4204-015003 | 20-Dec-00 | 26-Oct-00 | 55 | Negative | | | |
| 4204-015003 | 17-Jan-01 | 26-Oct-00 | 83 | Negative | | | |
| 4204-015003 | 14-Feb-01 | 26-Oct-00 | 111 | Negative | | | |
| 4204-015003 | 14-Mar-01 | 26-Oct-00 | 139 | Negative | | | |
| 4204-015003 | 9-May-01 | 26-Oct-00 | 195 | Negative | | | |
| 4204-015003 | 6-Jun-01 | 26-Oct-00 | 223 | Negative | | | |
| 4204-015003 | 21-Aug-03 | 26-Oct-00 | 1029 | | | 0.5 | |
| **4204-015003** | **21-Aug-03** | **26-Oct-00** | **223** | **Negative** | | **0.5** | |
| 4204-015004 | 6-Nov-00 | 28-Nov-00 | -22 | Positive | Negative | | |
| 4204-015004 | 28-Nov-00 | 28-Nov-00 | 0 | | | <0.50 | |
| 4204-015004 | 30-Nov-00 | 28-Nov-00 | 2 | Negative | | | |
| 4204-015004 | 5-Dec-00 | 28-Nov-00 | 7 | Negative | | | |
| 4204-015004 | 13-Dec-00 | 28-Nov-00 | 15 | Negative | | | |
| 4204-015004 | 20-Dec-00 | 28-Nov-00 | 22 | Negative | | | |
| 4204-015004 | 27-Dec-00 | 28-Nov-00 | 29 | Negative | | | |
| 4204-015004 | 24-Jan-01 | 28-Nov-00 | 57 | Negative | | | |
| 4204-015004 | 21-Feb-01 | 28-Nov-00 | 85 | Negative | | | |
| 4204-015004 | 7-Mar-01 | 28-Nov-00 | 99 | | | < 0.5 | |
| 4204-015004 | 21-Mar-01 | 28-Nov-00 | 113 | Negative | | | |
| 4204-015004 | 18-Apr-01 | 28-Nov-00 | 141 | Negative | | | |
| 4204-015004 | 16-May-01 | 28-Nov-00 | 169 | Negative | | | |
| 4204-015004 | 11-Jul-01 | 28-Nov-00 | 225 | Negative | | | |
| 4204-015004 | 8-Aug-01 | 28-Nov-00 | 253 | Negative | | | |
| **4204-015004** | **8-Aug-01** | **28-Nov-00** | **253** | **Negative** | | | |

| SID | Test Date | Xplant Date | Test - Xplant | HBsAg | Anti HBs | HBV DNA | Death |
|---|---|---|---|---|---|---|---|
| 4409-001002 | 14-Apr-98 | 14-Dec-98 | -244 | Positive | | 599 | |
| 4409-001002 | 17-Dec-98 | 14-Dec-98 | 3 | Negative | 3405 | | |
| 4409-001002 | 18-Dec-98 | 14-Dec-98 | 4 | Negative | 4173 | | |
| 4409-001002 | 21-Dec-98 | 14-Dec-98 | 7 | | 5578 | | |
| 4409-001002 | 22-Dec-98 | 14-Dec-98 | 8 | Negative | | | |
| 4409-001002 | 1-Jan-99 | 14-Dec-98 | 18 | Negative | | | |
| 4409-001002 | 7-Jan-99 | 14-Dec-98 | 24 | | 2397 | | |
| 4409-001002 | 28-Jun-99 | 14-Dec-98 | 196 | Negative | 964 | | |
| 4409-001002 | 25-Oct-99 | 14-Dec-98 | 315 | Negative | 3735 | | |
| 4409-001002 | 18-Jan-00 | 14-Dec-98 | 400 | Negative | 1448 | | |
| 4409-001002 | 16-Jan-01 | 14-Dec-98 | 764 | Negative | 664 | | |
| 4409-001002 | 5-Nov-01 | 14-Dec-98 | 1057 | Negative | 789 | | |
| 4409-001002 | 4-Nov-02 | 14-Dec-98 | 1421 | Negative | 1298 | | |
| 4409-001002 | 6-Oct-03 | 14-Dec-98 | 1757 | Negative | 306 | | |
| 4409-001002 | 15-Dec-03 | 14-Dec-98 | 1827 | Negative | 5723 | | |
| **4409-001002** | **15-Dec-03** | **14-Dec-98** | **1827** | **Negative** | **5723** | | |
| 4409-002001 | 4-May-98 | 23-Nov-98 | -203 | Positive | | < 2.5 | |
| **4409-002001** | **4-May-98** | **23-Nov-98** | **-203** | **Positive** | | **< 2.5** | **18-Dec-98** |
| 4409-002003 | 14-Nov-98 | 3-Jan-99 | -50 | Positive | | | |
| 4409-002003 | 16-Dec-98 | 3-Jan-99 | -18 | | | 171.3 | |
| 4409-002003 | 16-Jan-99 | 3-Jan-99 | 13 | Negative | > 150 | | |
| 4409-002003 | 21-Jan-99 | 3-Jan-99 | 18 | Negative | | | |
| 4409-002003 | 28-Jan-99 | 3-Jan-99 | 25 | Negative | | | |
| 4409-002003 | 4-Feb-99 | 3-Jan-99 | 32 | Negative | | | |
| 4409-002003 | 10-Feb-99 | 3-Jan-99 | 38 | Negative | Positive | | |
| 4409-002003 | 11-Feb-99 | 3-Jan-99 | 39 | Negative | > 150 | | |
| 4409-002003 | 17-Feb-99 | 3-Jan-99 | 45 | | > 150 | | |
| 4409-002003 | 26-Feb-99 | 3-Jan-99 | 54 | | | 1.5 | |
| 4409-002003 | 11-Mar-99 | 3-Jan-99 | 67 | Negative | | 4.8 | |
| 4409-002003 | 25-Mar-99 | 3-Jan-99 | 81 | Negative | > 150 | | |
| 4409-002003 | 6-Apr-99 | 3-Jan-99 | 93 | Positive | 90 | | |
| 4409-002003 | 8-Apr-99 | 3-Jan-99 | 95 | Positive | 100 | | |
| 4409-002003 | 21-Apr-99 | 3-Jan-99 | 108 | Positive | 60 | | |
| 4409-002003 | 29-Apr-99 | 3-Jan-99 | 116 | Positive | | | |
| 4409-002003 | 6-Aug-99 | 3-Jan-99 | 215 | Positive | Negative | 23535 | |
| 4409-002003 | 17-Aug-99 | 3-Jan-99 | 226 | | Negative | | |
| 4409-002003 | 23-Aug-99 | 3-Jan-99 | 232 | Positive | | | |
| 4409-002003 | 15-Feb-00 | 3-Jan-99 | 408 | Positive | | 2440649 | |
| 4409-002003 | 5-Aug-00 | 3-Jan-99 | 580 | Negative | | 148868 | |
| 4409-002003 | 2-Feb-01 | 3-Jan-99 | 761 | Positive | | 200141 | |
| 4409-002003 | 16-Nov-01 | 3-Jan-99 | 1048 | Positive | | 9089 | |
| 4409-002003 | 3-Jul-02 | 3-Jan-99 | 1277 | Positive | | | |
| 4409-002003 | 30-Jul-02 | 3-Jan-99 | 1304 | | | 23798 | |
| 4409-002003 | 6-Jan-03 | 3-Jan-99 | 1464 | Positive | | 6860 | |
| 4409-002003 | 8-Apr-03 | 3-Jan-99 | 1556 | Positive | | 12200 | |
| 4409-002003 | 17-Sep-03 | 3-Jan-99 | 1718 | Positive | Negative | | |
| 4409-002003 | 29-Jan-04 | 3-Jan-99 | 1852 | Positive | Negative | | |
| 4409-002003 | 30-Jan-04 | 3-Jan-99 | 1853 | | | 341 | |
| 4409-002003 | 5-Apr-04 | 3-Jan-99 | 1919 | Positive | Negative | 238 | |
| 4409-002003 | 28-May-04 | 3-Jan-99 | 1972 | Positive | | 239 | |
| 4409-002003 | 28-Jul-04 | 3-Jan-99 | 2033 | Positive | Negative | 452 | |
| 4409-002003 | 28-Jul-04 | 3-Jan-99 | 2033 | Positive | Negative | 452 | |
| **4409-002003** | **28-Jul-04** | **3-Jan-99** | **2033** | **Positive** | **Negative** | **452** | |

| SID | Test Date | Xplant Date | Test - Xplant | HBsAg | Anti HBs | HBV DNA | Death |
|---|---|---|---|---|---|---|---|
| 4409-002004 | 26-Aug-98 | 18-Feb-99 | -176 | Positive | | Negative | |
| 4409-002004 | 25-Mar-99 | 18-Feb-99 | 35 | Negative | > 150 | | |
| 4409-002004 | 19-Apr-99 | 18-Feb-99 | 60 | Negative | | | |
| **4409-002004** | **19-Apr-99** | **18-Feb-99** | **60** | **Negative** | | | |
| 4409-002005 | 17-Nov-98 | 23-Feb-99 | -98 | Positive | | | |
| 4409-002005 | 30-Mar-99 | 23-Feb-99 | 35 | Negative | | | |
| **4409-002005** | **30-Mar-99** | **23-Feb-99** | **35** | **Negative** | | | **10-Dec-00** |
| 4409-002006 | 8-Jul-98 | 3-Mar-99 | -238 | Positive | | | |
| 4409-002006 | 5-Apr-99 | 3-Mar-99 | 33 | Negative | > 150 | | |
| **4409-002006** | **5-Apr-99** | **3-Mar-99** | **33** | **Negative** | **> 150** | | |
| 4409-002007 | 1-Mar-99 | 10-Mar-99 | -9 | Positive | | | |
| 4409-002007 | 13-Apr-99 | 10-Mar-99 | 34 | Negative | > 150 | | |
| **4409-002007** | **13-Apr-99** | **10-Mar-99** | **34** | **Negative** | **> 150** | | |
| 4409-003002 | 17-Mar-98 | 9-Dec-98 | -267 | Positive | | | |
| 4409-003002 | 10-Dec-98 | 9-Dec-98 | 1 | | 3393 | | |
| 4409-003002 | 11-Dec-98 | 9-Dec-98 | 2 | | 10434 | | |
| 4409-003002 | 12-Dec-98 | 9-Dec-98 | 3 | | | < 0.01 | |
| 4409-003002 | 14-Dec-98 | 9-Dec-98 | 5 | | | < 0.01 | |
| 4409-003002 | 15-Dec-98 | 9-Dec-98 | 6 | | | < 5 | |
| 4409-003002 | 16-Dec-98 | 9-Dec-98 | 7 | | 3751 | < 5 | |
| 4409-003002 | 18-Dec-98 | 9-Dec-98 | 9 | | 6331 | | |
| 4409-003002 | 21-Dec-98 | 9-Dec-98 | 12 | | 2397 | | |
| 4409-003002 | 29-Dec-98 | 9-Dec-98 | 20 | | 4310 | | |
| 4409-003002 | 13-Jan-99 | 9-Dec-98 | 35 | | 3082 | | |
| 4409-003002 | 2-Feb-99 | 9-Dec-98 | 55 | | 1232 | | |
| 4409-003002 | 23-Mar-99 | 9-Dec-98 | 104 | | 432 | | |
| 4409-003002 | 4-Jun-99 | 9-Dec-98 | 177 | | 542 | | |
| 4409-003002 | 30-Jun-99 | 9-Dec-98 | 203 | | | < 5 | |
| 4409-003002 | 27-Sep-99 | 9-Dec-98 | 292 | | 560.5 | 1080.1 | |
| 4409-003002 | 14-Dec-99 | 9-Dec-98 | 370 | | 829 | | |
| 4409-003002 | 7-Feb-01 | 9-Dec-98 | 791 | | 1072 | | |
| 4409-003002 | 1-Mar-02 | 9-Dec-98 | 1178 | | 246 | | |
| 4409-003002 | 14-Mar-03 | 9-Dec-98 | 1556 | | 596 | | |
| 4409-003002 | 20-Jan-04 | 9-Dec-98 | 1868 | | > 150 | Negative | |
| 4409-003002 | 27-Jan-04 | 9-Dec-98 | 1875 | | > 150 | Negative | |
| **4409-003002** | **27-Jan-04** | **9-Dec-98** | **1875** | | **> 150** | **Negative** | |
| 4409-003009 | 10-Dec-98 | 9-Feb-99 | -61 | Positive | | | |
| 4409-003009 | 29-Jan-99 | 9-Feb-99 | -11 | | | 4883 | |
| 4409-003009 | 10-Feb-99 | 9-Feb-99 | 1 | | 40 | | |
| 4409-003009 | 11-Feb-99 | 9-Feb-99 | 2 | Negative | 1315.3 | | |
| 4409-003009 | 16-Feb-99 | 9-Feb-99 | 7 | | 4216 | | |
| 4409-003009 | 17-Feb-99 | 9-Feb-99 | 8 | | 9330 | | |
| 4409-003009 | 3-Mar-99 | 9-Feb-99 | 22 | | | < 5 | |
| 4409-003009 | 26-May-99 | 9-Feb-99 | 106 | | 2289 | | |
| 4409-003009 | 28-Jul-99 | 9-Feb-99 | 169 | | 2162 | | |
| 4409-003009 | 27-Sep-99 | 9-Feb-99 | 230 | | 16.9 | | |
| **4409-003009** | **27-Sep-99** | **9-Feb-99** | **230** | | **16.9** | | **1-Feb-00** |
| 4409-003013 | 3-Mar-99 | 4-Mar-99 | -1 | Negative | | | |
| 4409-003013 | 5-Mar-99 | 4-Mar-99 | 1 | | 2678.9 | | |
| **4409-003013** | **5-Mar-99** | **4-Mar-99** | **1** | | **2678.9** | | |
| 4409-003015 | 11-Mar-99 | 13-Mar-99 | -2 | Positive | | | |
| **4409-003015** | **11-Mar-99** | **13-Mar-99** | **-2** | **Positive** | | | |

| SID | Test Date | Xplant Date | Test - Xplant | HBsAg | Anti HBs | HBV DNA | Death |
|---|---|---|---|---|---|---|---|
| 4409-005007 | 15-Dec-98 | 16-Dec-98 | -1 | | | 1172 | |
| 4409-005007 | 16-Dec-98 | 16-Dec-98 | 0 | Positive | | | |
| 4409-005007 | 17-Dec-98 | 16-Dec-98 | 1 | Positive | 34 | | |
| 4409-005007 | 18-Dec-98 | 16-Dec-98 | 2 | Positive | 1 | | |
| 4409-005007 | 19-Dec-98 | 16-Dec-98 | 3 | Positive | < 1 | | |
| 4409-005007 | 20-Dec-98 | 16-Dec-98 | 4 | Negative | 2086 | | |
| 4409-005007 | 21-Dec-98 | 16-Dec-98 | 5 | Negative | 10094 | | |
| 4409-005007 | 22-Dec-98 | 16-Dec-98 | 6 | Negative | 4800 | | |
| 4409-005007 | 23-Dec-98 | 16-Dec-98 | 7 | Negative | Not Done | | |
| 4409-005007 | 26-Dec-98 | 16-Dec-98 | 10 | Negative | 204 | | |
| 4409-005007 | 29-Dec-98 | 16-Dec-98 | 13 | Positive | 119 | | |
| 4409-005007 | 9-Jan-99 | 16-Dec-98 | 24 | | | > 5 | |
| 4409-005007 | 12-Jan-99 | 16-Dec-98 | 27 | | | > 5 | |
| 4409-005007 | 5-Feb-99 | 16-Dec-98 | 51 | | | < 5 | |
| 4409-005007 | 12-Feb-99 | 16-Dec-98 | 58 | | | > 5 | |
| 4409-005007 | 19-Apr-99 | 16-Dec-98 | 124 | | | 5.5 | |
| 4409-005007 | 27-Jul-99 | 16-Dec-98 | 223 | Positive | | < 2.7 | |
| 4409-005007 | 4-Oct-99 | 16-Dec-98 | 292 | Positive | Negative | | |
| 4409-005007 | 1-Dec-99 | 16-Dec-98 | 350 | Positive | | | |
| 4409-005007 | 14-Mar-00 | 16-Dec-98 | 454 | Positive | | | |
| 4409-005007 | 11-May-00 | 16-Dec-98 | 512 | | | 1075.1 | |
| 4409-005007 | 13-Sep-00 | 16-Dec-98 | 637 | Positive | | 2282.8 | |
| 4409-005007 | 12-Jan-01 | 16-Dec-98 | 758 | Positive | | 889.1 | |
| 4409-005007 | 27-Feb-01 | 16-Dec-98 | 804 | | | 2097.1 | |
| 4409-005007 | 20-Mar-01 | 16-Dec-98 | 825 | Positive | | | |
| **4409-005007** | **20-Mar-01** | **16-Dec-98** | **825** | **Positive** | | | **17-Apr-01** |
| 4409-005010 | 1-Apr-98 | 6-Mar-99 | -339 | Positive | | < 0.7 | |
| 4409-005010 | 9-Mar-99 | 6-Mar-99 | 3 | | 4351 | | |
| 4409-005010 | 10-Mar-99 | 6-Mar-99 | 4 | | 3723 | | |
| 4409-005010 | 11-Mar-99 | 6-Mar-99 | 5 | Negative | 3466 | | |
| 4409-005010 | 12-Mar-99 | 6-Mar-99 | 6 | Negative | 3902 | | |
| 4409-005010 | 15-Mar-99 | 6-Mar-99 | 9 | Negative | 3060 | < 0.5 | |
| 4409-005010 | 17-Mar-99 | 6-Mar-99 | 11 | Negative | | < 0.5 | |
| 4409-005010 | 22-Mar-99 | 6-Mar-99 | 16 | Negative | | | |
| 4409-005010 | 29-Mar-99 | 6-Mar-99 | 23 | Negative | | | |
| 4409-005010 | 7-Sep-99 | 6-Mar-99 | 185 | Negative | | | |
| 4409-005010 | 19-Oct-99 | 6-Mar-99 | 227 | | 93 | | |
| 4409-005010 | 13-Dec-99 | 6-Mar-99 | 282 | Negative | | | |
| 4409-005010 | 3-Mar-00 | 6-Mar-99 | 363 | Negative | | | |
| 4409-005010 | 26-Jan-01 | 6-Mar-99 | 692 | Negative | | | |
| 4409-005010 | 12-Mar-02 | 6-Mar-99 | 1102 | Negative | | | |
| 4409-005010 | 18-Jun-02 | 6-Mar-99 | 1200 | Negative | | | |
| **4409-005010** | **18-Jun-02** | **6-Mar-99** | **1200** | **Negative** | | | |
| 4409-005011 | 13-Aug-98 | 7-Mar-99 | -206 | Positive | | 3110 | |
| 4409-005011 | 7-Mar-99 | 7-Mar-99 | 0 | | | < 5 | |
| 4409-005011 | 9-Mar-99 | 7-Mar-99 | 2 | | | < 5 | |
| 4409-005011 | 10-Mar-99 | 7-Mar-99 | 3 | | | < 5 | |
| 4409-005011 | 12-Mar-99 | 7-Mar-99 | 5 | | 1205 | | |
| 4409-005011 | 13-Mar-99 | 7-Mar-99 | 6 | Negative | 963 | | |
| 4409-005011 | 14-Mar-99 | 7-Mar-99 | 7 | Negative | 1026 | < 0.5 | |
| 4409-005011 | 15-Mar-99 | 7-Mar-99 | 8 | Negative | 1298 | < 0.5 | |
| 4409-005011 | 16-Mar-99 | 7-Mar-99 | 9 | | 1380 | | |

| SID | Test Date | Xplant Date | Test - Xplant | HBsAg | Anti HBs | HBV DNA | Death |
|---|---|---|---|---|---|---|---|
| 4409-005011 | 17-Mar-99 | 7-Mar-99 | 10 | Negative | | | |
| 4409-005011 | 22-Mar-99 | 7-Mar-99 | 15 | Negative | | | |
| 4409-005011 | 29-Mar-99 | 7-Mar-99 | 22 | Negative | | | |
| 4409-005011 | 20-Apr-99 | 7-Mar-99 | 44 | Negative | | | |
| 4409-005011 | 8-Sep-99 | 7-Mar-99 | 185 | Negative | | | |
| 4409-005011 | 5-Oct-99 | 7-Mar-99 | 212 | | 30 | | |
| 4409-005011 | 1-Nov-99 | 7-Mar-99 | 239 | Negative | | | |
| 4409-005011 | 3-Mar-00 | 7-Mar-99 | 362 | Negative | | | |
| 4409-005011 | 4-Apr-00 | 7-Mar-99 | 394 | | | Negative | |
| 4409-005011 | 10-Sep-00 | 7-Mar-99 | 553 | Negative | | | |
| 4409-005011 | 14-May-03 | 7-Mar-99 | 1529 | | 1235 | Negative | |
| 4409-005011 | 3-Jun-03 | 7-Mar-99 | 1549 | Negative | | | |
| 4409-005011 | 14-Dec-03 | 7-Mar-99 | 1743 | Negative | | | |
| 4409-005011 | 16-Dec-03 | 7-Mar-99 | 1745 | Negative | | Negative | |
| **4409-005011** | **16-Dec-03** | **7-Mar-99** | **1745** | **Negative** | | **Negative** | |
| 4409-005012 | 28-Sep-98 | 18-Mar-99 | -171 | Positive | | 218 | |
| 4409-005012 | 18-Mar-99 | 18-Mar-99 | 0 | | | < 0.5 | |
| 4409-005012 | 19-Mar-99 | 18-Mar-99 | 1 | | 3572 | | |
| 4409-005012 | 20-Mar-99 | 18-Mar-99 | 2 | | 4535 | | |
| 4409-005012 | 21-Mar-99 | 18-Mar-99 | 3 | | 3493 | | |
| 4409-005012 | 22-Mar-99 | 18-Mar-99 | 4 | | 2628 | | |
| 4409-005012 | 26-Mar-99 | 18-Mar-99 | 8 | | 3836 | | |
| 4409-005012 | 31-Mar-99 | 18-Mar-99 | 13 | Negative | | | |
| 4409-005012 | 5-Apr-99 | 18-Mar-99 | 18 | Negative | | | |
| 4409-005012 | 14-Apr-99 | 18-Mar-99 | 27 | Negative | | | |
| 4409-005012 | 21-Apr-99 | 18-Mar-99 | 34 | Negative | | | |
| 4409-005012 | 31-Aug-99 | 18-Mar-99 | 166 | | 574 | | |
| 4409-005012 | 17-Sep-99 | 18-Mar-99 | 183 | Negative | | | |
| 4409-005012 | 18-Jan-00 | 18-Mar-99 | 306 | Negative | | Negative | |
| 4409-005012 | 15-Feb-00 | 18-Mar-99 | 334 | | 24 | | |
| 4409-005012 | 18-Apr-00 | 18-Mar-99 | 397 | Negative | | | |
| 4409-005012 | 30-Apr-01 | 18-Mar-99 | 774 | Negative | | | |
| 4409-005012 | 30-Apr-02 | 18-Mar-99 | 1139 | Negative | | Negative | |
| 4409-005012 | 16-Apr-03 | 18-Mar-99 | 1490 | Negative | 468 | Negative | |
| 4409-005012 | 31-Dec-03 | 18-Mar-99 | 1749 | Negative | | | |
| 4409-005012 | 15-Jan-04 | 18-Mar-99 | 1764 | Negative | | Negative | |
| **4409-005012** | **15-Jan-04** | **18-Mar-99** | **1764** | **Negative** | | **Negative** | |
| 4409-006009 | 28-Feb-95 | 4-Feb-99 | -1437 | | | 1.6 | |
| 4409-006009 | 14-Jan-99 | 4-Feb-99 | -21 | Positive | | | |
| 4409-006009 | 2-Mar-99 | 4-Feb-99 | 26 | Negative | Positive | | |
| 4409-006009 | 6-May-99 | 4-Feb-99 | 91 | Negative | Positive | | |
| 4409-006009 | 6-May-99 | 4-Feb-99 | 91 | Negative | Positive | | |
| 4409-010005 | 12-Dec-94 | 27-Mar-99 | -1566 | Negative | | | |
| 4409-010005 | 23-Feb-99 | 27-Mar-99 | -32 | | | < 5 | |
| 4409-010005 | 3-Mar-99 | 27-Mar-99 | -24 | Negative | | | |
| 4409-010005 | 4-Mar-99 | 27-Mar-99 | -23 | | 3025 | | |
| 4409-010005 | 8-Mar-99 | 27-Mar-99 | -19 | | 2239 | | |
| 4409-010005 | 15-Mar-99 | 27-Mar-99 | -12 | | 1210 | | |
| 4409-010005 | 22-Mar-99 | 27-Mar-99 | -5 | Negative | | | |
| 4409-010005 | 23-Mar-99 | 27-Mar-99 | -4 | | | < 5 | |
| 4409-010005 | 29-Mar-99 | 27-Mar-99 | 2 | | 665 | | |
| 4409-010005 | 8-Apr-99 | 27-Mar-99 | 12 | | 1089 | | |

| SID | Test Date | Xplant Date | Test - Xplant | HBsAg | Anti HBs | HBV DNA | Death |
|---|---|---|---|---|---|---|---|
| 4409-010005 | 9-Apr-99 | 27-Mar-99 | 13 | | | < 5 | |
| 4409-010005 | 26-Apr-99 | 27-Mar-99 | 30 | Negative | | < 5 | |
| 4409-010005 | 3-May-99 | 27-Mar-99 | 37 | Negative | | | |
| 4409-010005 | 10-May-99 | 27-Mar-99 | 44 | Negative | | < 5 | |
| 4409-010005 | 16-Aug-99 | 27-Mar-99 | 142 | Negative | 1089 | | |
| 4409-010005 | 22-Nov-99 | 27-Mar-99 | 240 | Negative | 666 | | |
| 4409-010005 | 7-Feb-00 | 27-Mar-99 | 317 | Negative | 363 | | |
| 4409-010005 | 6-Mar-00 | 27-Mar-99 | 345 | | 182 | | |
| 4409-010005 | 1-May-00 | 27-Mar-99 | 401 | Negative | | | |
| **4409-010005** | **1-May-00** | **27-Mar-99** | **401** | **Negative** | | | |
| 4409-010007 | 31-Mar-99 | 13-Mar-99 | 18 | Negative | 2541 | < 5 | |
| 4409-010007 | 5-Apr-99 | 13-Mar-99 | 23 | Negative | 3812 | < 5 | |
| 4409-010007 | 12-Apr-99 | 13-Mar-99 | 30 | Negative | | < 5 | |
| 4409-010007 | 26-Apr-99 | 13-Mar-99 | 44 | Negative | 1452 | < 5 | |
| 4409-010007 | 30-Aug-99 | 13-Mar-99 | 170 | Negative | 3751 | | |
| 4409-010007 | 13-Dec-99 | 13-Mar-99 | 275 | Negative | 1452 | | |
| 4409-010007 | 7-Feb-00 | 13-Mar-99 | 331 | | 266 | | |
| 4409-010007 | 20-Mar-00 | 13-Mar-99 | 373 | Negative | | | |
| 4409-010007 | 18-Sep-00 | 13-Mar-99 | 555 | Negative | | | |
| **4409-010007** | **18-Sep-00** | **13-Mar-99** | **555** | **Negative** | | | |
| 4409-011001 | 24-Mar-98 | 22-Feb-99 | -335 | Positive | | | |
| 4409-011001 | 15-Apr-98 | 22-Feb-99 | -313 | | | 0 | |
| 4409-011001 | 1-Apr-99 | 22-Feb-99 | 38 | | Positive | | |
| **4409-011001** | **1-Apr-99** | **22-Feb-99** | **38** | | **Positive** | | |
| 4409-016001 | 17-Dec-98 | 17-Mar-99 | -90 | Positive | | < 0.7 | |
| 4409-016001 | 19-Feb-99 | 17-Mar-99 | -26 | Negative | | | |
| 4409-016001 | 16-Mar-99 | 17-Mar-99 | -1 | | | < 0.7 | |
| 4409-016001 | 22-Mar-99 | 17-Mar-99 | 5 | Negative | | | |
| 4409-016001 | 21-Apr-99 | 17-Mar-99 | 35 | Negative | Positive | 1.6 | |
| 4409-016001 | 8-Dec-00 | 17-Mar-99 | 632 | | | < 5 | |
| 4409-016001 | 21-Jan-03 | 17-Mar-99 | 1406 | Negative | Negative | < 0.017 | |
| 4409-016001 | 21-Jan-03 | 17-Mar-99 | 1406 | Negative | Negative | < 0.017 | |
| **4409-016001** | **21-Jan-03** | **17-Mar-99** | **1406** | **Negative** | **Negative** | **< 0.017** | |
| 4409-016002 | 24-Feb-98 | 15-Feb-99 | -356 | | | < 0.7 | |
| 4409-016002 | 24-Dec-98 | 15-Feb-99 | -53 | Positive | | | |
| 4409-016002 | 19-Feb-99 | 15-Feb-99 | 4 | Negative | Positive | | |
| 4409-016002 | 6-Aug-99 | 15-Feb-99 | 172 | Negative | Positive | | |
| 4409-016002 | 4-Oct-99 | 15-Feb-99 | 231 | Negative | Positive | | |
| 4409-016002 | 16-Mar-00 | 15-Feb-99 | 395 | Negative | Positive | | |
| 4409-016002 | 16-Mar-00 | 15-Feb-99 | 395 | Negative | Positive | | |
| 4409-016002 | 16-May-00 | 15-Feb-99 | 456 | Negative | Positive | | |
| 4409-016002 | 16-May-00 | 15-Feb-99 | 456 | Negative | Positive | | |
| 4409-016002 | 3-Aug-00 | 15-Feb-99 | 535 | Negative | Positive | | |
| 4409-016002 | 23-Jan-01 | 15-Feb-99 | 708 | Negative | Negative | < 0.017 | |
| 4409-016002 | 16-Aug-01 | 15-Feb-99 | 913 | Negative | Negative | | |
| 4409-016002 | 10-Dec-03 | 15-Feb-99 | 1759 | Negative | | | |
| **4409-016002** | **10-Dec-03** | **15-Feb-99** | **1759** | **Negative** | | | |
| 4409-016005 | 9-Dec-97 | 22-Feb-99 | -440 | Positive | | < 0.7 | |
| **4409-016005** | **9-Dec-97** | **22-Feb-99** | **-440** | **Positive** | | **< 0.7** | |
| 4409-016010 | 1-Mar-99 | 14-Mar-99 | -13 | Positive | | | |
| 4409-016010 | 5-Mar-99 | 14-Mar-99 | -9 | | | 1459 | |
| 4409-016010 | 29-Aug-99 | 14-Mar-99 | 168 | | Positive | | |

| SID | Test Date | Xplant Date | Test - Xplant | HBsAg | Anti HBs | HBV DNA | Death |
|---|---|---|---|---|---|---|---|
| 4409-016010 | 29-Aug-00 | 14-Mar-99 | 534 | Negative | Positive | | |
| 4409-016010 | 13-Mar-01 | 14-Mar-99 | 730 | Positive | | | |
| 4409-016010 | 26-Mar-01 | 14-Mar-99 | 743 | | | 113.7 | |
| 4409-016010 | 12-Jun-01 | 14-Mar-99 | 821 | Positive | Negative | | |
| 4409-016010 | 4-Sep-01 | 14-Mar-99 | 905 | | | 840.021 | |
| 4409-016010 | 5-Jan-02 | 14-Mar-99 | 1028 | Positive | Negative | | |
| 4409-016010 | 29-Apr-02 | 14-Mar-99 | 1142 | Positive | | 1000 | |
| 4409-016010 | 25-Jul-02 | 14-Mar-99 | 1229 | Negative | | 1000 | |
| **4409-016010** | **25-Jul-02** | **14-Mar-99** | **1229** | **Negative** | | **1000** | |
| 4409-016015 | 16-Nov-98 | 8-Apr-99 | -143 | Positive | | | |
| 4409-016015 | 17-Mar-99 | 8-Apr-99 | -22 | | | < 0.7 | |
| 4409-016015 | 11-Oct-99 | 8-Apr-99 | 186 | Negative | Positive | | |
| 4409-016015 | 18-Jan-00 | 8-Apr-99 | 285 | Negative | Positive | | |
| 4409-016015 | 29-Mar-00 | 8-Apr-99 | 356 | Negative | Positive | | |
| **4409-016015** | **29-Mar-00** | **8-Apr-99** | **356** | **Negative** | **Positive** | | |
| 4409-018001 | 1-Dec-98 | 23-Jan-99 | -53 | Positive | | | |
| 4409-018001 | 17-Jan-99 | 23-Jan-99 | -6 | | | < 5 | |
| 4409-018001 | 23-Jan-99 | 23-Jan-99 | 0 | | 304 | | |
| 4409-018001 | 24-Jan-99 | 23-Jan-99 | 1 | | 2675 | | |
| 4409-018001 | 25-Jan-99 | 23-Jan-99 | 2 | | 1541 | | |
| 4409-018001 | 26-Jan-99 | 23-Jan-99 | 3 | | 1087 | | |
| 4409-018001 | 27-Jan-99 | 23-Jan-99 | 4 | Negative | 718 | | |
| 4409-018001 | 28-Jan-99 | 23-Jan-99 | 5 | | 544 | | |
| 4409-018001 | 29-Jan-99 | 23-Jan-99 | 6 | | 466 | | |
| 4409-018001 | 31-Jan-99 | 23-Jan-99 | 8 | | 357 | | |
| 4409-018001 | 1-Feb-99 | 23-Jan-99 | 9 | | 262 | | |
| 4409-018001 | 4-Feb-99 | 23-Jan-99 | 12 | | 1613 | | |
| 4409-018001 | 7-Feb-99 | 23-Jan-99 | 15 | | 1116 | | |
| 4409-018001 | 12-Feb-99 | 23-Jan-99 | 20 | | 581 | | |
| 4409-018001 | 22-Feb-99 | 23-Jan-99 | 30 | | 767 | | |
| 4409-018001 | 1-Mar-99 | 23-Jan-99 | 37 | | 855 | | |
| 4409-018001 | 8-Mar-99 | 23-Jan-99 | 44 | | 601 | | |
| 4409-018001 | 22-Mar-99 | 23-Jan-99 | 58 | | 650 | | |
| 4409-018001 | 12-Apr-99 | 23-Jan-99 | 79 | Negative | 561 | < 5 | |
| 4409-018001 | 15-Jan-04 | 23-Jan-99 | 1818 | Negative | | | |
| **4409-018001** | **15-Jan-04** | **23-Jan-99** | **1818** | **Negative** | | | |
| 4409-020002 | 8-Feb-99 | 22-Mar-99 | -42 | Positive | | 6 | |
| 4409-020002 | 8-Apr-99 | 22-Mar-99 | 17 | Negative | | | |
| **4409-020002** | **8-Apr-99** | **22-Mar-99** | **17** | **Negative** | | | **16-Apr-99** |
| 4409-028004 | 6-Jan-98 | 12-Feb-99 | -402 | | | Positive | |
| 4409-028004 | 7-Apr-98 | 12-Feb-99 | -311 | Negative | | | |
| 4409-028004 | 18-Aug-99 | 12-Feb-99 | 187 | | | Negative | |
| 4409-028004 | 8-Feb-00 | 12-Feb-99 | 361 | Negative | | | |
| 4409-028004 | 9-Feb-00 | 12-Feb-99 | 362 | | 409.75 | Negative | |
| 4409-028004 | 16-Aug-00 | 12-Feb-99 | 551 | Negative | 417.23 | | |
| 4409-028004 | 28-Sep-01 | 12-Feb-99 | 959 | Negative | 744.26 | | |
| 4409-028004 | 20-Aug-02 | 12-Feb-99 | 1285 | Negative | 332.97 | | |
| 4409-028004 | 13-May-03 | 12-Feb-99 | 1551 | Negative | | Negative | |
| **4409-028004** | **13-May-03** | **12-Feb-99** | **1551** | **Negative** | | **Negative** | |
| 4409-028005 | 9-Feb-99 | 17-Feb-99 | -8 | Positive | | < 5 | |
| 4409-028005 | 17-Feb-99 | 17-Feb-99 | 0 | Positive | | | |
| **4409-028005** | **17-Feb-99** | **17-Feb-99** | **0** | **Positive** | | | **17-Feb-99** |

| SID | Test Date | Xplant Date | Test - Xplant | HBsAg | Anti HBs | HBV DNA | Death |
|---|---|---|---|---|---|---|---|
| 4409-079001 | 18-Nov-98 | 5-Mar-99 | -107 | Positive | | < 0.7 | |
| 4409-079001 | 6-Mar-99 | 5-Mar-99 | 1 | Negative | > 1600 | | |
| 4409-079001 | 7-Mar-99 | 5-Mar-99 | 2 | Negative | 1506 | | |
| 4409-079001 | 9-Mar-99 | 5-Mar-99 | 4 | Negative | > 1600 | | |
| 4409-079001 | 12-Mar-99 | 5-Mar-99 | 7 | Negative | | | |
| 4409-079001 | 22-Mar-99 | 5-Mar-99 | 17 | Negative | > 1600 | | |
| 4409-079001 | 1-Apr-99 | 5-Mar-99 | 27 | | 1379 | | |
| 4409-079001 | 5-Apr-99 | 5-Mar-99 | 31 | Negative | | | |
| **4409-079001** | **5-Apr-99** | **5-Mar-99** | **31** | **Negative** | | | |
| 4409-218001 | 1-Mar-99 | 9-Mar-99 | -8 | Positive | | | |
| 4409-218001 | 18-May-99 | 9-Mar-99 | 70 | Negative | > 150 | | |
| 4409-218001 | 1-Jul-99 | 9-Mar-99 | 114 | Negative | | | |
| **4409-218001** | **1-Jul-99** | **9-Mar-99** | **114** | **Negative** | | | |
| 4409-219008 | 28-Jan-97 | 16-Apr-99 | -808 | | | 440 | |
| 4409-219008 | 26-Mar-97 | 16-Apr-99 | -751 | Positive | | | |
| 4409-219008 | 20-Apr-99 | 16-Apr-99 | 4 | | 8517 | | |
| **4409-219008** | **20-Apr-99** | **16-Apr-99** | **4** | | **8517** | | |
| 4409-221001 | 14-Sep-98 | 16-Mar-99 | -183 | | | < 100 | |
| 4409-221001 | 23-Oct-98 | 16-Mar-99 | -144 | Positive | | | |
| 4409-221001 | 15-Apr-99 | 16-Mar-99 | 30 | Negative | 755 | | |
| **4409-221001** | **15-Apr-99** | **16-Mar-99** | **30** | **Negative** | **755** | | |

## Appendix 2

## Patient Summaries Nabi-4204 and Nabi-4409

| SID | Xplant Date | HBsAg serology Xplant | HBsAg | Anti HBs | HBV DNA | Death | HBV-Related | AE | Clin F/U | Assessment | Eval Ser/Clin |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 4204-001001 | 19-Dec-99 | 1553 | Negative | | | | | | 1633 | 56 year old Asian Indian male with a history of HBV-related HCC liver failure. At surgery he was of unknown replicative status (HBeAg-positive but HBV DNA < 5 pg/mL. There was no serological recurrence through 1212 days and no clinical recurrence through 1633 days. Liver biopsies in Jan 2001, Feb 2002, and Apr 2003 immunostains for HBsAg and HBcAg negative. Liver biopsy March / April 2004 showed minimal steatosis and no rejection - evaluable | Yes |
| 4204-001002 | 6-Feb-00 | 1458 | Negative | 66 | | | | | 1673 | 45 year old White male Rn, no serological recurrence through 1458 days and no clinical recurrence through 1673 days - evaluable | Yes |
| 4204-001003 | 6-Jul-00 | 258 | Negative | | | | | | 1395 | 58 year old white male Rr, serology follow-up to 258 days and clinical follow-up to 1395 days with no recurrence - evaluable | No/Yes |
| 4204-001004 | 20-Jan-01 | 27 | Negative | Positive | | 17-Mar-01 | Yes | Sepsis | 56 | 51 yr white male Nn, died day 56 secondary to bacterial sepsis. Had no recurrence at time of death, but investigator stated that death was related to the HBV infection - evaluable with follow-up censored by death at Day 56 post transplantation | Yes |
| 4204-001005 | 23-Jan-01 | 476 | Negative | 5340 | | | | | 1154 | 54 year old white male Rn, had no recurrence by serology for 476 days and by clinical criteria for 1154 days - evaluable | No/Yes |
| 4204-001006 | 23-Mar-01 | 1207 | Negative | 766 | < 357 | | | | 1280 | 58 year old asian male Rn, no serological recurrence through 1207 days and no clinical recurrence through 1280 days - evaluable | Yes |
| 4204-001007 | 3-Apr-01 | 1268 | Negative | 67 | < 357 | | | | 1275 | 54 year old white female Rn, was HBsAg positive through 62 days post transplant but then became negative and had no recurrence - evaluable | Yes |
| 4204-002001 | 13-Jul-00 | 1083 | Negative | Positive | < 200 | | | | 1094 | 52 year old black male Nn, had no recurrence - evaluable | Yes |
| 4204-002002 | 20-Sep-00 | 839 | Negative | Negative | | | | | 1081 | 51 year old white male Nn, no recurrence - evaluable | Yes |
| 4204-002003 | 2-Feb-01 | 532 | Negative | | < 0.017 | | | | 1159 | 63 year old asian male Rn, no serological recurrence at 532 days and no clinical recurrence at 1159 days - evaluable | No/Yes |
| 4204-002004 | 4-Feb-01 | 23 | Negative | | | | | | 34 | 41 year old white male Nn, no recurrence in first 34 days but withdrew consent and withdrew from study - not evaluable | No |
| 4204-002005 | 17-Feb-01 | 906 | Positive | | 1600000 | | | | 1089 | 47 year old asian male Rn, HBIg discontinued 249 days after transplantation and had recurrence by 906 days post transplantation. On combination antiviral therapy and as of Nov 05 was doing well clinically - not evaluable as Nabi-HB discontinued at 249 days | No |
| 4204-002006 | 22-Feb-01 | 2 | Negative | | | 24-Feb-01 | | ICH | 2 | 45 year old asian male Nn, died secondary to intracranial hemorrhage 2 days after transplantation - not evaluable | No |
| 4204-003001 | 11-Apr-00 | 365 | Negative | | Negative | | | | 1086 | 45 year old white male Rn, no serological recurrence at 365 days and no clinical recurrence at 1086 days - evaluable | No/Yes |
| 4204-004001 | 10-May-00 | 22 | Negative | | | 15-Jun-00 | | Sepsis | 37 | 71 year old white female Rr, did not have recurrence, but had bacterial sepsis and died 37 days post transplantation - evaluable with follow-up censored by death at Day 37 | Yes |
| 4204-004002 | 31-Jul-00 | 7 | Positive | | | 23-Aug-00 | | New Onset UGI Bleed | 24 | 69 year old white male Rr, died secondary to a new upper gastrointestinal hemorrhage 24 days post transplantation - not evaluable due to death within 30 days of transplantation | No |
| 4204-004003 | 10-Jan-01 | 615 | Negative | | | 29-Sep-02 | | | 628 | 43 year old asian male Nn, no serological evidence of recurrence for 615 days and no clinical evidence of recurrence for 628 days. Died secondary to bacterial sepsis 628 days post transplantation - evaluable through 628 days | Yes |
| 4204-004004 | 14-May-01 | 1092 | Negative | > 150 | < 100 | | | | 1671 | 56 year old white male Rr, no serological recurrence at 1092 days and no clinical recurrence at 1671 days- evaluable | Yes |
| 4204-005001 | 20-May-00 | 1449 | Negative | | | | | | 1671 | 53 year old black male Rn, no serological recurrence through 1449 days and no clinical recurrence through 1671 days - evaluable | Yes |
| 4204-005002 | 23-Jun-00 | 1187 | Negative | | | | | | 1637 | 50 year old white male Rn, no recurrence - evaluable | Yes |
| 4204-009001 | 2-Jun-00 | 739 | Negative | 139 | | | | | 1660 | 31 year old white male Rn, no serological recurrence through 739 days and no clinical recurrence through 1660 days - evaluable | Yes |
| 4204-011001 | 5-Jan-01 | 1103 | Negative | | < 160 | | | | 1104 | 49 year old asian male replicative status unknown pre-transplant but appears to be negative post-transplant, no recurrence - evaluable | Yes |

| SID | Xplant Date | HBsAg serology Xplant | HBsAg | Anti HBs | HBV DNA | Death | HBV-Related | AE | Clin F/U | Assessment | Eval Ser/Clin |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 4204-012001 | 30-Jan-00 | 862 | Negative | 1519 | | | | | 1125 | 47 year old asian male Nn, had a single HBsAg-positive serology on day 81 but remainder negative (at a minimum through 862 days) therefore is classified as no recurrence - evaluable | Yes |
| 4204-012002 | 23-May-00 | 1093 | Negative | 4404 | | | | | 1094 | 48 year old asian male Rn, withdrew consent for additional procedures but allowed follow-up information to be collected; no recurrence - evaluable | Yes |
| 4204-012003 | 17-Apr-01 | 1098 | Negative | 85 | | | | | 1099 | 60 year old white male Rr, no recurrence - evaluable | Yes |
| 4204-013001 | 31-Aug-00 | 1365 | Negative | 61 | | | | | 1569 | 51 year old white female Rn, no serological recurrence through 1365 days and no clinical recurrence through 1569 days - evaluable | Yes |
| 4204-015001 | 23-Aug-00 | 635 | Positive | | < 0.5 | | | | 1169 | 48 year old hispanic male Rn, for whom HBIg was discontinued at 252 days and then became HBsAg-positive by 635 days post transplantation. Tenefovir was started in June 2004 and patient is reported to be doing well clinically. Not evaluable as Nabi-HB was discontinued on day 252. | No |
| 4204-015002 | 26-Oct-00 | 532 | Negative | | < 100 | | | | 1080 | 59 year old asian male Nn, no serological recurrence through 532 days - evaluable | No/Yes |
| 4204-015003 | 26-Oct-00 | 223 | Negative | | 0.5 | | | | 1030 | 47 year old male Nn, no serological recurrence through 223 days and no clinical recurrence through 1030 days. Died Nov 2003 - evaluable | No/Yes |
| 4204-015004 | 28-Nov-00 | 253 | Negative | | | | | | 254 | 56 year old asian male Nn, had no recurrence through 253 days of follow-up, but was lost to follow-up prior to 2 years and is therefore not evaluable | No |

| | | | |
|---|---|---|---|
| Eval. By Serology | 18 | Recurred | 0 |
| Eval. By Clinical | 24 | Recurred | 0 |

Nabi-4409 New Transplants Summary

| SID | Xplant Date | HBsAg serology Xplant | HBsAg | Death | HBV-Related | AE | Clin F/U | Assessment | Eval Ser/Clin |
|---|---|---|---|---|---|---|---|---|---|
| 4409-001002 | 14-Dec-98 | 1827 | Negative | | | | 1827 | 54 year old White male was HBeAg-positive and had HBV DNA 599 pg/mL pre-transplantation. Treated with HBIg monotherapy. Had no recurrence by serology or clinical parameters for 1827 days post transplantation - evaluable | Yes |
| 4409-002001 | 23-Nov-98 | -203 | Positive | 18-Dec-98 | | Septic Shock | 25 | 41 year old white male was HBeAg-negative and had HBV DNA < 2.5 pre-transplantation. Developed bacterial sepsis and died 25 days post transplantation. Not evaluable as patient died within 30 days of transplantation | No |
| 4409-002003 | 3-Jan-99 | 93 | Positive | | | | 2032 | 49 year old Asian male HBeAg-negative with HBV DNA 171 pg/mL pre-transplantation. Treated with concomitant lamivudine. Liver biopsies on 29 May 1999 and 4 Aug 2000 (146 and 579 days post-transplantation, respectively) were HBsAg- and HBcAg-positive by immunostains, and showed mild active fibrosis, consistent with recurrent HBV-related liver disease - evaluable | Yes |
| 4409-002004 | 18-Feb-99 | 60 | Negative | | | | 1785 | 54 year old Asian male had no recurrence by serology for 60 days and was clinically well at 1,785 days post transplantation. Received concomitant lamivudine - evaluable | No/Yes |
| 4409-002005 | 23-Feb-99 | 35 | Negative | 10-Dec-00 | | | 656 | 45 year old White male had first OLT for HBV-related liver failure Aug 1996. He was HBsAg-positive pre-transplantation but became HBsAg-negative until 17 Nov 98 when he became HBsAg-positive and was HBeAg-negative. He was re-transplanted on 23 Feb 1999. The patient was treated with HBIg monotherapy and remained HBsAg-negative at the last serology 35 days post-transplantation but remained clinically well until his death 656 days after transplantation. His death was not HBV-related. Evaluable until date of death. | Yes |
| 4409-002006 | 3-Mar-99 | 33 | Negative | | | | 1772 | 58 year old Black male HBeAg-negative pre-transplantation. Treated with HBIg monotherapy and remained HBsAg-negative through last serology 33 days post-transplantation. Had no clinical evidence of recurrence through 1772 days of follow-up. Not evaluable by serology but evaluable based on clinical follow-up. | No/Yes |
| 4409-002007 | 10-Mar-99 | 34 | Negative | | | | 1765 | 54 year old Asian male was HBeAg-negative pre-transplantation. Treated with HBIg monotherapy and was HBsAg-negative at last serology 34 days post-transplantation. Had no clinical evidence of recurrence through 1765 days of follow-up. Not evaluable by serology, but evaluable based on clinical follow-up. | No/Yes |
| 4409-003002 | 9-Dec-98 | -267 | | | | | 1874 | 40 year old Asian female HBeAg-negative and HBV DNA not detected pre-transplantation. Treated with concomitant lamivudine. No post-transplantation HBsAg serology available. There was no clinical recurrence for 1874 days of follow-up - not evaluable by serology but evaluable by clinical | No/Yes |
| 4409-003009 | 9-Feb-99 | 2 | | 1-Feb-00 | | | 269 | 58 year old Asian male HBeAg-negative and HBV DNA not detectable pre-transplantation. Treated with concomitant lamivudine. No clinical evidence of recurrence when the patient died due to a malignancy 269 days post-transplantation - evaluable clinically until date of death at Day 269 post-transplantation. | Yes |
| 4409-003013 | 4-Mar-99 | 1 | | | | | 1 | 41 year old White female received emergent transplant. After receipt of one dose of Nabi-HB was found to be HBsAg-negative. Patient was discontinued from study. Not evaluable due to lack of evidence patient was HBsAg-positive pre-transplantation. | No |
| 4409-003015 | 13-Mar-99 | -2 | Positive | | | | 1721 | 54 year old White male HBeAg-negative pre-transplantation. Treated with HBIg monotherapy. No HBsAg serologies post-transplantation. No clinical evidence of recurrence at 1721 days post-transplantation. Not evaluable by serology, but evaluable clinically. | No/Yes |

Orange = Recurrence

| SID | Xplant Date | HBsAg serology Xplant | HBsAg | Death | HBV-Related | AE | Clin F/U | Assessment | Eval Ser/Clin |
|---|---|---|---|---|---|---|---|---|---|
| 4409-005007 | 16-Dec-98 | 13 | Positive | 17-Apr-01 | Yes | | 852 | 42 year old White male HBeAg-positive and HBV DNA 1172 pg/mL pre-transplantation. Treated with 10 doses of HBIg and then changed to lamivudine monotherapy. A liver biopsy 16 Jun 2000 (548 days post-transplantation) revealed recurrent cirrhosis with lamivudine-resistant HBV. The patient died 852 days post-transplantation with what was considered to be HBV-related liver failure. Not evaluable since the vast majority of treatment was lamivudine monotherapy. | No |
| 4409-005010 | 6-Mar-99 | 1200 | Negative | | | | 1200 | 50 year old White male HBeAg-negative and HBV DNA not detectable pre-transplantation. Treated with HBIg monotherapy. Liver biopsy 3 Feb 2000 (334 days post-transplantation) showed no evidence of rejection. There was no serological or clinical evidence of recurrence for 1200 days post transplantation. Evaluable by serology and clinical f/u | Yes |
| 4409-005011 | 7-Mar-99 | 1745 | Negative | | | | 1745 | 22 year old White male HBeAg-negative but HBV DNA 3110 pg/mL pre-transplantation. Treated with concomitant lamivudine. No serological or clinical evidence of recurrence 1745 days post transplantation. | Yes |
| 4409-005012 | 18-Mar-99 | 1764 | Negative | | | | 1768 | 59 year old Asian female HBeAg-positive and HBV DNA 218 pg/mL pre-transplantation. Treated with concomitant lamivudine. Liver biopsy 15 Sep 1999 (181 days post-transplantation) showed n evidence of hepatitis or rejection. No serological or clinical evidence of recurrence 1768 days post transplantation - evaluable by serology and clinically | Yes |
| 4409-006009 | 4-Feb-99 | 91 | Negative | | | | 1213 | 39 year old White male HBeAg-negative. Treated with HBIg monotherapy. No evidence of recurrence by serology through 91 days post-transplantation and no clinical evidence of recurrenc for 1213 days post-transplantation. Not evaluable by serology but is clinically evaluable. | No/Yes |
| 4409-010005 | 27-Mar-99 | 401 | Negative | | | | 1731 | 40 year old White female HBeAg-negative, HBV DNA < 5 pg/mL pre-transplantation. Pt had liver failure due to Budd-Chiari syndrome. Received an anti-HBc antibody-positive donor liver. Therefore was treated with HBIg monotherapy. Not evaluable as the pt did not have HBV-related liver failure. | No |
| 4409-010007 | 13-Mar-99 | 555 | Negative | | | | 1556 | 48 year old White male HBV DNA < 5 pg/mL pre-transplantation. Patient had HCV-related liver failure and received an anti-HBc antibody-positive donor liver. Therefore was treated with HBIg monotherapy. Not evaluable as the pt did not have HBV-related liver failure | No |
| 4409-011001 | 22-Feb-99 | -313 | | | | | 66 | 50 year old Black male HBV DNA-negative. Treated with HBIg monotherapy. No post-transplantation HBsAg serology available. No clinical evidence of recurrence 66 days post-transplantation. Not evaluable due to inadequate follow-up | No |
| 4409-016001 | 17-Mar-99 | 1406 | Negative | | | | 1406 | 50 year old Hispanic male had the first OLT 12 Feb 1999. Due to hepatic artery thrombosis required second OLT 17 Mar 1999. Patient was HBeAg-positive pre-transplantation #1. Treated with concomitant lamivudine. No evidence of recurrence by serology or clinical evidence of recurrence through 1406 days post-transplantation. Evaluable | Yes |
| 4409-016002 | 15-Feb-99 | 1759 | Negative | | | | 1759 | 52 year old Asian male HBeAg-negative and HBV DNA-negative pre-transplantation. Treated with concomitant lamivudine. A liver biopsy 21 Jul 2000 (522 days post-transplantation) showed mild t moderate rejection. No serological evidence of recurrence and no clinical evidence of recurrence through 1759 days post-transplantation. Evaluable | Yes |

Orange = Recurrence

Nabi-4409 New Transplants Summary

| SID | Xplant Date | HBsAg serology Xplant | HBsAg | Death | HBV-Related | AE | Clin F/U | Assessment | Eval Ser/Clin |
|---|---|---|---|---|---|---|---|---|---|
| 4409-016005 | 22-Feb-99 | -440 | Positive | | | | 80 | 52 year old White male HBeAg-negative, HBV DNA-negative. Not evaluable by serology as no HBsAg serology recorded post-transplantation and not evaluable clinically the duration of follow-up is inadequate | No |
| 4409-016010 | 14-Mar-99 | 1229 | Negative | | | | 1229 | 59 year old Asian male HBeAg-positive and HBV DNA 1459 pg/mL pre-transplantation. Treated with HBIg monotherapy for 184 days. Remained HBsAg-negative through Day 534 post-transplantation but then became HBsAg-positive until 1229 days post-transplantation (also had HBV DNA 1000 pg/mL through Day 1229). Evaluable case of recurrence due to discontinuation of Nabi-HB at 184 days. | Yes |
| 4409-016015 | 8-Apr-99 | 356 | Negative | | | | 356 | 40 year old White male HBV DNA <0.7 pg/mL pre-transplantation. Treated with 7 doses of HBIg and then lamivudine monotherapy. Not evaluable due to inadequate HBIg | No |
| 4409-018001 | 23-Jan-99 | 1818 | Negative | | | | 1818 | 43 year old Asian male HBeAg-positive but HBV DNA < 5 pg/mL pre-transplantation. Treated with HBIg monotherapy. No evidence of serological or clinical recurrence through 1818 days post-transplantation. Evaluable by serology and clinical follow-up | Yes |
| 4409-020002 | 22-Mar-99 | 17 | Negative | 16-Apr-99 | | | 25 | Patient died 25 days post-transplantation. Not evaluable due to death within 30 days and inadequate follow-up | No |
| 4409-028004 | 12-Feb-99 | 1551 | Negative | | | | 1697 | 57 year old White male HBeAg-negative. The patient had numerous HBsAg serologies going bac to 1996 and all are negative. In early 1996 a HBeAg was positive, but a repeat one month later was HBeAg-negative and the patient had measurable anti-HBe antibody. Immunohistology stain o the native liver (at the time of transplantation) was negative for HBsAg and HBcAg. The patient is therefore not evaluable | No |
| 4409-028005 | 17-Feb-99 | 0 | Positive | 17-Feb-99 | Yes | Primary Non-functioning Graft | 1 | Died one day post-transplantation due to non-functioning graft. Not evaluable | No |
| 4409-079001 | 5-Mar-99 | 31 | Negative | | | | 59 | Not evaluable due to inadequate follow-up | No |
| 4409-218001 | 9-Mar-99 | 114 | Negative | | | | 70 | Not evaluable due to inadequate follow-up | No |
| 4409-219008 | 16-Apr-99 | -751 | | | | | 28 | Not evaluable due to inadequate follow-up and no HBsAg serology post-transplantation. | No |
| 4409-221001 | 16-Mar-99 | 30 | Negative | | | | 73 | Not evaluable due to inadequate follow-up | No |

Orange = Recurrence

| | | | |
|---|---|---|---|
| Eval By Serology | 11 | Recurred | 1 |
| Eval by Clinical | 17 | Recurred | 1 |

**Attachment 4**

**Draft Package Insert**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use Nabi-HB Intravenous (Nabi-HB IV) safely and effectively. See full prescribing information for Nabi-HB IV.**

**Nabi-HB® Intravenous**
**Hepatitis B Immune Globulin (Human), Intravenous**
***Solvent/Detergent Treated and Filtered***
**Initial U.S. Approval: 200X**

**----------INDICATIONS AND USAGE----------**
Nabi-HB Intravenous (Nabi-HB IV) is indicated for the prevention of hepatitis B clinical disease in HBsAg-positive liver transplant recipients (1).

**----------DOSAGE AND ADMINISTRATION----------**
The suggested dose and dose-schedule for Nabi-HB IV administration to maintain the target minimum trough levels is as follows: (2)

| Weeks Post Transplant | Minimum Trough anti-HBs Level | Usual Dose Necessary |
|---|---|---|
| 0 – 2 | 500 IU/L | 10,000 IU anhepatically and then daily |
| 2 – 12 | 250 IU/L | 10,000 IU weekly or every 2 weeks* |
| >12 | 100 IU/L | 10,000 IU monthly** |
| * Depending on measured anti-HBs titer<br>** After one year some patients may achieve minimum trough levels with longer dosing intervals | | |

**----------DOSAGE FORMS AND STRENGTHS----------**
30 mL, single use vial (>208 IU/mL) in a carton containing greater than 5,000 IU (3).

**----------CONTRAINDICATIONS----------**
- History of anaphylactic or severe systemic reaction to human globulin (4).
- IgA deficient individuals may have the potential to develop IgA antibodies and have an anaphylactoid reaction (4).

**----------WARNINGS AND PRECAUTIONS----------**
- Anaphylactoid reactions in patients with isolated IgA deficiency (5.1).
- Risk of transmission of infectious agents from human plasma (5.2).

**----------ADVERSE REACTIONS----------**
Most common adverse reactions (incidence >2 %) are back pain, leg pain, and nausea (6).

**To report SUSPECTED ADVERSE REACTIONS, contact Nabi Biopharmaceuticals at 1-800-458-4244 or *www.nabi.com* or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch***

**----------DRUG INTERACTIONS----------**
- Effect on vaccination with live virus vaccines is not known. May be necessary to revaccinate persons while on Nabi-HB IV therapy (7.1)
- Nabi-HB IV should not be administered intravenously with other drugs (7.2).

**----------USE IN SPECIFIC POPULATIONS----------**

- Nabi-HB IV should be given to a pregnant woman only if clearly indicated (8.1).
- Caution should be exercised when Nabi-HB IV is administered to a nursing mother (8.3).
- Nabi-HB IV should only be given to IgA deficient persons or persons with unknown IgA levels if the expected benefits outweigh the potential risks (5.1).

**See 17 for PATIENT COUNSELING INFORMATION**

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**FULL PRESCRIBING INFORMATION: CONTENTS***

**1 INDICATIONS AND USAGE**
**2 DOSAGE AND ADMINISTRATION**
**3 DOSAGE FORMS AND STRENGTHS**
**4 CONTRAINDICATIONS**
**5 WARNINGS AND PRECAUTIONS**
**5.1 Anaphylactoid Reactions**
**5.2 Risk of Transmission of Infections Agents from Human Plasma**
**6 ADVERSE REACTIONS**
**7 DRUG INTERACTIONS**
**7.1 Vaccinations**
**7.2 Concomitant Adminstration with Lamivudine**
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**8 USE IN SPECIFIC POPULATIONS**
**8.1 Pregnancy**
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**10 OVERDOSAGE**
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**12 CLINICAL PHARMACOLOGY**
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**14 CLINICAL STUDIES**
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**15 REFERENCES**
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**17.1 Allergies**
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**17.4 Children**
**17.5 Older Adults**

* Sections or subsections omitted from full prescribing information are not listed

## FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

Nabi-HB IV is indicated for the prevention of hepatitis B clinical disease in HBsAg-positive liver transplant recipients.

Nabi-HB IV is indicated for intravenous use.

## 2 DOSAGE AND ADMINISTRATION

Intravenous drug products should be inspected visually for particulate matter and discoloration prior to administration.

The required volume (see below for dosage recommendation) should be calculated and withdrawn from the vial(s) using aseptic technique and transferred into 250 mL sterile saline. Infusion should be via infusion pump and should not be less than one hour in duration.

Infusions of Nabi-HB IV are generally well tolerated when given over at least one hour, and patients are generally not premedicated. However, pre-infusion medication, and an extended infusion time should be considered for patients with a history of high sensitivity to intravenous administration of hepatitis B immune globulin (HBIG).

Nabi-HB IV should be given via a separate infusion line. No other medications should be mixed with Nabi-HB IV.

The goal of the dose regimen of Nabi-HB IV is to achieve the minimum trough anti-HBs levels (measured by enzyme immunoassay) reported to be associated with successful repression of HBV following liver transplantation.[3]

The suggested dose and dose-schedule for Nabi-HB IV administration to maintain the target minimum trough levels are shown in Table 1:

**Table 1. Usual Doses and Intervals Necessary to Achieve Minimum Trough Anti-HBs Levels**

| Weeks Post Transplant | Minimum Trough anti-HBs Level | Usual Dose Necessary |
|---|---|---|
| 0 – 2 | 500 IU/L | 10,000 IU anhepatically and then daily |
| 2 – 12 | 250 IU/L | 10,000 IU weekly or every 2 weeks* |
| >12 | 100 IU/L | 10,000 IU monthly** |

* Depending on measured anti-HBs titer
** After one year some patients may achieve minimum trough levels with longer dosing intervals

The recommended dosage for patients receiving combination antiviral therapy:
Nabi-HB 20,000 IU intra-operative and 10,000 IU/day for seven days for early HBsAg neutralization. Patients with active replication at the time of transplantation have the highest HBIG dose requirements to achieve these targets and have prolonged exposure to circulating

HBsAg within the first week of liver transplantation. In order to obtain neutralizing anti-HBs titers in the early post liver transplantation period, additional 10,000 IU doses of HBIG should be considered.

After the first 12 weeks post-transplantation, 10,000 IU Nabi-HB IV should be administered monthly to maintain trough antibody levels above 100 IU/L. The trough anti-HBs antibody levels should be monitored and the dose and administration schedule should be supplemented with additional doses of Nabi-HB IV as necessary to maintain a trough level of 100 IU/L.

**These are guidelines only. For each patient, the frequency of Nabi-HB IV should be based on serum anti-HBs levels.**

Titers should be assayed using a quantitative enzyme-linked immunosorbant assay (EIA), a monoclonal in conjunction with a quantitation panel and HBe(rDNA) EIA for HBsAg, anti-HBs and HBeAg respectively.

## 3 DOSAGE FORMS AND STRENGTHS

Nabi-HB® IV, Hepatitis B Immune Globulin (Human) Intravenous, is supplied in carton containing greater than 5,000 IU in a 30 mL, single use vial (>208 IU/mL).

## 4 CONTRAINDICATIONS

Individuals known to have had an anaphylactic or severe systemic reaction to human globulin should not receive Nabi-HB IV, Hepatitis B Immune Globulin (Human), or any other human immune globulin. Nabi-HB IV contains less than 100 micrograms IgA per mL. Individuals who are deficient in IgA may have the potential to develop IgA antibodies and have an anaphylactoid reaction. The physician must weigh the potential benefit of treatment with Nabi-HB IV against the potential for hypersensitivity reactions.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Anaphylactoid Reactions

Because of possible anaphylactoid reactions in patients with isolated immunoglobulin A deficiency, Nabi-HB IV should only be given to IgA deficient persons or persons with unknown IgA levels if the expected benefits outweigh the potential risks.

### 5.2 Risk of Transmission of Infectious Agents from Human Plasma

**Nabi-HB IV is made from human plasma. Products made from human plasma may contain infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. The risk that such products can transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current viral infections, and by inactivating and/or reducing certain viruses. The Nabi-HB IV manufacturing process includes a solvent/detergent treatment step (using tri-*n*-butyl phosphate and Triton® X-100) that is effective in inactivating known enveloped viruses such as HBV, HCV, and HIV. Nabi-HB IV is filtered using a Planova® 35 nm Virus Filter that is effective in reducing the levels of**

**some enveloped and non-enveloped viruses. These two processes are designed to increase product safety. Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other health care provider to Nabi Biopharmaceuticals at 1-800-458-4244. The physician should discuss the risks and benefits of this product with the patient.**

## 6 ADVERSE REACTIONS

In the five prospective trials conducted by Nabi, 206 patients who received 1,320 infusions of 10,000 IU Nabi-HB IV were evaluated for safety. Of the 324 adverse events reported, 150 (46%) were considered mild, 113 (35%) moderate, 59 (18%) severe, and 2 (1%) were of unknown intensity. The most frequently reported adverse events thought to be related to Nabi-HB IV were back pain (32 events, 10%), leg pain (7 events, 2%), and nausea (6 events, 2%), which were all resolved.

Only one (2%) of the 46 reported serious adverse events was considered probably related to administration of the product. This event was similar in nature to the back pain experienced by the same patient during and after infusions of study product.

As of June 2006 there have been 30 adverse events reported to Nabi, since Nabi-HB® received marketing approval for post-exposure prophylaxis (administered by intramuscular injection) in 1999. Twenty-one (21) of these adverse events were for Nabi-HB administered by intravenous infusion, and it is estimated that approximately 60,000 intravenous infusions of Nabi-HB, generally of 10,000 IU per administration were given between 1999 and 2006.

No anaphylactic reactions have been reported with Nabi-HB IV or the intramuscular preparation, Nabi-HB®. However, these reactions, although rare, have been reported following the injection of human immune globulins.[2]

## 7 DRUG INTERACTIONS

### 7.1 Vaccinations

The effect of infusions of Nabi-HB IV on vaccination with live virus vaccines is not known. It may be necessary to revaccinate persons who receive a live virus vaccine while on Nabi-HB IV therapy.

### 7.2 Concomitant Administration with Lamivudine

Drug interaction studies have not been performed. However, in a study to evaluate concomitant administration of Nabi-HB IV with oral lamivudine, no drug-drug interactions among the 30 peri-operative transplant recipients were observed.[1] Interactions with other drugs have not been studied.

### 7.3 Admixture with Other Drugs

There are no available data on admixture of Nabi-HB IV and other drugs, or simultaneous intravenous administration with other drugs. Nabi-HB IV should not be mixed with other drugs.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Animal reproduction studies have not been conducted with Nabi-HB IV. It is also not known whether Nabi-HB IV can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nabi-HB IV should be given to a pregnant woman only if clearly indicated.

### 8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Nabi-HB IV is administered to a nursing mother.

### 8.4 Pediatric Use

Safety and effectiveness in the pediatric population have not been established.

### 8.5 Geriatric Use

Clinical studies of Nabi-HB IV did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

## 10 OVERDOSAGE

Overdosage effects of Nabi-HB IV have not been observed. Much higher doses than the 10,000 IU per day recommended for the first week post transplantation have been reported without incident. McGory, *et al.*[3], successfully administered 20,000 IU per day (5,000 IU q6h) during the first week following transplantation in patients with actively replicating virus. Doses up to 50,000 IU per day have been reported.[3]

## 11 DESCRIPTION

Nabi-HB IV, Hepatitis B Immune Globulin (Human) Intravenous, is a sterile solution of immunoglobulin (5 ±1% protein) containing antibodies to hepatitis B surface antigen (anti-HBs). It is prepared from plasma obtained from individuals with high titers of anti-HBs. The plasma is processed using a modified Cohn 6 / Oncley 9 cold-alcohol fractionation process[4,5] with two added virus reduction steps described below. Nabi-HB IV is formulated in 0.075 M sodium chloride, 0.15 M glycine, and 0.01% polysorbate 80, at pH 6.2. The product is supplied as a nonturbid, clear to opalescent, sterile liquid in a single dose vial. It contains no preservative and is intended for single use by intravenous administration.

The manufacturing steps for Nabi-HB IV are designed to reduce the risk of transmission of viral disease. The solvent/detergent treatment step, using tri-*n*-butyl phosphate and Triton® X-100, is effective in inactivating known enveloped viruses such as hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV)[6]. Virus filtration, using a Planova® 35 nm Virus Filter, is effective in reducing some known enveloped and non-enveloped viruses[7]. The inactivation and reduction of known enveloped and non-enveloped model viruses were validated in laboratory studies as summarized in the following tables:

**Table 2a - Summary Characteristics of the Viruses used in the Validation Studies[8]**

| Virus | Family | Envelope | Genome | Size (nm) | Shape | Model |
|---|---|---|---|---|---|---|
| Pseudorabies Virus (PrV) | Herpesviridae | Yes | DNA | 150 - 200 | Spherical | Human Herpes virus |
| Human Immunodeficiency Virus (HIV) | Retroviridae | Yes | RNA | 80 - 130 | Spherical | Relevant pathogen |
| Bovine Viral Diarrhea Virus (BVD) | Flaviviridae | Yes | RNA | 60 - 70 | Spherical | Hepatitis C |
| West Nile Virus (WNV) | Flaviviridae | Yes | RNA | 60 - 70 | Spherical | Relevant pathogen |
| Encephalomyocarditis Virus (EMC) | Picornaviridae | No | RNA | 28 -30 | Icosahedral | Hepatitis A |
| Hepatitis A Virus (HAV) | Picornaviridae | No | RNA | 28 -30 | Icosahedral | Hepatitis A |
| Porcine Parvovirus (PPV) | Parvoviridae | No | DNA | 18 - 26 | Icosahedral | Human Parvovirus B19 |

**Table 2b – Summary of $Log_{10}$ Reduction Values Obtained in Virus Studies[8]**

| Process Step Validated | PrV | HIV | BVD | WNV | EMC | PPV |
|---|---|---|---|---|---|---|
| Precipitation and Separation Of Fraction III | 3.7 | > 5.9 | 3.6 | NT | 4.4 | 3.9 |
| Depth Filtration of Fraction III Centrifugate, | NT | NT | NT | NT | > 6.6 | 5.4 |
| S/D Treatment of Redissolved Fraction II Paste | *> 6.5 | *> 6.3 | *> 6.9 | *> 6.8 | NT | NT |
| Nanofiltration (35 nm) | *> 5.7 | *> 7.4 | > 6.9 | NT | 3.0[a] | 0.7[a] |
| Cumulative Clearance | > 15.8 | > 17.5 | > 17.4 | NT | > 11.0[a] | 9.3[a] |

NT = Not Tested. Results marked with an asterisk (*) indicate virus removed to the limit of detection in all replicates tested.
[a] cumulative clearance for EMC and PPV does not include reduction observed for nanofiltration

Product potency is expressed in international units (IU) by comparison to the World Health Organization (WHO) standard. Each milliliter (mL) of product contains a minimum of >208 IU anti-HBs/mL. The potency of each milliliter of Nabi-HB IV exceeds the potency of anti-HBs in a U.S. reference hepatitis B immune globulin (FDA). The U.S. reference has been tested by Nabi against the WHO standard and found to be equal to 208 IU/mL.

## 12 CLINICAL PHARMACOLOGY

The ability of hepatitis B immune globulin (HBIG) to prevent hepatitis B clinical disease in HBsAg – positive liver transplant recipients is well established in the literature, and is the minimum standard of care.

Early efforts when moderate doses and limited duration of HBIG administration were used following transplantation were disappointing.[9-11] However, later studies demonstrated that larger doses and indefinite administration of HBIG reduced HBV recurrence to between 25% and 36%, with the best results found in patients who were negative for active virus replication (HBeAg and HBV DNA negative) at the time of transplantation.[3, 12-17]

It was suggested by several studies that a minimum trough level of >100 IU/L was associated with prevention of recurrence of HBV in the majority of patients. Failures occurred most commonly in HBeAg-positive or HBV DNA-positive patients. The target minimum trough anti-HBs level of >100 IU/L was associated with approximately 75% success in prevention of HBV recurrence, compared to 20% without HBIG treatment.[12-17] McGory et al,[3] reported that an aggressive treatment regimen at the University of Virginia (UVA) resulted in successful suppression of HBV in 25 of 27 (93%) orthotopic liver transplant recipients treated for 2 to 55 months (average of 21 months) after transplantation. This low recurrence rate was observed in spite of the fact that 67% of the patients were HBeAg or HBV DNA positive. The target minimum trough levels suggested by the authors were >500 IU/L for the first 7 days post transplantation, >250 IU/L from day 8 to 90, and >100 IU/L thereafter.

Measurement of anti-HBs titers demonstrated that HBIG was consumed rapidly during the first several days following transplantation, and the half-life gradually increased, becoming relatively stable by approximately 12 weeks post-transplantation. Data from 309 infusions of HBIG administered to 27 transplant recipients demonstrated that the mean CL decreased from 13.5 L/D/kg during the first two weeks to 0.002 L/D/kg at least 90 days post-transplantation. The mean Vd decreased from 6.2 L/kg to 0.03 L/kg, and the T½ increased from 0.7 days to 14.1 days. High inter-patient variability in HBIG elimination observed during the first 30 days post-transplantation decreased with time.

HBsAg and quantitative anti-HBs results were correlated for 14 patients during the first week post-transplantation, 19 patients from 8 to 90 days, and for 25 patients >90 days post-transplantation. During the first week post-transplantation, HBsAg was always detectable when anti-HBs levels were ≤300 IU/L. Only when anti-HBs titers were >500 IU/L was HBsAg routinely undetectable. Between 8 and 90 days post-transplantation, HBsAg was undetectable in 112 of 114 samples from 19 patients with a titer of >250 IU/L. Five patients with a titer <250 IU/L had detectable serum HBsAg. After 90 days, HBsAg was detected once 18 months post transplantation in one patient with an anti-HBs titer of 58 IU/L. All other sera samples (n >500) obtained from this patient had anti-HBs titers between 11 and >8000 IU/L and all were HBsAg-negative.

Based on the positive results reported by McGory, *et al.*[3], a dose of approximately 10,000 IU of Nabi-HB IV per infusion was used in the five studies conducted by Nabi, aimed at maintaining a trough level of > 500 IU/L. Nabi-HB IV demonstrated greater than 98%

absolute efficacy using a dose of 10,000 IU per infusion with a variable infusion frequency similar to that used by McGory[3], and similar results were seen.

### 12.1 Mechanism of Action

The anti-HBs contained in Nabi-HB IV neutralize HBV by binding to the surface antigen, thereby preventing virus from binding and hence, entering the hepatocyte, which is necessary for virus replication.

### 12.2 Pharmacodynamics

Treatment of patients with Nabi-HB IV and lamivudine was dictated by monitoring serum levels of antibody, with dose levels and duration of dosing being altered accordingly. Target levels were achieved that prevented HBsAg recurrence; see Table 3. The patients were divided into 3 groups based on the HBV replication status at the time of lamivudine initiation and the time of liver transplantation. The Nn Group consisted of patients who were non-replicators at the time of lamivudine initiation and at the time of liver transplantation; the Rn Group consisted of patients who were replicators at the time of lamivudine initiation but non-replicators at the time of, or within two weeks prior to, transplantation; and the Rr Group consisted of patients who were replicators at both evaluations.

**Table 3: Nabi-HB IV with Concomitant Lamivudine**
**Number of Patients Below Specified Anti-HBs Levels/Effectiveness[1]**

| Study Period | Anti-HB (IU/L) | Nn[2] Patients | Rn[3] Patients | Rr[4] Patients | HBsAg Recurrence |
|---|---|---|---|---|---|
| Day 1 - 2 | < 300 | 5/10 (50%) | 8/11 (50%) | 6/6 (100%) | 0 |
| Day 3 - 4 | < 300 | 1/9 (11%) | 3/11 (27%) | 6/6 (100%) | 0 |
| Day 5 | < 300 | 0/9 (0%) | 1/11 (9%) | 1/5 (20%) | 0 |
| Day 6 - 7 | < 300 | 0/9 (0%) | 0/11 (0%) | 2/6 (33%) | 0 |
| Day 8 - 30 | < 200 | 0/9 (0%) | 0/11 (0%) | 2/5 (40%) | 0 |
| Day 31 - Week 12 | < 200 | 0/8 (0%) | 0/11 (0%) | 2/4 (50%) | 0 |
| Weeks 13 -24 | < 100 | 0/7 (0%) | 0/10 (0%) | 1/4 (25%) | 0 |
| Weeks 25 - 36 | < 100 | 0/7 (0%) | 0/1 (0%)0 | 1/4 (25%) | 0 |

[1] Dickson, RC, *et al.*, Liver Transplantation 12:124-133, 2006

[2] Nn = Native non-replicators

[3] Rn = Native Replicators, who became non-replicators as a result of treatment

[4] Rr = Native Replicators, who remained replicators despite treatment

### 12.3 Pharmacokinetics

The pharmacokinetics of HBIG was studied by comparing the Dickson study (Nabi-4204) to the McGory study. The McGory study evaluated intravenous HBIG as monotherapy, while in Nabi-4204, Nabi-HB IV and lamivudine was co-administered. Examination of the anti-HB titers obtained in these two studies provides a mechanism to evaluate the effect of lamivudine on HBIG pharmacokinetic parameters. A standard one-compartment pharmacokinetic model parameterized in terms of clearance and volume of distribution was used for the analysis.

**Table 4: Comparison of pK Parameters by HBV Replication Status**

| pK Parameter | Period (days) | Geometric Mean | | |
|---|---|---|---|---|
| | | Nn[1] | Rn[2] | Rr[3] |
| Clearance (CL) (L/hr) | 1-2 | 0.070 | 0.134 | 3.260 |
| | 3-7 | 0.046 | 0.064 | 0.450 |
| | 8-30 | 0.014 | 0.014 | 0.024 |
| | >30 | 0.007 | 0.007 | 0.013 |
| Half-life (T½) (hr) | 1-2 | 59.1 | 27.3 | 0.7 |
| | 3-7 | 83.6 | 57.4 | 5.1 |
| | 8-30 | 266.2 | 270.2 | 123.4 |
| | >30 | 445.7 | 544.6 | 204.4 |
| Volume of Distribution (Vd) (L) | 1-2 | 5.99 | 5.29 | 3.31 |
| | 3-7 | 5.55 | 5.29 | 3.31 |
| | 8-30 | 5.55 | 5.29 | 4.23 |
| | >30 | 4.59 | 5.29 | 3.69 |

[1] Nn = Native non-replicators

[2] Rn = Native Replicators, who became non-replicators as a result of treatment

[3] Rr = Native Replicators, who remained replicators despite treatment

No significant effect from lamivudine could be determined on either clearance or volume of distribution parameters.

## 14 CLINICAL STUDIES

The Nabi-HB IV database is based on both new transplant and maintenance phase patient studies. The pivotal data are from two studies in 62 new transplant recipients. These data are supported by 4 studies in which Nabi-HB IV was administered to 173 maintenance phase patients. The combined evaluable database consists of 214patients as summarized in Table 5.

**Table 5: Nabi-HB IV Evaluable Patients**

| Study | Study Type | Recurrence Rate (%) |
|---|---|---|
| Nabi-4204[1] (Dickson) | New OLT | 0/24 (0%) |
| Nabi-4409[1] (Expanded Access) | New OLT | 1/17 (6%) |
| Nabi-4409 (Expanded Access) | Maintenance-phase | 0/121 (0%) |
| Nabi-2906 (Safety and pK #1) | Maintenance-phase | 0/21 (0%) |
| Nabi-4203 (Safety and pK #2) | Maintenance-phase | 0/21 (0%) |
| Nabi-4406 (Compassionate Use) | Maintenance-phase | 0/10 (0%) |
| **TOTAL** | **ALL STUDIES** | **1/214 (0.5%)** |

[1] Represents all patients who have at least 2 years of clinical follow-up data

Evidence of efficacy of Nabi-HB IV to prevent recurrence of HBV in new transplant recipients is based on the data from two clinical studies in which Nabi-HB IV was administered to orthotopic liver transplant patients. The results for these studies were compared to historical efficacy rates.

In most cases, the standard of care for patients who are shown to be HBsAg-negative by several observations is to follow them clinically and obtain serology only when clinically indicated. Barring major changes in the health or immune status of the HBsAg-negative patient (particularly those who are native non-replicators or replicators pre-lamivudine but not replicating at transplantation), the frequency, and therefore, need to continually test for HBsAg seroconversion, decreases with time from transplantation. Therefore, calculations of efficacy were based on clinical status at last known clinical observation, as well as, serology.

### 14.1 New Transplant Patient Studies

**Dickson Study (Nabi-4204)**

A prospective, multi-center trial of HBV prophylaxis was conducted in patients undergoing OLT. Nabi-HB IV in combination with lamivudine was administered to determine anti-HBs titers required to neutralize HBsAg, to determine whether suppression of HBV replication by lamivudine prior to OLT affects Nabi-HB IV pharmacokinetics, and to evaluate the efficacy of lower dose Nabi-HB from 12 to 36 weeks post-transplantation with follow-up extended to at least 2 years.

Twenty-four (24) of the 28 patients with an evaluable clinical endpoint were followed clinically for ≥ 2 years. The 0% recurrence is less than 45%, the literature rate for recipients of lamivudine; see Table 6.

There were also no recurrences among the 18 patients who either died > 30 days post transplantation or had serology data ≥ 2 years following transplantation. Again, the 0% recurrence is significantly less than 45%. The 18 patients were followed for a mean of 2.8 years; see Table 7.

**Expanded Access Study (Nabi-4409)**

This open-label expanded access study included 121 maintenance-phase patients and 32 newly transplanted patients to be evaluated for recurrence of HBV infection by HBsAg. Nabi-HB IV was well tolerated in this study, and adverse events were consistent with those reported previously.

Seventeen of the 24 patients with an evaluable clinical endpoint were followed clinically for ≥ 2 years. There was 1 clinical recurrence among the 17 patients (5.9%), less than 45%, the reference rate for recipients treated with lamivudine monotherapy (relative efficacy = 86.9%); see Table 6.

There was 1 recurrence among the 11 patients (9.0%) who either died at least 30 days post transplantation or had serology data at least 2 years following transplantation. The 9.0% recurrence is also less than 45%, (relative efficacy = 79.8%). The 11 patients were followed for a mean of 3.2 years; see Table 7.

**Pooled Database of New Transplant Patients**

For the combined database of new transplant patients in both the Dickson study and the Expanded Access Study, there was 1 recurrence among the 41 patients who either had clinical follow-up for at least 2 years or died at least 30 days post transplantation. The observed recurrence of 2.4% (1 of 41) was less than the 45% with lamivudine monotherapy (relative efficacy of 94.6%); see Table 6. The 1 recurrence in 70.7 person-years, yields a person-time recurrence rate of 1.4 per 100 person-years.

Similarly, there was 1 recurrence among the 29 patients who either had serology follow-up for at least 2 years or died at least 30 days post transplantation. The observed recurrence of 3.4% (1 of 29) was significantly less than the 45% with lamivudine monotherapy (relative efficacy 92.3%); see Table 7. The 1 recurrence in 36 person-years, yields a person-time recurrence rate of 2.8 per 100 person-years.

**Table 6: Efficacy of Nabi-HB with Lamivudine Compared to Lamivudine Monotherapy for Evaluable Population based on Follow-up[1]**

| Study | Recurrences (Relative Efficacy[2]) | p-value[3] |
|---|---|---|
| Dickson | 0/24 (100%) | < 0.0001 |
| Expanded Access | 1/17 (86.9%) | 0.0012 |
| Pooled | 1/41 (94.6%) | < 0.0001 |

[1] **New OLT Patients with ≥ 2 Years of Clinical Follow-up**
[2] Relative efficacy assuming lamivudine recurrent rate = 0.45 (details of lamivudine recurrence rate of 0.45 is provided in Section 5.3.2) .
[3] p-value is based on one-sample comparison of recurrent rate to Lamivudine recurrent rate of 0.45.

**Table 7: Efficacy of Nabi-HB with Lamivudine Compared to Lamivudine Monotherapy for Modified All Patients Population based on Serology[1]**

| Study | Recurrences (Relative Efficacy[2]) | p-value[3] |
|---|---|---|
| Dickson | 0/18 (100%) | < 0.0001 |
| Expanded Access | 1/11 (79.8%) | 0.028 |
| Pooled | 1/29 (92.3%) | < 0.0001 |

[1] **New OLT Patients with HBsAg Serology ≥ 2 years.**
[2] Relative efficacy assuming lamivudine recurrent rate = 0.45 (details of lamivudine recurrence rate of 0.45 is provided in Section 5.3.2).
[3] p-value is based on one-sample comparison of recurrent rate to lamivudine recurrent rate of 0.45.

## 14.2 Studies in Maintenance-Phase Liver Transplant Recipients

Four studies were conducted that evaluated a total of 173 maintenance-phase liver transplant recipients. Two of the studies were designed primarily to assess the pharmacokinetics of Nabi-HB IV, however, efficacy was also assessed. All patients were at least 6 months post-transplantation, and while all were HBsAG-positive prior to transplantation, all remained HBsAg-negative post-transplantation. From the third study it was concluded that monthly intravenous administration of Nabi-HB IV was successful in maintaining a negative HBsAg status in 10 maintenance-phase transplant recipients, intravenous infusions of Nabi-HB IV were generally well tolerated, and adverse events were consistent with those reported previously.

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## 16 HOW SUPPLIED/STORAGE AND HANDLING

Nabi-HB IV, Hepatitis B Immune Globulin (Human) Intravenous, is supplied as:

| NDC Number | Contents |
|---|---|
| XXXXXXXXXX | Carton containing greater than 5,000 IU in a 30 mL, single use vial (>208 IU/mL) |

**Storage**
Refrigerate between 2 to 8°C (36 to 46°F).
Do not freeze.
Do not use after expiration date.
Use within 6 hours after the vial has been removed from refrigeration.

## 17 PATIENT COUNSELING INFORMATION

Nabi-HB IV is injected into the vein to prevent infection by the hepatitis B virus in patients who have had a liver transplant. Nabi-HB IV is generally well tolerated. Some patients may occasionally experience back pain, leg pain, or nausea.

In deciding to use this medicine, patients must be advised of the risks of taking the medicine weighed against the benefits. For Nabi-HB IV, the following should be considered:

### 17.1 Allergies

Tell your doctor if you have ever had any unusual or allergic reaction to hepatitis B or any other immune globulin. Also tell your health care professional if you are allergic to any other substances, such as foods, preservatives, or dyes.

### 17.2 Pregnancy

Studies on effects in pregnancy have not been done in either humans or animals.

### 17.3 Breastfeeding

It is not known whether Nabi-HB IV passes into breast milk. Although most medicines pass into breast milk in small amounts, many of them may be used safely while breast-feeding. Mothers who are taking this medicine and who wish to breastfeed should discuss this with their doctor.

### 17.4 Children

Although there is no specific information comparing the use of Nabi-HB IV in children with use in other age groups, this medicine is not expected to cause different side effects or problems in children that it does in adults.

### 17.5 Older Adults

Many medicines have not been studied specifically in older people. Therefore, it may not be know whether they work exactly the same way they do in younger adults or if they cause different side effects in older people. There is no specific information comparing use of Nabi-HB IV in the elderly with use in other age groups.

Manufactured by:
Nabi® Biopharmaceuticals
Boca Raton, FL 33487

**U.S. License No. 1687**
**Part No**. XX.XXXX.XX
Month 200X

***INSERT BAR CODE***

**Attachment 5**

**April 5, 2006 FDA Meeting Minutes**

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

APR 28 2006

Our reference/tracking number: CRMTS 5625

Nabi Biopharmaceuticals
Attn: Lewis Pollack, Ph.D.
12276 Wilkins Ave.
Rockville, MD 20852

Dear Dr. Pollack:

Attached is a copy of the memorandum summarizing your April 5, 2006 meeting with CBER. Please note that although cited as attachments to the summary, we have not included copies of materials which you supplied. This memorandum constitutes the official record of the meeting.

If you have any questions, please contact Michael Wiack at 301-827-5307.

Sincerely yours,

Franklin T. Stephenson

Franklin Stephenson, M.S.
Acting Chief
Regulatory Project Management Branch
Division of Blood Applications
Office of Blood Research and Review
Center for Biologics
Evaluation and Research

**FOOD AND DRUG ADMINISTRATION**
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

**Official Meeting Minutes**

**Date:** April 14, 2006
**From:** Michael Wiack/OBRR/DBA, HFM-380
**To:** File of CRMTS 5625
**Subject:** Nabi Biopharmaceuticals Hepatitis B Immune Globulin Intravenous (Human) STN 125073/0

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**Meeting Date:** April 5, 2006 **Time:** 10:00 – 11:30

**Location:** Teleconference

CBER Meeting Leader: Basil Golding, M.D.
Recorder: Michael Wiack

**FDA Participants:**
Dr. Basil Golding OBRR/DH
Dr. Toby Silverman OBRR/DH
Dr. Charles Maplethorpe OBRR/DH
Dr. Jessica Kim OBE/DB
Dr. Mei-ying Yu OBRR/DH
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**Nabi Participants**
Lewis Pollack, Ph.D.
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Michael Harlow, BS

In an amendment to BLA 125073/0 dated February 17, 2006, Nabi requested a meeting with FDA to "obtain agreement on key points summarized at the December 1, 2005 meeting; the recurrence rate for Lamivudine monotherapy historical control, agreement on patient inclusion criteria for reanalysis of the Nabi 4204 and 4409 databases and the proposed protocol."

After introductions, Dr. Rasmussen began the discussion and stated the data submitted by Nabi demonstrates compelling statistical evidence for the efficacy of their product. New studies have been published supporting the need to maintain HBIG therapy after transplant. Nabi is willing to conduct the proposed clinical trial as a Post Market Commitment. If CBER is not willing to approve Nabi's BLA we would like to take up Dr. Epstein's offer to take this to BPAC.

**Discussion of Sponsor Questions:**

1. *Do you agree with the calculated historical rate for Lamivudine monotherapy of 45%?*

FDA Response: We do not agree with your calculated historical rate. Nabi proposes to use a point estimate which does not satisfy the most conservative scenario as had been discussed at the December 1, 2005 meeting. To take into consideration the variability of the point estimate, a number less than or equal to the lower limit of the 95% confidence interval should be used. The method that Nabi provided gives 35%.

2. *Have we provided sufficient information characterizing the patient population to allow FDA to work with us in developing a consensus database?*

FDA Response: Nabi has not provided sufficient data. There are numerous missing data points for HBsAg measurements in both studies. FDA made the following conclusions based on the data submitted:

a) There were 4 deaths within the first 30 days after transplant, and there were 4 deaths before 2 years after transplant that were not attributable to HBV recurrence. Therefore, these 8 subjects can be removed from the analysis, leaving 54 subjects in the database.
b) For 23 of 54 subjects, the data support the maintenance of HBsAg seronegativity to month 24; however, only 19 of these 23 HBsAg seronegatives received combined Lamivudine + HBIG therapy.
c) For 4 of 54 subjects, there is clear evidence of HBsAg seroconversion before month 24; these subjects are 4204-002003, 4202-15001, 4409-002003, and 4409-005007.
d) For 4 of 54 subjects, the data do not support maintenance of HBsAg seronegativity at month 24, and are consistent with HBsAg seroconversion by month 24. These subjects are 4204-001004 (death at month 2 judged HBV related), 4204-002005 (HBsAg positive at month 37), 4409-003002 (HBV DNA positive at month 10), and 4409-016010 (HBsAg positive from months 25 to 39). The data for subject 4409-003002 are difficult to interpret because there is only one HBsAg measurement at day -267 (positive) and no additional HBsAg measurements reported despite monitoring of anti-HBs levels and HBV DNA measurements out to day +1875. The HBV DNA measurement appears to be negative, except for a reading of 1080.1 at day +292. Lacking data to the contrary, subject 4409-003002 should be classified as a treatment failure based on the day 292 HBV DNA measurement.
e) For 23 of 54 subjects, there were inadequate data to show that the subjects maintained HBsAg seronegativity to month 24, because HBsAg measurements were not submitted for time points up to or after month 24.

3. *Do you agree that the protocol is designed appropriately to demonstrate efficacy of Nabi HBIgIV?*

FDA Response: The protocol is adequate for monitoring HBV recurrence in OLT subjects receiving lamivudine + HBIG prophylaxis, but it should be conducted prior to licensure for the OLT indication.

BPAC Agenda:

- This BLA will be on the agenda of the July BPAC meeting. This will be an open session and scheduled for 2½ hours
- Nabi will have 30 minutes and will speak before CBER does
- Time will be scheduled for public comment
- CBER will present questions to the committee. One question will most likely be to the effect "do you recommend licensure of this product?"

**Attachments/Handouts:**

Nabi information package dated February 17, 2006.

**Attachment 6**

**Nabi's Responses to the April 5, 2006 Meeting Minutes**

**FDA Comment:**

*We do not agree with your calculated historical rate. Nabi proposes to use a point estimate, which does not satisfy the most conservative scenario as had been discussed at the December 1, 2005 meeting. To take into consideration the variability of the point estimate, a number less than or equal to the lower limit of 95% confidence interval should be used. The method that Nabi provided gives 35%.*

**Nabi Response:**

At FDA's request, Nabi provided a meta-analysis of recurrence rates of HBV-related liver disease post liver transplant for lamivudine monotherapy (from the literature). Nabi and the FDA are in agreement with the methodology utilized for the overall estimate of recurrence rate for lamivudine monotherapy (the method and the literature used are provided in Attachment 4). The method yielded a rate of 45% with lower and upper 95% confidence limits of 35% and 54%, respectively. The 45% recurrence rate for lamivudine monotherapy was used as the historic control against which to compare the efficacy of the combination of lamivudine and Nabi-HB in prevention of recurrence of HBV-related clinical disease in HBsAg-positive transplant patients (the results are given in Tables 4-5 and 4-6 of Attachment 3).

The FDA would prefer using the lower 95% confidence limit (35%) for lamivudine monotherapy as the basis for comparison to Nabi-HB IV. There is no precedence for this request, nor is there any scientific or statistical justification for using the lower bounds. The meta-analysis demonstrated a 45% recurrence rate on lamivudine monotherapy, and that is the rate that should form the basis for the historical control. Nabi believes that 45% represents a very conservative rate. If anything, the recurrence rate on lamivudine has increased (up to 80%). However, if you use the 35%, the effect does not go away and is still significant and clinically meaningful. In order to test the robustness of the conclusion, we conducted a sensitivity analysis using the conservative recurrence rate of 35% for lamivudine monotherapy. As it appears from Tables 1 and 2, the sensitivity analysis is consistent with the results obtained when the point estimate rate of 45% for lamivudine monotherapy was utilized. So, even if one uses a 35% recurrence rate, the effect does not go away and is still highly statistically significant and clinically meaningful. However, as stated above, we do not believe that the 35% recurrence rate is appropriate.

**Table 1: New OLT patients with at least 2 years of Clinical Follow-up**

| Study | Recurrent Rate (%) | Reference Recurrent Rate | P-value |
|---|---|---|---|
| Nabi-4204 | 0/24 (0%) | 35% | <0.0001 |
| Nabi-4409 | 1/17 (6%) | 35% | 0.013 |
| Pooled | 1/41 (2%) | 35% | <0.0001 |

**Table 2: New OLT patients with at least 2 years of HBsAg Serology**

| Study | Recurrent Rate (%) | Reference Recurrent Rate | P-value |
|---|---|---|---|
| Nabi-4204 | 0/18 (0%) | 35% | 0.0009 |
| Nabi-4409 | 1/11 (9%) | 35% | 0.12 |
| Pooled | 1/29 (3%) | 35% | 0.0001 |

**FDA Comment:**

*Nabi has not provided sufficient data. There are numerous missing data points for HBsAg measurements in both studies. The conclusions FDA made based on the data submitted and Nabi's comments to each point is below.*

A. *There were 4 deaths within the first 30 days after transplant, and there were 4 deaths before 2 years after transplant that were not attributable to HBV recurrence. Therefore, these 8 subjects below can be removed from the analysis, leaving 54 subjects in the database.*

**Nabi Response:**

The efficacy database is comprised of 62 new transplant patients, from studies Nabi-4204 and Nabi-4409. This patient population is referred to as the All Patients Population, and it includes all patients who have been enrolled and were HBsAg negative after OLT. In addition, we have the Modified All Patients population, which is a subset of the All Patients population with a minimum of at least two-year follow-up data on serology. There are 29 patients in this population, and the two-year follow-up requirement is in line with the recommendation from the March 2004 BPAC meeting. Lastly, we note that in most cases, the standard of care for patients who are shown to be HBsAg negative by several observations is to follow them clinically and obtain serology only when clinically indicated. There are 41 patients in this population.

The tables following (Table 3, Table 4, and Table 5) summarize the reasons patients were considered non- evaluable. The database is reduced from 62 to 56 based on the reasons given in Table 3. Only 29 of the 56 patients have a

minimum of two-year follow-up data on serology. The evaluable database consisted of 41 patients (Table 4 and Table 5). Additional details can be found in Attachment 3 and Appendices 1 and 2.

Nabi-4204 was a prospective, well conducted, NIH funded, multi-center trial of HBV prophylaxis in patients undergoing OLT. Nabi-4204 was originally designed to study the co-administration of Nabi-HB and lamivudine for 36 weeks. After the BPAC meeting in March 2004, Nabi made every effort to capture additional data to satisfy the BPAC recommendation of 2-year follow data, and was generally successful.

With the exception of the 2 patients who died within 30 days of transplantation, follow-up information was obtained for 28 patients, including one patient who withdrew consent at day 34 and one patient who relocated on day 254. All patients included in Nabi-4204 received Nabi-HB manufactured in Boca Raton, Florida.

Most patients enrolled in Nabi-4204 continued indefinitely to receive both Nabi-HB (generally 5,000 IU monthly) and lamivudine. However, investigators at two sites elected to discontinue Nabi-HB approximately 8 to 17 months after transplantation.

The database for Nabi-4204, which began with 30 enrolled patients, is comprised of 24 evaluable patients. Eighteen of these patients had serology data ≥ 2 years following transplantation.

**Table 3: Patients Excluded from Analysis –All Patients Population**

| Patient ID | Reason for Exclusion |
|---|---|
| 4409-002001<br>4409-003013<br>4409-003015<br>4409-016005<br>4409-028005<br>4409-219008 | No HBsAg serology was recorded post-transplant. Thus, there was no evidence the patient was HBsAg negative post-transplant. |

**Table 4: Summary of Non-Evaluable Patients for Nabi 4204 –Evaluable Population**

| Database Began with 30 Patients | | |
|---|---|---|
| **Patient ID** | **Reason Subtracted from Total** | **New Total** |
| 4204-002006<br>4204-004002 | Patients died within 30 days after transplant | 28 |
| 4204-015001 | Nabi-HB was discontinued at 252 days for economic reasons | 27 |
| 4204-002005 | Nabi-HB was discontinued at 249 days for economic reasons | 26 |
| 4204-015004 | Patient has less than 2-years follow-up (lost to follow-up at 254 days) | 25 |
| 4204-002004 | Patient has less than 2-years follow-up (withdrew consent at 43 days) | 24 |
| **Therefore, the database for Nabi-4204 is Comprised of 24 Evaluable Patients** | | |

The other efficacy study, Nabi- 4409, was an expanded access study, which due to a market shortage of licensed hepatitis B immune globulin, was approved by the FDA to provide Nabi-HB IV to transplant recipients (newly transplanted, and maintenance-phase transplant recipients) while FDA reviewed the BLA for the post-exposure prophylaxis indication. A total of 32 new transplant recipients and 121 maintenance-phase transplant recipients were evaluated. In the original study, there was no recurrence of HBV-related disease among the maintenance-phase patients, and only 1 recurrence among the newly transplanted patients. Given the nature of this study, obtaining follow-up information on patients in 4409 was more difficult than for the well-controlled study 4204. A follow-up study (Nabi-4409EXT) was designed to collect extended follow-up information in line with the recommendation from the March 2004 BPAC meeting. The database for Nabi-4409 is comprised of 17 clinically evaluable new transplant patients. Serology data at least 2 years following transplantation were available for 11 patients. A listing of all HBsAg serology by patient and a summary containing an assessment pertaining to evaluability outcome are in Attachment 3, Appendices 1 and 2, respectively.

**Table 5: Summary of Non-Evaluable Patients for Nabi-4409 –Evaluable Population**

| Database Began with 32 Patients | | |
|---|---|---|
| **Patient ID** | **Reason Subtracted from Total** | **New Total** |
| 4409-002001<br>4409-028005<br>4409-020002 | Patients died within 30 days after transplant | 29 |
| 4409-003013<br>4409-028004 | Patient was discovered on the day of transplantation to have been HBsAg-negative pre-transplant | 27 |
| 4409-010005<br>4409-010007 | Patient received a HBV-positive donor liver, but was not infected with HBV pre-transplantation | 25 |
| 4409-005007 | Patient received only 10 doses of Nabi-HB IV with the last dose given within 8 days after liver transplantation; thereafter, the patient was treated with lamivudine monotherapy. | 24 |
| 4409-011001<br>4409-016005<br>4409-016015<br>4409-079001<br>4409-218001<br>4409-219008<br>4409-221001 | Patients had less than 2 years follow-up data available | 17 |
| **Therefore, the database for Nabi-4409 is Comprised of 17 Evaluable Patients** | | |

The total of the two databases (Nabi-4409 with 17 patients and Nabi-4204 with 24 patients) leaves us with our database of 41evaluable patients, 29 of which have serology results >2 years post-transplantation.

The pivotal data are from two studies in 62 new transplant recipients (Nabi-4204 and Nabi 4409). These data are supported by 4 studies (Nabi-2906, Nabi-4203, Nabi-4406 and Nabi-4409), in a total of 173 maintenance phase patients. Nineteen patients participated in more than one of the aforementioned studies, accounting for a total of 29 repeats in patient count. Therefore, there were a total of 206 unique patients among the five studies. Based on BPAC criteria, 6 patients in nabi-4204 and 15 patients in Nabi-4409 were excluded from the efficacy assessments, therefore, resulting in the combined database of 214 evaluable patients. These are summarized in Table 6.

**Table 6: Nabi-HB IV Evaluable Patients**

| Study | Study Type | Recurrence Rate % |
|---|---|---|
| Nabi-4204[1] | New OLT | 0/24 (0%) |
| Nabi-4409[1] | New OLT | 1/17 (6%) |
| Nabi-4409 | Maintenance-phase | 0/121 (0%) |
| Nabi-4203 | Maintenance-phase | 0/21 (0%) |
| Nabi-2906 | Maintenance-phase | 0/21 (0%) |
| Nabi-4406 | Maintenance-phase | 0/10 (0%) |
| **Total** | **All Studies** | **1/214 (0.5%)** |

[1]This represents all patients who have at least 2 years of clinical follow-up data

The 41 evaluable new transplant patients are sufficient to demonstrate statistically significant superiority as compared with historical controls ($p<0.001$). Also, an efficacy database of 41 new transplant patients, an additional 173 maintenance patients and safety data from thousands of patients who received the drug post-licensure compares very favorably to patient numbers used for licensure of certain other orphan drug indications. For example, the approval in April 2006 of Genzyme Corporation's Myozyme (alglucosidase alfa), a recombinant formulation of the human enzyme acid a-glucosidase, was on the basis of a single open-label study of 18 infants, that compared the effects of Myozyme treatment with historical mortality and morbidity data. A second open label study of 21 patients up to 3.5 years of age was felt to be insufficient to determine a treatment effect. **In contrast, only 1 of 214 (0.5%) patients in the combined Nabi-HB IV database seroconverted.**

In addition, as discussed at the December 2005 meting with FDA, we conducted a time-to-recurrence analysis using all patients enrolled. Nabi recognizes that FDA did not previously review this analysis; however, it is submitted here to address comments in the April 2006 FDA letter. The outcome used in the analysis is time to recurrence. Computed from the beginning of date of infusion with study medication, the time to recurrence for each patient was either the "event time" of their first *recurrence* (from HBsAg negative after OLT to HBsAg positive) or censored at the earliest of death, or the date of last contact. A total of 1 recurrence occurred between enrollment and month 3 in Nabi-4409. Only patients who were HBsAg- after OLT were included in the efficacy calculation. The following patients and the reasons for exclusion from the analysis are presented above in Table 3.

Figure 1 shows the Kaplan-Meier estimates of the time-to-recurrence distributions in Nabi-4204 and Nabi-4409. The vertical scale of the figure indicates that the

recurrence-free proportion is 100% and 94.1% for Nabi-4204 and Nabi-4409 respectively. The data are displayed in Table 7.

**Figure 1: Kaplan-Meier estimates of the time-to-recurrence distributions in Nabi-4202 and Nabi-4409**

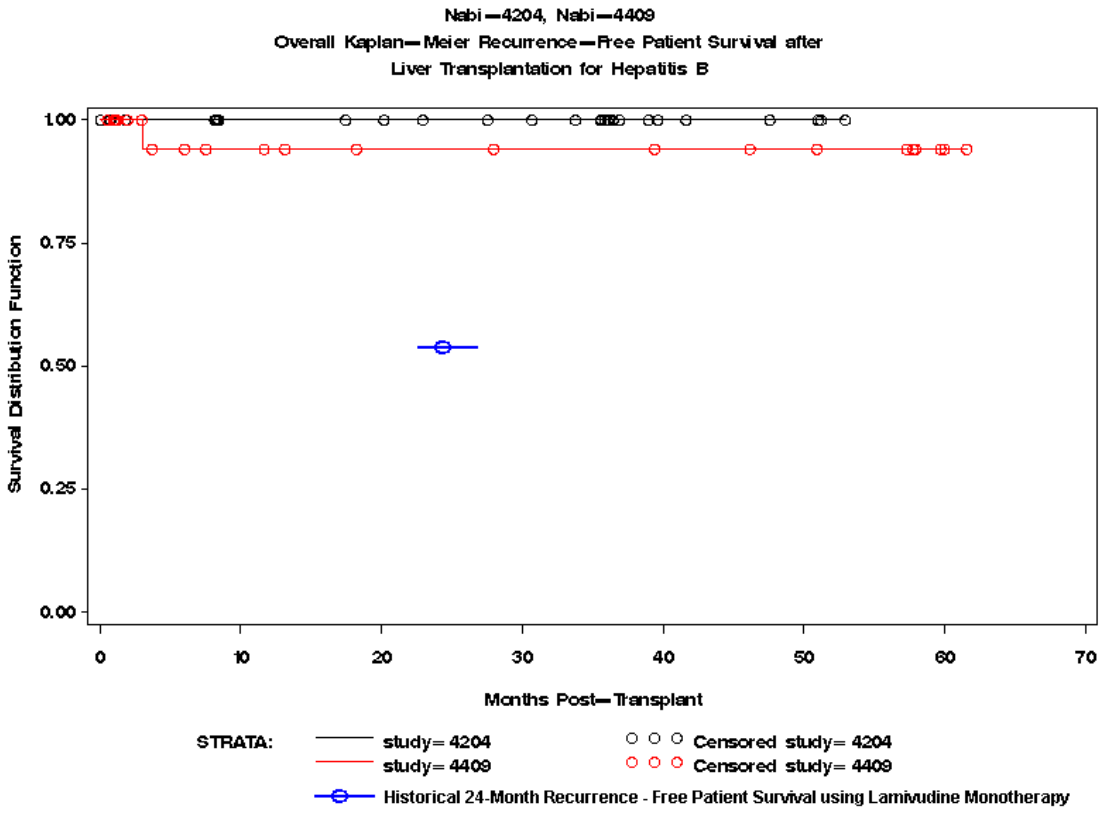

**Table 7: Recurrent Event for All Patients Population**

| Time Interval (Months) | Number of Recurrent Events | Cumulative Recurrent Events | Number Censored | Number Remaining on Study |
|---|---|---|---|---|
| **Nabi-4204** | | | | |
| 0 - 3 | 0 | 0 | 5 | 25 |
| 4 - 7 | 0 | 0 | 0 | 25 |
| 8 - 11 | 0 | 0 | 4 | 21 |
| 12 - 15 | 0 | 0 | 0 | 21 |
| 16 - 19 | 0 | 0 | 1 | 20 |
| 20 - 23 | 0 | 0 | 2 | 18 |
| **Nabi-4409** | | | | |
| 0 - 3 | 1 | 1 | 10 | 16 |
| 4 - 7 | 1 | 1 | 2 | 14 |
| 8 - 11 | 1 | 1 | 1 | 13 |
| 12 - 15 | 1 | 1 | 1 | 12 |
| 16 - 19 | 1 | 1 | 1 | 11 |
| 20 - 23 | 1 | 1 | 0 | 11 |

It is of interest to compare the recurrence-free Kaplan-Meier estimates from the two studies with that of lamivudine monotherapy. This was accomplished by using the log hazard ratio and its variance. The results of the comparison are displayed in Table 8.

**Table 8: Results of The Comparison of Nabi-HB IV with Lamivudine Compared to Lamivudine Monotherapy for All Patients Population with Recurrence**

| Study | Treatment | Number of Patients | Recurrence | p-value[2] |
|---|---|---|---|---|
| Nabi-4204 | Nabi-HB IV + lamivudine | 30 | 0[1] | |
| Literature | lamivudine alone | 94 | 42 | <0.0001 |
| Nabi-4409 | Nabi-HB IV + lamivudine | 26 | 1 | |
| Literature | lamivudine alone | 94 | 42 | <0.0001 |

[1]To calculate the log hazard ratio and its variance, the zero recurrence was replaced by $10^{-6}$.
[2]p-values are based on the log hazard ratio and its variance.

The data indicate a highly significant statistical reduction in the risk of recurrence when Nabi-HB IV plus lamivudine was compared to lamivudine alone.

**FDA Comment:**

B. *For 23 of 54 patients, the data support the maintenance of HBsAg seronegativtiy to month 24; however, only 19 of these 23 HBsAg seronegatives received combined Lamivudine plus HBIg therapy.*

**Nabi Response:**

The well-established standard of care is combination therapy; since this is the most effective treatment to prevent HBV recurrences in transplant patients. Nineteen (19) patients received the combination of Nabi-HB and lamivudine, whereas 4 patients received Nabi-HB monotherapy. Combining the 19 and the 4 patients represent the most conservative approach, as the efficacy hurdle for Nabi-HB IV monotherapy in these 4 patients is in fact higher, since BPAC and the medical community have accepted that lamivudine has some effect in this patient population.

**FDA Comment:**

C. *For 4 of 54 subjects, there is clear evidence of HBsAg seroconversion before month 24, and are consistent.*

**Nabi Response:**

The table below (Table 9) summarizes the reasons why the 4 patients questioned are or are not treated as a treatment failure.

**Table 9: Responses to the 4 Patients Questioned in Part C**

| Patient No. | Nabi Response |
|---|---|
| 4204-002003 | Although there is one positive HBsAg result at day 375, there were 15 negative results, including data at days 430 and 532. Therefore, the one positive result on day 375 most likely was due to a lab error. |
| 4202-15001 | Nabi-HB IV was discontinued for economic reasons on day 252. At that time, HBsAg was negative. The fact that the patient seroconverted and became HBsAg positive on day 635 argues strongly for the efficacy of Nabi-HB IV and illustrates the need for continued treatment with Nabi-HB; hence, this event actually support the efficacy of the drug and should not be considered as a treatment failure. |
| 4409-002003 | Nabi agrees that this is a treatment failure. |
| 4409-005007 | Nabi-HB IV was discontinued on day 8 after 10 doses and the patient received lamivudine monotherapy thereafter. Therefore, this is not a treatment failure. |

**FDA Comment:**

D. *For 4 of 54 subjects, the data do not support maintenance of HBsAg seronegativity at month 24, and are consistent with HBsAg seroconversion by month 24.*

**Nabi Response:**

The table below (Table 10) summarizes the reasons why the 4 patients questioned are or are not treated as a treatment failure.

**Table 10: Responses to the 4 Patients Questioned in Part D**

| Patient No. | Nabi Response |
|---|---|
| 4204-001004 (Death at month 2 judged HBV related) | This patient died from bacterial sepsis. Although the investigator stated that the death was HBV related, the 5 HBsAg measurements made prior to death were all negative. This strongly argues against this being a treatment failure. |
| 4204-002005 (HBsAg positive at month 37) | Nabi-HB IV was discontinued at day 249 for economic and logistic reasons. Patient was seronegative then, and remained seronegative until day 906, where HBV recurred. The fact that the patient seroconverted and became HBsAg positive after discontinuation of Nabi-HB argues for the efficacy of Nabi-HB, and illustrates the need for continued treatment; hence, it cannot be considered a treatment failure. |
| 4409-003002 (HBV DNA positive at month 10) | There is no clinical evidence of recurrence through day 1875. There was an isolated DNA positive result at day 292, preceded by negative DNA earlier and through day 1875. DNA positive results are expected; if the patient is clinically well and HBsAg negative, a single positive DNA measurement is meaningless. FDA agreed that HBsAg, not DNA, should be used as a surrogate for efficacy. |
| 4409-016010 (HBsAg positive from months 25-39) | Nabi-HB IV was discontinued at day 184, and was seronegative then and until month 25, where HBV recurred. This argues for the efficacy of Nabi-HB IV, illustrates the need for continued treatment with Nabi-HB IV and cannot be considered a treatment failure. |

**FDA Comment:**

E. *For 23 of 54 subjects, there were inadequate data to show that the subjects maintained HBsAg seronegativity to month 24, because HBsAg measurements were not submitted for time points up to or after month 24.*

**Nabi Response:**

Nabi-4204 was originally designed for 36 weeks. After the March 2004 BPAC meeting, Nabi made every effort to capture additional data to satisfy the BPAC recommendation of 2-year follow data. Data was missing for a number of patients so we used the last observation carried forward method to fill in for missing values. So, for example, if a patient has month 12 serology data, but is missing month 13 data, then the month 12 data is substituted for month 13 data. Some patients did not have serology data for 2 years, but were monitored clinically for at least two years. We believe that if patients were clinically well without symptoms of recurrent liver disease, and had normal liver transaminases, then it is reasonable to assume that such patients had not seroconverted. This assumption is reasonable as there is a strong correlation between recurrence of HBsAg positivity and signs and symptoms of liver disease. This close correlation is the reason HBsAg has been widely accepted as a surrogate marker for efficacy. Nonetheless, faced with FDA's criticism, we did two separate analyses, namely one for patients who had clinical data for at least two years, and one for patients who also serology data for at least two years. Both analyses unequivocally demonstrate that Nabi-HB + lamivudine is statistically superior to lamivudine alone.

Nabi agrees with FDA's comment that there were missing serology data for 23 patients (and therefore 31 patients had serology data). In fact 29 patients comprise the Nabi-HB IV serology database. However, we maintain this is a sufficient database for approval for an orphan indication like this (see response to Section A).

**FDA Comment:**

*The protocol is adequate for monitoring HBV recurrence in OLT subjects receiving Lamivudine plus HBIG prophylaxis, but it should be conducted prior to licensure for the OLT indication.*

**Nabi Response:**

The proposed protocol should be a Post Marketing Phase 4 Commitment for the following reasons (see Attachment 3, Risk/Benefit analysis for additional details):

1) **The Data in the Nabi IV BLA meet all BPAC recommendations:**

a) Pivotal Study Should be From Time of Transplantation.

The pivotal data are from two studies in 62 new transplant recipients (Nabi-4204 and Nabi 4409). These data are supported by 4 studies (Nabi-2906, Nabi-4203, Nabi-4406 and Nabi-4409), in a total of 173 maintenance phase patients.

b) Pharmacokinetics Data Should be Captured That Can be Used to Guide Therapeutic Dosing

Nabi-HB IV pharmacokinetic data in both new transplant and maintenance patients support the proposed dosing recommendations, which correspond roughly to the EMEA guidelines. Target trough levels were achieved in new transplant patients in Nabi-4204 (Dickson study); i.e., 300 IU/ml in weeks 1-7, 200 IU/mL for weeks 8-12, and 100 IU/mL thereafter. These levels prevented seroconversion and were similar to those shown to be efficacious in the McGory study, which FDA had accepted as demonstrating efficacy. Pharmacokinetic comparisons to the McGory study show that co-administration with lamivudine does not interfere with Nabi-HB IV kinetics and provides additional support. Target trough levels were also observed in maintenance phase individuals in several studies.

c) Historical Control Should Ensure Comparability Between Study Arms in Terms of Baseline Risk Factors

Nabi used a very conservative estimate for lamivudine efficacy (45%, based on meta-analysis). The results of the meta-analysis are consistent with other reports from the literature. If anything, the recurrence rate has increased due to increased development of viral resistance, which is currently as high as 67% when administered post transplant.

d) Two-Year Follow-Up Required for Patients Receiving Concomitant Lamivudine

Follow-up data well exceed the 2-year recommendation (mean follow-up of 3.5 yrs). There was 1 recurrence among the 41 patients who either had clinical follow-up for at least 2 years (relative efficacy of 94.6%) and 1 recurrence among the 29 patients who either had serology follow-up for at least 2 years (relative efficacy 92.3%).

**2) The safety profile of Nabi-HB is excellent, with a very benign drug-related adverse event profile.**

The safety results demonstrate that intravenous administration of Nabi-HB is safe and well tolerated in transplant recipients who have undergone transplantation due to hepatitis B-related liver failure. In the five trials of intravenous administration of the product (Nabi-2906, -4406, -4409, -4203, and -4204), 206 patients received a total of 1,320 infusions of Nabi-HB IV. The data base safety is comprised of multiple infusions administered to over 200 patients and is substantial and more than adequate to establish that Nabi-HB IV is safe and well-tolerated in this population, particularly in light of the relatively small number of transplant procedures performed in hepatitis B positive patients. Additionally, Nabi-HB has been used widely off-label for prevention of recurrent hepatitis B-related clinical disease in liver transplant recipients in the US since its approval in 1999 (estimated 60,000 infusions). Upon examination of the patient population no significant demographic trends were noted. The paucity of reports of adverse events (and lack of treatment failures) provides further support for the safety (and efficacy) of Nabi-HB IV.

**3) The need for standardized prescribing information is critical and immediate for patient health and safety.**

Nabi-HB IV is currently being used off-label as a standard of care, and it is therefore essential that there is proper prescribing information available to physicians for optimal treatment recommendations. Right now, since there is not a product approved for this indication, prescription practices are highly variable, which is many cases have resulted in recurrence of hepatitis B infections, often resulting in liver failure, need for new liver transplantation or even death (as illustrated in Nabi-4409 and Nabi-4204, and further documented in the enclosed paper by Hayashi et al. 2006). We contend that most of these re-infections could have been avoided if Nabi-HB had been continued, emphasizing the need to provide guidelines in the label.

4) **The Nabi-HB IV exceeds that used for regulatory approval of other orphan drug indications.**

5) **Nabi is willing to conduct a Phase 4 study to assess efficacy of Nabi-HB IV and concomitant antiviral treatment in new liver transplant recipients (similar in design to Nabi-4204). However, requiring this study pre-approval would delay label recommendations by 5 years.**

   0.5 year study planning and initiation
   1-year enrolment
   2-years follow-up
   0.5-year data analysis and BLA preparation
   1-year FDA review and approval

   During this time period patients will continue to be at significant risk for recurrences (Hayashi *et. al*. 2006). That is not in the best interest of the American public.

**Attachment 7**

**Proposed Phase IV Protocol**

**Multi-Center Efficacy Study to Assess Intravenous Nabi 5% Hepatitis B Immune Globulin (Nabi-HB) Used in Combination with Lamivudine for Patients with Hepatitis B Virus (HBV) Associated Liver Disease Undergoing Liver Transplantation**

PROTOCOL NABI-4206
PROTOCOL DATE: 9 June 2006

PRINCIPAL INVESTIGATORS: Multicenter

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## 1.0 INTRODUCTION

Hepatitis B virus associated liver disease had previously been considered a relative contraindication to liver transplantation given the significant recurrence rate and poor outcome associated with allograft infection. Passive immunization with intravenous (IV) high dose hepatitis B immune globulin (HBIg) has been shown to decrease HBV recurrence after liver transplantation. Individualized IV HBIg dosing to keep the anti-HBs titer > 500 IU/L (Abbott assay) was shown by McGory, et al, to prevent HBV recurrence in almost 90% of patients undergoing liver transplantation for hepatitis B.[1] However, they noted high inter-patient variability in HBIg pharmacokinetics in the first 90 days after liver transplantation. The standard deviation for the HBIg clearance (Cl), volume of distribution (VD), and half-life ($t_{1/2}$) was frequently greater than the mean in the first 30 days. In patients with successful transplants variability decreased with time after transplantation, and by 90 days after transplantation the pharmacokinetics had stabilized. Early dosing was further complicated by the effect of the HBeAg status on the pharmacokinetics of HBIg. The $t_{1/2}$ of HBIg was statistically shorter for patients with HBeAg than those without HBeAg in both the first seven days and first three months after transplant, although increased dosing for patients with HBeAg was only required during the first seven days. Retrospective data from this study suggested that the titer of anti-HBs required for prevention of recurrent hepatitis B decreased with time. In the first week post-transplant, HBsAg was detected when anti-HBs titers were < 300 IU/L and never detected when anti-HBs were > 500 IU/L. Between weeks two through 12, HBsAg was detected when anti-HBs titers were < 250 IU/L and detected in only 2/114 samples when titers were > 250 IU/L. After 90 days, HBsAg was detected once in a patient with an anti-HBs titer of 58 IU/L at 1.5 years after liver transplant, while it has not been detected in over 500 samples (27 patients) with titers ranging from 11 IU/L to > 8000 IU/L. These data indicate that success of HBIg in preventing recurrent hepatitis Bpost-transplant is related to anti-HBs titer and that variability in pharmacokinetics of HBIg during the initial post-transplant period may be related to the virus load at the time of transplant. Other studies have demonstrated a high rate of recurrent hepatitis B when H-BIG is discontinued a few months after transplantation. Current data suggest that HBIg needs to be administered long-term or indefinitely, but the optimal dose regimen remains unknown.

Nabi has developed two HBIg formulations (Nabi-HB™, and Nabi-HB Intravenous). These new formulations contain specific anti-HBs antibody, with no added non-specific immunoglobulin. The manufacturing process for both Nabi-HB products includes both a virus filtration and a solvent-detergent treatment step, designed to remove or inactivate enveloped and non-enveloped viruses such as HBV, HCV, and HIV. The two products are identical except for the potency of anti-HBS. Nabi-HB for intramuscular administration has a minimum potency of 312 IU/mL and Nabi-HB Intravenous has a minimum potency of 208 IU/mL. Both products contain a total concentration of 5% protein, and neither product contains thimerosal.

In a study of Nabi-HB given to OLT patients at least six months post transplant, 21 patients received an infusion of Nabi-HB every 28 days (total of 112 infusions over two to ten months). All patients were followed during the 28-day intervals between infusions for safety and pharmacokinetic parameters. All doses were administered intravenously at 180 IU/kg (12,500 IU per 70 kg) as an approximately 280 mL infusion given over at least one hour using an

infusion pump. Serum samples for anti-HBs levels for at least the first three infusions were collected on Days 0 (pre and post infusion), 1, 3, 7, and 14 of each dosing interval and on the Termination day. Patients were allowed to extend their participation in the study for up to six additional infusions, during which anti-HBs levels were drawn only pre and post infusion. One hundred adverse events were reported in the 21 patients over the 112 patient-months. Nine (9%) of these were serious and 27 (27%) were either related to the study drug administration or were of unknown relationship; one of the serious adverse events was considered to be related. The most common (N = 23) adverse event was muscle/joint pain which occurred in six (29%) patients. Seventeen (74%) of these events were considered related to the study drug, and 14 (82%) of those were experienced by patients with a history of such reactions to infusions of hepatitis B immune globulin.

The University of Virginia enrolled six patients in the Nabi-HB study. In their experience, one hour infusions were possible in four patients using Nabi-HB, but in none of the six when they received the Abbott product. In addition, all patients required premedication while receiving Abbott H-BIG, while this was only required in two of the six patients while receiving Nabi-HB. In these patients, who were at least six month post transplant, the pharmacokinetics of the two products appeared to be similar.

Several studies have demonstrated that lamivudine successfully decreases viral replication in patients with chronic hepatitis B. However, with prolonged administration, lamivudine resistant mutants frequently emerge. A recent article by Markowitz, et al demonstrated that a combination of lamivudine and H-BIG prevented recurrent hepatitis B in all 14 patients undergoing liver transplantation for hepatitis B. H-BIG was given as 10,000 IU intravenously during the anhepatic phase, 10,000 IU IV daily for the next 6 days, biweekly while in the hospital, and then monthly. Lamivudine was given at 150 mg daily beginning either before or shortly after liver transplantation and continued indefinitely. The combination of Lamivudine and IV HBIg is now widely used in liver transplantation centers.[2]

Dickson, et al., conducted a prospective, multi-center study between Dec 1999 and May 2001 to assess Nabi-HB in combination with lamivudine in 30 adult patients undergoing liver transplantation for HBV-induced liver disease.[3] Adults undergoing LT for chronic HBV received lamivudine prior to or at LT, and Nabi-HB 20,000 IU on day of LT, 10,000 on days 1-7, weeks 4 and 8, and 5,000 every 4 weeks thereafter. Replicative status based on serum HBV DNA (>5 pg/mL = replicator (R) or =5 pg/mL = nonreplicator (N) was determined at initiation of lamivudine (R or N) and within 2 weeks of LT (r or n), resulting in 3 groups: Nn, Rn, Rr.

A total of 30 patients (10 Nn, 13 Rn, 6 Rr, 1 unknown) mean age of 52 years underwent LT. All subjects were HBsAg-positive at the time of transplantation. HBsAg neutralization was achieved with anti-HBs > 300 IU/L during week 1 and > 200 IU/L during weeks 2-12. Pre-LT suppression of HBV replication resulted in similar dose requirements and pK in the Rn and Nn groups within 1 week after LT. Comparatively, the Rr group had greater HBIg requirements during weeks 1-12 due to greater anti-HBs clearance and shortened $t_{1/2}$ during the entire 36 week follow-up.

Four patients died within the first 8 weeks (post-transplantation days 3, 37, 24, and 58 respectively). Two patients withdrew consent but agreed to provide follow-up information. One subject relocated on study day 199 and was lost to follow-up. One Rn subject underwent re-transplantation at day 2, and one Nn subject underwent re-transplantation at week 28.

The mean duration of follow-up from transplantation for the remaining 24 patients was 1241 (range 628 to 1673) days. Twenty-three (23) of 24 patients (96%) remained either HBsAg-negative or had no clinical evidence of HBV-related liver disease. The one (Rn) patient who had HBsAg seroconversion received Nabi-HB for 252 days and was HBsAg-negative at the time Nabi-HB was discontinued. There are no HBsAg serologies between 252 and 634 days post-transplantation. However, 383 days after discontinuation of Nabi-HB the patient was HBsAg-positive. The prospective study was designed to assess pharmacokinetics of Nabi-HB in patients administered concomitant lamivudine. Further, the prospective portion of the study was 36 weeks for each subject. Additional information on HBV status was collected retrospectively.

This prospective, confirmatory study is designed to assess recurrence of HBV-related liver disease among adult patients undergoing liver transplantation for HBV-induced liver disease. On the day of transplantation patients will be administered a total of 20,000 IU of Nabi-HB; 10,000 IU while anhepatic and 10,000 IU following reperfusion (before leaving the OR). Daily doses of 10,000 IU will be administered on post-transplantation days 1-7. However additional doses may be administered as necessary to maintain a trough anti-HBs titer =300 IU/L. Single doses will be administered at the beginning of week 4 and the beginning of week 8 However additional doses may be administered as necessary to maintain a trough anti-HBs titer =200 IU/L. Thereafter, through the end of study participation 24 months after transplantation, each patient will be administered a minimum of 10,000 IU every 4 weeks. Additional doses will be administered if necessary to maintain a trough anti-HBs level of = 100 IU/L.

The dose and schedule of intravenous Nabi-HB administration above is a guideline designed so that there is a high likelihood the target trough anti-HBs titers will be achieved for each patient. However, some patients, particularly those with a large virus load, may require additional doses of Nabi-HB. During the course of the study, expected trough anti-HBs levels will extrapolated by the investigator from measured anti-HBs titers in order to estimate the need to adjust the dose or schedule to achieve the target trough anti-HBs titer. The target trough anti-HBs titer is =300 IU/L in the first week post-transplantation, at least 200 IU/L during weeks 2-12 post-transplantation, and at least 100 IU/L thereafter. Each subject will participate in the study for 2 years (approximately 108 weeks).

## 2.0 STUDY OBJECTIVES

### 2.1 Primary Objective

- To assess efficacy of concomitant Nabi-HB and anti-viral (lamivudine if not receiving another anti-viral pre-study) in preventing recurrence of HBV-related liver disease in patients undergoing liver transplantation for hepatitis B.

## 2.2 Secondary Objective(s)

- To determine if a monthly dose of 10,000 IU Nabi-HB beginning 12 weeks after transplantation will maintain a trough anti-HBs titer = 100 IU/L.
- To assess emergence of lamivudine or HBIg resistance.
- To assess the importance of HBV genotype and pre-LT mutations on post LT outcome

## 3.0 INSTITUTIONAL REVIEW BOARD

Institutional Review Board approval of the protocol and Informed Consent document must be obtained from a properly constituted IRB and evidence of that approval must be provided, in writing, prior to initiation of the study.

## 4.0 INFORMED CONSENT

The investigator will be responsible for obtaining signed, written informed consent from each patient and ensuring that each patient has received a copy of the signed consent form.

## 5.0 STUDY POPULATION

### 5.1 Patient Eligibility

Patients who require liver transplantation for hepatitis B-related end-stage liver disease will be considered for enrollment in this study, including patients with co-existent HDV infection or hepatocellular carcinoma (HCC) (see Inclusion Criteria 3). Patients with co-existent HDV infection are included because despite a lower risk of recurrent hepatitis B, prophylaxis against HBV recurrence is needed. Patients who require re-transplantation for recurrent hepatitis B or with chronic liver disease and recurrent HBV on lamivudine may be included if tests reveal no evidence of lamivudine resistance. Patients with co-existent HCV infection will be excluded because of the invariable recurrence of HCV infection.

### 5.2 Inclusion Criteria

Eligible patients must:

1) Be 18 years old or greater, either male or female, of any ethnic background
2) Be positive for HBsAg. Patients may be either positive or negative for anti-HDV, HBeAg, and HBV DNA (<u>in this protocol, all HBV DNA will be tested by PCR</u>)
3) Be diagnosed with HBV-related liver disease including either:

   HBsAg positive cirrhosis, or

   HBsAg positive and presence of hepatocellular carcinoma (HCC) with no evidence of vascular invasion or extrahepatic spread, and either:

   - a single tumor no larger than 5 cm in diameter, or
   - no more than three tumors, the largest of which is no greater than 3 cm in diameter
4) Have received at least one dose of lamivudine (100 mg PO qd) prior to transplantation
5) Fulfill UNOS minimal listing criteria

6) Have received approval for liver transplantation at the respective participating center and are listed and felt to be within three months of liver transplantation
7) If requiring retransplantation for primary graft nonfunction or hepatic artery thrombosis, retransplantation must take place within the first four weeks of the initial transplant with no evidence of recurrent hepatitis B
8) Be able and willing to give written informed consent. A legal guardian must be available to provide consent for patients with Grade 3 or 4 hepatic encephalopathy
9) If a woman of childbearing potential, have a negative serum β-HCG pregnancy test within 14 days prior to starting lamivudine therapy and within 14 days prior to transplant and agree to practice contraception during the study (a total of 108 weeks)

### 5.3 Exclusion Criteria

Eligible patients must not:

1) Require retransplantation for recurrent hepatitis B
2) Have chronic hepatitis B liver disease with a history of breakthrough infection not suppressed by current antiviral therapy
3) Have other causes of liver disease including chronic hepatitis C
4) Have HCC and do not meet Inclusion Criterion #3, or who require systemic chemotherapy
5) Be seropositive for HIV infection
6) Be using experimental devices or receiving experimental drugs
7) Be participating in any other clinical treatment trial with an investigational drug within 30 days prior to liver transplantation or plan to receive an investigational drug during this study

## 6.0 STUDY PLAN

### 6.1 Design

This is a prospective, multi-center, confirmatory study using concomitant high dose intravenous Nabi-HB in combination and lamivudine in patients undergoing OLT for HBV-related liver disease. The participating centers will enroll a total of 50 patients. Patients will be identified prior to transplantation and be considered for the study if they have evidence of HBV-induced liver disease and meet the enrollment criteria. Patients will be enrolled in this study when they are listed as Status 2 or 3 and felt to be within 12 weeks of liver transplantation. Determination of replicative status will be performed at the time of enrollment and repeated at 12 week intervals if the patient is not yet transplanted. Replicative HBV will be defined as the presence of either HBeAg or serum HBV DNA by $>10^4$ for HBeAg-negative patients and $=10^5$ for HBeAg-positive patients. Each patient is expected to participate in this study for 108 weeks following transplantation.

Intravenous Nabi-HB, 10,000 IU, will be administered to patients intra-operatively (Day 0) during the anhepatic phase, following reperfusion, daily on Days 1-7, once during Week 4, once during Week 8 (for a total of 11 – 10,000 IU doses), and then 10,000 IU will be administered at the beginning of months 3-24. Blood for trough anti-HBs levels will be collected prior to

infusion on post-transplantation Days 1, 2, 5, during Weeks 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108. Anti-HBs levels will be determined using an enzyme immunoassay (EIA, Abbott).

Patients with a 6 week trough level <300 IU/L will receive 10,000 IU Nabi-HB every 4 weeks for the remainder of the study. Between Weeks 6 and 12, if the anti-HBs level is projected to be <200 IU/L prior to the next infusion, an additional 10,000 IU of Nabi-HB will be given intravenously as soon as possible prior to the next scheduled infusion. If, during the interval from 13 to 108 weeks, the anti-HBs level is projected to be < 100 IU/L prior to the next infusion, an additional 10,000 IU of Nabi-HB will be given intravenously as soon as possible prior to the next scheduled infusion.

Patients not already receiving an antiviral for suppression of HBV at the time of enrollment will be started on lamivudine 100 mg PO daily. Patients already receiving lamivudine will be continued on lamivudine. All patients must receive at least one dose lamivudine 100 mg PO prior to transplantation, and must be maintained on lamivudine for the duration of the study unless testing demonstrates emergence of lamivudine resistance.

## 6.2 Record Keeping and Monitoring

All relevant patient data will be recorded in the case report forms (CRFs) or via an electronic data capture (EDC) system. Henceforth, data capture form (DCF) will refer to either paper CRF or EDC. Instructions for entering study information to the DCF will be provided by Nabi. Data must be entered on the DCF in a timely manner. Source documents along with Paper CRFs must be available for possible monitoring. A copy of each paper CRF will be maintained at the site for a minimum of two years. The investigator is responsible for the accuracy of all data entered in the DCFs.

## 6.3 Study Drugs and Administration

### *6.3.1 Study Drugs*

*Nabi-HB Intravenous*

Hepatitis B Immune Globulin (Human), Nabi-B™ Intravenous, is a sterile solution of immunoglobulin (5 ±1% protein) containing antibodies to hepatitis B surface antigen (anti-HBs). It is prepared from plasma obtained from individuals with high titers of anti-HBs. The plasma is processed using a modified Cohn 6 / Oncley 9 cold-alcohol fractionation process with two added virus reduction steps described below.[4,5] Nabi-HB™ Intravenous is formulated in 0.075 M sodium chloride, 0.15 M glycine, and 0.01% polysorbate 80, at pH 6.2. The product is supplied as a nonturbid, clear to opalescent, sterile liquid in a single dose vial. It contains no preservative and is intended for single use by intravenous administration.

The manufacturing steps for Nabi-HB™ Intravenous are designed to reduce the risk of transmission of viral disease. The solvent/detergent treatment step, using tri-*n*-butyl phosphate and Triton® X-100, is effective in inactivating known enveloped viruses such as hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV)[6]. Virus filtration, using a Planova® 35 nm Virus Filter, is effective in reducing some known enveloped and non-enveloped viruses[7]. The inactivation and reduction of known enveloped and non-enveloped model viruses were validated in laboratory studies as summarized in Table 1.

**Table 1 Log Reduction of Test Viruses**

| Test Virus: | HIV | BVD | PRV | EMC | PPV |
|---|---|---|---|---|---|
| Model Virus: | HIV | HCV | HBV | Hepatitis A | PVB19 |
| Envelope/Genome: | **YES/RNA** | yes/RNA | yes/DNA | no/RNA | **NO/DNA** |
| **Manufacturing Step** | | | | | |
| Precipitation of Cohn Fraction III | > 5.9 | 3.6 | 3.7 | 4.4 | 3.9 |
| Cuno Filtration | NT | NT | NT | > 6.6 | 5.4 |
| Solvent/Detergent | > 4.2 | > 6.9 | > 6.4 | NT | NT |
| Nanofiltration | > 7.4 | > 6.9 | > 5.7 | 3.0 | 0.7 * |
| Cumulative | > 17.5 | > 17.4 | > 15.8 | > 14.0 | 9.3 |

BVD = Bovine Viral Diarrhea Virus PVB19 = Parvovirus B19 NT = not tested
EMC = Encephalomyocarditis Virus PPV = Porcine Parvovirus
HIV = Human Immunodeficiency Virus PRV = Pseudorabies Virus
* Value not included in cumulative clearance

Product potency is expressed in international units (IU) by comparison to the World Health Organization (WHO) standard. Each milliliter (mL) of product contains a minimum of > 208 IU anti-HBs/mL. The potency of each milliliter of Nabi-HB™ Intravenous exceeds the potency of anti-HBs in a U.S. reference hepatitis B immune globulin (FDA). The U.S. reference has been tested by Nabi® against the WHO standard and found to be equal to 208 IU/mL.

Nabi-HB™ Intravenous is made from human plasma. Products made from human plasma may contain infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. The risk that such products can transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current viral infections, and by inactivating and/or reducing certain viruses. The Nabi-HB™ Intravenous manufacturing process includes a solvent/detergent treatment step (using tri-*n*-butyl phosphate and Triton® X-100) that is effective in inactivating known enveloped viruses such as HBV, HCV, and HIV. Nabi-HB™ Intravenous is filtered using a Planova® 35 nm Virus Filter that is effective in reducing the levels of some enveloped and non-enveloped viruses. These two processes are designed to increase product safety. Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products.

*Lamivudine*
Lamivudine is a synthetic nucleoside analogue with activity against HBV through incorporation of the monophosphate form into viral DNA by HBV polymerase, resulting in DNA chain termination. Lamivudine has been approved for the treatment of chronic hepatitis B infection, but not for prophylaxis of OLT patients against HBV recurrence.

### *6.3.2 Packaging and Labeling*

*Nabi-HB*
Nabi-HB is provided in 30 mL vials.

*Lamivudine*
Lamivudine is available for oral administration in 100 mg tablets (bottle of 60) and in a 5 mg/mL solution (plastic bottle of 240 mL).

### *6.3.3 Dosage Preparation*

*Nabi-HB*
All doses of Nabi-HB are determined by using the minimal label potency; not an assayed potency for the specific lot of Nabi-HB being used.

Prior to preparation, Nabi-HB should be allowed to equilibrate at room temperature for at least 15 minutes. Contents of the vial should be inspected for particulate matter and discoloration prior to administration. The vial must not be shaken and the contents of the vial must be administered within six hours of removal from refrigeration. Nabi-HB should not be mixed with other medications in the same intravenous infusion system or intravenous lines during infusion.

10,000 IU Dose
Using aseptic technique, the appropriate volume for a 10,000 IU dose is drawn into a syringe and added to 250 mL sterile saline (0.9%).

*Lamivudine*
Patients will receive either a single 100 mg tablet or 20 mL of the oral solution. In patients with renal insufficiency, the dose of Lamivudine will be adjusted according to the creatinine clearance (CrCl) as outlined in the table in the following section. If the patient is unable to take oral medications, the Lamivudine solution will be given via a nasogastric tube.

### *6.3.4 Dosage Administration*

Study drugs are to be administered only under the supervision of the investigator or sub-investigator(s) identified on form FDA 1572.

*Nabi-HB*
Infusions of 10,000 IU Nabi-HB are administered to all patients at the specified intervals for the first 4 weeks of the study. Those patients with a 6 week trough level < 300 IU/L will receive 10,000 IU Nabi-HB every 4 weeks for the remainder of the study. For intravenous infusions, the 10,000 IU dose of Nabi-HB in 250 mL of saline typically should be infused over *no less than* one hour using an infusion pump.

Infusions of 10,000 IU Nabi-HB are administered beginning at 12 weeks after liver transplantation to all patients with a 6 week trough level ≥ 300 IU/L. In addition, if a patient's anti-HBs level is projected to be < 200 IU/L prior to the next infusion during the first 12 weeks of the study, or < 100 IU/L prior to the next infusion thereafter, an additional 10,000 IU of Nabi-HB will be given intravenously as soon as possible prior to the next scheduled infusion. Patients may be medicated with meperidine 25-50 mg IV, diphenhydramine 50 mg IV or hydrocortisone 50 mg IV one-half hour before Nabi-HB is administered. Alternatively, sites may medicate patients using their institution's standard procedure. If back pain or spasm develops, the infusion will be discontinued until the symptoms resolve. Patients may then

receive an initial or additional doses of the medication and the Nabi-HB will be restarted at one-half the infusion rate. If no adverse event occurrs during the initial infusion, withdrawal of the medications prior to Nabi-HB infusion will be attempted during subsequent infusions. It is anticipated the majority of patients will be able to receive Nabi-HB infusions over no less than one hour without the need for medication pre-infusion.

*Lamivudine*
Lamivudine will be given as a dose of 100 mg p.o. daily either by a single tablet (100 mg) or by 20 mL of the oral solution (5 mg/mL). During the perioperative period, lamivudine solution will be given via a nasogastric tube if the patient is unable to take oral medications. Patients will be treated for at least the duration of the study period. Patients with breakthrough infection will be tested for underlying HBV mutations. Lamivudine will be continued and [entecavir] will be added.

In patients with renal insufficiency, the dose of lamivudine will be adjusted according to the creatinine clearance (CrCl) as outlined below.

| **Renal Function** | **Lamivudine Dose** | | | |
|---|---|---|---|---|
| CrCl mL/min | Initial Dose mg qd | Maintenance Dose mg qd | Solution mL | % daily dose |
| > 50 | 100 | 100 | 20 | 100% |
| 30-49 | 100 | 50 | 10 | 50% |
| 15-29 | 100 | 25 | 5 | 25% |
| 5-14 | 35 | 15 | 3 | 15% |
| < 5 | 35 | 10 | 2 | 10% |
| Estimated Creatinine clearance: | $\frac{140 - \text{age (years)} \times \text{weight (kg)}}{72 \times \text{serum Cr (mg/dl)} \times 1.0 \text{ (men) or } 0.85 \text{ (women)}}$ | | | |

*6.3.5 Storage Requirements*

*Nabi-HB*
Nabi-HB must be stored refrigerated at 2-8°C (36-46°F) in a secured area until used. Precautions should be taken to protect against freezing and heating.

*Lamivudine*
Tightly closed bottles of either lamivudine tablets or solution should be stored at controlled room temperature of 20-25$^{o}$ C.

*6.3.6 Study Drug Accountability*

*Nabi-HB*
The Investigator or designee is required to inventory all Nabi-HB shipments upon receipt and acknowledge receipt by signing and dating the accompanying letter and returning it to Nabi in the enclosed postage paid envelope. He/she is also responsible for maintaining accurate inventory records of all study drug using the Investigational Supplies Inventory Forms provided by Nabi.

*Lamivudine*
Doses of lamivudine will be accounted for using pharmacy records.

*6.3.7 Retrieval of Study Drug*

*Nabi-HB*
At the termination of the study or at the request of Nabi, the investigator must return all used and unused vials of Nabi-HB to Nabi. This return will be documented on both the Investigational Supplies Inventory Form and the Study Drug Return Form supplied by Nabi. All study drug returns to Nabi must be accompanied by a completed Study Drug Return Form.

*Lamivudine*
There will be no retrieval of lamivudine bottles.

## 6.4 Study Methods

Each patient must review and sign an Informed Consent form before participating in this study.

The following procedures regarding the patients will take place on the days indicated (see Attachment I, Time and Events Schedule).

*6.4.1 Screening and Enrollment (up to 12 weeks prior to transplant unless specified)*

a. Review patient status for compliance with Inclusion/Exclusion Criteria
b. Obtain signed Informed Consent
c. Conduct physical exam and obtain medical history
d. Obtain results for anti-HDV, anti-HCV, anti-HBs, anti-HBe, HBsAg, HBeAg, and HBV DNA. If HBV DNA-detectable then do assess for HBV genotype and HBV mutants.
e. Obtain 10 mL of blood for AST, ALT, Total Bilirubin, BUN, creatinine and stored serum
f. Begin lamivudine therapy
g. For women of child-bearing potential, obtain a serum sample for pregnancy test (β-HCG) within 14 days prior to starting lamivudine therapy and within 14 days prior to transplantation. The patient must also agree to practice contraception during the study.
h. Adverse Events (AE) including Serious Adverse Events (SAE) defined in Sections 7.1 and 7.2 will be collected from Enrollment (when an informed consent is signed) through the first 12 weeks following transplantation. Only Serious Adverse Events resulting in death will be collected after Week 12.

*6.4.2 Day 0 (Day of Transplantation)*

a. Obtain 10 mL of blood for HBeAg, anti-HBe, and HBV DNA, HBV mutations prior to transplantation.
b. Administer 10,000 IU Nabi-HB IV during the anhepatic phase of surgery.
c. Administer 10,000 IU Nabi-HB IV following reperfusion (before leaving the OR).

*6.4.3 Days 1-7 Post transplantation*

a. On Days 1, 2, and 5 prior to the infusion of Nabi-HB obtain 20 mL of blood from all patients for:
   - anti-HBs level, HBsAg, and HBV DNA
   - AST, ALT, Total Bilirubin, BUN, creatinine
b. Administer 10,000 IU Nabi-HB IV to all patients.

*6.4.4 Weeks 2, 3, 4, 6, and 8 post transplantation*

a. Obtain 10 mL of blood for HBV DNA, HBsAg, and anti-HBs level. During weeks 2, 3 and 8 obtain the blood prior to Nabi-HB infusion.
b. Obtain 10 mL of blood for AST, ALT, Total Bilirubin, BUN, and creatinine
c. Weeks 4 and 8 only: Administer 10,000 IU Nabi-HB IV.

*6.4.5 Nabi-HB Dose Adjustment*

Between Weeks 6 and 12:
If the 6-Week trough level < 300 IU/L patients will receive 10,000 IU Nabi-HB every 4 weeks for the remainder of the study.

If the anti-HBs level is projected to be < 200 IU/L prior to the next infusion, an additional 10,000 IU of Nabi-HB will be given intravenously as soon as possible prior to the next scheduled infusion.

Between Weeks 13 and 108:
If the anti-HBs level is projected to be < 100 IU/L prior to the next infusion, an additional 10,000 IU of Nabi-HB will be given intravenously as soon as possible prior to the next scheduled infusion.

*6.4.6 Weeks 12, 24, 36, 48, 60, 72, 84, 96, 108 post transplant*

a. Obtain 10 mL of blood for HBV DNA, HBsAg, and anti-HBs level. Obtain the blood prior to Nabi-HB infusion. If HBV DNA is detectable, at next scheduled blood sampling obtain blood for assessment of HBV mutants.
b. Obtain 10 mL for stored serum to replace lost or damaged specimen.
c. Obtain 10 mL of blood for AST, ALT, Total Bilirubin, BUN, and creatinine

## 6.5 Laboratory Tests

All laboratory evaluations will be performed at the study site.

## 7.0 ADVERSE EVENTS

### 7.1 Adverse Event Recording

An adverse event (AE) is any unfavorable, harmful or pathological change in a research patient as indicated by physical signs, symptoms and/or clinically significant laboratory abnormalities that occur in association with the use of a product (trial related), and may or may not be related to the administration of the product. This definition includes intercurrent illnesses, injuries, exacerbation of pre-existing conditions, and events occurring as a result of product abuse or overdose. Stable pre-existing conditions and elective procedures to address such conditions are not adverse events. A change in a laboratory variable is considered an adverse event if it was considered by the attending physician to be clinically significant, or if it caused (or should have caused) the clinician to reduce or discontinue the use of the product, institute a further diagnostic evaluation, or institute therapy. Additionally, this definition of an adverse event does not include inpatient or outpatient elective surgery for a condition that was present prior to the start of the trial, and which has not worsened unexpectedly during the trial.
The illness, not the treatment, is the AE (e.g. "appendicitis" is an AE, not "appendectomy").

An adverse event (AE) is any unfavorable, harmful or pathological change in a research subject, administered an investigational product (IP), as indicated by physical signs, symptoms and/or clinically significant laboratory abnormalities that may occur in association with the use of a product (trial-related), whether or not considered product-related. This definition includes intercurrent illnesses, injuries, exacerbation of pre-existing conditions, and events occurring as a result of product abuse or overdose. Planned procedures to address stable pre-existing conditions as well as any elective procedure are not adverse events. A change in a laboratory variable is considered an adverse event if it leads to a change in the subject's functional status, or is considered by the attending physician to be clinically significant or if it caused (or should have caused) the clinician to reduce or discontinue the use of the product or institute therapy. The illness, not the treatment, is the AE (e.g. "appendicitis" is an AE, <u>not</u> "appendectomy").

Following administration of the IP, study personnel will actively solicit adverse events. Assessment for seriousness and relationship to the study drug will be carried out by the investigator or sub-investigator. All AEs occurring [specify length of time] after administration of the IP must be recorded on the AE CRF/eCRF page, and followed to resolution or as specified per protocol. [specify length of time AEs will be followed after study closure].

All deaths that occur while the subject is on the study will be reported to the Sponsor through the serious adverse event reporting system. In addition, investigators may report to the Sponsor, any reaction they deem to be related to the IP, at any time.

#### *7.1.1 Expected Adverse Events Related to Liver Transplantation*

Liver transplantation is a complex procedure that is associated with frequent and varied complications. For example, acute cellular rejection may occur in as many as 70% of patients undergoing liver transplantation. Similarly, infectious complications, such as cytomegalovirus infection, and metabolic and systemic disturbances such as diabetes mellitus, hypertension, and renal failure may result from post-transplant immunosuppressive medications. Most of the anticipated complications are managed by routine treatment regimens that have been developed

at each transplant center. **The following list details direct complications of surgery or side effects of medications that are generally not unexpected following liver transplantation, and will not be considered adverse events for this study within the context of liver transplantation.** However, clinical judgement will ultimately be exercised to determine if those adverse events listed below are related to the study drugs or to the transplantation itself.

a. *Complications Related to Surgery/Post Operative Procedures*
    a. Hepatic artery or portal vein thrombosis
    b. Bile leak/stricture
    c. Hematoma
    d. Abscess
    e. Bleeding following liver biopsy
b. *Infectious*
    a. Bacterial – wound infections, sepsis/line infections, Legionella, Listeria, Mycobacteria, Nocardia
    b. Fungal – Aspergillus, Cryptococcus, Histoplasma, Coccidioides, Blastomyces, Rhizopus
    c. Viral – CMV, EBV, HSV, VZV
c. *Medication Related*
    a. Osteopathic – osteonecrosis, fractures
    b. Cardiovascular – hypertension
    c. Gastrointestinal – anorexia, diarrhea, nausea, vomiting
    d. Hepatologic – cholestasis, veno-occlusive disease
    e. Renal – elevation of BUN, blood urea, or creatinine
    f. Metabolic – hyperkalemia, hypomagnesemia, hyperglycemia
    g. Malignancy – lymphomas, Kaposi's Sarcoma, carcinomas
    h. Hematologic – anemia
    i. Neurologic – tremors, paresthesias, hyperesthesias, headaches, seizures, psychosis/delirium
    j. Ocular – cataracts, retinal changes
    k. General – fever, Cushinoid features, hypertrichosis, gingival hyperplasia, rash, alopecia, hirsutism

**All Adverse events (except those noted above) must be recorded on the Adverse Event Case Report Form page.**

### 7.2 Serious Adverse Event

A SERIOUS ADVERSE DRUG EXPERIENCE is any adverse drug experience that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious

adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

**The following will not be considered serious adverse events:** any event that results in hospitalization or prolongs an existing hospitalization if the reason for that hospitalization or prolongation was for:

a. Administration of a blood transfusion
b. Administration of study procedures
c. Obtaining a liver biopsy
d. An expected adverse event related to liver transplantation as noted in Section 7.1.1.

For the purpose of this study, a serious adverse drug experience is also called a serious adverse event or SAE. All SAEs should be reported to the Nabi Product Safety Surveillance Group (NPSSG) during the interval from each investigational product injection through the following 42 days, and thereafter only SAEs which result in death will be collected. Any SAE considered to be probably related to the study drug should also be reported regardless of timing during the study. All SAEs must be reported to the NPSSG within 24 hours of learning of the event at:

Telephone: 301-255-6934, or 301-255-6931

Fax: 800-303-3874,

Pager: 1-800-314-0474 or 1-800-314-0473.

Reports of SAEs should be faxed to Nabi on the provided SAE Worksheets and give full details of the experience, including an assessment of the relationship of the event to the investigational product, action taken regarding the investigational product, and outcome. In addition, the Principal Investigator is responsible for reporting all serious adverse events (SAE) to the Institutional Review Board.

Discharge summaries and/or death certificates to support the data on the SAE worksheet should be sent to the Product Safety Surveillance Group as soon as they become available. Any necessary follow-up reports should be submitted as soon as the information becomes available.

**All SAEs must be recorded on the Adverse Event DCF page.**

## 8.0 ANALYSES

### 8.1 Sample Size and Power

Recurrence of HBV-related liver disease (defined as seroconversion from HBsAg-negative to HBsAg-positive) at two years among transplant recipients treated with concomitant Nabi-HB and lamivudine is given as $\theta_A$ and recurrence of HBV-related liver disease (defined as seroconversion from HBsAg-negative to HBsAg-positive) at two years among transplant recipients treated with lamivudine monotherapy is given as $\theta$. Based on a meta-analysis of

published original articles on HBV-related liver disease, the recurrence rate among transplant recipients treated with lamivudine monotherapy is 0.45.
StatXact software was used to perform an exact, two-sided, one-sample calculation for the required sample size with $\theta_A = 0.25$ and $\theta = 0.45$. Using an $\alpha$ level of 0.05, a power of 80%, and a drop-out rate of 10%, it is estimated that 50 subjects are required for the study.

### 8.2 Efficacy

The primary analysis population will include subjects satisfying the following:

1. HBsAg positive at Transplant.
2. Survival beyond 30 days.
3. All subjects will be HbsAG-positive prior to transplantation. Almost all transplant recipients [who receive a HBV-negative liver] will become HbsAg-negative shortly after transplantation. Seroconversion is defined as going from the initial HbsAg-negative serostatus post-transplantation to HbsAG-postive. There must be evidence that the subject seroconverts from HbsAG negative to HbsAg positive post-transplant.
4. There must be evidence of either clinical follow-up or serology (HBsAg) at 2 years post liver transplantation.

Let $\theta_A$ be the true recurrence rate for transplant recipients treated with concurrent Nabi-HB and lamivudine. The reference rate of recurrence with lamivudine monotherapy is 0.45. The hypothesis to be tested is:

$$H_0: \theta_A = 0.45 \textit{ vs. } H_1: \theta_A \neq 0.45$$

A test of the hypothesis will utilize a one-sample, two-sided binomial comparison conducted with StatXact-6 software.

Descriptive statistics will be used to analyze secondary efficacy outcomes (for example, emergence of lamivudine or HBIg resistance).

### 8.3 Safety Analysis

Safety data tabulation and analyses will examine changes from baseline to end of treatment. The principle of treatment emergence will be employed for the analysis of adverse experiences (AE) data. Treatment emergence is defined to be any event that occurred during treatment and was not present at baseline, or one that represents an exacerbation of a condition present at baseline. Adverse experience data will be listed individually and summarized by body system and preferred terms within a body system for each treatment group using the MedDRA dictionary. Serious and/or unexpected AEs may also be discussed on a case-by-case basis.

Graphical assessment of laboratory parameters over time will be displayed by showing means by time. Shift tables will be used to show proportions of subjects with changes in laboratory outcomes among low, normal, and high ranges between study entry and end of treatment.

## 9.0 WITHDRAWAL FROM STUDY

Should a patient withdraw from the study for any reason, the reason will be recorded. If withdrawal is the result of a serious adverse event, the patient will be followed until the condition has resolved, as determined by the investigator. Evaluation for adverse events at 14 days following administration of the last infusion of Nabi-HB should be completed for any patient who withdraws from the study.

## 10.0 REFERENCES


1. McGory RW, Ishitani MB, Oliveira WM et al. Improved outcome of orthotopic liver transplantation for chronic hepatitis B cirrhosis with aggressive passive immunization. Transplantation 1996; 61(9):1358-1364.

2. Markowitz JS, Martin P, Conrad AJ et al. Prophylaxis against hepatitis B recurrence following liver transplantation using combination lamivudine and hepatitis B immune globulin. Hepatology 1998; 28(2):585-589.

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4. Cohn EJ, Strong LS, Hughes WL et al. Preparation and Properties of Serum and Plasma Proteins. IV. A System for the Separation into Fractions of the Protein and Lipoprotein Components of Biological Tissues and Fluids. J Am Chem Soc 1946; 68:459-479.

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6. Horowitz B. Investigations into the application of tri(*n*-butyl)phosphate/detergent mixtures to blood derivatives. Morgenthaler J, editor. *Virus Inactivation in Plasma Products*[56], 83-96. 1989. *Curr Stud Hematol Blood Transfus.*

7. Burnouf T. Value of virus filtration as method for improving the safety of plasma products. Vox Sang 1996; 70:235-236.

## 11.0 AGREEMENT WITH PROTOCOL

I, _____, agree to conduct protocol Nabi-4206, "Multi-Center Efficacy Study to Assess Intravenous Nabi 5% Hepatitis B Immune Globulin (Nabi-HB) Used in Combination with Lamivudine for Patients with Hepatitis B Virus (HBV) Associated Liver Disease Undergoing Liver Transplantation", as described in the above protocol. I understand that no deviations from the above protocol may be made without the permission of the sponsor, Nabi Biopharmaceuticals.

**ACCEPTED AND AGREED**:

Investigator

_____ _____

Signature Date

## 12.0 ATTACHMENT I TIME AND EVENTS SCHEDULE

| | Screening | Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Week 2 | Week 3 | Week 4 | Week 6 | Week 8 | Week 12 | Week 24 | Week 36 | Week 48 | Week 60 | Week 72 | Week 84 | Week 96 | Week 108 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Informed Consent & Medical History** | x | | | | | | | | | | | | | | | | | | | | | | |
| **Physical Exam** | x | | | | | | | | | | | | | | | | | | | | | | |
| **B-HCG (females), anti-HCV** | x [1] | | | | | | | | | | | | | | | | | | | | | | |
| **Anti-HDV, anti-HBe, HBeAg** | x | x [2] | | | | | | | | | | | | | | | | | | | | | |
| **HBV DNA** | x [5] | x [2] | x | x | | | x | | | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| **ALT, AST, total bilirubin, BUN, creatinine** | x | | x | x | | | x | | | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| **HBsAg** | x | | x | x | | | x | | | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| **Nabi-HB Infusion (10,000 IU)** | | x [3] | x | x | x | x | x | x | x | | | x | | x | | | | | | | | | |
| **Nabi-HB Infusion (10,000 IU)** | | | | | | | | | | | | | | | <----------monthly----------> | | | | | | | | |
| **Lamivudine, 100 mg po daily** | <----------daily----------> | | | | | | | | | | | | | | | | | | | | | | |
| **Anti-HBs Serology [4]** | x | | x | x | | | x | | | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| **AEs, and Concomitant Medications** | <----------x----------> | | | | | | | | | | | | | | | | | | | | | | |
| **SAEs** | <----------all SAEs----------> | | | | | | | | | | | | | | | <-----AEs resulting in death------> | | | | | | | |

1. If female of child-bearing potential, a negative serum β-HCG pregnancy test must be obtained within 14 days prior to starting lamivudine therapy and within 14 days prior to transplantation.
2. Obtain blood for HbeAg, anti-Hbe, and HBV DNA, HBV mutations on the day of transplantation prior to transplantation
3. On Day 0, Nabi-HB is administered during the anhepatic phase of surgery and again following reperfusion
4. Anti-HBs samples will be collected prior to Nabi-HB infusions
5. Within 14 days of transplantation

**All studies to be performed on Weeks 4 through 108 can be done ± 3 days of scheduled time**

**Attachment 8**

**Selected References**