

Issue Summary
Blood Products Advisory Committee
Gaithersburg, Maryland
July 13, 2006

Topic I: FDA Review of Nabi Pharmaceuticals' Hepatitis B Immune Globulin Intravenous (H) (HBIGIV) for Prevention of Recurrent HBV Disease after orthotopic liver transplantation (OLT)

Issue: FDA seeks to be advised on the adequacy of a retrospective analysis of Hepatitis B Immune Globulin Intravenous (HBIGIV) for prevention of recurrent HBV disease after orthotopic liver transplantation (OLT) to demonstrate effectiveness.

Background:

Hepatitis B Immune Globulin (Intramuscular) (Nabi), (HBIGIM), is indicated for treatment of acute exposure to blood containing HBsAg, perinatal exposure of infants born to HBsAg-positive mothers, sexual exposure to HBsAg-positive persons and household exposure to persons with acute HBV infection.

Nabi seeks an additional indication for use of the product as immunoprophylaxis against liver graft re-infection with hepatitis B virus (HBV) for patients undergoing orthotopic liver transplantation (OLT) for HBV disease.

A March 2004 BPAC voted to accept the surrogate endpoint, "maintenance of HBsAg seronegativity," for this indication. The BPAC commented that HBIG monotherapy should have 1 year follow-up data, and use of HBIG in combination with an HBV antiviral (lamivudine) should have 2 years follow-up data. Specific analytic plans were not discussed.

Nabi submitted an analysis of data from subjects in two studies who received HBIG from the time of OLT and were receiving the HBV antiviral lamivudine. Study 4204 was conducted under an IND sponsored by Dr. Roland Dickson of the Mayo Institute (Orlando). The objective of study 4204 was to measure the pharmacokinetics of Nabi HB over a 9 month treatment period in HBV OLT subjects concomitantly receiving lamivudine. Study 4409, sponsored by Nabi, was an open protocol for the use of the product in 153 HBV reactive OLT subjects. Neither study was designed as a pivotal efficacy study. The studies were not prospectively designed to evaluate HBsAg serology as a surrogate endpoint at 2 years of follow-up and thus did not include prospective plans for analysis of this endpoint.

Summary of Nabi Pharmaceuticals' License Application

Nabi's submission included its review of the medical literature, known to be subject to publication biases, for lamivudine monotherapy after OLT for HBV disease. Nabi identified 5 papers they deemed suitable for conducting a meta-analysis for the purpose of deriving a historical control failure rate, as shown in the following table:

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Table 2.1-1 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	13/39	41%

Nabi's meta-analysis found an HBV weighted recurrence rate (θ_A) of 45% for lamivudine monotherapy with a 95% confidence interval of 35 - 54%.

The data from studies 4204 and 4409 are missing HBsAg measurements for many time periods for a number of subjects (see below). Nabi states that if patients were "clinically stable," (a term that was not agreed upon) then clinicians did not monitor HBsAg. Therefore, Nabi classifies subjects with missing HBsAg data and who are "clinically stable" as being HBsAg seronegative (successes). This is a primary difference between patient care and rigorous clinical research and is an example of the most anti-conservative approach to imputing missing data. Nabi presents the HBsAg seronegativity data from these two studies in two ways according to: 1) whether data on "clinical stability" (indicating assumed HBsAg seronegativity) are available, or 2) whether HBsAg data are available for the entire 2 year monitoring period. In either case, these are highly selected samples from the original data. The following 2 tables present Nabi's analyses:

**Sponsor's Analysis of Studies 4204 & 4409
(Clinical Stability Endpoint)**

Table 3.3-1: Database for Efficacy of Nabi-HB with Lamivudine Compared to Lamivudine Monotherapy (New OLT patient with = 2 years of Clinical Follow-up or Death > 30 days post transplantation)		
Study	Recurrences Relative efficacy assuming $\theta_A = 0.45$	p-value
4204	0/24 100%	<0.0001
4409	1/17 86.9%	0.0012
Pooled	1/41 94.6%	<0.0001

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**Sponsor's Analysis of Studies 4204 & 4409
(HBsAg Serological Endpoint)**

Table 3.3-2: Database for Efficacy of Nabi-HB with Lamivudine Compared to Lamivudine Monotherapy (New OLT patient with = 2 years of Clinical Follow-up or Death > 30 days post transplantation)		
Study	Recurrences Relative efficacy assuming $\theta_A = 0.45$	p-value
4204	0/18 100%	<0.0001
4409	1/11 79.8%%	0.028
pooled	1/29 92.3%	<0.0001

Although Nabi calculated “p” values for their analysis, this process is not justified as inferential statistics have very limited meaning when the mechanism of treatment assignment is known to be nonrandom [Greenland, *Epidemiology*, 1990].

The next table, prepared by CBER, presents data points of available HBsAg serological data and is followed by CBER’s analysis. Nabi’s analysis differs substantially from CBER’s analysis. These differences are highlighted later in this document and include a description of discrepancies between CBER’s and Nabi’s retrospective analyses. (See page 10).

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The following table, prepared by CBER, presents the HBsAg serologic data:

SID	Month																										
	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23		24	
4204-001001		5	1	1	1		1		1	1					1												Neg month 52
4204-001002		4	1	1	1	1	1	1	1	1					1												Neg month 49
4204-001003		1	5	1	1				1	1	1	2															?
4204-001004			5																								death HBV related
4204-001005			5	1										1													?
4204-001006			2	1	1	1	1	1	1	1	1	1	1														Neg month 41
4204-001007			5	5	5	2	1	1	1	1	1	1		1			1						1				Neg month 43
4204-002001			1	4	1	1	1	1	1	1	1	1	1	1													Neg month 37
4204-002002			1	5	1	1	1	1	1	1	1	1	1	1													Neg month 28
4204-002003			1	5	1	1	1	1	1	1	1	1	1			1			1								?
4204-002004			1	6																							?
4204-002005			1	6	1	1	1	1	1	1	1	1	1	1													Pos month 37
4204-002006			1																								died
4204-003001			1	5	1	1	1	1	1	1	1	1	1	1													?
4204-004001			1	2																							died
4204-004002			1																								died
4204-004003			4	1	1	1	1	1	1	1	1	1	1				1	1					1				died
4204-004004			4	1	1	1	1	1	1	1	1	1	1			1		1								1	Neg month 37
4204-005001			5	4	1		1	1	1	1	1	1	1		1	1		1		1		1					Neg month 49
4204-005002			1	5	1	1	1	1	1	1	1	1	1	1			2		1	1	1						Neg month 40
4204-009001			1	2	1	1																					Neg month 25
4204-011001			1	3	1	1	1	1	1	1	1	1	1		1				1	1							Neg month 37
4204-012001			1	2	1	1	1	1	1	1	1	1	1				1										Neg month 29
4204-012002			1	3	1																						Neg month 37
4204-012003			1	3	1	1	1	1	1	1	1	1	1	1			1		1			1					Neg month 27
4204-013001			4	1	1	1	1	1	1	1	1	1	1		1								1				Neg month 36
4204-015001			5	1	1	1	1	1	1	1	1	1	1												1		?
4204-015002			5	1	1	1	1	1	1	1	1	1	1							1							?
4204-015003			5	1	1	1	1	1	1	1	1	1	1														?
4204-015004			1	5	1	1	1	1	1	1	1	1	2														?
4409-002003			3	3	2	4				2					1								1				Pos months 26-68
4409-002004				1	2																						?
4409-005011			6	1					1	1				1								1					Neg month 59
4409-005012			3	1					1					1													Neg month 59
4409-016001			1	1	1																						Neg month 47
4409-016002			1					1	1							2	2		1							1	Neg month 59
4409-016010			1																			1					Pos months 25-39
4409-003002																											Pos DNA Month 10
4409-003009			1																								died
4409-005007			10							1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Pos month 28 died month 29
4409-001002			4						1				1	1	1	1											Neg month 61
4409-002001																											died
4409-002005					2																						died
4409-002006					2																						?
4409-002007			1		2																						?
4409-003013			1																								?
4409-003015			2																								?
4409-005010			6						1			1		1												1	Neg month 41
4409-006009			1	1		2																					?
4409-010005			2		3			1			1	1	1		2												?
4409-010007			2	2				1			1	1	1									2					?
4409-011001																											?
4409-016005																											?
4409-016015								1			1		2														?
4409-018001			1		1																						Neg month 61
4409-020002																											died
4409-028004															1							1					Neg month 52
4409-028005			1																								died
4409-079001			5	2																							?
4409-218001			1			1	2																				?
4409-219008																											?
4409-221001				2																							?

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Key to HBsAg Seroconversion table (above):

Numbers indicate the number of HBsAg measurement made in the month for the given subject.

A red background in the box indicates a positive HBsAg Measurement.

A red "X" (green "X" for red backgrounds) indicates death.

Hatched background indicates no further HBsAg measurements up to the 24 month time point.

A "?" in the comments section (at the end of each row) indicates there were no further HBsAg measurements at any time after the 24 month time point.

If there were additional HBsAg measurements after the 24 month time point, the comments section gives the month of the last negative HBsAg measurement if all subsequent HBsAg measurement were negative.

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FDA “Evaluable” Databases

The following section shows how FDA has derived the “Evaluable databases” for studies 4204 and 4409. These databases are for discussion purposes and are not meant to suggest that the inability to assess outcome in 11 of 30 subjects in Study 4204 and 21-24 subjects out of 32 subjects in Study 4409 and therefore excluding them from the analysis is a sound analytic approach:

Study 4204

30 subjects

2 subjects died within 30 days (4204-002006 and 4204-004002)

28 subjects

2 subjects were lost to follow-up (4204-002004 and 4204-015004)

26 subjects

2 subjects died in the interval 30 days to 2 yrs not HBV-related (4204-004001 and 4204-004003)

24 subjects

5 subjects inadequately monitored for HBsAg to 2 yrs (4204-001003, 4204-001005, 4204-003001, 4204-015002, 4204-015003)

19 subjects

These 19 “Evaluable” subjects are the following: 4204-001001, 4204-001002, 4204-001003, 4204-001006, 4204-001007, 4204-002001, 4204-002002, 4204-002003, 4204-002005, 4204-004004, 4204-005001, 4204-005002, 4204-009001, 4204-011001, 4204-012001, 4204-012002, 4204-012003, 4204-013001 and 4204-015001.

This study did not have a predefined analysis plan for HBsAg serologic status at 24 months. Within a range of analytic approaches to handling missing data, the 11 excluded subjects would have been counted as treatment failures.

Study 4409

Of the 153 subjects in this open label expanded access study, 32 were newly transplanted and compose the data set proposed for analysis.

32 subjects (which includes 22 subjects on HBIG monotherapy, i.e. no Lamivudine)

3 died within 30 days (4409-002001, 4409-028005 and 4409-020002)

29 subjects (19 HBIG monotherapy)

Excluded the following 4 subjects:

1. 4409-003013 discovered to be HBsAg neg at transplant
2. 4409-010005 not HBV infected but rec'd HBV+ liver
3. 4409-010007 not HBV infected but rec'd HBV+ liver
4. 4409-028004 no evidence of HBsAg pos prior to transplant

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25 subjects (15 HBIG monotherapy)

2 subjects died between 30 days and 2 yrs (4409-003009 and 4409-002005)

23 subjects (14 HBIG monotherapy)

12 subjects excluded for less than 2 yrs follow-up (4409-002004, 4409-002006, 4409-002007, 4409-003015, 4409-006009, 4409-011001, 4409-016005, 4409-016015, 4409-079001, 4409-218001, 4409-219008 and 4409-221001)

11 subjects (3 HBIG monotherapy)

8 Subjects on combined HBIG + Lamivudine therapy

These 8 subjects on combined HBIG + Lamivudine therapy are the following: 4409-002003, 4409-005007, 4409-005011, 4409-005012, 4409-016001, 4409-016002, 4409-016010, 4409-003002; the 3 subjects on HBIG monotherapy are the following: 4409-001002, 4409-005010 and 4409-018001.

This study also did not have a predefined analysis plan for HBsAg serologic status at 24 months. Within a range of analytic approaches to handling missing data, up to 24 excluded subjects would have been counted as treatment failures.

Pooled Data

For combined HBIG + Lamivudine therapy there are $19 + 8 = 27$ subjects in the "Evaluable" database for studies 4204 and 4409. If the 3 subjects on HBIG monotherapy are included, the "Evaluable" database contains $27 + 3 = 30$ subjects. As with other analytic approaches, appropriate pooling across data sets should be discussed with FDA prior to performing any combination or analysis.

FDA Classification of HBsAg Seroconverters

For 4 subjects, there is clear evidence of HBsAg seroconversion before month 24; these subjects are 4204-002003, 4202-015001, 4409-002003, and 4409-005007.

For 4 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 the following:

1. 4204-001004 (death at month 2 judged HBV related),
2. 4204-002005 (HBsAg positive at month 37),
3. 4409-003002 (HBV DNA positive at month 10), and
4. 4409-016010 (HBsAg positive from months 25 to 39).

The lack of regular HBsAg monitoring precludes the assignment of a time point for most of these HBsAg seroconversions; therefore, seroconversion before month 24 (i.e. surrogate

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endpoint failure) must be considered. This lack of regular HBsAg monitoring reflects a primary distinction between patient care and rigorous clinical research.

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 at baseline or on-study, despite the monitoring of anti-HBs levels and a single HBV DNA measurement. The HBV DNA measurement at day +292 reports a serum HBV DNA level of 1080 pg/ml which corresponds to 4×10^5 HBV genome equivalents per milliliter. Lacking data to the contrary subject 4409-003002 has been classified as a treatment failure based on the day +292 HBV DNA measurement.

Therefore, there are a total 8 subjects who are judged HBsAg seroconverters by month 24.

FDA Analysis

Based upon the above classification, CBER concludes that the database for the “Evaluable” subjects shows an observed recurrence rate of $8/27 = 0.2963$ (95% CI: 0.1375, 0.5018). The upper bound of the 95% CI does not exclude the sponsor’s point estimate of 45% for their meta-analysis of historical experience with lamivudine treatment alone. This, along with the substantial number of subjects with missing data for the surrogate endpoint (23 subjects) who were therefore excluded from the “Evaluable” database are inadequate to demonstrate efficacy of this product, leads CBER to the conclusion that the submitted data are inadequate to support licensure for this indication.

Nabi includes 3 subjects who received only HBIG monotherapy in their analysis. This may not be appropriate for a retrospective analysis to support an indication for use with a concomitant HBV antiviral drug (lamivudine), because such subjects may have specific contraindications for anti-HBV treatment and *baseline covariates for outcome* among subjects only receiving lamivudine may not coincide with baseline covariates for subjects receiving HBIG + Lamivudine combination therapy, i.e. they may represent a different patient population. If the 3 HBIG monotherapy subjects are included the observed recurrence rate becomes $8/30 = 0.27$ with a 95% CI of the recurrence rate = (0.12, 0.46).

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Analysis of FDA/Sponsor Discrepant Results

The FDA approach to this retrospective data analysis differed from the approach of Nabi in the following 3 ways:

1. **Deaths.** One way to handle deaths in this context is an *a priori* discussion of conservative approaches such as removing all non-HBV related deaths from analysis. An anti-conservative approach would include and count as successes these subjects with non-HBV related deaths. FDA followed a conservative approach and removed HBV non-related deaths from the database. Nabi followed an anti-conservative approach and included HBV non-related deaths in the database and counted them as successes if the previous HBsAg measurement was negative.
2. **Missing Data.** If HBsAg measurements were not available to satisfy the requirement for at least 2 yrs HBsAg monitoring for combined HBIG + Lamivudine therapy, Nabi counted subjects as successes if they were monitored clinically for at least 2 years and judged to be clinically stable. FDA removed these subjects from the database due to missing data. An even more conservative analysis would retain these subjects in the analysis and assume them to be failures.
3. **HBIG Discontinuation.** Seven subjects discontinued HBIG therapy prior to 2 yrs. Two of these seven HBsAg-seroconverted. Nabi anti-conservatively excluded the 2 of 7 subjects who were HBsAg seroconverters and included the 5 of 7 subjects who remained HBsAg negative. FDA did not exclude any of the 7 subjects for the reason of HBIG early discontinuation.

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For the **HBsAg serology** “Evaluable” subjects’ database, FDA and Nabi differ as shown in the table below.

It should be noted that neither of the studies submitted by Nabi was designed as a pivotal efficacy study. The studies were not prospectively designed to evaluate HBsAg serology at 2 years of follow-up as a surrogate endpoint and therefore did not include prospective plans for analysis of this endpoint.

Subject ID	FDA Inclusion Reason	FDA Exclusion Reason	Nabi Inclusion Reason	Nabi Exclusion Reason
4204-002003	HBsAg pos At month 13			HBsAg less than 2 yrs
4204-002005	HBsAg pos At month 37 (day 906)			HBIG Discontinued Day 249 HBsAg pos Day 906
4204-004001		Died before 2 yrs Not HBV-related	HBsAg neg Prior to death	
4204-004003		Died before 2 yrs Not HBV-related	HBsAg neg Prior to death	
4204-015001	HBsAg pos At month 22			HBIG Discontinued Day 252 HBsAg pos Day 635
4409-005007	HBsAg pos At all times			HBIG Discontinued After 10 doses
4409-003002	HBV DNA pos Month 10 1080 pg/ml			No HBsAg measurements
4409-003009		Died before 2 yrs Not HBV-related	HBsAg neg Prior to death	
4409-001002		HBIG monotherapy Not accepted	HBIG monotherapy Accepted	
4409-002005		Died before 2 yrs Not HBV-related	HBsAg neg Prior to death	
4409-005010		HBIG monotherapy Not accepted	HBIG monotherapy Accepted	
4409-018001		HBIG monotherapy Not accepted	HBIG monotherapy Accepted	

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Table 3.3-1 (Nabi Clinical Stability endpoint), presented above, differs from Nabi HBsAg serology database, just discussed, by including the following 12 additional subjects: 4204-001003, 4204-001005, 4204-002003, 4204-003001, 4204-015002, 4204-015003, 4409-002004, 4409-003002, 4409-002006, 4409-002007, 4409-003015 and 4409-006009. All, except subject 44009-003002, were excluded from the FDA analysis due to inadequate monitoring of HBsAg; subject 44009-003002 was included in the FDA analysis because he was HBV DNA positive at month 10.

QUESTIONS FOR THE COMMITTEE:

1. Please comment on Nabi's *post hoc* inclusion and exclusion criteria for the classification of subjects as successes or failures following HBIG administration in the setting of OLT.
2. Given the observational nature of the information provided, the data limitations (including a priori definitions), and the lack of analysis plan, is inference about the outcomes of Nabi/s HBIG administration in this setting appropriate?
3. Do the submitted data from retrospective chart reviews, an uncontrolled PK assessment and an open label access program demonstrate efficacy of Hepatitis B Immune Globulin (H) (HBIG) (Nabi-HB™) for the OLT HBV immunoprophylaxis indication?