

Hepatitis B Immune Globulin
Intravenous (Human)(Nabi-HB™
Intravenous) to Prevent HBV
Recurrence after Orthotopic Liver
Transplantation (OLT) for
Hepatitis B disease

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FDA/CBER/OBRR/DH/CRB

87th BPAC, July 13, 2006

STN125073

Claim:

Intravenous administration of Hepatitis B Immune Globulin Intravenous (Human) (HBIGIV; Nabi-HB™ Intravenous) will prevent HBV recurrence after orthotopic liver transplantation (OLT) for hepatitis B disease when given with anti-HBV antiviral therapy

Current Indications for Hepatitis B Immune Globulin Intravenous (Human)(Nabi-HB[®])

- Acute exposure/needle-stick to blood containing HBsAg
- Sexual exposure to HBsAg-positive persons
- Perinatal exposure of infants born to HBsAg-positive mothers
- Household exposure to persons with acute HBV infection

Order of Presentation

- Background on IND studies conducted
- Failed attempt to use University of Virginia data (McGory study) as pivotal study for licensure
- Current attempt to retrospectively analyze Nabi's data for maintenance of HBsAg Seronegativity

IND 8452 Chronology

- Submitted June 1999; Objective: intravenous administration for OLT for HBV disease
- Conducted 4 studies
 1. **Study 2906.** Pharmacokinetics in 21 OLT subjects more than 3 months after OLT (i.e., at the earliest time when PK parameters have stabilized after OLT). The product was Nabi HB (CANGENE), a version of the product made at Cangene Corp. Dose: 180 IU/kg i.v.
 2. **Study 4406.** An open-label extension of study 2906 for 10 subjects, to provide product to these subjects.

IND 8452 Chronology (cont.)

- 3. Study 4203.** Pharmacokinetics in 21 OLT subjects more than 6 months after OLT (i.e., at a time when PK parameters have stabilized after OLT). The product was Nabi HB (Boca), the current version of the product manufactured in Boca Raton, FL. Dose: 10,000 IU i.v. monthly for 3 months.
- 4. Study 4409.** An open protocol for use of the product in 153 HBV OLT subjects; dose schedules and monitoring were not standardized

Nabi Proposal to Use a non-IND Study of another HBIG i.m. product to Demonstrate Efficacy

- McGory et al, *Transplantation* **61**(9):1358-1364(1995)
 - 27 HBsAg+; 17/27 HBeAg+ for OLT
 - Dose: 10,000 IU
 - anhepatic
 - daily d1-6
 - then target trough > 500 IU/L
-

FDA Response:

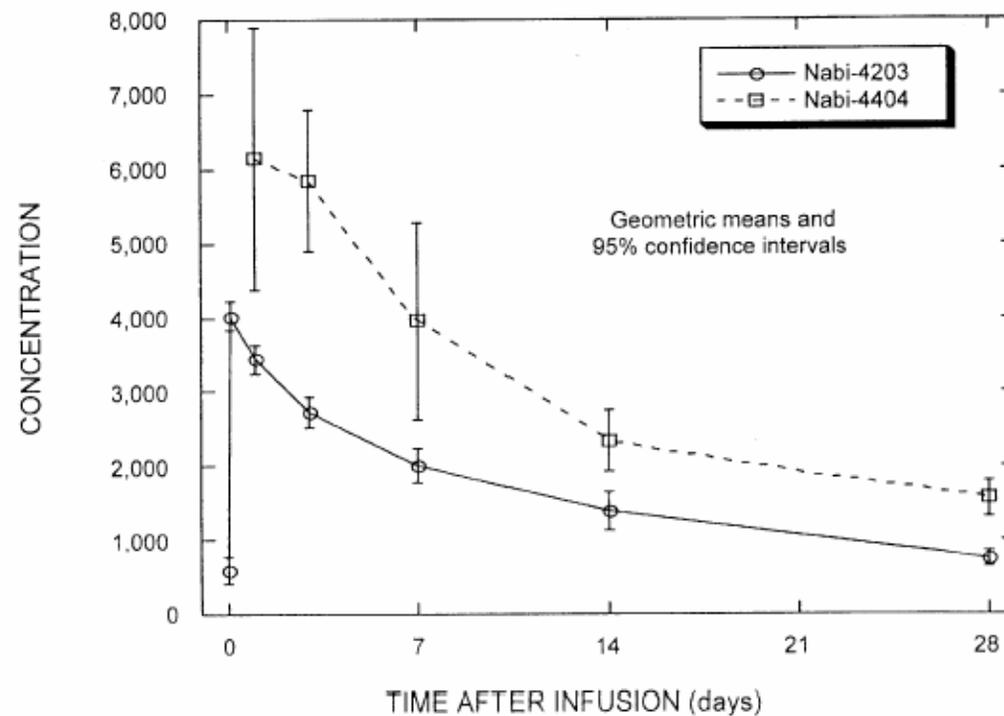
- A clinical benefit must be demonstrated
- Data must show that a similar result would be expected if the Nabi HBIGIV had been used

No Formal Demonstration of Clinical Benefit in Submitted McGory Study

- Control database not submitted
- Analysis was descriptive
- No hypothesis tested
- No prospectively described plan for analysis

Disparity in Serum anti-HBs Levels achieved in McGory(4404) vs. Study 4203

Non normalized Geometric Means



2003 Nabi proposed use of surrogate endpoint: HBsAg seronegativity

- Claimed HBsAg seronegativity is the clinical goal of therapy
- Requested retrospective analysis of data from past Nabi studies for licensure
- FDA brought HBsAg endpoint issue to March 2004 BPAC, which endorsed this endpoint with 2 provisions:
 - HBIGIV monotherapy needs 1 year follow-up
 - HBIGIV + Lamivudine needs 2 years follow-up

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Dickson PK
study

4204

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	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Neg month 52
4204-001002	4	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Neg month 49
4204-001003	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	?
4204-001004	5																									death HBV related
4204-001005	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	?
4204-001006	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Neg month 41
4204-001007	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	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	1	1	1	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	1	1	1	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	1	1	1	1	1	1	1	1	1	1	1	1	?
4204-002004	1	6																								?
4204-002005	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Pos month 37
4204-002006	1																									died
4204-003001	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	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	1	1	1	1	1	1	1	1	1	1	1	died
4204-004004	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Neg month 37
4204-005001	1	4	1	1	1	1	1	1	1	1	1	1	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	1	1	1	1	1	1	1	1	1	1	1	1	1	Neg month 40
4204-009001	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Neg month 25
4204-011001	1	3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Neg month 37
4204-012001	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Neg month 29
4204-012002	1	3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Neg month 37
4204-012003	1	3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Neg month 27
4204-013001	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Neg month 36
4204-015001	1	1	1	1	1	1	1	1	1	1	1	1	1	1	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	1	1	1	1	1	1	1	1	1	1	1	1	1	?
4204-015003	5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	?
4204-015004	1	5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	?
4409-002003	3	3	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Pos months 26-68
4409-002004	1	1	2																							?
4409-005011	6	1																								Neg month 59
4409-005012	3	1																								Neg month 59
4409-016001	1	1	1																							Neg month 47
4409-016002	1	1																								Neg month 59
4409-016010	1																									Pos months 25-39
4409-003002																										?
4409-003009	1																									Pos DNA Month 10
4409-005007	10																									Pos month 26 died month 29
4409-001002	4																									Neg month 61
4409-002001																										died
4409-002005			2																							died
4409-002006			2																							?
4409-002007	1		2																							?
4409-003013	1																									?
4409-003015	1																									?
4409-005010	6																									Neg month 41
4409-006009	1	1		2																						?
4409-010005	2	3			1																					?
4409-010007	2	2																								?
4409-011001																										?
4409-016005																										?
4409-016015																										?
4409-018001	1		1																							Neg month 61
4409-020002																										died
4409-028004																										Neg month 52
4409-028005	1																									died
4409-079001	5	2																								?
4409-218001	1			1	2																					?
4409-219008																										?
4409-221001			2																							?

4409

Open Protocol

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
4204-001004		5	X																							death HBV related
4204-002003	1	5	1	1	1	1	1	1	1	1			1		1				1							?
4204-002005		6	1	1	1	1	1	1	1	1																Pos month 37
4204-015001		5	1	1	1	1	1	1	1	1													1			?
4409-002003		3	3	2	4				2						1						1					Pos months 26-
4409-016010	1																			1						Pos months 25-
4409-003002																										?
																										Pos DNA Month 10
4409-005007		10							1		1		1				1						1			Pos month 28 ded month 29

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4204

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	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Neg month 52
4204-001002	4	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Neg month 49
4204-001003	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	?
4204-001004	5																									death HBV related
4204-001005	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	?
4204-001006	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Neg month 41
4204-001007	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	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	1	1	1	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	1	1	1	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	1	1	1	1	1	1	1	1	1	1	1	1	?
4204-002004	1	6																								?
4204-002005	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Pos month 37
4204-002006	1																									died
4204-003001	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	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	1	1	1	1	1	1	1	1	1	1	1	died
4204-004004	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Neg month 37
4204-005001	1	4	1	1	1	1	1	1	1	1	1	1	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	1	1	1	1	1	1	1	1	1	1	1	1	1	Neg month 40
4204-009001	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Neg month 25
4204-011001	1	3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Neg month 37
4204-012001	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Neg month 29
4204-012002	1	3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Neg month 37
4204-012003	1	3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Neg month 27
4204-013001	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Neg month 36
4204-015001	1	1	1	1	1	1	1	1	1	1	1	1	1	1	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	1	1	1	1	1	1	1	1	1	1	1	1	1	?
4204-015003	5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	?
4204-015004	1	5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	?
4409-002003	3	3	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Pos months 26-68
4409-002004	1	1	2																							?
4409-005011	6	1																								Neg month 59
4409-005012	3	1																								Neg month 59
4409-016001	1	1	1																							Neg month 47
4409-016002	1	1																								Neg month 59
4409-016010	1																									Pos months 25-39
																										?
																										Pos DNA Month 10
4409-003002																										
4409-003009	1																									died
4409-005007	10																									Pos month 26 died month 29
4409-001002	4																									Neg month 61
4409-002001																										died
4409-002005			2																							died
4409-002006			2																							?
4409-002007	1		2																							?
4409-003013	1																									?
4409-003015	1																									?
4409-005010	6																									Neg month 41
4409-006009	1	1		2																						?
4409-010005	2	3			1																					?
4409-010007	2	2				1																				?
4409-011001																										?
4409-016005																										?
4409-016015																										?
4409-018001	1		1																							Neg month 61
4409-020002																										died
4409-028004																										Neg month 52
4409-028005	1																									died
4409-079001	5	2																								?
4409-218001	1			1	2																					?
4409-219008																										?
4409-221001			2																							?

4409

Open Protocol

Historical Control for HBIGIV + Lamivudine

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	16/39	41%

Nabi states that their meta-analysis results in an HBV 2-year recurrence rate (θ_A) of 45% for lamivudine monotherapy with a lower bound of the 95% confidence interval at 35%.

Prevention of HBV Recurrence using Lamivudine Monotherapy

Anna Lok, M.D., U. of Michigan, March 2004 BPAC

- More economical and convenient compared to HBIG
- Recurrence at 1 yr 10%-30%, increases to 30%-40% at 3 yr due to emergence of resistant mutations
- Lamivudine resistant mutants can result in rapidly progressive liver disease and death
- Lamivudine monotherapy is insufficient for the prevention of recurrent hepatitis B post-LT.

Liver Transplantation for Hepatitis B – 2004

Anna Lok, M.D., U. of Michigan, March 2004 BPAC

- Recurrence rate < 10 % using combination prophylaxis of HBIG + lamivudine
- Graft and patient survival similar if not better than patients transplanted for other liver disease

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

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

FDA Analysis of Study 4204

30 subjects

2 subjects died within 30 days

28 subjects

2 subjects were lost to follow-up

26 subjects

2 subjects died in the interval 30 days to 2 yrs not HBV-related

24 subjects

5 subjects inadequately monitored for HBsAg to 2 yrs

19 subjects

FDA Analysis of Study 4409

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

3 died within 30 days

29 subjects (19 HBIGIV 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

25 subjects (15 HBIGIV monotherapy)

2 subjects died between 30 days and 2 yrs

23 subjects (14 HBIGIV monotherapy)

12 subjects excluded for less than 2 yrs follow-up

11 subjects (3 HBIGIV monotherapy)

8 Subjects on combined
HBIGIV + Lamivudine therapy

FDA Evaluable Database for Studies 4204 and 4409

- a) 19 subjects from study 4204
- b) 8 subjects from study 4409
- c) 27 subjects in pooled database
- d) If 3 HBIGIV monotherapy subjects from study 4409 are included, 30 subjects in pooled database

FDA Analysis

1. 8/27 HBsAg seroconversions in HBIGIV + Lamivudine group
29.6% HBsAg seroconversion, 95% CI (14%, 50%)
2. 8/30 HBsAg seroconversions if 3 HBIGIV monotherapy subjects included
27% HBsAg seroconversion, 95% CI (12%, 46%)

FDA: 8 HBsAg Seropositives

		Month																											
SD		-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			
1	4204-001004		5	X																								death	HBV related
2	4204-002003	1	5	1	1	1	1	1	1	1	1			1		1				1								?	
3	4204-002005		6	1	1	1	1	1	1	1	1																	Pos month 37	
4	4204-015001		5	1	1	1	1	1	1	1	1														1			?	
5	4409-002003		3	3	2	4				2						1								1				Pos months 26-4	
6	4409-016010	1																			1							Pos months 25-:	
7	4409-003002																											?	Pos DNA Month 10
8	4409-005007		10							1		1		1				1							1			Pos month 28 died month 29	

Comparison of FDA/Nabi Approach to Data Analysis (1)

Deaths. FDA removed HBV non-related deaths from the database. Nabi included HBV non-related deaths in the database and counted them as successes if the previous HBsAg measurement was negative.

Comparison of FDA/Nabi Approach to Data Analysis (2)

Missing Data. If HBsAg measurements were not available to satisfy the requirement for at least 2 yrs HBsAg monitoring for combined HBIGIV + 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. FDA's approach was consistent with Nabi's analysis plan submitted on September 3, 2003.

Comparison of FDA/Nabi Approach to Data Analysis (3)

HBIGIV Discontinuation. Seven subjects discontinued HBIGIV therapy prior to 2 yrs. Two of these seven HBsAg-seroconverted. Nabi excluded the 2 of 7 subjects who were HBsAg seroconverters and included the 5 of 7 subjects who remained HBsAg negative. FDA used an intent-to-treat approach, and did not exclude any of the 7 subjects for the reason of HBIGIV early discontinuation.

Alternative Failure Analyses

	Current Failures	Current and Deaths after 1 month	Current and all Deaths	Current and Missing Data subjects	Current And Both
Fail =	8	12	17	31	40
N =	27	31	36	50	59
Fail Rate	30%	39%	47%	62%	68%

FDA/Nabi Discrepancies

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)			HBIGIV Discontinued Day 249 HBsAg pos Day 906
4204-015001	HBsAg pos At month 22			HBIGIV Discontinued Day 252 HBsAg pos Day 635
4409-005007	HBsAg pos At all times			HBIGIV Discontinued After 10 doses
4409-003002	HBV DNA pos Month 10 1080 pg/ml			No HBsAg measurements

FDA/Nabi Discrepancies (cont.)

Subject ID	FDA Inclusion Reason	FDA Exclusion Reason	Nabi Inclusion Reason	Nabi Exclusion Reason
4409-001002		HBIGIV monotherapy not accepted	HBIGIV monotherapy accepted	
4409-005010		HBIGIV monotherapy not accepted	HBIGIV monotherapy accepted	
4409-018001		HBIGIV monotherapy not accepted	HBIGIV monotherapy accepted	
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	
4409-003009		Died before 2 yrs Not HBV-related	HBsAg neg Prior to death	
4409-002005		Died before 2 yrs Not HBV-related	HBsAg neg Prior to death	

Summary

1. No prospectively-designed clinical trial of Nabi-HB to demonstrate safety and efficacy for the HBV immunoprophylaxis indications in patients undergoing OLT for HBV disease
2. Attempt to use McGory data failed because Serum anti-HBs levels not comparable
3. HBsAg Seronegativity endpoint failed due to unacceptably high HBsAg seropositivity rate