

Blood Product Advisory Committee Meeting - July 13, 2006

Nabi Biopharmaceuticals

**Hepatitis B Immune Globulin (Human),
Intravenous
(Nabi-HB IV)**

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Purpose

To present substantial evidence that the safety and efficacy data, derived from the Nabi-HB IV clinical trials, support approval of BLA 125073 for the indication of:

“prevention of hepatitis B clinical disease in HBsAg-positive liver transplant recipients.”

Regulatory History

- 1994: Initial IND submitted
- 1995: Orphan Drug Designation
- 1997: FDA rejects suggested prospective, randomized, comparative study between Nabi-HB and Abbott H-BIG (not virally inactivated)
- 2001: Nabi-HB approved for post-exposure prophylaxis
- End of 2002: BLA for liver transplant indication submitted
- May 2003, May 2004, and June 2005: Complete Response Letters
- Aug. 2003, Dec. 2004, and Feb. 2006: Nabi Responses
- **March 2004: BPAC Outlines Criteria for Approval**
- Dec. 2005 and April 2006: Meetings to discuss Nabi-HB IV database vs. BPAC criteria
- **July 2006: FDA seeks BPAC advice**

Development Limitations

- Orphan Drug Designation: life threatening disease for very small patient population - 200 hepatitis B positive liver transplants in the US annually in ~125 transplant sites - limits size of clinical trials that can be performed
- As HBIG had become standard of care, a placebo-controlled study was not feasible
- No approved comparator
- Continuous evolving standard of care with introduction of antivirals; however, no antivirals approved for this indication
- Nabi started working with the FDA in the 90s; however, criteria for approval unclear until March 2004 BPAC meeting - retrospective data collection agreed upon with FDA after BPAC meeting

Rationale for Approval

- Two studies demonstrating efficacy and safety of Nabi-HB IV in new transplant patients (Nabi-4204 and Nabi-4409)
- Nabi-HB has been the standard of care for HBV liver transplants in the US for 7 years - 60,000 infusions administered establishing a favorable risk/benefit profile
- HBIG efficacy is well documented in literature, has been the standard of care in the US and ROW for 15 years, and is approved for prevention of recurrence of hepatitis B post-liver transplant in the EU and ROW
- Support for efficacy from studies in maintenance-phase patients

Rationale for Approval

Summary of Clinical Studies

Study	Study Type	Recurrence Rate (%)
Nabi-4204	New OLT	0/24 (0 %)
Nabi-4409	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%)

Rationale for Approval

- Lack of guidance in US Label has resulted in numerous examples of recurrence after premature discontinuation of Nabi-HB IV (Dickson et al. 2006; Hayashi et al. 2006)
- Approval would be consistent with FDA policy encouraging companies to seek label indications for drugs that are used off-label
- Orphan drug considerations
- **Meets standards in FDA guidance, “Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products”**

March 2004 BPAC Recommendations and May 2004 FDA Letter

- Pharmacokinetics data should be captured that can be used to guide therapeutic dosing.
- A historical control can be used for comparison in pivotal study.
- 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. 6 months or more after transplantation).
- In the case of HBIG monotherapy, a minimum of 1 year of follow-up time will be necessary.
- For HBIG / Lamivudine combination therapy, a minimum of 2 years of follow-up time will be necessary.

Nabi-4204 (Dickson) Pharmacokinetics

- 30 New Liver Transplant Recipients
 - Lamivudine 100 mg/day started pre-surgery & continued indefinitely
 - Nabi-HB base dose schedule:
 - 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
 - Additional doses or modification based on trough anti-HBs levels
 - After 2004 BPAC meeting, follow-up was extended beyond week 36 to comply with BPAC recommendations

Nabi-HB Pharmacokinetics with Concomitant Lamivudine

Number of Patients Below Specified Anti-HBs Levels

Study Period	Anti HBs Titer	Patients
Day 1-2	< 300	19/27 (70%)
Day 3-4	< 300	10/26 (38%)
Day 5	< 300	2/25 (8%)
Day 6-7	< 300	2/26 (8%)
Day 8-30	< 200	2/25 (8%)
Day 31-Week 12	< 200	2/23 (9%)
Weeks 13-24	< 100	1/21 (5%)
Weeks 25-36	< 100	1/21 (5%)

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

Dosing Recommendation for Nabi-HB IV

Weeks Post-Transplant	Minimum Trough anti-HBs Level	Recommended Dose
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

Nabi-4204 Pharmacokinetics

BPAC Recommendation: Pharmacokinetics data should be captured that can be used to guide therapeutic dosing:

- Target trough levels are generally achieved with the dose schedule suggested, although adjustments based on trough anti-HBs levels may be required.

March 2004 BPAC Recommendations and May 2004 FDA Letter

- Pharmacokinetics data should be captured that can be used to guide therapeutic dosing.
- A historical control can be used for comparison in pivotal study.
- 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. 6 months or more after transplantation).
- In the case of HBIG monotherapy, a minimum of 1 year of follow-up time will be necessary.
- For HBIG / Lamivudine combination therapy, a minimum of 2 years of follow-up time will be necessary.

Recurrence Rates - Literature Review

1-Year Recurrence Rates

Study	No or Short-term (<3 months) Treatment # Patients (%)	HBIG Monotherapy # Patients (%)
Samuel (1993)	111/150 (74%)	75/209 (36%)
Terrault (1996)	21/28 (75%)	4/24 (17%)
Muller (1991)	11/11 (100%)	6/23 (26%)
McGory (1996)	---	2/27 (7%)
Grazi (1996)	8/10 (80%)	4/25 (16%)
Nyman (1997)	4/4 (100%)	3/14 (21%)
Overall	155/203 (76%)	94/322 (29%)
95% CL	(68%, 80%)	(24%, 34%)

Recurrence Rates – Literature Review

2-Year Recurrence Rates

Study	Lamivudine Only	Lamivudine + HBIG
Anselmo (2002)	13/20 (65%)	10/89 (11%)
Bain (1996)	2/3 (67%)	---
Chan (2004)	6/20 (30%)	---
Mutimer (2000)	5/12 (42%)	---
Perrillo (2001)	16/39 (41%)	---
Marzano (2001)	---	1/25 (4%)
Markowitz (1998)	---	0/14 (0%)
Starkel (2002)	---	0/8 (0%)
Overall	42/94 (45%)	11/136 (8%)
95% CL	(35%, 54%)	(4%, 14%)

Historical Recurrence Rate

- No evidence that baseline risk factors have substantially changed from those in published literature
- Nabi assigned a conservative estimate of recurrence (45%, 2-year recurrence rate) on lamivudine monotherapy for analyses – if anything, the recurrence rate on chronic use of lamivudine has increased

March 2004 BPAC Recommendations and May 2004 FDA Letter

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- A historical control can be used for comparison in pivotal study.
- 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. 6 months or more after transplantation).
- In the case of HBIG monotherapy, a minimum of 1 year of follow-up time will be necessary.
- For HBIG / Lamivudine combination therapy, a minimum of 2 years of follow-up time will be necessary.

Nabi-4204 (Prospective Study of Nabi-HB IV + Lamivudine)

- Nabi-4204 was a prospective study that assessed the pharmacokinetics, efficacy and safety of Nabi-HB IV with concomitant lamivudine in new liver transplant recipients, conducted under investigator held IND and funded by the NIH
- Following the 2004 BPAC meeting, follow-up was extended from 36 weeks to greater than 2 years (median follow-up of 3.0 years for serology)

Assumptions for Efficacy Analysis Based on BPAC Recommendations and Agreed upon with FDA

- **HBsAg can be used as a surrogate marker for efficacy as it correlates well with clinical liver disease**
 - the corollary is that if the patient is clinically well, it is reasonable to assume that the patient is sero-negative (if no measurements of HBsAg). Because of this, HBsAg measurements are not standard clinical practice in patients who are clinically well
- **HBV DNA is not a good marker and should not be used**
 - it will always be present if the assay is sufficiently sensitive
 - no correlation has been demonstrated between DNA status and prognosis

Assumptions for Efficacy Analysis Based on BPAC Recommendations

- Retrospective analysis plan was submitted to FDA, and after the March 2004 BPAC meeting was discussed on numerous occasions
- Patients included in the analysis were HBsAg negative after OLT and had a minimum of at least two years follow-up data on Nabi-HB and lamivudine
- Two analysis populations were evaluated:
 - At least two years follow-up data with serology
 - At least two years clinical follow-up (this is consistent with clinical practice; if patients are clinically well without signs of liver disease, serology is not monitored)

Nabi-4204

Nabi's Analysis, Based on Clinical Data

30 new liver transplant recipients:

- Nabi excluded the following patients from the analysis:
 - 2 patients died within 30 days of transplant (4204-002006 and 4204-004002)
 - 2 patients had Nabi-HB discontinued for economic reasons from 8 to 17 months post-transplants (4204-015001 and 4204-002005)
 - 2 patients followed for less than 2 years (4204-015004 and 4204-002004)
- Therefore, **24** patients were included in Nabi's clinically evaluable analysis.
 - **0/24 (0%) recurrences is statistically significantly better than 42/94 (45%) recurrences on lamivudine monotherapy (p<0.0001)**
- FDA also excluded 2 patients who died between days 30 and 730 (4204-004001 and 4204-004003) – that would make 22 evaluable patients
 - **0/22 (0%) recurrences is still statistically significantly better than 42/94 (45%) recurrences on lamivudine monotherapy (p<0.0001)**
- An additional 6 patients did not have 2-year serology data and were excluded from the serology database

Disputed Patients - Nabi-4204

Four patients were classified by FDA as treatment failures – Nabi disagrees

1. Patient (#4204-015001)

- Discontinued Nabi-HB on day 252 (HBsAg negative) for economic reasons, but continued on lamivudine monotherapy
- Recurrence of Hep. B on day 636, that is >1 year after discontinuation of Nabi-HB
- **FDA counted this patient as a failure of Nabi-HB in their analysis, even though this patient demonstrates the need for concomitant Nabi-HB**
- Nabi excluded the patient from analysis

2. Patient (#4204-002005)

- Discontinued Nabi-HB on day 249 (HBsAg negative) for economic reasons; continued on lamivudine monotherapy
- Recurrence of Hep. B on day 906, that is >2 years after discontinuation of Nabi-HB.
- **The FDA counted this patient as a failure of Nabi-HB in their analysis, even though this patient demonstrates the need for concomitant Nabi-HB**
- Nabi excluded the patient from analysis

Disputed Patients - Nabi-4204

3. Patient (#4204-001004)

- Died from bacterial sepsis on day 56
- HBsAg negative at time of death
- Therefore, should be censored at day 56

4. Patient (#4204-002003)

- HBsAg negative for 14 measurements up through day 532 with exception of one positive value on day 375
- As all measurements before and after were negative, and as the patient was clinically well without signs of recurrence throughout day 1159, the positive value on day 375 represents a lab error
- **Therefore, the patient should be classified as a treatment success, not failure**

Nabi-4409 (Expanded Access Study of Nabi-HB + Lamivudine)

- Nabi-4409 was an expanded access study to assess the pharmacokinetics, efficacy and safety of Nabi-HB IV with concomitant lamivudine in new (n = 32) as well as maintenance (n = 121) liver transplant recipients
- Following the 2004 BPAC meeting follow-up was extended to greater than 2 years (median follow-up of 4.8 years for serology)

Nabi-4409 – New Liver Transplant Patients

32 new liver transplant recipients:

- Nabi excluded the following patients from the analysis:
 - 3 patients died within 30 days of transplant (4409-002001, 4409-028005, 4409-020002)
 - 2 patients were discovered on the day of transplant to have been HBsAg negative pre-transplant (4409-003013, 4409-028004)
 - 2 patients received a HBV-positive donor liver, but was not HBV positive pre-transplantation (4409-010005, 4409-010007)
 - 1 patient only received 10 doses of Nabi-HB with last dose given two weeks after transplant (4409-005007)
 - 7 patients had less than 2 years of follow-up data available (4409-011001, 4409-016005, 4409-016015, 4409-079001, 4409-218001, 4409-219008, 4409-221001)
- Hence, **17 patients that were treated with Nabi-HB + lamivudine and had at least 24 months follow-up** were included in Nabi's analysis. There was 1 recurrence among these patients (94% efficacy)
 - **1/17 (6%) recurrence is statistically significantly better than 42/94 (45%) recurrences on lamivudine monotherapy ($p = 0.012$)**
- An additional 6 patients did not have 2-year serology data and were excluded from the serology database

Disputed Patients - Nabi-4409

The following 4 patients were classified by the FDA as treatment failures:

1. Patient (#4409-005007)

- Only received 10 doses of Nabi-HB, the last one two weeks after liver transplantation. Continued on lamivudine monotherapy.
- Developed recurrence of HBV 548 days post-LT. Died 852 days post-LT from ESLD.
- **The FDA counted this patient as a failure of Nabi-HB in their analysis**, even though this patient demonstrates the need for concomitant Nabi-HB.
- **Nabi excluded the patient from analysis.**

2. Patient (#4409-016010)

- Discontinued Nabi-HB for economic reasons on day 184;
- HbSAg negative on day 534.
- Seroconverted on day 730; ~ 30 months after discontinuation of Nabi-HB.
- **Again, the FDA counted this patient as a failure of Nabi-HB in their analysis**, when this case actually demonstrates the need for concomitant Nabi-HB.

Disputed Patients - Nabi-4409

3. Patient (#4409-003002)

- Patient was clinically well through day 1874, no HBsAg data were recorded. Positive for HBV DNA at month 10.
- Although FDA agreed that HBV DNA should not be used as it does not correlate to prognosis, **the FDA counted this patient as a failure in their analysis.**
- As the patient was clinically well throughout 6 yrs, **Nabi believes the patient should be counted as a clinical success.**

4. Patient (#4409-002003)

- This patient was the only true failure on Nabi-HB.
- Despite treatment with Nabi-HB + lamivudine, the patient became HBsAg positive 146 days after LT.
- **Nabi agrees with the FDA that this is a treatment failure.**

Efficacy Based on Serology

Efficacy in New Liver Transplant Patients With at Least 2 Years of HBsAg Serology or Death > 30 Days Post-Transplant

Study	Recurrence Rate (%)	Efficacy (relative to lamivudine monotherapy)	p-value*
Nabi-4204	0/18 (0%)	100%	<0.0001
Nabi-4409	1/11 (9%)	80%	0.028
Pooled	1/29 (3%)	92%	<0.0001

* p-value is based on one-sample comparison of efficacy rate compared to lamivudine monotherapy recurrence rate of 45%

Efficacy Based on Clinical Status

Efficacy in New Liver Transplant Patients With at Least 2 Years of Clinical* Follow-up or Death > 30 Days Post-transplant

Study	Recurrence Rate (%)	Efficacy (relative to lamivudine monotherapy)	p-value**
Nabi-4204	0/24 (0%)	100%	<0.0001
Nabi-4409	1/17 (6%)	87%	0.0012
Pooled	1/41 (2%)	95%	<0.0001

* It is assumed that if clinically well with normal liver enzymes, patient would be HBsAg negative, and therefore, a treatment success

** p-value is based on one-sample comparison of efficacy rate compared to lamivudine monotherapy recurrence rate of 45%

Recurrence Rates

2-Year Recurrence Rates

Study	Lamivudine + Nabi-HB IV	Lamivudine + HBIG
Anselmo (2002)	---	10/89 (11%)
Marzano (2001)	---	1/25 (4%)
Markowitz (1998)	---	0/14 (0%)
Starkel (2002)	---	0/8 (0%)
Nabi-4204	0/24 (0%)	---
Nabi-4204	0/18 (0%)	---
Nabi-4409	1/17 (0%)	---
Nabi-4409	1/11 (0%)	---
Overall (rate, 95% CI)	1/41 (2%, 0 – 13) 1/29 (3%, 0 -18%)	11/136 (8%, 4 – 14%)

Additional Supporting Clinical Data

Hayashi et al.: *Importance of Continued Hepatitis B Immunoglobulin in Prevention of Reinfection Following Liver Transplantation. Liver Transplantation (submitted 2006)*

- Analysis of **20** hepatitis B positive patients, who underwent liver transplantation in UCI Medical Center between 1994 – 2001
 - **3** died in immediate post-operative period and **1** was lost to follow-up, leaving 16 patients with at least 2 years of follow-up data
 - **16** patients were followed for a mean of ~84 months (~7 years)
 - **10** continued on Nabi-HB + lamivudine for a mean of ~80 months. None developed recurrence of hep. B
 - **6** discontinued Nabi-HB (1 due to side effects, 5 due to cost of treatment or logistics)
 - **Of the 6 patients who discontinued Nabi-HB, 3/6 developed recurrence of hepatitis B**

Additional Supporting Information

Narratives for 3 Patients Who Showed Recurrence of Hepatitis B in Hayashi Study

Patient 1:

- Received Nabi-HB + lamivudine ~ 38 months post-liver transplant and was well with no signs of recurrent Hep. B.
- Discontinued Nabi-HB as he returned to his native country.
- When he returned to the US six months later, he had sero-converted and was HBsAg positive.
- Started high dose Nabi-HB and became sero-negative.
- Patient is still on Nabi-HB + antivirals 91 months post-liver transplant and is doing well.

Patient 2:

- Received Nabi-HB + lamivudine for ~ 22 months post-liver transplant and did well with no signs of Hep. B.
- Discontinued Nabi-HB treatment as insurance carrier stopped reimbursement due to off-label, but continued on lamivudine.
- 24 months later (46 months post-transplant), patient sero-converted (HBsAg positive) and developed severe liver disease.
- **Died 62 months post-liver transplant.**

Additional Supporting Information

Narratives for 3 Patients Who Showed Recurrence of Hepatitis B in Hayashi Study (*continued*)

Patient 3:

- Received Nabi-HB + lamivudine for ~ 12 months post-liver transplant and was well with no signs of recurrent Hep. B.
- Left the area and discontinued Nabi-HB as well as lamivudine.
- **Returned 24 months later with clinical signs and symptoms of fulminant liver failure and HBsAg positive.**

Note: All three patients who showed recurrence were non-replicators, indicating that it is very difficult to predict who are at risk.

Differences in FDA/Nabi Approach

- Nabi and FDA met on several occasions to discuss the analysis.
- The following were agreed upon: use of HBsAg as surrogate for efficacy, exclusion of deaths within 30 days of OLT, retrospective data collection, and meta-analysis approach to historical recurrence rate on lamivudine.
- Remaining differences:
 - Deaths
 - Missing data
 - Nabi-HB discontinuation

Differences in FDA/Nabi Approach to DEATHS

- FDA excluded all non-HBV related deaths that occurred < 2 years. Nabi censored four non-HBV related deaths that were surface antigen negative at time of death.
- If non-HBV-related deaths are excluded (as FDA did), this changes results for clinical analysis from 1/41 to 1/37 ($p < 0.0001$) and the serology database from 1/29 to 1/25 ($p < 0.0001$) and does not affect overall outcome relative to the lamivudine monotherapy.

Differences in FDA/Nabi Approach to MISSING DATA

- Nabi made every effort to follow the 2004 BPAC recommendations and collected clinical and serology data on subjects who participated in Nabi-4204 and Nabi-4409. Some missing data are to be expected in retrospective databases.
- Nabi included subjects who were clinically stable in the clinical database. We agree that this could be viewed as reflecting clinical practice rather than rigorous scientific research; however, this is standard of care, and therefore relevant.
- FDA's comment regarding missing data does not apply to the serology data base.

Differences in FDA/Nabi Approach to Nabi-HB DISCONTINUATION

FDA counted subjects who sero-converted after discontinuing Nabi-HB for economic or logistical reasons as failures; this is not appropriate. Excluding these subjects, as Nabi did, is the right scientific approach and is not anti-conservative.

Summary

Nabi's BLA submission positively responds to all BPAC recommendations:

- 1. Pivotal study should be from time of transplantation**
Nabi provided data on new transplant patients
- 2. Pharmacokinetics data should be captured that can be used to guide therapeutic dosing**
pK data from Nabi-4204 provides guide to dosing
- 3. Historical control can be used for comparison in pivotal study**
Meta-analysis of lamivudine monotherapy was used for historic control, using a conservative 45% recurrence rate
- 4. Two-year follow-up required for subjects receiving concomitant lamivudine**
Follow-up data in new transplant patients well exceed the 2 year recommendation

Summary – Risk/Benefit

- Favorable Adverse Event profile – 30 AEs in over 60,000 infusions since 1999
- No reports of off-label efficacy failure (based on MedWatch forms)
- Approximately 80% recurrence prior to HBIG; 45% recurrence with lamivudine monotherapy
- In clinical trials, less than 3% failure rate in 41 new transplant patients with Nabi-HB and concomitant lamivudine; 0% failure rate in 173 maintenance patients

Questions for BPAC - #1

“Post hoc inclusion and exclusion criteria”

- Inclusion and exclusion criteria were based on BPAC recommendations.
- Nabi met with the Agency several times to discuss the analyses. Many issues were resolved.
- Remaining issues are subject of today's meeting; e.g., inclusion of subjects who discontinued Nabi-HB as failures and relevance of clinical database.

Questions for BPAC- #2

Observational nature of information, data limitations, and lack of analysis plan

- The clinical database, while observational in nature, follows standard of care, and is therefore relevant.
- HBsAg has been accepted as surrogate by FDA and BPAC. **Therefore, the serology database is not observational and stands on its own merits.**
- Analysis plan based on BPAC recommendations.

Questions for BPAC - #3

Are retrospective data, including from an expanded access program and pK study sufficient to demonstrate efficacy?

- Nabi and FDA agreed to retrospective data collection.
- Efficacy was demonstrated in the pooled serology database ($p < 0.0001$).
- Clinical database and data from maintenance patients support serology findings ($p < 0.0001$).
- **The statistical analysis should not be invalidated by counting subjects who sero-converted after discontinuing Nabi-HB as failures, as FDA did.**

FDA Issue Summary

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 633
4409-003007	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	

Questions for BPAC - #3 (Cont.)

Sensitivity Analysis

- If assuming a 35% recurrence rate on lamivudine, Nabi's pooled recurrence rate of 1/29 patients (3%--Serology) or 1/41 patients (2%--Clinical) is still highly statistically significantly superior $p < 0.0001$
- Even assuming a 35% recurrence rate on lamivudine, and if you exclude patients who died before 2 years of non-HBV related disease (n=4) and patients who received monotherapy (n=3), the combination of Nabi-HB + lamivudine is still highly statistically superior to lamivudine alone ($p = 0.002$ for serology, $p < 0.0001$ clinical)

Questions for BPAC - #3 (cont.)

- Approval of Nabi-HB IV is warranted and not anti-conservative given that:
 - Despite retrospective nature of databases, Nabi-4204 and Nabi-4409 clearly demonstrate efficacy
 - BPAC recommendations were followed
 - Nabi-HB is standard of care and has been so for years
 - This is an Orphan Drug Indication
 - Myozyme was recently approved as a treatment for Pompe Disease based on an open-label study in 19 patients; there are 300 new cases per year in the US of this disease
 - FDA's stated desire to bring standard of care off-label uses on label
 - **The need to prevent premature discontinuation, which puts patients at significant risk; doing the study the FDA requests will delay the labeled indication by 5 years**

Post-approval Commitment

Nabi is willing to conduct a Phase 4 study to assess efficacy of Nabi-HB and concomitant anti-viral 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 enrollment
- 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 and death (Hayashi et.al. 2006; Dickson et al. 2006)

Conclusion

- Non-standardized dose administration is not in the public health interest and places patients at risk for HBV liver re-infection and subsequent risk of death
- Nabi study data supports the following labeling claim:

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