

**Statistical Review for the Nabi
Biopharmaceuticals,
Hepatitis B Immune Globulin
Intravenous (HBIGIV)**

Blood Product Advisory Committee Meeting

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Outline

- Background
- Efficacy
- Goal of the Analysis
- Issues
- Summary

Background

- FDA received a BLA (Biologic License Application) from Nabi Biopharmaceuticals(2002):
 - Hepatitis B Immune Globulin Intravenous (HBIGIV)
 - For the Prevention of Recurrent HBV Disease after orthotopic liver transplantation (OLT)
- Nabi conducted six **open** label and **non-randomized** studies.

Regulatory Background

March 2004 BPAC Recommendations

Efficacy Data

1. The first HBIGIV infusion should be received by the first week from the most recent transplant date
2. Compare HBIGIV plus Lamivudine vs. Lamivudine monotherapy
3. Primary endpoint: HBsAg recurrence rate with two years following transplantation

Nabi Studies with Efficacy Data

- Study 4204: 30 OLT subjects receiving HBIGIV plus Lamivudine
- Study 4409: 10 OLT subjects receiving HBIGIV plus Lamivudine and 22 OLT subjects receiving HBIGIV monotherapy

Total sub-sample of interest is **40** OLT subjects receiving HBIGIV plus Lamivudine

Goal of the Analysis

HBsAg recurrence rate of the new treatment (NABI-HBIGIV) with Lamivudine

is less than

HBsAg recurrence rate of the Lamivudine monotherapy.

Issues

HBsAg recurrence rate of NABI-HBIGIV: Dr. Maplethorpe	√
Method to estimate the HBsAg recurrence rate of Lamivudine, the historical control	Slides 8 ~15
Method to determine the efficacy of NABI-HBIGIV plus Lamivudine vs. Lamivudine monotherapy	Slides 16~19

HBsAg recurrence rate of Lamivudine, the Historical Control

- No universally accepted information on the clinical benefit of Lamivudine monotherapy
- Nabi proposed to use published studies to estimate the historical control rate
 - Non-comparability of published studies
 - Internal validity/quality of the published study is questionable
- Nabi proposed to use 30% for the HBsAg recurrent rate of Lamivudine monotherapy

HBsAg recurrence rate of Lamivudine, the Historical Control(2)

- FDA recommended Nabi to apply a scientific method (e.g., a meta-analysis) to estimate the HBsAg recurrence rate of Lamivudine monotherapy
- Nabi submitted the following published studies:

Author	Before 2004 BPAC	After 2004 BPAC
Anselmo	65% (13/20)	65% (13/20)
Bain	50% (2/4)	67% (2/3)
Chan	NA	30% (6/20)
Mutimer	39% (5/13)	42% (5/12)
Perrillo	32% (12/37)	41% (16/39)
Grellier	75% (9/12)	NA

HBsAg recurrence rate of Lamivudine, the Historical Control(3)

Study	Recurrence rate	95% Confidence Interval (CI)
Anselmo	65% (13/20)	(43%, 82%)
Bain	67% (2/3)	(21%, 94%)
Chan	30% (6/20)	(15%, 52%)
Mutimer	42% (5/12)	(20%, 68%)
Perrillo	41% (16/39)	(27%, 57%)

HBsAg recurrence rate of Lamivudine, the Historical Control (4)

- How to account the heterogeneity in a meta analysis?
 - Random effects model (Assumes true effect estimates vary across studies) can include the study as a random effect
- What other methods?
 - Weighted pooled point estimate and appropriate confidence interval

HBsAg recurrence rate of Lamivudine, the Historical Control (5)

Technical method for meta analysis proposed by Nabi

- A **point estimate** (weighted mean) by combining the five studies (weight: the inverse of the estimated variance of the observed recurrence rate in each study)
- Nabi concluded, “A 45% rate of recurrence for HBsAg-positive OLT recipients treated with lamivudine monotherapy and followed for at least 2 years”

Note: CI not provided by Nabi

HBsAg recurrence rate of Lamivudine, the Historical Control (6)

Study	Recurrence rate	Estimated variance	Proportion of weight*	Weighted recurrence rate
Anselmo	0.65 (13/20)	0.011	0.216	0.140
Bain	0.67 (2/3)	0.074	0.033	0.022
Chan	0.30 (6/20)	0.011	0.234	0.070
Mutimer	0.42 (5/12)	0.020	0.121	0.051
Perrillo	0.41 (16/39)	0.006	0.396	0.162
Over all (Nabi)			1.00	0.45

*: Proportion of weight allocated to each trial

Result of Retrospective Analysis For the historical control

Study	Recurrence rate	95% Confidence Interval
Anselmo	65% (13/20)	(43%, 82%)
Bain	67% (2/3)	(21%, 94%)
Chan	30% (6/20)	(15%, 52%)
Mutimer	42% (5/12)	(20%, 68%)
Perrillo	41% (16/39)	(27%, 57%)
Over all (FDA)	45%	(27%, 62%)*
Over all (Nabi)	45%	(35%, 54%)*

* Note: differences due to calculations based on formulas used

The Efficacy of NABI-HBIGIV with Lamivudine vs. Lamivudine alone

Synopsis of two studies of interest (4204 & 4409):

- Single arm trial compared to the historical control (**non-randomized trial**)
- Efficacy data values were **retrospectively collected**
- Sample size was not based on study power
- Study objective was **not statistically hypothesized**

The Efficacy of NABI-HBIGIV with Lamivudine vs. Lamivudine alone (2)

Considering HBsAg recurrence data from study 4204 and 4409, as per Dr. Maplethorpe

- Study 4204: 19 evaluable subjects on combined HBIGIV plus Lamivudine therapy
- Study 4409: 8 evaluable subjects on combined HBIGIV plus Lamivudine therapy

Total 27 evaluable subjects on combined HBIGIV plus Lamivudine therapy

The Efficacy of NABI-HBIGIV with Lamivudine vs. Lamivudine alone (3)

FDA's retrospective analysis results:

Study	Observed recurrence rate	95% Confidence Interval
4204	4/19=21%	(6%, 46%)
4409	4/8=50%	(16%, 84%)
Pooled	8/27 = 30%	(14%, 50%)

The Efficacy of NABI-HBIGIV with Lamivudine vs. Lamivudine alone (4)

Including THREE select HBIGIV monotherapy subjects from study 4409 and pooling these subjects with retrospective analysis

Study	Observed recurrence rate	95% Confidence Interval
4204	4/19=21%	(6%, 46%)
4409	4/11=36%	(11%, 69%)
Pooled	8/30 = 27%	(12%, 46%)

Summary

Issues

- Meta analysis-historical control of Lamivudine monotherapy
 - In applying a meta analysis the **variability** of a point estimate should be taken into consideration.
- Efficacy of NABI-HBIGIV plus Lamivudine vs. Lamivudine monotherapy
 - Nabi proposed HBIGIV efficacy based on **two** arm
 - FDA recommends **single** arm in analysis (open label and non-randomized studies with retrospectively collected data compared to the historical control)

Summary

Conclusions

- HBsAg recurrence rate of Lamivudine monotherapy
 - Historical weighted point estimate = 45% HBsAg recurrence rate
 - 95% confidence interval: (27%, 62%)
- HBsAg recurrence rate in HBIGIV with Lamivudine group
 - Single arm point estimate (8/27) = 30% HBsAg recurrence rate
 - 95% confidence interval: (14%, 50%)