



Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Biostatistics

Statistical Review and Evaluation – BLA (Mid-Cycle Review Memo)

BLA/Supplement Number: 125389/0

Product Name: Immune Globulin Intravenous Human 10% (Biotest-IGIV)

Indication(s): For the treatment of Primary Immune Deficiency Disorders (PIDD)

Applicant: Biotest Pharmaceuticals Corporation (BPC)

Date(s): CBER Receipt Date: 20-11-2010

Review Priority: Standard

Statistical Branch: CBER/OBE/DB/Therapeutics Evaluation Branch

Primary Statistical Reviewer: Jessica (Jeongsook) Kim, Ph.D./HFM-219

Concurring Reviewer: Estelle Russek-Cohen, Ph.D., Acting division director
Therapeutics Evaluation Branch/HFM-215

Medical Office/Division: OBRR/DH/CRB

Clinical Reviewer(s): Mitchell Frost, MD./HFM-392

Project Manager: Pratibha Rana/HFM-380

Table of Contents

1. EXECUTIVE SUMMARY	ERROR! BOOKMARK NOT DEFINED.
2. INTRODUCTION	ERROR! BOOKMARK NOT DEFINED.
2.1 OVERVIEW	ERROR! BOOKMARK NOT DEFINED.
2.2 DATA SOURCES.....	ERROR! BOOKMARK NOT DEFINED.
3. STATISTICAL EVALUATION	ERROR! BOOKMARK NOT DEFINED.
3.1 EVALUATION OF EFFICACY	ERROR! BOOKMARK NOT DEFINED.
3.1.1 STUDY DESIGN AND ENDPOINTS-----	4
3.1.2 EFFICACY ASSESSMENTS -----	4
3.1.3 PATIENT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS-----	4
3.1.4 STATISTICAL METHODOLOGIES-----	4
3.1.5 RESULTS AND CONCLUSIONS-----	4
3.2 EVALUATION OF SAFETY	5
3.3 GENDER, RACE, AGE AND OTHER SPECIAL/SUBGROUP POPULATIONS	5
4. SUMMARY AND CONCLUSIONS	5
DISTRIBUTION LIST.....	6

1. EXECUTIVE SUMMARY

This submission is a biologic license application by Biotest Pharmaceuticals Corporation (BPC) including an open-label, phase III, safety, efficacy, and pharmacokinetic study of nabi-IGIV 10% Immune globulin intravenous (human) in subjects with primary immune deficiency disorders (PIDD). The primary efficacy endpoint is the rate of serious bacterial infections (SBIs) per person-year for the following types of infections: bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess. A one-sided 99% upper confidence limit for the rate of SBIs per person-year needs to be less than 1 to meet the FDA's efficacy requirement for IGIV products. As for the safety evaluation, the one-sided 95% upper confidence limit for the proportion of infusions with one or more temporally associated Adverse Events (AEs) needs to be less than 40%.

There was a single SBI (bacterial pneumonia) with no deaths during the study. The infusion related adverse events in this study were lower than the FDA's criterion.

Complete analyses will be reported in the final review memo. This statistical review memo serves as the mid-cycle review commitment for BLA 125389/0.

2. INTRODUCTION

2.1 OVERVIEW

Product Information

Immune Globulin Intravenous (IGIV) isolated from human plasma is a treatment modality for a majority of patients with PID. Biotest's rationale for developing this new IGIV 10% product (Biotest-IGIV 10% will not contain a sugar stabilizer) are to: 1) develop a higher concentration that allows for reduced volume load, reduced infusion time, and reduced associated costs of administering this type of medication, and 2) supplement existing IGIV supply in the US, thereby reducing the risk of IGIV shortages that could negatively impact the management of PID. Biotest states that Biotest-IGIV 10% is expected to reduce serious bacterial infection (SBI) rates in patients with PID when compared to historically compiled infection data in subjects from the pre-IgG treatment era.

Biotest Immune Globulin Intravenous (Human) 10% herein referred to as Biotest –IGIV (originally named Nabi – IGIV) is a highly purified, sterile, preparation of concentrated immunoglobulin G (IgG) antibodies. Biotest – IGIV is manufactured at Biotest's facility in Boca Raton, FL using a modified Cohn/Oncley process. This investigational IGIV is expected to be similar in safety and efficacy to historically compiled data. Examples of other IgG products currently on the market are Gammaguard®, Gamimune® N (10%), Gamunex® (10%) and Flebogamma®(5%).

Clinical Study Reviewed

Nabi-7101: A Phase 3, multicenter, open-label study to assess the efficacy of Nabi-IGIV 10% in preventing serious bacterial infection (SBIs: bacteremia/sepsis, bacterial meningitis,

osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess) compared to historical control data (as determined by requirements established by the US Food and Drug Administration: by demonstration of an upper 99% confidence limit for a serious infection rate per person-year of <1.0), to assess safety by evaluating adverse events (AEs) and laboratory measurements, and to evaluate the pharmacokinetic (PK) properties of Biotest-IGIV 10%.

2.2 DATA SOURCE

This BLA is an eCTD submission. The data are stored in FDA E-Room. The primary datasets used are “AE.xpt (Adverse events), DM.xpt (Demography), and IF.xpt (Serious infection)” for study Nabi-7101.

3. STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

3.1.1 STUDY DESIGN AND ENDPOINTS

NABI-7101 Study : Open Label, Phase III Safety, Efficacy, and Pharmacokinetic Study of Nabi-IGIV 10% [Immune Globulin Intravenous(Human)] in Subjects with Primary Immune Deficiency Disorders (PIDD)

Duration of treatment:

Subjects will be dosed every 3 to 4 weeks and observed for a total of 12 months. The enrollment period is expected to be 6-12 months. The total duration of the study will be approximately 18 to 24 months (24 Sep 2007~ 24 Jul 2009).

Primary efficacy endpoint:

The rate of serious bacterial infections (SBIs) per person-year for the following types of infections: bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess.

- Infections at more than one site caused by the same pathogen occurring simultaneously or within a time-frame consistent with causal association will be considered to be a single serious infectious episode.
- Only SBIs that occurred during or after the first Nabi-IGIV 10% infusion and before or on the final visit date (i.e., occurred during the study) were included in this rate.
- Serious bacterial infections other than those previously identified or which occurred after the final clinical visit during the follow-up safety visit were not included in the primary efficacy analysis.
- Person-years for each subject was computed as the number of days from the first infusion date to the final visit date of study completion (i.e., 364 days), early termination, or death, whichever occurred first, divided by 365.25.

Secondary efficacy endpoints:

- Time to first infection
- Days off school/work due to infections
- Days with visits to physician's office or emergency room
- Hospitalizations due to infection
- Days on antibiotics.

3.1.2 EFFICACY ASSESSMENTS

There was a single SBI (bacterial pneumonia) during the study. The corresponding one-sided upper 99% confidence limit is lower than the FDA's criterion.

3.1.3 PATIENTS DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS**Number of Subjects:**

Sixty subjects, with PK parameters in a subset of 20 (10 on the 3-week and 10 on the 4-week treatment schedule) were planned. There were 63 subjects (32 women and 31 men) in the Safety, 58 subjects in the Intent-to-Treat (ITT), and 51 in the Per-Protocol (PP) population. 52 subjects completed the one-year study, and 11 subjects terminated early from the study.

3.1.4 STATISTICAL METHODOLOGIES**Study Hypothesis:**

$H_0: \lambda = \lambda_0$ vs. $H_1: \lambda = \lambda_1 < \lambda_0$, where λ is SBI event per person-year. The sample size calculation used $\lambda_0 = 1$, i.e., 1 event per person-year. Assuming the true underlying event rate, λ_1 , is 0.5 per subject per year and for 80% power, a one-sided test at the 0.01 significance level, a sample size of 60 subjects was planned (a drop-out rate of 20%).

The primary outcome is the rate of serious bacterial infections per person-year. Computed from the beginning of Day 0, person-time for each subject is either the "event time" of their first serious bacterial infection or censored at the earliest of death, drop-out, or 52 weeks (elapsed time from first infusion to study completion) for those with no serious bacterial infections. The SAS procedure GENMOD and StatXact was proposed to estimate the infection rate and develop the appropriate one-sided 99% upper confidence bound. Efficacy is measured by the upper confidence limit, and a value less than 1.0 will be considered evidence of efficacy.

Secondary analyses of this same outcome will be based on time to the serious bacterial infections. Kaplan-Meier product limit estimates will be used to describe the time-to-event distributions. Descriptive statistics will be provided for secondary outcomes.

Study population: The intent-to-treat (ITT) population for the analysis of study endpoints will be defined as all subjects who receive any amount of the correct study medication.

3.1.5 RESULTS AND CONCLUSIONS

RESULTS:

Efficacy: There was only a single SBI during the study for a rate of SBI per person-years of 0.017(1/58).

Safety: 52 subjects (83%) completed this 1-year study.

There were no deaths during the study. There were 11 serious adverse events (SAEs) in 7 subjects (11.1%).

CONCLUSIONS: The infusion of Biotest-IGIV 10% met the major efficacy and safety objectives of the study and met the requirement defined by the FDA guidance.

3.2 EVALUATION OF SAFETY

Assessment of the overall incidence of all adverse events during the treatment phase and infusion-related events with at least 72 hours after the infusion of the IP were analyzed. The one-sided 95% upper confidence limit for the proportion of infusions with an AE will be calculated.

4. SUMMARY AND CONCLUSIONS

The infusion of Biotest-IGIV 10% met the major efficacy and safety objectives of the study and met the requirement defined by the FDA guidance. There was a single (bacterial pneumonia) SBI with no deaths during the study. Study related adverse events were lower than the FDA's criterion. Complete analyses will be reported in the final review memo.

This statistical review memo serves as the mid-cycle review commitment for BLA 125389/0.

DISTRIBUTION LIST

cc:

Original/HFM-380/Rana Pratibha

DCC/HFM-99

HFM- 215 /Chron.

HFM-392/Nisha Jain, MD., OBRR/DH/CRB

HFM-215/Christopher Egelebo, RPM, OBE/DB

HFM-215/Estelle Russek-Cohen, Ph.D., OBE/DB

HFM-215/Henry Hsu, Ph.D., OBE/DB