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

## Statistical Review and Evaluation – BLA (FINAL)

**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: November 20, 2010

**Review Priority:** Standard

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## **1. EXECUTIVE SUMMARY**

The submission is a biologic license application by Biotest Pharmaceuticals Corporation (BPC) including an open-label, phase III, multi-center (15 centers), safety, efficacy, and pharmacokinetic study (Nabi-7101) of Nabi-IGIV 10% Immune globulin intravenous (human: proposed trade name: Bivigam) in subjects with primary immune deficiency disorders (PIDD). The primary efficacy endpoint is the rate of Serious Bacterial Infections (SBIs) occurring after the first infusion of Nabi-IGIV and before or on the final clinical visit date per person-year. The rate of SBI is defined as total number of SBIs divided by the total person-year for the following types of infections: bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess. The primary safety endpoint is the proportion of infusions with one or more infusion-related (TAAE: temporally associated with an infusion, i.e., within 72 hours of the infusion) adverse events (AEs).

### **1.1 CONCLUSIONS AND RECOMMENDATIONS**

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, FDA recommends that a one-sided 95% upper confidence limit for the proportion of infusions with one or more temporally associated AEs should be less than 40%.

There were two SBIs (two subjects with bacterial pneumonia) during the study for a rate of SBI per person-years of 0.035(2 out of 58) for intent-to-treat (ITT) and 0.04(2 out of 51) for per-protocol (PP) population. There was no death during the study, Nabi-7101. The proportion of infusions with one or more infusion related adverse events in this study were lower than the FDA's acceptance criterion. The safety of the proposed product was confirmed by one open label study.

### **1.2 BRIEF OVERVIEW OF CLINICAL STUDIES**

The submission includes one pivotal study (Nabi-7101) results from an open label, phase III safety, efficacy, and pharmacokinetic study of Nabi-IGIV 10% [Immune Globulin Intravenous (Human)] in subject with primary immune deficiency disorders (PIDD). The scheduled treatments were Biotest-IGIV 10%, 300 to 800 mg/kg at 3- or 4-week intervals depending on the subject's previous schedule for approximately 12 months and subjects were followed-up for an additional 3 months (total of 15 months). The total duration of the study was 22 months. The submitted study, Nabi-7101, met the efficacy/safety criteria recommended in the FDA's guidance document for the industry for Immune Globulin Intravenous product (Study results are summarized in Table 2.7.3.2-1 for efficacy and in Table 12.7 for safety).

### **1.3 MAJOR STATISTICAL ISSUES AND FINDINGS**

The one-sided upper 99% confidence of the rate of SBI per person year using one-sample Poisson rate method from StatXact generates 0.157 for ITT population and 0.165 for PP population. The sponsor applied the generalized linear model procedure for a Poisson distribution and generated 0.136 for ITT and 0.143 for PP for the rate of SBI per person year. These minor numerical discrepancies could be due to the different statistical method applied in the calculation, which did not impact on the study success conclusion. The second SBI was confirmed by the sponsor after it was being identified by Dr. Mitchell Frost from FDA/OBRR

and the corresponding document was submitted to FDA in STN 125389/0.8. Corresponding data files were re-submitted and the study results were confirmed by this reviewer.

## **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 10% (originally named Nabi – IGIV 10%) is a highly purified, sterile, preparation of concentrated immunoglobulin G (IgG) antibodies. Biotest – IGIV 10% 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%).

#### **Proposed clinical use**

Biotest-IGIV is indicated for the treatment of PIDD associated with defects in humoral immunity. These include, but are not limited to, congenital X-linked a gammaglobulinemia, common variable immunodeficiency, and severe combined immunodeficiencies.

#### **Clinical Study Reviewed**

**Nabi-7101:** A phase III, multicenter (15 centers), 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% (<http://www.fda.gov/cber/guidelines.htm>).

### **Inclusion Criteria**

1. Male or female, age  $\geq 6$  and  $\leq 75$ , with a documented and confirmed pre-existing diagnosis of chronic primary immune deficiency with a history of an abnormally low total IgG level (e.g.,  $< 500$  mg/dL) and deficient antibody production before chronic therapy (ie, X-linked agammaglobulinemia, common variable immunodeficiency, Hyper IgM Syndrome with IgG deficiency, etc).
2. Currently on IGIV replacement therapy at a fixed interval and dosage with a total monthly dose of IGIV between 300 and 800 mg/kg that has been stable for at least 3 months prior to screening.
3. Documented (within 3 months) plasma IgG trough level of  $>500$  mg/dL on current IgG therapy (IgG levels may be obtained at screening if previous results not available).
4. Medical records documenting infections and treatment within the previous 2 years need to be available for review.
5. Subject or legal guardian(s) must have given written informed consent/assent.
6. If a menstruating female, have a negative serum or urine pregnancy test within 7 days prior to the first dose of Nabi-IGIV and agree to use an acceptable method of contraception or be at least one year post-menopausal or surgically sterile.

### **Exclusion Criteria**

1. Received any blood product (other than IGIV) within the last 3 months prior to screening or received any investigational agent (other than IGIV) within the last four weeks prior to receiving Nabi-IGIV.
2. Known history of medically significant adverse reactions to other IgG or blood products.
3. Known selective IgA deficiency, history of allergic reaction to products containing IgA or has a history of antibodies to IgA.
4. Known significant proteinuria and/or has a history of acute renal failure/or severe renal impairment (BUN or creatinine more than 1.5 times the upper limit of normal).
5. Known history or current diagnosis of deep venous thrombosis.
6. Known medical condition that is known to cause secondary immune deficiency, such as chronic lymphocytic leukemia, lymphoma, multiple myeloma, HIV infection, AIDS, or chronic or recurrent neutropenia (absolute neutrophil count less than  $500 \text{ mm}^3$ ).
7. Current daily use of corticosteroids ( $> 10$  mg of prednisone equivalent /day for  $> 30$  days), immunosuppressants or immunomodulators. (Intermittent
8. Known non-controllable arterial hypertension (systolic blood pressure  $> 160$  mmHg and /or diastolic blood pressure  $>100$  mmHg.)
9. Known anemia at screening (hemoglobin  $<10$  g/dL).
10. Subject is pregnant or lactating.
11. Known history of illicit drug use within 3 months prior to the administration of Nabi-IGIV and for the study duration.
12. Have any condition judged by the study physician to preclude participation in the study, including any psychological disorder, which might hinder compliance.
13. Known active viral or bacterial infection or symptoms/signs consistent with such an infection within the two weeks prior to the initial dose of investigational product infusion. Subjects may be on antibiotics as long as signs/symptoms of infection have been absent for two weeks prior to the initial infusion of Nabi- IGIV.
14. Expectation of non-compliance with the protocol procedures and visit schedule.

### **Analysis populations**

Safety: subjects who received study treatment, Biotest-IGIV

ITT: subjects who received any amount of study treatment and had at least one record in the subject diary after first infusion

*NOTE: “Dr. Rubinstein’s study participation was terminated by letter dated May 20, 2008. BPC has made the prospective decision to exclude Dr. Rubinstein’s subjects from the Intent-to-Treat (ITT) population in the final statistical analysis. This decision has been predicated on 1) the significance and excessiveness of the protocol violations and deviations at the site, and 2) the insufficient number of infusions each subject received necessary to elicit the intended effect. BPC believes these circumstances demonstrate Dr. Rubinstein’s study data to be neither robust nor reliable for inclusion in the ITT population. Consequently, the subjects will only be included in the safety Assessment. Since there are NO missing data for subjects who were enrolled and treated in other sites, the ITT population in this study includes all subjects who received any amount of study treatment except those from Dr. Rubinstein’s site”*

PP: ITT subjects excluding those with major protocol violations

PK: safety population subjects who volunteered to provide PK samples

## **2.2 DATA SOURCES**

This BLA is an eCTD submission. The data are stored in FDA E-Room. The primary datasets used for this statistical review memo are SAS Derived Dataset (ADAE.xpt (Adverse events), ADSL.xpt (Subject level analysis dataset: Demography), and ADIF1.xpt ~ADIF6.xpt (Serious infections)” for the efficacy and safety analysis for the proposed product, Biotest-IGIV 10%, in the study Nabi-7101.

## **3. STATISTICAL EVALUATION**

### **3.1 EVALUATION OF EFFICACY**

#### **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) to assess the efficacy, safety, and PK properties of Biotest IGIV 10% in preventing serious bacterial infections (SBIs).

**Study design:** This was an open-label study in 15 centers. Biotest-IGIV 10%, 300 to 800 mg/kg at 3- or 4- week intervals depending on the previous schedule for approximately 12 months and subjects were followed-up for an additional 3 months (total of 15 months).

**Study subjects:** There were 63 subjects in the safety, 58 subjects in the Intent-to-Treat (ITT), and 51 in the Per-Protocol (PP) population with 32 women and 31 men with a mean age of 41 years. There were 44 subjects between 18 and 64 years of age (69.8%), 4 children (6.3%) between 6 and 11 years of age, 6 adolescents (9.5%) between 12 and 17 years of age, and 9

subjects (14.3%) over 65 years old (See Reviewer’s Table 1 in page 8 of this review). The following table summaries the demographic information of the 63 subjects.

Reviewer’s table 1. Demographic Characteristics

Parameter (n=63)	No. of subjects (%) n=63
Gender	32 (50.8%): female 31 (49.2%): male
Race	7 (11.1%) : Hispanic or Latino 56 (88.9%) : Not Hispanic or Latino
Age (yrs)	41.16: Mean 19.68: Standard deviation 6 to 75: Range
6-11	4 (6.3%)
12-17	6 (9.5%)
18-64	44 (69.8%)
65 and older	9 (14.3%)

**Data Sets Analyzed:**

A total of 63 subjects are included in the Safety population. Subjects from Site 50160 were excluded from the ITT population due to significant, excessive protocol violations and an insufficient number of infusions per subject to elicit the intended effect. Thus, a total of 5 subjects were excluded resulting in a total of 58 (92.1%) subjects in the ITT population. There were 7 subjects with major protocol violations for a PP population of 51.

**Duration of treatment:**

Subjects were dosed every 3 to 4 weeks and treated for approximately 12 months with an observation period of approximately 15 months.

**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.

## **STATISTICAL METHODOLOGIES**

### **Study Hypothesis:**

H<sub>0</sub>:  $\lambda = \lambda_0$  vs. H<sub>1</sub>:  $\lambda = \lambda_1 < \lambda_0$ , where  $\lambda$  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,  $\lambda_1$ , 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.

For the secondary analyses for the 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. The primary efficacy analysis is done based on the ITT population.

## **RESULTS AND CONCLUSIONS**

### **Primary Efficacy Analysis**

There were two SBIs during the study (two subjects with each having one bacterial pneumonia episode) in total 53.54 person-years for ITT and 51.10 for PP population resulting in an SBI rate per person-years of 0.035 (2 out of 58) and 0.04 (2 out of 51) respectively. The one-sided upper 99% confidence limit for SBI rate per person-year was 0.136 and 0.143 (by generalized linear model) and 0.157 and 0.1645 (by StatXact) for ITT and PP, respectively, which was less than 1 SBI per person-year defined as FDA's acceptance criterion.

**Table 2.7.3.2-1 Primary Efficacy Analysis: Serious Bacterial Infections**

Parameter	ITT (N=58)	PP (N=51)
Total number of SBIs <sup>a</sup>	2	2
Total person-years <sup>b</sup>	53.54	51.10
Rate of SBIs <sup>c</sup>	0.035	0.040
Upper 99% confidence limit <sup>d</sup>	≤0.136*	≤0.143**
Evaluation time in person-years		
Mean (SD)	0.923 (0.2341)	1.002 (0.0194)
Median	0.999	1.002
Minimum, Maximum	0.18, 1.06	0.92, 1.06

SBI = serious bacterial infections; SD = standard deviation.

<sup>a</sup> Only serious bacterial infections defined by FDA in protocol appendix B and occurring after the first infusion of Nabi-IGIV 10% and before or on the final visit date of Nabi-IGIV 10% are included.

<sup>b</sup> Person-years: Person-time in years with 2 decimals = (the Final Clinical Visit Date - the Day 0 date+1) / 365.25, where the final clinical visit date is defined as the specimen collection date of the final clinical visit for Urinalysis, or the specimen collection date for the clinical laboratory tests at the final clinical visit and Day 0 date is the start date of the first Nabi-IGIV 10% infusion.

<sup>c</sup> Rate of SBIs = total number of SBIs/total person-years.

<sup>d</sup> A one-sided 99% upper confidence limit was obtained by using the generalized linear model procedure for a Poisson distribution.

**Reviewer's comment:** *The one-sided upper 99% confidence of the rate of SBI per person year using one-sample Poisson rate method of StatExact generates 0.157 for ITT population and 0.1645 for PP population. The numerical discrepancies identified could be due to the different statistical method applied in the calculation, which did not impact on the study success conclusion. This reviewer verified summary statistics for the primary efficacy variable presented in Table 11-2.*

*The sponsor included inequality notation for the calculated confidence limits such as ≤0.136\* for ITT and ≤0.143\*\* for PP population, which should be modified as without the inequality notation.*

### Secondary Efficacy Analysis

Secondary efficacy endpoints included time to first SBI, time to first infection of any kind/seriousness, days on antibiotics (excluding prophylaxis), days off school/work due to infections, all confirmed infections of any kind or seriousness, and hospitalizations due to infection. Study results of the secondary efficacy analysis were reported using descriptive statistics (No hypothesis testing is conducted). Since there were only two SBIs, analysis for the time to first SBIs may not provide any meaningful information (subject-(b)(6)-: first treatment on 4/28/2008 and culture finding on 3/6/2009 and subject -(b)(6)-: first treatment on 4/28/2008 and culture finding on 3/6/2009).

Mean days off school/work due to infection was 2.1 for ITT and 2.3 for PP population. Subjects in the study Nabi-7101 had average of 2.4 confirmed infections of any kind or seriousness for

ITT and 2.6 for PP population. On the average, about one fourth of the year antibiotics were taken for both ITT and PP populations (Days on antibiotics per subject per year: 82.73 for ITT and 83.45 for PP). There were 2 subjects out of 58 for ITT population and 2 subjects out of 51 for PP population hospitalized for 11 days in total due to infection.

The following tables are from the sponsor's report and summary statistics were confirmed by this reviewer.

**Table 11-4: Days off School/Work and Number of Infections of Any Kind or Seriousness**

Parameter	ITT (N=58)	PP (N=51)
<b>Days off school/work due to infections</b>		
Total days	122	117
Mean (SD) per subject	2.1 (4.84)	2.3 (5.10)
Median (range) per subject	0 (0 - 24)	0.0 (0 - 24)
Days per subject per year [90% CI] <sup>f</sup>	2.28 [1.96; 2.64]	2.29 [1.96; 2.66]
<b>Infections of any kind or seriousness<sup>a</sup></b>		
	(n = 57)	(n = 51)
Total infections	197	189
Mean (SD) per subject	3.5 (3.54)	3.7 (3.55)
Median (range) per subject	3.0 (0 - 14)	3.0 (0 - 14)
Infections per subject per year [90% CI] <sup>c</sup>	3.70 [3.28; 4.15]	3.70 [3.27; 4.16]
<b>Confirmed<sup>b</sup> infections of any kind or seriousness</b>		
	(n = 57)	(n = 51)
Total infections	139	132
Mean (SD) per subject	2.4 (2.67)	2.6 (2.68)
Median (range) per subject	2.0 (0 - 14)	2.0 (0 - 14)
Infections per subject per year [90% CI] <sup>c</sup>	2.61 [2.26; 2.99]	2.58 [2.23; 2.97]

**Table 11-8: Days on Antibiotics**

Parameter	ITT	PP
<b>All subjects<sup>a</sup></b>		
No. of subjects	(n = 58)	(n = 51)
Total days on antibiotics <sup>a</sup>	4429	4264
Mean (SD) per subject	76.4 (118.25)	83.6 (124.04)
Median (range) per subject	28.0 (0 - 372)	32.0 (0 - 372)
Days per subject per year [90% CI] <sup>b</sup>	82.73 [80.70; 84.79]	83.45 [81.37; 85.57]

**Table 11-10: Hospitalization Due to Infection**

Parameter	ITT (N=58)	PP (N=51)
<b>Subjects with hospitalization</b>		
	2	2
No. of days hospitalized due to infection	11	11
Mean (SD) per subject	0.2 (1.02)	0.2 (1.08)
Median (range) per subject	0 (0 - 6)	0 (0 - 6)
Days per subject per year [90% CI]	0.21 [0.12; 0.32]	0.22 [0.13; 0.34]

SD = standard deviation

### 3.2 EVALUATION OF SAFETY

There were no deaths during the study. The mean treatment duration was 317.3 days with a range of 66 to 386 days. There were 11 serious adverse events (SAEs) in 7 subjects (11.1%). Assessment of the overall incidence of all adverse events during the treatment phase and infusion-related events (TEAEs) within 72 hours after the infusion (TAAEs) of the proposed product, Biotest-IGIV 10% were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 10.0. The one-sided 95% upper confidence limit for the proportion of infusions with a TAAE was 30.6% and met the FDA’s acceptance criterion, < 40%.

A summary of Serious Adverse Event (SAE) incidence rates and SAE incidence rates per infusion were analyzed. There were 40 subjects (64%) with TEATs related to study treatment. There were 7 subjects (11%) with SAEs, 1 of which considered related to the study treatment, and there were no deaths. This reviewer verified sponsor’s summary statistics provided in the following tables.

**Table 12-3: Summary of Adverse Events: AEs, TEAEs, SAEs, AEs Resulting in Withdrawal, TAAEs, and PDAEs – Safety Population**

Parameter	No. of Subjects (%) (N=63)
Number of subjects with ≥1 AE	59 (93.7%)
Total number of AEs	940
Number of subjects with ≥1 TEAE	59 (93.7%)
Total number of TEAEs	937
Number of subjects with ≥1 treatment-related TEAE	40 (63.5%)
Number of subjects with ≥1 SAE	7 (11.1%)
Total number of SAEs	11
Number of subjects with ≥1 treatment-related SAE	1 (1.6%)
Number of subjects with ≥1 AE leading to withdrawal <sup>a</sup>	2 (3.2%)
Total number of TEAEs leading to withdrawal <sup>a</sup>	5
Number of subjects with ≥1 treatment-related TEAE leading to withdrawal	2 (3.2%)
Number of subjects with ≥1 TAAE	47 (74.6%)
Total number of TAAEs	431
Number of subjects with ≥1 PDAE	41 (65.1%)
Total number of PDAEs	336

<sup>a</sup> AEs for which Nabi-IGIV 10% was discontinued or which the subject was withdrawn from the study. TAAEs = AEs temporally associated with infusions; PDAEs = pre-defined AEs (i.e. infusion-related defined events).

**Table 12-7: Proportion of Infusions with  $\geq 1$  TAAEs – Safety Population**

<b>Time Point</b>	<b>All Infusions</b>
Total subjects	63
Proportion during infusion and up to 1 h post-infusion	
Weighted mean percent	12.2%
Upper 95% confidence limit	$\leq 14.3\%$
Proportion 1 to 24 h post-infusion	
Weighted mean percent	16.2%
Upper 95% confidence limit	$\leq 18.6\%$
Proportion 24 to 48 h post-infusion	
Weighted mean percent	5.4%
Upper 95% confidence limit	$\leq 6.9\%$
Proportion 48 to 72 h post-infusion	
Weighted mean percent	4.0%
Upper 95% confidence limit	$\leq 5.4\%$
Proportion during and up to 72 h post-infusion	
Weighted mean percent	27.7%
Upper 95% confidence limit	$\leq 30.6\%$

Infusions with  $>1$  TAAE are only counted once.

TAAEs = AEs temporally associated with infusions

### 3.3 GENDER, RACE, AGE AND OTHER SPECIAL/SUBGROUP POPULATIONS

Two SBIs were cases of bacterial pneumonia. One occurred in a 21 year old male subject and the second occurred in a 49 year old female subject. For the pediatric population, there was no subject aged  $<2$  and there were 9 subjects aged 2 to 16. For the elderly group, there were 9 subjects aged 65 and older. Two SBIs were identified to the age group 17 to 64 (0.05= 2 out of 40). Due to the small number of subjects enrolled in each age group, the study NABI-7101 does not include any comparisons of efficacy responses among different age groups. The same reason was applied to the subpopulation analysis for gender and race in the study NABI-7101.

## 4. SUMMARY AND CONCLUSIONS

### 4.1 Statistical Issues and collective evidence

The sponsor has submitted the results of a single, open-arm, Phase III trial with 63 subjects to support the efficacy of the proposed product, Immune Globulin Intravenous Human 10% (Biotest-IGIV) for the treatment of Primary Immune Deficiency Disorders (PIDD). Based on the sponsor's dataset this reviewer identified a single subject (subject ID (b)(6)) with single SBI (bacterial pneumonia). During the review process, Dr. Mitchell Frost (clinical reviewer from FDA/CBER/OBRR) determined additional SBI (bacterial pneumonia) from the subject (subject ID (b)(6)), which is recognized by the sponsor in later amendment to this BLA. There was no death during the study and study related adverse events were lower than the FDA's criterion. The sponsor included inequality notation for the calculated confidence limits for the primary efficacy

endpoint as  $\leq 0.136$  for ITT and  $\leq 0.143$  for PP population, which should be modified as without the inequality notation.

## **4.2 Conclusions and recommendation**

The infusion of Biotest-IGIV 10% met the primary efficacy and safety objectives of the study and met the requirement recommended the FDA: by demonstration of one sided upper 99% upper confidence limit for the rate of SBIs per person-year is less than 1 for efficacy and one-sided 95% upper confidence limit for the proportion of infusions with one or more temporally associated AEs is less than 40%. Other than minor inequality notation issue stated in Section 4.1, there is no outstanding statistical issue in the Biotest's pivotal study Nabi-7101 included in their Biologic License Application to seek FDA's approval for the proposed product, Biotest-IGIV, 10%.

## **DISTRIBUTION LIST**

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