Application Type	Original BLA
Application Number(s)	125389/o
Received Date(s)	11/3/2010
PDUFA Goal Date	9/2/2011
Division / Office	DH/OBRR
Priority Review	No
Reviewer Name(s)	Mitchell Frost, M.D.
Review Completion Date / Stamped Date	
Supervisory Concurrence	
Applicant	Biotest Pharmaceuticals Corporation
Established Name	Immune Globulin Intravenous (Human) 10%
(Proposed) Trade Name	Bivigam
Pharmacologic Class	Immune Globulin
Formulation(s), including Adjuvants, etc	N/A
Dosage Form(s) and Route(s) of Administration	BIVIGAM is a liquid solution containing 10% IgG (5g in 50mL solution, 10g in 100mL solution) to be administered intravenously
Dosing Regimen	300-800 mg/kg every 3-4 weeks
Indication(s) and Intended Population(s)	Primary Humoral Immunodeficiency

1. EXECUTIVE SUMMARY

This Clinical Review memo covers STN BL 125389/0, an original BLA submitted by Biotest Pharmaceutical Corporation (BPC) for Bivigam (Nabi Immune Globulin Intravenous (Human) 10% [Nabi-IGIV 10%]). Bivigam is a liquid 10% immune globulin intravenous (IGIV) product for the proposed indication for the treatment of primary humoral immunodeficiency (PI) to be administered intravenously (IV). BPC assumed ownership of Nabi-IGIV and its ongoing clinical trial, Nabi-7101, after the purchase of the Nabi Biopharmaceuticals (Nabi) business unit and manufacturing facility in Boca Raton, FL by Biotest AG of Dreieich, Germany. BPC chose not to change the name of the clinical trial or the investigational product.

Nabi-7101 was a phase 3, multicenter, open-label trial, with a total of enrollment of 63 subjects, ages 6 – 75 years. Subjects had documented immune deficiency with agammaglobulinemia or hypogammaglobulinemia and were receiving IV immune globulin replacement therapy every 3 or 4 weeks. The objective of the trial was to evaluate the safety and efficacy of Bivigam, and to characterize its pharmacokinetic (PK) properties.

During the trial, Bivigam was infused at a dose of 300-800 mg/kg per infusion at 3- or 4-week intervals, depending on the subject's previous immunoglobulin G (IgG) replacement schedule. Doses were adjusted in order to maintain serum trough total IgG concentrations > 500 mg/dL. Subjects received Bivigam for a total of 12 months and followed-up for an additional 3 months (total of 15 months). The total duration of the trial was 22 months.

Efficacy was based on the annual rate of acute serious bacterial infections (SBIs), defined as pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, visceral abscess, and bacterial meningitis, per subject per year.

Based upon the observed rate of SBI of 0.035/person-years with an upper one-sided 99% confidence limit ≤0.136 in the intent-to-treat (ITT) population (N=58), BPC has provided substantial evidence of the efficacy of Bivigam by meeting the pre-specified primary efficacy endpoint of ≤1 SBI/subject/year with an upper one-sided 99% confidence limit less than 1. Further, data for secondary endpoints are supportive of Bivigam's efficacy in that they are within the range of other US-licensed IGIV products for the same indication.

The overall safety profile of Bivigam is in line with other IGIV products as demonstrated by the tabulated TEAEs and TAAEs observed during the clinical trial. The most frequent TAAEs are also consistent with what is reported with the use of other IGIV products as well, both in the types of TAAEs and in the rates of their occurrence. Nabi-7101 had a pre-specified target endpoint for safety of an upper one-sided 95% confidence limit of less than 0.40 when calculating the observed proportion of infusions with one or more temporally-associated adverse events (TAAE) (an adverse event occurring within 72

hours during or after an infusion of Bivigam). BPC met this pre-specified safety endpoint with an upper one-sided confidence limit of less than 0.36.

With regard to dosing, Nabi-7101 began with the dosing schedule of 300 to 600 mg/kg. This dosing schedule was increased to 300 to 800 mg/kg in Amendment 1 to the protocol dated 17 Jul 2007 (original protocol dated 29 Mar 2007) "at the recommendation of several of the study's investigators at the Investigator Meeting on 13-14 July 2007". Thirteen of the 63 subjects in the Safety Population, approximately 20%, received doses in excess of 600 mg/kg. The data suggest a higher proportion of TAAEs at these higher doses. FDA Guidance document[1] recommends a minimum of 30 subjects to be studied at the highest dose to be recommended in the product's labeling. It is recommended that the labeling for the dosage of Bivigam be changed from the proposed 300 to 800 mg/kg every 3 to 4 weeks, to 300 to 600 mg/kg every 3 to 4 weeks.

Bivigam contains Polysorbate 80 (PS80) in higher concentration than other licensed IGIV products. PS80 is used as a stabilizer in Bivigam in lieu of a sugar stabilizer, as used in other immune globulin products. Sugar stabilizers, particularly sucrose, have been associated with renal dysfunction. PS80 has been reported to have a profound cardiovascular effect when given intravenously in a canine animal model, with resultant hypotension.

BPC is aware of the potential for hypotension with the infusion of Bivigam due to PS80 and plans for routine post-marketing surveillance. In Nabi-7101, 47 of the 63 subjects in the Safety Population had at least one episode of a drop in systolic blood pressure greater than 20 mmHg during an infusion. While none of these events led to a clinically relevant outcome, the study population included few pediatric and elderly subjects, and excluded pregnant subjects. These subpopulations will potentially receive Bivigam and may be at greater risk to develop hypotension from PS80.

It is recommended that Bivigam be approved for the proposed indication and that the issue of potential hypotension due to PS80 be addressed via a post-marketing study requirement.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

The PI diseases are characterized by hypogammaglobulinemia and/or defective antibody production and, as a consequence, increased susceptibility to infection. Replacement therapy with IgG purified from pools of plasma from multiple donors has been used since the early 1950s, first as intramuscular (IM) and more recently, as IGIV and subcutaneous (SC) immunoglobulin (IGSC).

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[1] FDA Guidance for Industry. Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) As Replacement Therapy for Primary Humoral Immunodeficiency.2005; November.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Treatments for PI involve treating infections, generally with antibiotics, and preventing infections. Antibiotics may also be used to prevent infections in PI; however, the mainstay of prevention lies in correcting immunodeficiencies. Bone marrow transplant (BMT) can be used, particularly in life-threatening immunodeficiencies, and can be curative. BMT is not always successful and requires a donor who is a suitable tissue match to the recipient. Post-transplant BMT requires immunosuppressive therapy and runs the risk of graft vs. host disease. Enzyme replacement with adenosine deaminase is another option, but is only useful in patients who lack this enzyme.

2.3 Safety and Efficacy of Pharmacologically Related Products

FDA's Guidance, *Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency* references available literature as stating that IGIV administration to individuals with PI have observed SBI rates of 0.5 per year, as opposed to four or more SBIs in those without IGIV replacement therapy.

IGIV products currently available carry the following warnings and precautions:
- Hypersensitivity, especially in those with known antibodies to IgA, as IGIV products may contain trace amounts of IgA
- Renal Failure
  - Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose.
- Hyperproteninemia, Increased Serum Viscosity, and Hyponatremia
- Thrombotic Events
  - FDA held a Public Workshop entitled *Risk Mitigation Strategies to Address Procoagulant Activity in Immune Globulin Products* in May 2011. FDA reported that following a retrospective analysis performed by FDA for thrombotic events occurring between 1998 and 2005, FDA noted that there were about 30 thrombotic events reported annually to FDA, with 18% being serious adverse events. Arterial events outnumbered venous events. Thrombotic events were associated with increased age and weight, cardiac and deep venous thrombosis risk factors. For arterial events, 44% occurred during infusion and 82% within the first 24 hours. Factor XIa has been implicated as the most likely procoagulant contaminant. Factor XIa has been shown through thrombin generation tests to be at increased levels in recent lots of an IGIV product recently reported by the manufacture to have had associated thrombotic events.
- Aseptic Meningitis Syndrome
- Hemolysis
- Transfusion-related Acute Lung Injury
- Transmissible Infectious Agents

- Laboratory Tests may be altered.
    - After infusion of IgG, the transitory rise of the various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation. Also, passive transmission of antibodies to erythrocyte antigens (e.g., A, B, and D) may cause a positive direct or indirect antiglobulin (Coombs') test.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

There is no previous human data for Bivigam.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A Type B, Pre-BLA meeting was held between BPC and FDA on April 28, 2009. During that meeting, it was noted that Bivigam contained as much as 33 times the level of PS80 as compared with other US-licensed IGIV products, and that animal toxicology studies report hypotension in a canine model when given PS80. BPC stated that they would make the assessment of risk for hypotension with Bivigam infusion based upon safety data from the ongoing clinical trial and would address any safety issues in the risk mitigation strategy.

FDA asked that at least three product lots be used in the clinical trial Nabi-7101 in order to assure that product characteristics and outcomes do not differ drastically between product lots. A discussion was also held regarding the BPC's plan to implement numerous changes to the manufacturing process, equipment, and facilities at the Boca Raton, FL manufacturing site, and the subsequent need for comparability data with the product used in the clinical study.

A Type C meeting was held June 25, 2009. FDA recommended that BPC utilize a "two and two conformance lot approach" due to the additional facility modifications at the manufacturing site. As such, the BLA submission included data for two conformance lots (Conformance Lots #1 and #2) with plans for submission of an amendment during the review period with additional data for Conformance Lots #3 and #4.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty.

3.2 Compliance with Good Clinical Practices

The Division of Inspections and Surveillance (DIS) conducted Biomedical Monitoring (BIMO) inspections of four of the nineteen clinical sites that enrolled subjects in Study Nabi-7101. The data from these three clinical sites account for approximately 39% of the total subjects enrolled in the trial. The inspection included specific questions in reference

to the study protocol and verification of the study data on safety and efficacy endpoints submitted by BPC in the BLA. DIS reported that the BIMO inspections revealed no problems that impact the data submitted in the application. Site 009 was discontinued by BPC and the data excluded from the ITT population. Data from this site was included in the safety population; see Section 6.1.9.1.3 "Subject Disposition". DIS reports that the inspection of Site 009 revealed that the clinical investigator conducted the protocol required safety follow up or documented the site's attempts to do so. Due to the discontinuation of the study some subjects were unwilling to return to the site.

3.3 Financial Disclosures

BPC has adequately disclosed financial arrangements with clinical investigators.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

BPC has been modifying its manufacturing facility which was scheduled to occur in two phases. The first phase (Jan 2009 through Dec 2009) has been completed and included changes to the facility and manufacturing equipment. In February 2010, BPC manufactured the first 2 conformance lots (i.e., Phase 1 comparability). These lots were manufactured at the anticipated commercial scale via the intended commercial process, were placed on stability, and release-tested. Data for these 2 conformance lots was submitted with the BLA.

BPC had planned to utilize a "two and two conformance lot approach" due to the planned facility modifications and once phase 2 of the modifications were complete, submit an amendment during the BLA review period with additional data for Conformance Lots #3 and #4, manufactured after the phase 2 facility modifications.

A delay has occurred and BPC does not anticipate the data from these later 2 conformance lots to be available until mid to late November 2011. Therefore, the Chemistry, Manufacturing, and Controls (CMC) review can not be completed and on that basis the application can not be approved.

4.2 Assay Validation

See 4.1 "Chemistry, Manufacturing, and Controls".

4.3 Nonclinical Pharmacology/Toxicology

There is an issue with the PS80 levels in the product that is discussed elsewhere in the review. See Section 6.1.11.5 "Adverse Events of Special Interest (AESI)". Also, the glycine concentration in Bivigam is higher than some other IGIV products in the market. On April 8, 2011 BPC was requested to submit a toxicological assessment on the clinical safety of glycine. On May 9, 2011 BPC responded by stating that they were in the

process of preparing a toxicological assessment on the safety of glycine for submission to the Agency when complete. This report has not yet been submitted.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

BIVIGAM is a replacement therapy in the patients with primary antibody deficiencies (e.g., agammaglobulinaemia, hypogammaglobulinaemia, common variable immunodeficiency [CVID], severe combined immunodeficiency [SCID].

4.4.2 Human Pharmacodynamics (PD)

No studies of PD parameters were conducted in the clinical development of Bivigam.

4.4.3 Human Pharmacokinetics (PK)

The PK population consisted of 21 volunteer subjects. None of the pediatric subjects agreed to participate in the profiling section of the protocol; however peak and trough data were collected for pediatric subjects, as well as adults, at infusions 1, 4, 8, and 12.

There was a rapid rise in total IgG during the infusion period for both cycles with the attainment of similar maximum concentrations at the end of the infusion. The concentration-time curves for the 2 cycles were similar, with values returning to pre-infusion at around Days 14 - 21. The terminal half life ($t_{1/2}$) for the total population was estimated at about 30 days.

Mean trough concentrations determined at infusions 1, 4, 8 and 12 for all subjects were above 500 mg/dL. There was one trough concentration measured below 500 mg/dL (487mg/dL) at Infusion 6 with the 4-week cycle. Mean trough/peak (pre-/post infusion) serum IgG concentrations (mg/dL) for infusions 1, 4, 8 and 12 in pediatric and adult subjects were compared as shown below.

Mean Trough/Peak (Pre-/Post Infusion) Serum IgG Concentrations (mg/dL) for Infusions 1, 4, 8, and 12 in Pediatric and Adult Subjects – Safety Population
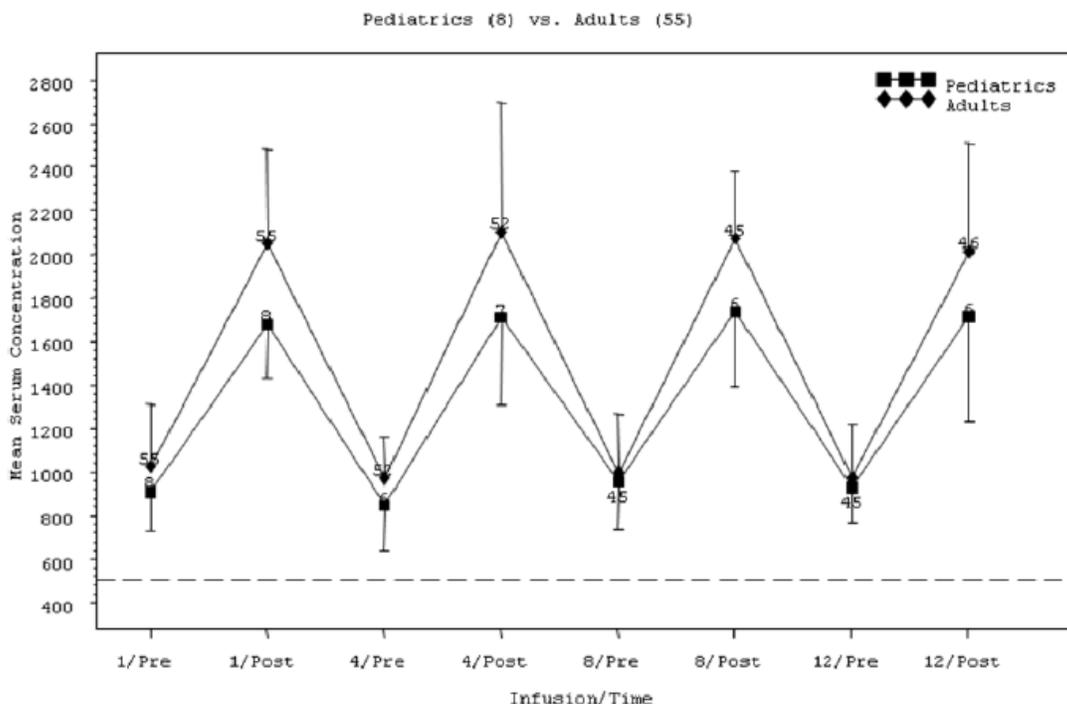
Source: Original BLA, NABI-7101 Clinical Study Report, page 72 of 141.

Average trough concentrations (and standard deviations) of total IgG and its subclasses (IgG1, IgG2, IgG3 and IgG4) were calculated from the 4th dose for the 4-week dosing cycle, and the 5th dose for the 3 week dosing cycle. These trough times (doses) correspond to those used for characterization of the full PK profile.

Entity	Serum Conc (mg/dL) ±SD 4-Week Dosing: Baseline	Serum Conc (mg/dL) ±SD 4-Week Dosing: 4th Dose	Serum Conc (mg/dL) ±SD 3-Week Dosing: Baseline	Serum Conc (mg/dL) ±SD 3-Week Dosing: 5th Dose
Total IgG	1001 ±262	927 ±171	1062 ±304	1018 ±197
IgG1	620 ±178	570 ±138	637 ±181	618 ±129
IgG2	301 ±107	265 ±63.3	332 ±151	286 ±56.2
IgG3	27.7 ±25.6	27.9 ±27.2	26.8 ±9.96	26.6 ±9.36
IgG4	23.8 ±19.8	20.0 ±14.9	28.9 ±22.8	30.2 ±27.2

Source: PK Review of Dr. Harold Boxenbaum, Table 2.

Total IgG PK estimates are shown below.

Total IgG Pharmacokinetic Estimates – PK Population

Statistic	3-Week Cycle (N=5)		4-Week Cycle (N=16)		Total (N=21)	
	Mean (SD)	CV%	Mean (SD)	CV%	Mean (SD)	CV%
C_{max} (mg/dL)	2184.00 (293.309)	13.4	2121.88 (425.256)	20.0	2136.67 (391.884)	18.3
T_{max}[a] (h)	4.050 (2.67 – 26.13)	NA	3.475 (2.58 – 78.58)	NA	3.500 (2.58 – 78.58)	NA
AUC_{tau} (h*mg/dL)	668,173.6 (118,197.53)	17.7	852,213.4 (155,333.93)	18.2	806,203.4 (165,545.09)	20.5
$t_{½}$ (day)	19.596 (4.1390)	21.1	33.484 (10.7244)	32.0	30.012 (11.2437)	37.5
CL (mL/kg/day)	1.97096 (0.224191)	11.4	1.41088 (0.462731)	32.8	1.55090 (0.479861)	30.9
Vz (L/kg)	0.05587 (0.013922)	24.9	0.06402 (0.015180)	23.7	0.06198 (0.014956)	24.1

Source: Original BLA, NABI-7101 Clinical Study Report, page 75 of 141.
AUC = area under the plasma concentration versus time curve; CL = total body clearance; Cmax = maximum concentration; CV = coefficient of variation; NA = not applicable; SD = standard deviation; Tmax = time of maximum concentration; t½ = terminal half-life; Vz = volume of distribution.
[a]Median and range, calculated from start of infusion.

4.5 Statistical

The statistical reviewer verified that the primary study endpoint analyses cited by the applicant were supported by the submitted data.

4.6 Pharmacovigilance

BPC has proposed to address pharmacovigilance of Bivigam through the collecting of adverse events (AE) from "all sources" and assessment of the data through BPC's Corporate Drug Safety department. BPC intends to summarize and report known IGIV class effects in periodic safety update reports (PSURs). With regard to the risk of hypotension due to PS 80, BPC intends to "specifically discuss and address any spontaneous AEs reported for hypotension in PSURs".

OBE and OBRR agree with the plan for routine pharmacovigilance as proposed by BPC. However, the study population included few pediatric and elderly subjects, and excluded pregnant subjects. These subpopulations will potentially receive Bivigam and may be at greater risk to develop hypotension from PS80. Pharmacovigilance data will need to specifically examine these at-risk populations and overall, it is recommended that the issue of potential hypotension due to PS80 be addressed via a post-marketing study or enhanced surveillance.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

Data from one clinical trial has been submitted in support of the proposed indication. Efficacy, safety and pharmacokinetic data will be reviewed from this trial, Nabi-7101.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

- Module 1
  - o 1.2 Cover Letters
  - o 1.3.3 Debarment Certification
  - o 1.3.4 Financial Disclosure
  - o 1.6 Meetings
  - o 1.9 Pediatric Administration Information
  - o 1.11.3 Efficacy Information Amendment
  - o 1.12.4 Request for Proprietary Name Review
  - o 1.12.11 Basis for Submission Statement
  - o 1.14 Labeling
  - o 1.16 Risk Management Plans
- Module 2
  - o 2.2 Introduction
  - o 2.5 Clinical Overview
  - o 2.7 Clinical Summary
- Module 4
  - o 4.2.3.7.6 Whitepaper Polysorbate 80
- Module 5
  - o 5.2 Tabular Listing of all Clinical Studies
  - o 5.3.5.1 Nabi-7101 (all documents)
  - o 5.4 Literature References

5.3 Table of Studies/Clinical Trials

Type of Study	Study Identifier	Objectives of the Study	Study Design and Type of Control	Test Product; Dosage Regimen; Route of Administration	Number of Subjects	Diagnosis of Subjects	Duration of Treatment
Efficacy, PK, Safety	Nabi-7101	Primary objective: prevention of SBIs (rate/person year = < 1.0). Secondary objectives: -Time to first SBI, -Days off school or work, -Infections of any type/seriousness, -Hospitalizations due to infection, -Days on antibiotics, -Safety, -PK.	Multicenter, open-label, Phase III	Biotest-IGIV 10%, IV; 300 to 800 mg/kg; 3- or 4-weekly, initial infusion rate = 0.3 mL/kg/hr; could be increased by 0.5 mL/kg/hr to maximum of 3.5 mL/kg/hr.	Safety = 63 ITT = 58 PP = 51	Pre-existing diagnosis of chronic PIDD (X-linked agammaglobulinemia, common variable immunedeficiency, hyper IgM syndrome with IgG deficiency) and history of an abnormally low total IgG level (<500 mg/dL) and deficient antibody production before chronic therapy.	12 months

Source: Original BLA, Module 5.2.
IgG = immunoglobulin G; IGIV = immunoglobulin intravenous; IgM = immunoglobulin M; ITT = intent-to-treat;
IV = intravenously; PIDD = Primary Immune Deficiency Disorders; PK = pharmacokinetics; PP = per protocol;
SBI = serious bacterial infection.

5.4 Consultations

5.4.1 Advisory Committee Meeting

No Advisory Committee Meeting was held.

5.4.2 External Consults/Collaborations

There were no external consultants or collaborators.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study NABI-7101

6.1.1 Objectives (Primary, Secondary, etc)

The objective of the study was to evaluate the efficacy, safety, PK of Bivigam in PI.

6.1.2 Design Overview

This was a phase 3, multicenter, open-label study with a 12-month study period.

6.1.3 Population

Subjects were eligible for study inclusion if they met all of the following inclusion criteria:
1. Male or female, age ≥6 and ≤75 years, with a documented and confirmed pre-existing diagnosis of chronic PI (i.e., X-linked agammaglobulinemia, common variable immunodeficiency, hyper IgM syndrome with IgG deficiency, etc.) with a history of an abnormally low total IgG level (i.e., <500 mg/dL) and deficient antibody production before chronic therapy.
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 had been stable for ≥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 have been obtained at screening if previous results are not available).
4. Medical records documenting infections and treatment within the previous 2 years were required to be available for review.
5. Subject or legal guardian(s) must have given written informed consent/assent.
6. If a menstruating female, must have had a negative serum or urine pregnancy test within 7 days prior to the first dose of Bivigam and agreed to use an acceptable method of contraception or be ≥1 year post-menopausal or surgically sterile.

Subjects were excluded from study participation if they met any of the following 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 4 weeks prior to receiving Bivigam.
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 had a history of antibodies to IgA.
4. Known significant proteinuria and/or had a history of acute renal failure/or severe renal impairment (blood urea nitrogen [BUN] or creatinine >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, human immunodeficiency virus (HIV) infection, AIDS, or chronic or recurrent neutropenia (absolute neutrophil count <500 mm3).
7. Current daily use of corticosteroids (>10 mg of prednisone equivalent/day for >30 days), immunosuppressants, or immunomodulators. (Intermittent corticosteroid use during the study was allowable, if medically necessary.)

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 was pregnant or lactating.
11. Known history of illicit drug use within 3 months prior to the administration of the investigational product and for the study duration.
12. Had 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 2 weeks prior to the initial dose of investigational product infusion. Subjects may have been on antibiotics as long as signs/symptoms of infection had been absent for 2 weeks prior to the initial infusion of the investigational product.
14. Expectation of non-compliance with the protocol procedures and visit schedule.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects received Bivigam infused at rates to provide a dose of 300-800 mg/kg per infusion. Infusions were administered at 3- or 4-week intervals, depending on the subject's previous IgG replacement schedule.

Subject's infusion rates were individualized under the following scheme: the initial infusion rate was 0.3 mL/kg/hr (30 mg/kg/hr) for 10 minutes; if this rate was well tolerated, the investigator could increase the rate to 0.5 mL/kg/hr (50 mg/kg/hr) for 20 minutes; barring subject intolerance, the investigator could increase the rate gradually every 20 minutes by 0.5 mL/kg/hr to the typical rate a subject was accustomed to receiving or to a maximum tolerated rate up to 3.5 mL/kg/hr (350 mg/kg/hr). Infusion time was not to exceed 8 hours.

If a non-life-threatening AE occurred during an infusion, the investigator could adjust the rate to one-half of the rate at the time of AE onset or to a "keep vein open" rate until symptoms subsided. Following the first infusion, the highest tolerated rate achieved at the first infusion was the target for subsequent infusions. Infusion rates higher than this target rate were only allowed under direct supervision and approval of the investigator.

Subjects were instructed not to introduce new medications at any time during the entire course of the study without first consulting the investigator. The investigator recorded any medications in the case report form (CRF) beginning with medications taken 30 days prior to the first study drug infusion. Subjects were queried at each visit about all medications taken since the previous visit.

Current use of daily corticosteroids (>10 mg of prednisone equivalent/day for >30 days), immunosuppressants, or immunomodulators was not allowed unless approved in advance by the medical monitor. Intermittent use of corticosteroids during the study was allowed

if medically necessary. The use of pre-medications was discouraged. If subjects required pre-medication (Tylenol®, Benadryl®, etc.) for recurrent reactions to immune globulins, they were allowed to continue those medications for this study. These medications were recorded as starting prior to the study.

Subjects on antibiotics were included in the study if they did not have any signs/symptoms of an acute viral or bacterial infection for 2 weeks prior to the initial infusion of study drug.

Other investigational drugs taken by the subject for possible or perceived effects against PI were prohibited.

6.1.5 Sites and Centers

Site #	Address	Principal Investigator
01	Institute for Allegry and Asthma, 11002 Veirs Mill Road #414, Wheaton, MD 20902	Martha White
02	University Hospital Case Medical Center, 11100 Euclid Avenue, RB&C Rm3131, Cleveland, OH 44106	Steven Strausbaugh (formerly Melvin Berger)
03	Allegy Associates of Palm Beach, 840 US Highway #1 Suite 235, North Palm Beach, FL 33408	Mark Stein
04	University of Alabama at Birmingham, 1717 6th Avenue, South, SRC-068, Birmingham, AL 35294	Harry Schroeder
05	Women & Childrens Hospital of Buffalo, Allergy Division, 239 Bryant Street, Buffalo, NY 14222	Mark Ballow
06	Rush University Medical Center, 1725 W. Harrison Street, Suite 117, Chicago, IL 60612	James Moy
07	Children's Hospital of Los Angeles, 4650 Sunset Boulevard, MS 75, Los Angeles, CA 90027	Joseph Church
08	Marietta Pulmonary Medicine, 55 Whitcher Street, Suite 420, Marietta, GA 30060	Wesley Bray
09	Montefiore Medical Center, 1525 Blondell Avenue, Suite 101, Bronx, NY 10461	Arye Rubinstein
10	St. Louis University Sciences Center, SSM Cardinal Glennon Children's Medical Center, 1465 South Grand Boulevard, Saint Louis, MO 63104	Alan P. Knutsen, MD
11	South Bend Clinic LLP, 211 North Eddy Street, South Bend, IN 46617	James Harris
12	Allergy/Immunology Research Center of North Texas, 7777 Forest Lane, Suite B-332, Dallas, TX 75230	Richard Wasserman
13	1st Allergy & Clinical Research Center, 7286 South Yosemite Street, Suite 180, Centennial, CO 80112	Isaac Melamed

Site #	Address	Principal Investigator
	Sites and Centers (continued)	
Site #	Address	Principal Investigator
14	Bellingham Asthma, Allergy & Immunology Clinic, 3015 Squalicum Parkway, Suite 180 Bellingham, WA 98225	David Elkayam
15	Precision Trials LLC, 3815 East Bell Road, Suite 4500, Phoenix, AZ 85032	Thomas Mirazi
16	AARA Research, 9900 N. Central Expressway, Suite 555, Dallas, TX 75231	William Lumry
17	Allergy, Asthma & Immunology Clinic, P.A., 1115 Kinwest Parkkway, Suite 100, Irving, TX 75063	Daniel Suez
18	Kentucky Lung Clinic, PSC, 200 Medical Center Drive, Suite 2M, Hazard, KY 41701	Firas Koura
19	Allergy & Asthma Center, 7247 West Central Avenue, Suite A, Toledo, OH 43617	Syed Rehman

Source: Adapted from Original BLA, 16.1.4 Description of Investigators Sites

6.1.6 Surveillance/Monitoring

Study Schedule – 21 Day Schedule

Infusion	Screening Visit	Infusion 1				Infusions 2,3,5,6,7,9,10, 11,13 – 17 Test times with **ONLY for Subjects in PK extension part At INFUSION 17				Infusion 4 Test times with * for PK subjects only					Day 21	Infusions 8 & 12				Final Clinical Visit	Final Safety Follow-up
Study Visit		Visit 1				V2,V3,V5-V7,V9-V11,V13-V17 (respectively)				Visit 4						Visit 8 & Visit 12					
Visit Day/Visit	Within 30 days	Day 0			Day 1-3	Day 0			Day 1-3	Day 0			Day 1-3*	Day 3*, 7*, 14*		Day 0			Day1-3*		
		Pre	IGIV	Post	Within 72h	Pre	IGIV	Post	Within 72h	Pre	IGIV	Post	Within 72h			Pre	IGIV	Post	Within 72h	Pre	Pre
Screening Procedures[a]	X																				
Hematology	X														8 only					X	
Chemistry	X					X[e]														X	X[e]
Urinalysis	X																			X	
Viral Testing[b]	X														X					X	X[b]
Physical Exam		X																		X	
Review & Collect Diary						X				X						X				X	
Vital Signs	X	≤30 min	X[f]	≤30 min		≤30 min	X[f]	≤30 min		≤30 min	X[f]	≤30 min				≤30 min	X[f]	≤30 min			
Back-up Serum, IgG Subclasses		15 min		15 min		15 min				15 min		15 min				15 min		15 min		15 min	
IGIV Infusion			X				X				X						X				

Infusion	Screening Visit	Infusion 1				Infusions 2,3,5,6,7,9,10, 11,13 – 17 Test times with **ONLY for Subjects in PK extension part At INFUSION 17				Infusion 4 Test times with * for PK subjects only					Day 21	Infusions 8 & 12				Final Clinical Visit	Final Safety Follow-up
Study Visit		Visit 1				V2,V3,V5-V7,V9-V11,V13-V17 (respectively)				Visit 4						Visit 8 & Visit 12					
Visit Day/Visit	Within 30 days	Day 0			Day 1-3	Day 0			Day 1-3	Day 0			Day 1-3*	Day 3*, 7*, 14*		Day 0			Day1-3*		
		Pre	IGIV	Post	Within 72h	Pre	IGIV	Post	Within 72h	Pre	IGIV	Post	Within 72h			Pre	IGIV	Post	Within 72h	Pre	Pre

Study Schedule – 21 Day Schedule (continued)

Infusion	Screening Visit	Infusion 1				Infusions 2,3,5,6,7,9,10, 11,13 – 17 Test times with **ONLY for Subjects in PK extension part At INFUSION 17				Infusion 4 Test times with * for PK subjects only					Day 21	Infusions 8 & 12				Final Clinical Visit	Final Safety Follow-up
Study Visit		Visit 1				V2,V3,V5-V7,V9-V11,V13-V17 (respectively)				Visit 4						Visit 8 & Visit 12					
Visit Day/Visit	Within 30 days	Day 0			Day 1-3	Day 0			Day 1-3	Day 0			Day 1-3*	Day 3*, 7*, 14*		Day 0			Day1-3*		
		Pre	IGIV	Pre	IGIV	Pre	IGIV	Post	Within 72h	Pre	IGIV	Post	Within 72h			Pre	IGIV	Post	Within 72h	Pre	Pre
Antibody Testing[c] And Total IgG serology	X[g]	15 min		15 min				15 min and 1h** post-infusion 17	X** (at Days 1,3,7,14 and 21 post-infusion 17)	15 min		15 min & 1h*	24h*	X*	X*	15 min		15 min		15 min[d]	
AEs			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[h]

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Infusion	Screening Visit	Infusion 1				Infusions 2,3,5,6,7,9,10, 11,13 – 17 Test times with **ONLY for Subjects in PK extension part At INFUSION 17				Infusion 4 Test times with * for PK subjects only					Day 21	Infusions 8 & 12				Final Clinical Visit	Final Safety Follow-up
Study Visit		Visit 1				V2,V3,V5-V7,V9-V11,V13-V17 (respectively)				Visit 4						Visit 8 & Visit 12					
Visit Day/Visit		Day 0			Day 1-3	Day 0			Day 1-3	Day 0			Day 1-3*	Day 3*, 7*, 14*		Day 0			Day1-3*		
	Within 30 days	Pre	IGIV	Post	Within 72h	Pre	IGIV	Post	Within 72h	Pre	IGIV	Post	Within 72h			Pre	IGIV	Post	Within 72h	Pre	Pre
Con Meds	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Distribute Diary				X				X				X						X			
Phone Call					X				X				X						X		

Source: Original BLA, NABI-7101 Clinical Study Report, page 35 and 36 of 141.

a Included obtaining ICF, medical and medication history, pregnancy test, Coombs test, SID assignment, and chest x-ray (if not available within 6 months prior to the first infusion)

b HBsAg, HCV, HCV NAT, HIV-1/HIV-2, HIV NAT, anti-Parvovirus B19 and B19 NAT (if antibody is positive at the baseline, NAT will be used for subsequent testing points)

c Anti-pneumococcal, anti-*H. influenzae* B, anti-tetanus

d Total IgG serology only

e BUN, creatinine, AST, ALT, LDH and total bilirubin at Visits 5, 9, 13, and final safety follow up visit

f Vital signs were recorded before (pre) each infusion, prior to each rate change of infusion, 5 to 10 minutes after each rate change, and approximately every 30 minutes once a stable infusion
rate was achieved, then 30 minutes after the infusion.

g Obtain total IgG serology sample at screening if previous results not available within the last 3 months

h All serious infections that occurred since the final clinical visit through the final safety follow up visit were recorded

Study Schedule – 28 Day Schedule

Infusion	Screening Visit	Infusion 1				Infusions 2,3,5,6,7,9,10, 11,13 Test times with **ONLY for Subjects in PK extension part At INFUSION 17				Infusion 4 Test times with * for PK subjects only					Day 21	Infusions 8 & 12				Final Clinical Visit	Final Safety Follow-up
Study Visit		Visit 1				V2,V3,V5-V7,V9-V11,V13-V17 (respectively)				Visit 4						Visit 8 & Visit 12					
Visit Day/Visit	Within 30 days	Day 0			Day 1-3	Day 0			Day 1-3	Day 0			Day 1-3*	Day 3*, 7*, 14*		Day 0			Day1-3*		
		Pre	IGIV	Post	Within 72h	Pre	IGIV	Post	Within 72h	Pre	IGIV	Post	Within 72h			Pre	IGIV	Post	Within 72h	Pre	Pre
Screening Procedures[a]	X																				
Hematology	X															8 only				X	
Chemistry	X					X[e]				X[c]										X	X[e]
Urinalysis	X																			X	
Viral Testing[b]	X															X				X	
Physical Exam		X																		X	
Review & Collect Diary						X				X						X				X	
Vital Signs	X	≤30 min	X[f]	≤30 min		≤30 min	X[f]	≤30 min		≤30 min	X[f]	≤30 min				≤30 min	X[f]	≤30 min			
Back-up Serum, IgG Subclasses		15 min		15 min		15 min				15 min		15 min				15 min		15 min		15 min	
IGIV Infusion			X				X				X						X				

Study Schedule – 28 Day Schedule (continued)

Infusion	Screening Visit	Infusion 1				Infusions 2,3,5,6,7,9,10,11,13 — Test times with **ONLY for Subjects in PK extension part At INFUSION 17				Infusion 4 — Test times with * for PK subjects only					Day 21	Infusions 8 & 12				Final Clinical Visit	Final Safety Follow-up
Study Visit		Visit 1				V2,V3,V5-V7,V9-V11,V13-V17 (respectively)				Visit 4						Visit 8 & Visit 12					
Visit Day/Visit	Within 30 days	Day 0			Day 1-3	Day 0			Day 1-3	Day 0			Day 1-3*	Day 3*, 7*, 14*		Day 0			Day1-3*		
		Pre	IGIV	Post	Within 72h	Pre	IGIV	Post	Within 72h	Pre	IGIV	Post	Within 72h			Pre	IGIV	Post	Within 72h	Pre	Pre
Antibody Testing[c] And Total IgG serology	X[g]	15 min		15 min				15 min and 1h** post-infusion 13	X** (at Days 1,3,7,14 and 21 post-infusion 13)	15 min		15 min & 1h*	24h*	X*	X*	15 min		15 min		15 min[d]	
AEs			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[h]
Con Meds	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Infusion	Screening Visit	Infusion 1				Infusions 2,3,5,6,7,9,10, 11,13 Test times with **ONLY for Subjects in PK extension part At INFUSION 17				Infusion 4 Test times with * for PK subjects only					Day 21	Infusions 8 & 12				Final Clinical Visit	Final Safety Follow-up
Study Visit		Visit 1				V2,V3,V5-V7,V9-V11,V13-V17 (respectively)				Visit 4						Visit 8 & Visit 12					
Visit Day/Visit	Within 30 days	Day 0			Day 1-3	Day 0			Day 1-3	Day 0			Day 1-3*	Day 3*, 7*, 14*		Day 0			Day1-3*		
		Pre	IGIV	Post	Within 72h	Pre	IGIV	Post	Within 72h	Pre	IGIV	Post	Within 72h			Pre	IGIV	Post	Within 72h	Pre	Pre
Distribute Diary				X				X				X						X			
Phone Call					X				X				X						X		

Source: Original BLA, NABI-7101 Clinical Study Report, page 37 and 38 of 141.

a Included obtaining ICF, medical and medication history, pregnancy test, Coombs test, SID assignment, and chest x-ray (if not available within 6 months prior to the first infusion)

b HBsAg, HCV, HCV NAT, HIV-1/HIV-2, HIV NAT, anti-Parvovirus B19 and B19 NAT (if antibody is positive at the baseline, NAT will be used for subsequent testing points)

c Anti-pneumococcal, anti-*H. influenzae* B, anti-tetanus

d Total IgG serology only

e BUN, creatinine, AST, ALT, LDH and total bilirubin at Visits 4, 7, 10, and final safety follow up visit

f Vital signs were recorded before (pre) each infusion, prior to each rate change of infusion, 5 to 10 minutes after each rate change, and approximately every 30 minutes once a stable infusion rate was achieved, then 30 minutes after the infusion.

g Obtain total IgG serology sample at screening if previous results not available within the last 3 months

h All serious infections that occurred since the final clinical visit through the final safety follow up visit were recorded

6.1.7 Endpoints and Criteria for Study Success

In design of this clinical trial, BPC followed the FDA Guidance document cited in Section 2.3 "Safety and Efficacy of Pharmacologically Related Products".

The primary efficacy parameter was the rate of SBIs per person-year for the following types of infections:
- Bacteremia/sepsis
- Bacterial meningitis
- Osteomyelitis/septic arthritis
- Bacterial pneumonia
- Visceral abscess

Only SBIs that occurred during or after the first Bivigam infusion and before or on the final visit date (i.e., occurred during the study) were included in this rate. Infections at >1 site caused by the same pathogen occurring simultaneously or within a time-frame consistent with causal association were considered to be a single serious infectious episode.

Secondary efficacy parameters included:
- Time to first SBI. Two parameters were analyzed:
  - The time to the first SBI as defined in the primary efficacy analysis
  - The time to the first infection of any kind/seriousness at any time after first Bivigam infusion and before or on the final clinical visit date
- Days off school/work due to infections
- All confirmed infections of any kind/seriousness
- Hospitalizations due to infection. Three parameters were analyzed:
  - the number of subjects with ≥1 hospitalization due to infection
  - the number of hospitalizations due to infection
  - the number of days of hospitalization due to infection
- Days on antibiotics, prophylaxis excluded

Pharmacokinetic evaluations:
For all subjects, blood samples were collected prior to the start of each infusion and at the final clinical visit for determination of total IgG with IgG subclasses (IgG1, IgG2, IgG3, and IgG4). Additionally samples for all subjects were collected prior to the start and 15 to 30 minutes after the end of Infusions 1, 4, 8, and 12 for determination of total IgG with IgG subclasses and specific antibodies against pneumococcal capsular polysaccaride (types 4, 6B, 9V, 14, 18C, 19F, 23F), *H. influenzae* B, and tetanus.

In a subset of subjects, blood samples were collected for PK profile assessments at the 4th (or 5th for the 3-week schedule) IgG infusion day (or subsequent infusion day). In addition, at certain study sites, during a PK extension portion of the study conducted on subjects that did not participate in the original PK portion of the study, PK parameters

were assessed at Infusion 13 for subjects on the 4-week infusion cycle or at Infusion 17 for subjects on the 3-week infusion cycle.

Sampling times used for the profile included the following:
- predose sample taken before the start of the infusion (all subjects)
- 15 minutes after the end of infusion
- 1 hour (± 5 minutes) after the end of infusion
- 24 hours (± 1 hour) after the end of infusion
- 3 days (± 6 hours) after the end of infusion
- 7 days (± 1 day) after the end of infusion
- 14 days (±1 day) after the end of infusion
- 21 days (±1 day) after the end of infusion: 3-week infusion schedule
- 28 days (±1 day) after the end of infusion: 4-week infusion schedule

These profile samples were assayed to determine the concentrations of total IgG and specific antibodies against pneumococcal capsular polysaccharide (types 4, 6B, 9V, 14, 18C, 19F, 23F), *H. influenzae* B, and tetanus.

6.1.8 Statistical Considerations & Statistical Analysis Plan

The ITT population was used for efficacy analyses. The primary outcome is the rate of SBIs per person-year. Person-year for each subject was computed from the first infusion date to the final clinical visit date, divided by 365.25.

The final clinical visit date was not collected directly and was 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.

If neither specimen date was available, the final clinical visit date was defined as the last infusion date + 21 or 28 days (depending on whether the patient was receiving a 3-week treatment cycle or a 4-week treatment cycle), the study completion (i.e., early termination date, or death), whichever occurred first. The data were assumed to arise from a Poisson process. Poisson regression was used to estimate the rate of SBI per person-year and develop the appropriate one-sided 99% upper confidence limit. Efficacy was measured by the upper confidence limit, and a value less than 1.0 was considered to be evidence for efficacy. During analysis, to take into account the observed intra-subject correlation of SBIs, the number of SBIs was only counted once in the same episode recorded in the CRF.

Descriptive statistics were provided and inferential analysis was performed for secondary efficacy parameters. Additionally, an exploratory analysis was performed to evaluate the correlation between trough level (low, medium, high) and number of infections of any kind/seriousness. For the time to the first SBI analysis, Kaplan-Meier product limit estimates were provided for the time to the first SBI/infection of any kind/seriousness distributions.

6.1.9 Study Population and Disposition

6.1.9.1 Populations Enrolled/Analyzed

The following analysis populations were used in study analyses:
- **Safety:** The Safety population consists of all subjects who received any amount of Bivigam. The Safety population was used for safety analyses.
- **Intent-To-Treat (ITT) Population:** The ITT population consists of all subjects who received any amount of Bivigam and reported at least once after first infusion recorded in the subject diary. The ITT population was used for efficacy analyses. (Subjects at Study Site #9 were only included in the Safety population, not in the ITT population. See Section 6.1.9.3 "Subject Disposition")
- **Per-Protocol (PP) Population:** The PP population for the analysis of study endpoints consists of all subjects who were assigned to ITT population without major protocol violations. The PP population was used for supportive efficacy analyses.
- **Pharmacokinetic (PK) Population:** The PK population included all subjects in the Safety population who volunteered to provide PK samples scheduled following the profile infusion or from trough concentrations collected during the study. None of the 10 pediatric subjects (children ages 6 – 11 years and adolescents ages 12 – 18 years) agreed to participate in the PK population.

6.1.9.1.1 Demographics

Parameter	Safety Pop. (N=63)
Gender	
Female	32 (50.8%)
Male	31 (49.2%)
Age (yr)	
Mean (SD)	41.2 (19.68)
Median	44.0
Min, Max	6, 75
Age group	
6-11 Years	4 (6.3%)
12-17 Years	6 (9.5%)
18-64 Years	44 (69.8%)
65 Years and Older	9 (14.3%)
Primary Diagnosis	
X-linked agammaglobulinemia	6 (9.5%)
Common variable immunodeficiency	51 (81.0%)
Other	6 (9.5%)
SBI history	8 (12.7%)
Bacterial pneumonia	7 (11.1%)
Other	1 (1.6%)

Source: Original BLA, NABI-7101 Clinical Study Report, page 61 of 141.

The study population had few pediatric and elderly subjects, and excluded pregnant patients. These subpopulations are all potential recipients of the product post-marketing. See further discussion of this topic in Section 4.6 "Pharmacovigilance".

6.1.9.1.2 Medical/Behavioral Characterization of the Enrolled Population

As would be expected with PI, most of the enrolled population had a history of other infections. The most common were sinusitis, upper respiratory tract infection and bronchitis. All subjects had multiple other diagnoses in their medical history to include other immune system disorders, such as anemia, arthritis, or autoimmune diseases and those involving the heart, digestive tract, or the nervous system, as well as malignancy.

6.1.9.1.3 Subject Disposition

A total of 63 subjects were enrolled in the study, 12 subjects discontinued from the study, and 52 subjects completed the study.
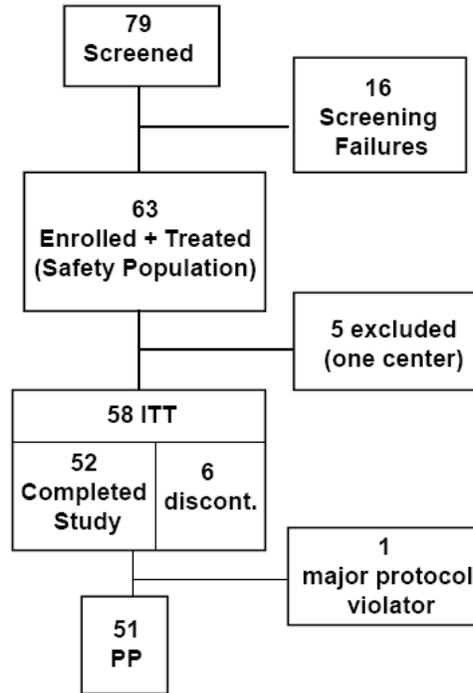
Source: Original BLA, NABI-7101 Clinical Study Report, page 57 of 141.

Number of Subjects	Reason for Discontinuation
3-Week Cycle	
5	Site 50160 (#9): BPC reports that the investigator elected to discontinue participation in the study after recurring protocol violations and deviations were brought to his attention. BPC states that these subjects were excluded from the ITT population in the final statistical analysis due to: 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 study data from Site 50160 to be neither robust nor reliable enough for inclusion in the ITT population (and there were no cases of SBI among these subjects). All 5 subjects at this discontinued site were receiving Bivigam on a 3-week cycle.
1	Protocol violation: Exclusion Criteria #11, Illicit drug use within 3 months of study drug administration
1	Based on subject's IgG levels, the investigator felt the subject was no longer in need of IgG therapy and withdrew the subject
1	AE: lethargy, headache, itching & tachycardia post first infusion
1	Withdrew consent, subject preferred other product
4-Week Cycle	
1	Lost to follow-up
1	Subject non-compliant with timely scheduling of appointments due to long commute

Source: Reviewer Tabulation from Original BLA

One subject on a 3-week cycle completed the study but was excluded from the PP population due to a violation of the inclusion criteria involving the use of an immunomodulatory drug (Arava). Thus there were a total of 7 subjects with major protocol violations.

6.1.10 Efficacy Analyses

6.1.10.1 Analyses of Primary Endpoint(s)

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

Source: Original BLA submission, NABI-7101 Clinical Study Report, page 62 of 141.
SBI = serious bacterial infections; SD = standard deviation.
[a]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.
[b]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.
[c]Rate of SBIs = total number of SBIs/total person-years.
[d]A one-sided 99% upper confidence limit was obtained by using the generalized linear model procedure for a Poisson distribution.

Two SBIs were cases of bacterial pneumonia. One occurred in a 21 year old male subject receiving 4-week treatment cycles (at a dose of approximately 500 mg/kg) and after receiving a total of 13 doses (treated in study for almost 1 year) developed left lower lobe pneumonia confirmed by CT scan. The subject was hospitalized and treated with intravenous antibiotics for 5 days, and another 5 days of oral antibiotics after discharge. With the exclusion of the subject's baseline total IgG serum concentration prior to Infusion #1 (977 mg/dL), all pre- and post-infusion total IgG serum concentrations were > 1000 mg/dL.

The second occurred in a 49 year old female subject, also on 4-week treatment cycles (at a dose of approximately 500 mg/kg). She developed a severe acute exacerbation of bronchitis and an acute respiratory failure secondary to pneumonia that was considered life threatening about 3 weeks after the 12th dose. She required intubation and was documented to have bilateral interstitial infiltrates by x-ray. She was discharged after approximately 2 weeks in the hospital and received her last dose of Bivigam. This subject had total IgG serum concentration trough levels that ranged from 487 – 956 mg/dL. The low of 487 mg/dL was recorded approximately 5 months prior to the SBI. All other recorded trough levels were > 600 mg/dL.

The investigator considered this to be an acute exacerbation of obstructive chronic bronchitis, acute respiratory failure, and bronchiectasis, and to be probably not related to the study drug. The investigator did not consider this to be an SBI. However, given the presence of initial pulmonary infiltrates, FDA considered this to be an SBI and requested BPC to reanalyze the data with the consideration of this subject as having developed an SBI. BPC agreed.

Based upon the rate of SBI of 0.035/person-years with an upper one-sided 99% confidence limit ≤0.136 in the ITT population (N=58), BPC has provided substantial evidence of the efficacy of Bivigam by meeting the pre-specified primary efficacy endpoint of ≤1 SBI/subject/year with an upper one-sided 99% confidence limit < 1.

6.1.10.2 Analyses of Secondary Endpoints

Confirmed Infections of Any Kind or Seriousness

Parameter	ITT (N=57)[*]	PP (N=51)
Total number of subjects	40	38
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]	2.61 [2.26; 2.97]	2.58 [2.23; 2.97]

Source: Adapted from Original BLA, NABI-7101 Clinical Study Report, page 64 of 141.
[*]The secondary efficacy analyses were performed on the ITT population with N=58 and PP =51. The documentations of "Other infections of any kind of seriousness" were collected from patient diaries provided at every visit. Patient (b)(6)- is a member of ITT population (n=58) but excluded from PP population (n=51) evaluation. BPC states that this subject was excluded due to multiple study visit compliance issues and was discontinued from the study after the infusion 3 visit and the diary information was not available due to patient compliance reasons. Consequently, BPC stated that they could not ascertain whether patient (b)(6)- did or did not have any other infection of any kind or seriousness and therefore decided to reduce the number of patients (patients with any information) for the evaluation.

Confirmed Infections of Any Kind or Seriousness by Category (ITT Population)

Infection	No. of Subjects (%)
Acute sinusitis	36 (25.9%)
Other respiratory infections	30 (21.6%)
Other	23 (16.5%)
Otitis media/ ear infections	15 (10.8%)
Bronchitis	14 (10.1%)
Acute exacerbation of chronic sinusitis	7 (5.0%)
GI-Infection	7 (5.0%)
Urinary tract infection	4 (2.9%)
Pneumonia	2 (1.4%)
Conjunctivitis	1 (0.7%)
Total	**139 (100%)**

Source: Adapted from Original BLA, NABI-7101 Clinical Study Report, page 65 of 141.

Number of Infections According to Trough IgG levels – ITT Population

Infections	Number of Subjects (%)			
	Low trough (600 – 900 mg/dL)	Medium trough (900 – 1200 mg/dL)	High trough (1200 – 1600 mg/dL)	Total
Total subjects	24	22	12	58
0 infections	8 (33%)	3 (14%)	4 (33%)	12 (26%)
1 – 5 infections	8 (33%)	10 (46%)	2 (17%)	20 (35%)
6 – 10 infections	2 (8.3%)	7 (32%)	3 (25%)	12 (21%)
11 – 15 infections	3 (13%)	1 (4.5%)	1 (8.3%)	5 (8.6%)
> 15 infections	2 (8.3%)	1 (4.5%)	2 (17%)	5 (8.6%)
Missing	1 (4.2%)[a]	0	0	1 (1.7%)

Source: Original BLA submission, NABI-7101 Clinical Study Report, page 66 of 141.
[a]1 subject with low trough values was missing the number of infections data

Days on Antibiotics

Parameter	ITT	PP
No. of subjects	(n=58)	(n=51)
Total days on antibotics[a]	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] [b]	82.73 [80.70; 84.79]	83.45 [81.37; 85.57]

Source: Adapted from Original BLA, NABI-7101 Clinical Study Report, page 67 of 141.
[a]Missing or partial antibiotics start date was manipulated to the earliest date after or on the first infusion date; missing or partial antibiotics stop date or ongoing was manipulated to the latest date before or on the end of study date.
[b]The 90% CI was obtained using the generalized linear model procedure for a Poisson distribution.

Of note is that 8 of the 58 subjects in the ITT population were on antibiotics for the entire duration of the study and that removing these subjects from the calculation of the primary efficacy analysis does not increase the upper one-sided 99% confidence interval for the rate of SBI in the remaining subjects above 1.0 SBI per person-year.

Hospitalization Due to Infection

Parameter	ITT (N=58)	PP (N=51)
Subjects with hospitalization	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]

Source: Original BLA, NABI-7101 Clinical Study Report, page 68 of 141.

The two subjects hospitalized due to infection are the same two subjects recorded with SBIs.

Days off School/Work due to Infections

Parameter	ITT (N=58)	PP (N=51)
No. of subjects with any days off	21	20
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 - 24)
Days per subject per year [90% CI][a]	2.28 [1.96; 2.64]	2.29 [1.96; 2.66]

Source: Adapted from Original BLA, NABI-7101 Clinical Study Report, page 64 of 141.
[a]The 90% CI was obtained using the generalized linear model procedure for a Poisson distribution.

Data for secondary endpoints are supportive of Bivigam's efficacy in that they are within the range of other US-licensed IGIV products for the same indication.

6.1.10.3 Subpopulation Analyses

BIVIGAM was evaluated in 9 pediatric subjects ages 6 - 16. This number of pediatric patients was too small for separate evaluation from the adult patients for safety or efficacy. BPC has requested a waiver for pediatric subjects < 2 years and a waiver for subjects 2 – 16 years. BPC has submitted a pediatric plan. Likewise, clinical studies of BIVIGAM did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

6.1.10.4 Dropouts and/or Discontinuations

See section 6.1.9.1.3 "Subject Disposition" for a complete description of dropouts and discontinuations. BPC handled subject dropouts and missing data in an appropriate manner.

6.1.11 Safety Analyses

6.1.11.1 Methods

The Safety population consists of all subjects who received any amount of Bivigam (N=63). AEs were actively solicited and all AEs occurring from the date of the first administration of Bivigam through 28 days after the last administration were to be recorded on the AE CRF page. AEs were captured by the subjects each day from Day 4 to Day 21 or 28, depending on scheduling of their next infusion, through the use of a home diary. Subjects recorded in the diary any complaints or problems experienced from when he/she left the clinic to 72 hours after the infusion. A member of the study staff

telephoned the subjects to review any AEs they may have had from the time they left the clinic until 72 hours after the infusion.

An AE was defined as any unfavorable, harmful, or pathological change in a subject administered an investigational product, as indicated by physical signs, symptoms, and/or clinically significant laboratory abnormalities that may have occurred in association with the use of the product (trial related), whether or not considered product-related. This definition included inter-current illnesses, injuries, exacerbation of pre-existing conditions, and events occurring as a result of product abuse or overdose.

A treatment emergent AE (TEAE) was defined to be any event which occurred during the observation period and was not present at baseline, or one which represented an exacerbation of a condition present at baseline.

AEs temporally associated with infusions (TAAE) are defined as those occurring between the start of Bivigam infusion and up to 72 hours following the infusion completion, regardless of other factors that may have impacted a possible causal association with product administration.

6.1.11.2 Overview of Adverse Events

Fifty-two subjects completed the 1-year study and all 52 had their highest doses > 400 mg/kg; 13 subjects had highest doses > 600 mg/kg and 5 subjects had highest doses > 800 mg/kg.

Treatment Exposure: Number of Infusions and Dose – Safety Population

Parameter	Total (N=63)
Total number of infusions	746
Per subject Mean (SD)	11.8 (4.10)
Median	13.0
Min, Max	1, 17
Dose per subject (mg/kg)	
Mean (SD)	499.6 (153.32)
Median	462.8
Min, Max	254, 1029
Highest dose per subject (mg/kg)	
Mean (SD)	517.4 (161.93)
Median	481.9
Min, Max	273, 1029
Number of infusions with highest dose	133
Per subject Mean (SD)	2.1 (2.63)
Median	1.0
Min, Max	1, 13

Source: Original BLA, NABI-7101 Clinical Study Report, page 78 of 141.

Summary of Adverse Events: AEs, TEAEs, SAEs, AEs Resulting in Withdrawal, and TAAEs – 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 SAE	7 (11.1%)
Total number of SAEs	11
Number of subjects with ≥1 AE leading to withdrawal[a]	2 (3.2%)
Total number of AEs leading to withdrawal[a]	5
Number of subjects with ≥1 TAAE	47 (74.6%)
Total number of TAAEs	431

Source: Adapted from Original BLA, NABI-7101 Clinical Study Report, page 80 of 141.
[a]AEs for which Bivigam was discontinued or which the subject was withdrawn from the study.
TAAEs = AEs temporally associated with infusions (within 72 hours from the start of the infusion)

The AEs leading to withdrawal were tachycardia, infusion site pain, headache, lethargy and pruritis. These are expected AEs for this product and the fact that it only involved 2 subjects, a minimal number, makes this a reasonable finding.

Treatment-Emergent Adverse Events (TEAEs) (≥5%) by MedDRA System Organ Class, Preferred Term and Worst Severity Classification
Population: Safety *(percentages are rounded to nearest integer)*

System Organ Class Preferred Term	Mild	Moderate	Severe	Total (N=63)
Number of Subjects with at least one TEAE	6 (10%)	20 (32%)	33 (52%)	59 (94%)
Blood and Lymphatic System				
Lymphadenopathy	1 (2%)	2 (3%)	0	3 (5%)
Ear and Labyrinth Disorders				
Ear Pain	2 (3%)	1 (2%)	1 (2%)	4 (6%)
Gastrointestinal Disorders				
Abdominal Pain	1 (2%)	1 (2%)	1 (2%)	3 (5%)
Abdominal Pain Upper	1 (2%)	1 (2%)	1 (2%)	3 (5%)
Diarrhea	4 (6%)	7 (11%)	2 (3%)	13 (21%)
Dyspepsia	2 (3%)	1 (2%)	0	3 (5%)
Mouth Ulceration	2 (3%)	1 (2%)	0	3 (5%)
Nausea	2 (3%)	5 (8%)	2 (3%)	9 (14%)

System Organ Class Preferred Term	Mild	Moderate	Severe	Total (N=63)
Vomiting	3 (5%)	2 (3%)	1 (2%)	6 (10%)
General Disorders and Administration Site Conditions				
Chills	2 (3%)	1 (2%)	0	3 (5%)
Fatigue	7 (11%)	8 (13%)	3 (5%)	18 (29%)
Infusion Site Reaction	3 (5%)	2 (3%)	0	5 (8%)
Malaise	0	2 (3%)	2 (3%)	4 (6%)
Edema Peripheral	2 (3%)	1 (2%)	0	3 (5%)
Pain	3 (5%)	3 (5%)	1 (2%)	7 (11%)
Pyrexia	4 (6%)	7 (11%)	1 (2%)	12 (19%)
Infections and Infestations				
Acute Sinusitis	1 (2%)	6 (10%)	0	7 (11%)
Bronchitis	1 (2%)	7 (11%)	4 (6%)	12 (19%)
Cellulitis	0	1 (2%)	2 (3%)	3 (5%)
Gastroenteritis	0	3 (5%)	0	3 (5%)
Gastroenteritis Viral	2 (3%)	3 (5%)	0	5 (8%)
Influenza	3 (5%)	0	1 (2%)	4 (6%)
Nasopharyngitis	1 (2%)	4 (6%)	0	5 (8%)
Otitis Externa	1 (2%)	2 (3%)	0	3 (5%)
Otitis Media	1 (2%)	3 (5%)	0	4 (6%)
Pharyngitis	3 (5%)	3 (5%)	1 (2%)	7 (11%)
Sinusitis	4 (6%)	14 (22%)	6 (10%)	24 (38%)
Upper Respiratory Tract Infection	6 (10%)	10 (16%)	0	16 (25%)
Urinary Tract Infection	3 (5%)	1 (2%)	1 (2%)	5 (8%)
Viral Upper Respiratory Tract Infection	1 (2%)	4 (6%)	1 (2%)	6 (10%)
Investigations				
Blood Pressure Diastolic Decreased	3 (5%)	0	0	3 (5%)
Blood Pressure Increased	4 (6%)	0	0	4 (6%)
Metabolism and Nutrition Disorders				
Dehydration	1 (2%)	2 (3%)	0	3 (5%)
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	1 (2%)	2 (3%)	0	3 (5%)
Back Pain	2 (3%)	3 (5%)	2 (3%)	7 (11%)
Fibromyalgia	0	1 (2%)	2 (3%)	3 (5%)
Myalgia	2 (3%)	2 (3%)	0	4 (6%)
Pain in Extremity	1 (2%)	2 (3%)	0	3 (5%)
Nervous System Disorders				
Dizziness	4 (6%)	2 (3%)	0	6 (10%)
Headache	9 (14%)	16 (25%)	7 (11%)	32 (51%)
Lethargy	2 (3%)	2 (3%)	1 (2%)	5 (8%)
Migraine	0	0	4 (6%)	4 (6%)

System Organ Class Preferred Term	Mild	Moderate	Severe	Total (N=63)
Respiratory, Thoracic and Mediastinal Disorders				
Asthma	1 (2%)	4 (6%)	0	5 (8%)
Cough	4 (6%)	9 (14%)	1 (2%)	14 (22%)
Nasal Congestion	4 (6%)	1 (2%)	0	5 (8%)
Pharyngolaryngeal Pain	7 (11%)	4 (6%)	2 (3%)	13 (21%)
Respiratory Tract Congestion	2 (3%)	1 (2%)	0	3 (5%)
Sinus Congestion	2 (3%)	2 (3%)	0	4 (6%)
Skin and Subcutaneous Tissue Disorders				
Dermatitis Contact	2 (3%)	0	1 (2%)	3 (5%)
Rash	3 (5%)	0	0	3 (5%)
Vascular Disorders				
Hot Flush	1 (2%)	2 (3%)	0	3 (5%)
Hypertension	0	4 (6%)	0	4 (6%)
Hypotension	1 (2%)	0	3 (5%)	4 (6%)

Source: Adapted from Original BLA, Biotest Pharmaceuticals Corporation Protocol: Nabi-7101, Table 14.3.2.5.1.

Adverse Events Temporally-Associated with Infusions (TAAEs) (≥5%) by MedDRA System Organ Class, Preferred Term and Worst Severity Classification Population: Safety *(percentages are rounded to nearest integer)*

System Organ Class Preferred Term	Mild	Moderate	Severe	Total (N=63)
Number of Subjects with at least one TAAE	11 (18%)	21 (33%)	15 (24%)	47 (75%)
Gastrointestinal Disorders				
Diarrhea	3 (5%)	0	1 (2%)	4 (6%)
Nausea	4 (6%)	1 (2%)	0	5 (8%)
General Disorders and Administration Site Conditions				
Fatigue	6 (10%)	7 (11%)	2 (3%)	15 (24%)
Infusion Site Reaction	3 (5%)	2 (3%)	0	5 (8%)
Infections and Infestations				
Sinusitis	1 (2%)	3 (5%)	1 (2%)	5 (8%)
Investigations				
Blood Pressure Diastolic Decreased	3 (5%)	0	0	3 (5%)
Blood Pressure Increased	4 (6%)	0	0	4 (6%)
Musculoskeletal and Connective Tissue Disorders				
Back Pain	0	2 (3%)	1 (2%)	3 (5%)
Fibromyalgia	0	1 (2%)	2 (3%)	3 (5%)
Myalgia	2 (3%)	1 (2%)	0	3 (5%)
Nervous System Disorders				
Dizziness	3 (5%)	1 (2%)	0	4 (6%)
Headache	8 (13%)	15 (24%)	4 (6%)	27 (43%)
Lethargy	2 (3%)	1 (2%)	1 (2%)	4 (6%)

System Organ Class Preferred Term	Mild	Moderate	Severe	Total (N=63)
Migraine	0	1 (2%)	2 (3%)	3 (5%)
Respiratory, Thoracic and Mediastinal Disorders				
Pharyngolaryngeal Pain	2 (3%)	1 (2%)	0	3 (5%)

Source: Adapted from Original BLA, Biotest Pharmaceuticals Corporation Protocol: Nabi-7101, Table 14.3.2.5.2.

The tabulated TEAEs and TAAEs are within the expected profile of the product.

Most Frequent (≥5%) TAAEs by Frequency – Safety Population (N=63)

TAAE	No. of Subjects (%)	No. of AEs (%AE of Total Infusions)[*]
Headache	27 (42.9%)	115 (15.4%)
Fatigue	15 (23.8%)	59 (7.9%)
Infusion site reaction	5 (7.9%)	5 (0.7%)
Nausea	5 (7.9%)	8 (1.1%)
Sinusitis	5 (7.9%)	5 (0.7%)
Blood pressure increased	4 (6.3%)	5 (0.7%)
Diarrhea	4 (6.3%)	4 (0.5%)
Dizziness	4 (6.3%)	4 (0.5%)
Lethargy	4 (6.3%)	4 (0.5%)
Back pain	3 (4.8%)	3 (0.4%)
Blood pressure diastolic decreased	3 (4.8%)	5 (0.7%)
Fibromyalgia[a]	3 (4.8%)	17 (2.3%)
Migraine	3 (4.8%)	8 (1.1%)
Myalgia	3 (4.8%)	4 (0.5%)
Pharyngolaryngeal pain	3 (4.8%)	3 (0.4%)

Source: Original BLA, NABI-7101 Clinical Study Report, page 82 of 141.
[*]Total Infusions = 746
Subjects reporting >1 TAAE are counted only once in each level (SOC or preferred term).
Related TAAEs included 'probably related', 'unknown', or missing.
[a]Symptoms occurring under pre-existing fibromyalgia.

The most frequent TAAEs are consistent with what is seen in other IGIV products.

Summary of TAAEs – Safety Population

Parameter	Total (N=63)
Total number of TAAEs	431
Number of subjects (%) with ≥1 TAAE	47 (74.6%)
During infusion or up to 1 h after	36 (57.1%)
1 – 24 h after infusion	32 (50.8%)
24 – 48 h after infusion	16 (25.4%)
48 – 72 h after infusion	20 (31.7%)
Number of infusions/subject with TAAE	
Mean (SD)	3.3 (4.12)
Median	2.0
Min, Max	0, 17
Number of TAAEs per infusion	
Mean (SD)	0.64 (0.944)
Median	0.23
Min, Max	0.0, 4.0

Source: Original BLA, NABI-7101 Clinical Study Report, page 83 of 141.

TAAEs per Infusion Rate - Population: Safety (N=63)

Infusion Rate (mL/kg/hr)	No. of Subjects[1]	No. of TAAE < 1 Hour Post Infusion[2]	No. of TAAE < 1 Hour /Subject[2]	Total No. of TAAE < 72 Hour Post Infusion[3]	Total No. of TAAE[3]/Subject
Mean Highest Infusion Rate Per Subject					
0.5 – 1.0	0	0	0.00	0	0.00
1.0 – 1.5	2	3	1.50	30	15.00
1.5 – 2.0	0	0	0.00	0	0.00
2.0 – 2.5	6	18	3.00	72	12.00
2.5 – 3.0	5	4	0.80	21	4.20
3.0 – 3.5	40	87	2.18	274	6.85
> 3.5	10	16	1.60	34	3.40
Total	**63**	**128**	**2.03**	**431**	**6.84**

Source: Original BLA, Biotest Pharmaceuticals Corporation Protocol: Nabi-7101, Table 14.3.1.5.

Proportion of Infusions with ≥1 TAAEs – Safety Population

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

Source: Original BLA, NABI-7101 Clinical Study Report, page 84 of 141.
Infusions with >1 TAAE are only counted once.

The table above demonstrates that BPC met the pre-specified safety endpoint of an upper
one-sided confidence limit of less than 0.40 for the observed proportion of infusions with
one or more temporally-associated AEs.

TAAEs by Dose – Safety Population (N=63)

Highest Dose		No. of subjects (%)	
		Total	With TAAEs
	< 300 mg/kg	3	1 (33.3%)
Low	300 – 400 mg/kg	8	7 (87.5%)
Medium	400 – 600 mg/kg	39	27 (69.2%)
High	600 – 800 mg/kg	8	7 (87.5%)
	> 800 mg/kg	5	5 (100%)

Source: Original BLA, NABI-7101 Clinical Study Report, page 86 of 141.

Approximately 20% of subjects received doses in excess of 600 mg/kg. The data suggest
a higher proportion of TAAEs at these higher doses. FDA Guidance document

recommends a minimum of 30 subjects to be studied at the highest dose to be recommended in the product's labeling. The proposed labeling of BPC will be recommended to be changed from 300 to 800 mg/kg every 3 to 4 weeks, to 300 to 600 mg/kg every 3 to 4 weeks.

Demographic and Baseline Characteristics of Subjects According to TAAEs –Safety Population (N=63)

Category	0 TAAEs (N=16)	1 – 10 TAAEs (N=36)	> 10 TAAEs (N=11)
Ethnicity n (%)			
Hispanic or Latino n (%)	3 (18.8%)	3 (8.3%)	1 (9.1%)
Race			
Asian n (%)	1 (6.3%)	0	0
White n (%)	15 (93.8%)	36 (100%)	11 (100%)
Gender			
Women n (%)	5 (31.3%)	19 (52.8%)	8 (72.7%)
Men n (%)	11 (68.8%)	17 (47.2%)	3 (27.3%)
Age (yr)			
Mean (SD)	36.6 (22.14)	42.2 (19.89)	44.5 (15.23)
Median	31.0	42.0	48.0
Min, Max	10, 71	6, 75	7, 61
Age group			
Children 6 – 11 yr n (%)	2 (12.5%)	1 (2.8%)	1 (9.1%)
Adolescents 12 – 17 yr n (%)	3 (18.8%)	3 (8.3%)	0
Adults 18 – 64 yr n (%)	8 (50.0%)	26 (72.2%)	10 (90.9%)
Elderly 65 yr and older n (%)	3 (18.8%)	6 (16.7%)	0
Primary diagnosis			
X-linked agammaglobulinemia n (%)	2 (12.5%)	3 (8.3%)	1 (9.1%)
Common variable immunodeficiency n (%)	14 (87.5%)	29 (80.6%)	8 (72.7%)
Other n (%)	0	4 (11.1%)	2 (18.2%)
SBI history			
Bacterial pneumonia n (%)	1 (6.3%)	5 (13.9%)	1 (9.1%)
Other n (%)	0	1 (2.8%)	0

Source: Original BLA, NABI-7101 Clinical Study Report, page 86 of 141.

The following viral tests were performed: parvovirus, HIV, HCV, and hepatitis B virus (HBV) at screening, prior to Infusions 8 and 12, and at the final safety follow-up visit. There was a single positive finding for parvovirus during the study. This subject is reported to have come in contact with acute Parvo B19 virus from working at a school greeting children where a child was reported to have symptomatic Fifth's disease. There were no other cases of Parvo B19 transmission with the IGIV batch concerned. There is no clear evidence of any viral transmission by Bivigam and it is plausible that this subject contracted the virus through interaction with an infected child, as suggested by BPC.

Overall, the safety profile appears consistent with other IGIV products with the exception of hypotension. See Section 6.1.11.5 "Adverse Events of Special Interest (AESI)" for further discussion of this topic.

6.1.11.3 Deaths

There were no deaths in the study.

6.1.11.4 Nonfatal Serious Adverse Events

There were 11 serious adverse events (SAE) in 7 subjects (11.1%) most of which (5 subjects) occurred >72 hours post-infusion. Two SAEs in 1 subject (mild vomiting and moderate dehydration) were considered related to the study treatment by the investigator. No SAE resulted in a dose change, dose interruption, or discontinuation from the study, and all of the SAEs resolved.

Summary of SAEs

Parameter Category	No. of Subjects (N=63)
Number of Subjects with at least one SAE	
During Infusion and up to 1 hour post-infusion[1]	0 (0%)
1 to 24 Hours post-infusion	1 (2%)
24 to 48 Hours post-infusion	0 (0%)
48 to 72 Hours post-infusion	1 (2%)
More than 72 Hours post-infusion	5 (8%)
Total	**7 (11%)**
Total Number of SAEs	
During Infusion and up to 1 hour post-infusion[1]	0
1 to 24 Hours post-infusion	2
24 to 48 Hours post-infusion	0
48 to 72 Hours post-infusion	1
More than 72 Hours post-infusion	8
Total	**11**

Source: Adapted from Original BLA, Biotest Pharmaceuticals Corporation Protocol: Nabi-7101, Table 14.3.2.1.6.
[1]Post-infusion means after the infusion has been completed

SAEs by MedDRA System Organ Class, Preferred Term
Population: Safety (N=63) *(percentages are rounded to nearest integer)*

System Organ Class Preferred Term	No. of Subjects (%)
Gastrointestinal Disorders	
Colitis	1 (2%)
Intestinal Obstruction	1 (2%)
Vomiting	1 (2%)
Infections and Infestations	
Appendicitis	1 (2%)
Obstructive Chronic Bronchitis with Acute Exacerbation	1 (2%)
Pneumonia Bacterial	1 (2%)
Injury, Poisoning and Procedural Complications	
Hip Fracture	1 (2%)
Metabolism and Nutrition Disorders	
Dehydration	1 (2%)
Psychiatric Disorders	
Mental Status Changes	1 (2%)
Respiratory, Thoracic and Mediastinal Disorders	
Acute Respiratory Failure	1 (2%)
Vascular Disorders	
Hypotension	1 (2%)

Source: Adapted from Original BLA, Biotest Pharmaceuticals Corporation Protocol: Nabi-7101, Table 14.3.2.3.4.

There were two subjects who experienced SAEs within 72 hours of Bivigam infusion. One subject developed a case of appendicitis approximately 2 to 3 days after Infusion #13. The second subject was a 7-year old male child who developed vomiting and moderate dehydration on the same day. Between 1 and 24 hours after Infusion #10, the subject experienced malaise followed by vomiting and dehydration the next day. The dehydration was associated with anuria. The subject was given promethazine (12.5 mg every 4 hours) for nausea but continued to vomit throughout the day and was taken to the emergency room. The subject was treated with IV fluids (900 cc normal saline) for dehydration and ondansetron for nausea and vomiting. No action was taken with study drug. The subject's condition improved and he was discharged home from the emergency room. The subject continued in the study and received 3 subsequent infusions of Bivigam.

More than half of the SAEs reported appear to be unrelated to the product.

6.1.11.5 Adverse Events of Special Interest (AESI)

Hypotension Related TEAEs

Bivigam contains PS80 in higher concentration than other licensed IGIV products.

Concentration of PS80 in IGIV Products and Nabi-IGIV 10%

Product Name/Concentration (Sponsor)	PS80 Concentration
Gammaplex/(b)(4) (BPL)	---(b)(4)---
-------(b)(4)------------------	--(b)(4)--
-----(b)(4)--------------	--(b)(4)--
IgPro20/20% (CSL)	--(b)(4)-
Bivigam®/10% (Biotest)	---(b)(4)-

Source: Mid-cycle memo of Dr. Evi Struble, pg. 3

This issue was discussed with BPC at a pre-BLA meeting dated April 23, 2009 where FDA stated that PS80 has been reported to have a profound cardiovascular effect when given intravenously in a canine animal model, with a 60% drop in mean blood pressure and left ventricular maximum DP/DT for at least 30 minutes. The BPC's response was that they would assess this cardiovascular effect based on safety data from their ongoing clinical trial. In their BLA submission, BPC has noted from animal studies that the effects of PS80 on myocardial contractility are "immediate, with onset occurring within minutes after administration. The effects disappear within 1 h after dosing is stopped."

BPC has reported that there were a total of 7 subjects with TEAEs related to hypotension that were reported. In 3 of these, hypotension was reported to have only a diastolic component. The sponsor submitted narratives of the 4 remaining subjects in which there were reported drops in systolic blood pressure. These narratives are presented below:

- **Subject (b)(6)** had a serious cardiovascular TEAE during the study 9 days after the last (Infusion 7) dose of Nabi-IGIV 10%. She experienced an acute hypotensive episode with accompanying symptoms of lightheadedness, fatigue, and blurred vision. Her relevant medical history included transient ischemic attacks, migraine headache, type II diabetes mellitus, and hypercholesterolemia. The subject visited her primary care physician also complaining of a poison ivy rash. Her blood pressure was 57/35. She was admitted to the hospital and treated with normal saline. No etiology was determined for this hypotensive episode. The PI noted that this event was not related to study drug and that the subject recovered from the hypotensive episode.
- **Subject (b)(6)** had a baseline blood pressure of 116/71 mmHg. This subject had 1 low blood pressure reading of 83/69 approximately 1 h after the start of Infusion 8. This rebounded to 112/78 for the next measurement. The rest of the blood pressure measurements were lower than baseline but within normal limits. The PI indicated that the changes in blood pressure were not related to study treatment and there was no decrease in blood pressure on re-exposure to study drug.
- **Subject (b)(6)** had a baseline reading of 125/73 mmHg. One blood pressure reading on the dosing date of August was 97/54. The PI determined that this

blood pressure reading was not clinically significant. There was no decrease in blood pressure on re-exposure to study drug.
- **Subject (b)(6)** had a baseline blood pressure of 100/72. This subject had a hypotensive episode from 3 – 4 Sep 2008 which the investigator considered severe in intensity and not related to study drug. This episode did not occur within 72 h of the last infusion.

No TEAEs of bradycardia or decreased heart rate was reported in the BLA submission. There were no changes in blood pressure that were reported to have led to treatment change in dosing regimen or discontinuation of dosing with Bivigam. BPC has concluded that the conduct of normal pharmacovigilance activities would be "appropriate to control a remaining potential risk which may be derived from PS80 in Biotest IGIV."

In an Information Request BPC was asked to submit a spreadsheet that includes all subjects who experienced a drop in systolic blood pressure of 20 mmHg or more during any infusion of Bivigam. It was asked that the spreadsheet include medical history, TAAEs reported during the infusion, the times of infusion and any change in infusion rate during the drop in blood pressure.

On April 22, 2011, BPC submitted the requested information as part of Amendment 0008 to the Bivigam BLA. Review of the data finds that 47 subjects experienced 1 or more drops in systolic blood pressure of 20 mmHg or more during any infusion of Bivigam. Some were isolated and others were sustained longer. It does not appear that any decreases in blood pressure were clinically significant and none were associated with any changes to the infusion. Fourteen of the 47 subjects experienced TAAEs during the drops in blood pressure, none were related to the cardiovascular system. Five of the 14 subjects who experienced TAAEs during the drops in blood pressure complained of headache, which was the most common complaint of the 14 subjects.

Due to the above findings, a post-marketing study to further evaluate the potential for hypotension during Bivigam infusion is recommended. See Section 4.6 "Pharmacovigilance" for further discussion of this topic.

6.1.11.6 Clinical Test Results

Results of hematology, chemistry and urinalysis testing did not suggest any evidence of intravascular hemolysis.

6.1.11.7 Dropouts and/or Discontinuations

There were only two dropouts/discontinuations due to AEs. The types of AEs seen and their rate of occurrence are as would be expected. It is unlikely that the dropouts/discontinuations that occurred would have impacted the safety results had they not occurred.

7. INTEGRATED OVERVIEW OF EFFICACY

Not applicable, see Section 5.1 "Review Strategy".

8. INTEGRATED OVERVIEW OF SAFETY

Not applicable, see Section 5.1 "Review Strategy".

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Bivigam is Pregnancy Category C. Animal reproduction studies have not been conducted with Bivigam. It is also not known whether Bivigam can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Give Bivigam to a pregnant woman only if clearly needed. Bivigam crosses the placenta from maternal circulation increasingly after 30 weeks of gestation.

9.1.2 Use during Lactation

It is not know whether Bivigam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Bivigam is administered to a nursing woman.

9.1.3 Pediatric Use and PREA Considerations

Bivigam was evaluated in 9 pediatric patients (4 children ages 6 – 11 years and 5 adolescents ages 12 – 16 years) with PI. This number of pediatric patients is too small for separate evaluation from the adult patients for safety or efficacy. PREA is triggered by this application. BPC has requested a waiver for subjects < 2 years and a deferral for the remaining pediatric age categories. BPC has submitted a pediatric plan. This plan has not been reviewed by the Pediatric Review Committee (PeRC) thus far.

9.1.5 Geriatric Use

Clinical studies of Bivigam did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

10. CONCLUSIONS

In design of this clinical trial, BPC followed the FDA Guidance document *Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency* which recommends that "the efficacy of an investigational IGIV compare the frequency of SBIs during a period of regular administration of the test product to a historically-based standard". The recommended period of administration and observation is 12

months and efficacy can be shown based on the historical data, by "demonstration of a SBI rate per person-year less than 1.0". It is recommended that the level of statistical significance be at the 0.01 level, or the upper one-sided 99% confidence limit be less than 1.0 The Guidance states that a sample size of 40 to 50 subjects would generally be adequate.

Based upon the rate of SBI of 0.035/person-years with an upper one-sided 99% confidence limit ≤0.136 in the ITT population (N=58), BPC has provided substantial evidence of the efficacy of Bivigam by meeting the pre-specified primary efficacy endpoint of ≤1 SBI/subject/year with an upper one-sided 99% confidence limit < 1. Further, data for secondary endpoints are supportive of Bivigam's efficacy in that they are within the range of other US-licensed IGIV products for the same indication.

The safety profile of Bivigam is in line with other IGIV products as demonstrated by the tabulated TEAEs and TAAEs observed during the clinical trial. The most frequent TAAEs are also consistent with what is reported with the use of other IGIV products as well, both in the types of TAAEs and in the rates of their occurrence. The FDA Guidance recommends that a target endpoint for safety be an upper one-sided 95% confidence limit of less than 0.40 when calculating the observed proportion of infusions with one or more TAAE. BPC met this pre-specified safety endpoint with an upper one-sided confidence limit of less than 0.36.

With regard to dosing, Nabi-7101 began with the dosing schedule of 300 to 600 mg/kg. This dosing schedule was increased to 300 to 800 mg/kg in Amendment 1 to the protocol dated 17 Jul 2007 (original protocol dated 29 Mar 2007) "at the recommendation of several of the study's investigators at the Investigator Meeting on 13-14 July 2007". Thirteen of the 63 subjects in the Safety Population, approximately 20%, received doses in excess of 600 mg/kg. The data suggest a higher proportion of TAAEs at these higher doses. FDA Guidance document recommends a minimum of 30 subjects to be studied at the highest dose to be recommended in the product's labeling. The labeling for the dosage of Bivigam is recommended to be changed from the proposed 300 to 800 mg/kg every 3 to 4 weeks, to 300 to 600 mg/kg every 3 to 4 weeks.

Bivigam contains PS8 in higher concentration than other licensed IGIV products. PS80 has been reported to have a profound cardiovascular effect when given intravenously in a canine animal model, with a 60% drop in mean blood pressure and left ventricular maximum DP/DT for at least 30 minutes. BPC is aware of the potential for hypotension with the infusion of Bivigam and plans for routine post-marketing surveillance. In Nabi-7101, 47 of the 63 subjects in the Safety Population had at least one episode of a drop in systolic blood pressure greater than 20 mmHg during an infusion. While none of these events led to a clinically relevant outcome, the study population included few pediatric and elderly subjects, and excluded pregnant subjects. These subpopulations will potentially receive Bivigam and may be at greater risk to develop hypotension from PS80. Pharmacovigilance data will need to specifically examine these at-risk populations

and overall, it is recommended that the issue of potential hypotension due to PS80 be addressed via a post-marketing study requirement.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

11.2 Risk-Benefit Summary and Assessment

Data submitted to the BLA supplement establish a substantial likelihood of benefit in the target population of adults with PI. There currently do not appear to be any additional clinically significant risks with the use of the product over other IGIV products currently licensed; therefore, the overall benefit-risk profile is favorable. There remains the unknown potential for clinically significant hypotension during infusion which is discussed elsewhere in this review and is recommended to be addressed post-marketing.

11.3 Discussion of Regulatory Options

11.4 Recommendations on Regulatory Actions

On a clinical basis, Bivigam is recommended for approval with a post-marketing requirement.

11.5 Labeling Recommendations

The first revision to the proposed labeling was sent back to BPC. BPC has yet to respond.

11.6 Recommendations on Post-marketing Actions

A post-marketing study is recommended to address the high concentration of PS 80 and the potential for hypotension during infusion of Bivigam. See Section 4.6 "Pharmacovigilance".