DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

Mid-cycle Review Memo:

TO: STN 125389/0

SPONSOR: Biotest Pharmaceuticals Corporation

PRODUCT: Nabi-IGIV 10% Immune Globulin Intravenous (Human)

FROM: Mitchell Frost, M.D.

SUBJECT: Mid-cycle review of BLA (STN 125389/0)

TO: Pratibha Rana Regulatory Project Manager

THROUGH: Nisha Jain, M.D., Clinical Review Branch Chief

EXECUTIVE SUMMARY:

BLA 125389 is an original BLA submission for Bivigam (Nabi-IGIV 10%), a 10% IGIV product first owned by Nabi Biopharmaceuticals. Ownership was transferred to Biotest Pharmaceutical Corporation upon their purchase of Nabi along with IND 13353. Under IND 13353, the phase 3 Study Nabi-7101 was completed. Nabi-7101 was performed to evaluate the safety and efficacy of Nabi-IGIV 10%, as well as to characterize its pharmacokinetics, in subjects with a diagnosis of humoral Primary Immune Deficiency Disorders (PIDD) from congenital X-linked agammaglobulinemia, common variable immunodeficiency and hyper IgM syndrome with immunoglobulin G (IgG) deficiency. The primary efficacy endpoint was 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

- Visceral abscess

Bivigam met the guidelines for clinical benefit (≤1 SBI/subject/year) and safety (proportion of infusions with more than 1 TAAE had an upper bound for the one-sided 95% CI of less than 40% for all time points). However, Bivigam contains polysorbate 80 in higher concentration than other licensed IGIV products. Polysorbate 80 has been associated with a cardiovascular effect exhibited as hypotension in canine models. Although the sponsor addressed this issue in the submission, an information request will be sent to the sponsor to tabulate all subjects who experienced a drop in systolic blood pressure of more than 20 mmHg.

Further, the sponsor will be requested to recalculate the primary efficacy endpoint adding an additional subject the one already designated as developing an SBI during the study period.

LETTER READY COMMENTS:

1. Your study has a total of ten pediatric subjects which is inadequate for licensure for a pediatric indication. In general, 20 pediatric subjects ages 2 – 16 should be studied for pediatric indication.
2. You have requested a waiver for < 2 years of age and 2 – 5 years of age. FDA denies your request. Please amend your submission to include pediatric deferral for ages 2 – 16 and submit a pediatric plan that adds 10 more subjects ages 2 – 16 (5 pediatric subjects ages 2 – 5 and 5 ages 6 – 16).
3. FDA considers Subject ---(b)(6)------ to meet the criteria of a SBI. Please reanalyze the primary efficacy endpoint taking this subject into consideration. In addition, please recalculate all other parameters that may be affected by including this subject in the primary efficacy analysis (e.g., time to first SBI).
4. Please submit a spreadsheet extracted from Appendix 16.2.7 which includes all subjects who experienced a drop in systolic blood pressure of 20 mmHg or more during any infusion. Please include in this spreadsheet the following:
    a. Medical history
    b. Any symptoms reported during the infusion
    c. A denotation of the exact time the infusion began
    d. Whether the rate of infusion was changed at any time and during the changes in the blood pressure.

INTRODUCTION:

The purpose of phase 3 Study Nabi-7101 was to evaluate the safety and efficacy of Nabi Immune Globulin Intravenous (Human) 10% (Nabi-IGIV 10%), and to characterize its pharmacokinetic (PK) properties. Subjects included in the study had a diagnosis of

humoral Primary Immune Deficiency Disorders (PIDD) from congenital X-linked agammaglobulinemia, common variable immunodeficiency and hyper IgM syndrome with immunoglobulin G (IgG) deficiency. The primary efficacy endpoint was 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
- Visceral abscess

Biotest Pharmaceutical Corporation (BPC) was formed after the purchase of the former Nabi Biopharmaceuticals (Nabi) business unit and manufacturing facility in Boca Raton, FL by Biotest AG of Dreieich, Germany. As a result, the ownership of the Nabi-7101 clinical study was transferred to Biotest Pharmaceuticals, and it was confirmed in a communication from the Food and Drug Administration (FDA) on 11 Jan 2008 that IND 13353 for this clinical study had been successfully transferred to Biotest Pharmaceuticals. However, since the clinical study was ongoing, Biotest Pharmaceuticals decided to continue to refer to this study as “Nabi-7101” and the investigational product as “Nabi-IGIV”.

Nabi-IGIV 10% contains sodium chloride, glycine, and polysorbate-80; it does not contain sucrose or albumin in its formulation. Pathogen inactivation steps consist of chemical (solvent/detergent) treatment and nanofiltration.
Nabi-7101 used doses that were adjusted in order to maintain serum trough total IgG concentrations > 500 mg/dL. This was done by targeting trough concentrations of > 600 mg/dL and proportionally changing subsequent doses as needed (e.g., if a trough was 400 mg/dL, the next dose was 50% higher).

As recommended by the FDA during the Type C meeting of June 25, 2009, Biotest has utilized a “two and two conformance lot approach” due to additional facility modifications at the Boca Raton, FL manufacturing site. As such, the BLA includes 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. Biotest is expecting to manufacture the additional two conformance lots in February 2011 and to submit the BLA amendment at the end of April/beginning of May 2011.

STUDY NABI-7101:

Title

“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)”

Study Objectives

Primary Objective
To assess the efficacy of Nabi-IGIV 10% in preventing SBIs compared to historical control data (as per FDA Guidance: by demonstration of a serious infection rate per person-year of < 1.0).

Secondary Objectives

- To assess the safety of Nabi-IGIV 10% by evaluating adverse events (AEs) and laboratory measurements
- To assess efficacy by the following variables:
  - Time to first SBI
  - Days off school/work due to infections
  - All infections of any type/seriousness
  - Hospitalizations due to infection
  - Days on antibiotics
- To evaluate the PK properties of Nabi-IGIV 10%.

Study Design

The Phase 3 study design was open-label, involved 15 centers and 63 subjects ages 6 – 75. Subjects had documented immune deficiency with agammaglobulinemia or hypogammaglobulinemia and were receiving intravenous (IV) immune globulin replacement therapy every 3 or 4 weeks. Table 1 describes days of each infusion for both the 3 and 4 –week cycles:

Table 1: Days of Each Infusion for 3 and 4-Week Cycles

3 Week Cycle																		
Infusion	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	Final
Day	0	21 (±7)	42 (±7)	63 (±7)	84 (±7)	105 (±7)	126 (±7)	147 (±7)	168 (±7)	189 (±7)	210 (±7)	231 (±7)	252 (±7)	273 (±7)	294 (±7)	315 (±7)	336 (±7)	357 (±7)

4 Week Cycle														
Infusion	1	2	3	4	5	6	7	8	9	10	11	12	13	Final
Day	0	28 (±7)	56 (±7)	84 (±7)	112 (±7)	140 (±7)	168 (±7)	196 (±7)	224 (±7)	252 (±7)	280 (±7)	308 (±7)	336 (±7)	364 (±7)

Source: Sponsor's BLA submission, nabi-7101-report-body.pdf, page 28 of 141.

Each subject was to receive a total Nabi-IGIV 10% infusion of 300-800 mg/kg per month administered as an infusion every 3 or 4 weeks (dependent upon the subject's previous IgG replacement schedule) for approximately 1 year. All subjects had blood samples collected prior to each infusion and at the final clinical visit for trough total IgG and IgG

subclass (IgG1, IgG2, IgG3, and IgG4) levels. Additionally, at Infusions 1, 4, 8, and 12 all subjects also had blood samples taken as follows:

- Prior to Infusions 1, 4, 8 and 12:
  Anti-pneumococcal antibody, anti-*Haemophilus influenzae* B antibody, and anti-tetanus antibody
- 15 – 30 minutes after Infusions 1, 4, 8 and 12:
  Total IgG and IgG subclass levels
  Anti-pneumococcal antibody, anti-*Haemophilus influenzae* B antibody, and anti-tetanus antibody

Twenty subjects (approximately 10 each on a 21-day or 28-day dosing schedule) willing to participate in the PK portion of the study had additional blood samples drawn during Infusion 4 (or 5) or if participating in the PK extension phase of the study, Infusion 13 (or 17) at 15 minutes, 1 hour (± 5 min), 24 hours (± 1 hr), 3 days (± 6 hr), 7 days (± 1 day), 14 days (± 1 day), and 21 days (± 1 day) [28 days (± 1 day) for subjects on a 28 day cycle] post-infusion for total IgG, anti-pneumococcal capsular polysaccharide antibody, anti-*Haemophilus influenzae* B antibody and anti-tetanus antibody testing. No subjects participated in both the PK portion of the study during Infusion 4 (or 5) and also participated in the PK extension phase of the study. At least 8 subjects 12 years of age or older from each dosing schedule were planned to be evaluated for PK.

Doses were adjusted in order to maintain serum trough total IgG concentrations > 500 mg/dL. This was done by targeting trough concentrations of > 600 mg/dL and proportionally changing subsequent doses as needed (e.g., if a trough was 400 mg/dL, the next dose was 50% higher).

All subjects were evaluated for AEs and serious AEs (SAEs) from the first infusion through Day 21 or Day 28 (depending on the infusion schedule) of the last infusion for the duration of the study.

Home diaries were the source documents for all subject-reported AEs, which were recorded on the case report forms (CRF). The subjects recorded in their home diaries any AEs, complaints, or problems experienced from when they left the clinic to 72 hours after the infusion and each day from Day 4 to Day 21 or 28, depending on infusion scheduling. Diary entries included documentation of AE start and stop dates and times, as well as event severity.

The total duration of the study was expected to be 21 to 27 months. The enrollment period was expected to be 6-12 months. Individual subjects were dosed every 3 to 4 weeks for approximately 12 months, with an observation period of approximately 15 months. The date of first enrollment was 24 Sept 2007 and the date of last completed was 24 Jul 2009.

Inclusion/Exclusion Criteria

Inclusion Criteria
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 PIDD (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 Nabi-IGIV 10% and agreed to use an acceptable method of contraception or be ≥1 year post-menopausal or surgically sterile.

Exclusion Criteria
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 Nabi-IGIV 10%.
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.

Treatments Administered

All subjects enrolled in the study received Nabi-IGIV 10% administered by means of an infusion pump for infusion rates at 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.

The initial infusion rate was 0.3 mL/kg/hr (30 mg/kg/hr) for 10 minutes. If this rate was well tolerated, the rate could have been increased to 0.5 mL/kg/hr (50 mg/kg/hr) for 20 minutes. If the subject continued to show no signs of intolerance, the rate could have been gradually increased every 20 minutes by 0.5 mL/kg/hr to the typical rate a subject was accustomed to receiving or a maximum tolerated rate up to 3.5 mL/kg/hr (350 mg/kg/hr). In this way, infusion rates were individualized for each subject. Infusion time was not to exceed 8 hours.

If a non-life-threatening AE occurred during an infusion, the rate could have been adjusted 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 to be the target for subsequent infusions. Infusion rates higher than this target rate were only allowed under direct supervision and approval of the investigator.

Concomitant Medications

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 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. It was not anticipated that such subjects would be candidates for this study. 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 to be 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 PIDD were prohibited.

Schedule of Events

Table 2: 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
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	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]
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: Sponsor's BLA submission, nabi-7101-report-body.pdf, 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

Table 3: 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				

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 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	
Distribute Diary				X				X				X						X			
Phone Call					X				X				X						X		

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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

Criteria for Evaluation

Efficacy
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 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. 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 Nabi-IGIV 10% 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
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 to be 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 polysaccaride (types 4, 6B, 9V, 14, 18C, 19F, 23F), *H. influenzae* B, and tetanus.

Safety
Safety assessments included medical history, physical examination, vital signs, baseline chest x-ray, AEs, laboratory tests, pregnancy tests, viral safety tests, and Coombs tests.

Statistical Methods
The intent-to-treat (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.

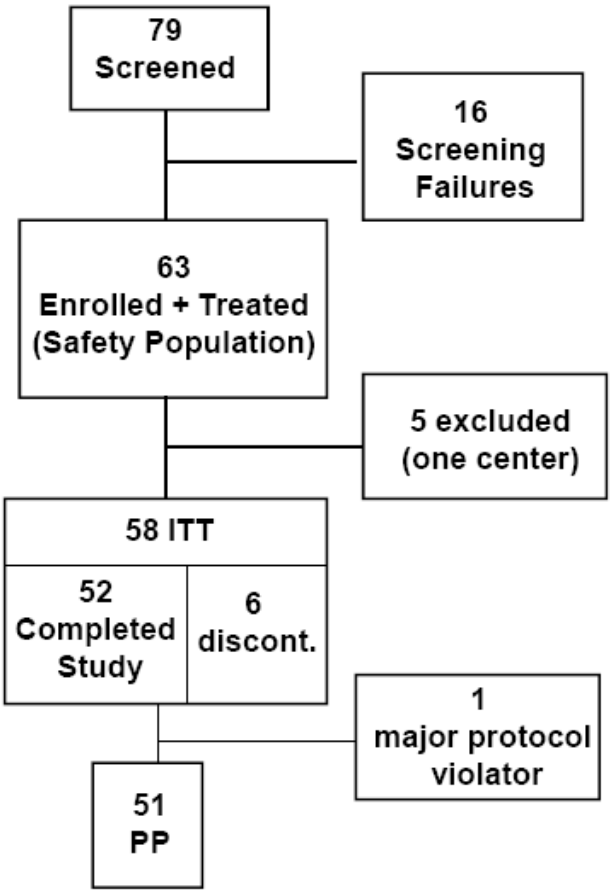
If neither specimen date was available, the final clinical visit date was defined as the last infusion date + 21 or 28 days (depending on whether the patient was receiving a 3-week treatment cycle or a 4-week treatment cycle), the study completion (i.e., early termination date, or death), whichever occurred 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 have been provided for the time to the first SBI/infection of any kind/seriousness distributions.

Study Results

Subject Disposition
A total of 63 subjects were enrolled in the study, 12 subjects discontinued from the study, and 52 subjects completed the study. Figure 1 depicts the overall disposition of all subjects and Table 4 provides the reasons for discontinuation.

Figure 1: Subject Status Flow Chart



Source: Sponsor's BLA submission, nabi-7101-report-body.pdf, page 56 of 141.

Table 4: Reasons for Subject Discontinuation

Number of Subjects	Reason for Discontinuation
3-Week Cycle	
5	Site 50160: The investigator elected to discontinue participation in the study after recurring protocol violations and deviations were brought to his attention. Site 50160 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. Biotest 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 Nabi-IGIV 10% 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: Tabulated from sponsor submission data

One subject on a 3-week cycle completed the study but was excluded from the Per Protocol 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.

Demographic Data
The demographic data is depicted in Table 5.

Table 5: Demographic and Baseline Characteristics – Safety Population

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: Sponsor's BLA submission, nabi-7101-report-body.pdf, page 61 of 141.

Primary Efficacy Results

The primary efficacy parameter was the rate of SBIs per person-year for the ITT population. The sponsor reported 1 SBI in 53.54 person-years, resulting in an SBI rate of 0.017 events per person-year (Table 6). The one-sided upper 99% confidence limit for this rate is reported as ≤0.101, thereby meeting FDA Guidance for efficacy, by demonstration of a serious infection rate per person-year of < 1.0. This was evaluated over close to 1 person-year with a mean (SD) of 0.923 (0.2341).

<u>Reviewer's Comments:</u> Based on this calculation alone, Bivigam was successful at meeting the primary efficacy endpoint.

Table 6: Primary Efficacy Analysis: Serious Bacterial Infections

Parameter	ITT (N=58)	PP (N=51)
Total number of SBIs[a]	1	1
Total person-years[b]	53.54	51.10
Rate of SBIs[c]	0.017	0.020
Upper 99% confidence limit[d]	≤0.101	≤0.105
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: Sponsor's BLA submission, nabi-7101-report-body.pdf, 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.

The one SBI reported was a case of left lower lobe pneumonia confirmed by CT scan in a subject who had been receiving 4-week treatment cycles, had received a total of 13 doses prior to the event, and was reported as having adequate IgG levels.

Secondary Efficacy Results
Descriptive statistics were not calculated for time to SBI since there was only one data point. Table 7 summarizes the probability of 1 tear without SBI and without infection of any kind/seriousness as well as the time to first infection of any kind/seriousness.

Table 7: Time to First SBI and Time to First Infection of Any Kind/Seriousness

Parameter	ITT (N=58)	PP (N=51)
Time to first SBI[a] (days)		
Number of subjects without SBI (Censored)	57 (98.3%)	50 (98.0%)
Probability of 1 year without SBI	98.0% 97.9%	98.0% 97.9%
95% CI for probability of 1 year without SBI[b]	86.4%, 99.7%	86.1%, 99.7%
Time to first infection of any kind/seriousness[a] (days)		
Median	100	100
95% CI for median[b]	(70, 151)	(54, 151)
Number of subjects without infection (Censored)	15 (25.9%)	11 (21.6%)
Probability of 1 year without infection	22.1%	21.6%
95% CI for probability of 1 year without infection[b]	12.0%, 34.1%	11.6%, 33.6%

Source: Sponsor's BLA submission, nabi-7101-report-body.pdf, page 63 of 141.
SBI = serious bacterial infection.
[a]Time to first SBI/infection in days was computed from the first Nabi-IGIV 10% infusion date to either the 'event time' of their first SBI or censored at the final visit date for subjects with no SBI. The final visit date was defined as the specimen collection date of the final visit for urinalysis, or the specimen collection date for the clinical laboratory tests at the final visit.
[b]Kaplan-Meier method was applied to calculate the probability of 1 year without SBI and its 95% CI.

There were a total of 21 subjects who had days off of school or work due to infections. A total of 42 subjects had infections of some kind and 15 subjects had none. In evaluations of subjects who developed infections of any kind/seriousness, the ITT population equals 57, not the 58 that it is in all other evaluations of the ITT population. The sponsor has explained that this is due to a single patient who had "compliance issues" and diary information was unavailable. The sponsor reduced the total of the ITT population by 1 for these calculations.

The sponsor reports that during data review and evaluation it became apparent to them that some reports of infections included diaries with ambiguous entries which were not clearly infections but rather symptoms starting on similar days. Therefore, the number of infections was classified as confirmed (yes to the question "Was this an infection?") infections and non-confirmed (no to the question "Was this an infection?"). Most subjects (40) still had confirmed infections but the mean number of infections (2.4) and infections per subject per year (2.61, 90% CI: 2.26; 2.99) were lower. Table 8 depicts the rates of days off school/work due to infections and of infections of any kind/seriousness among the ITT and PP populations. Table 9 gives a breakdown of the types of infections recorded.

Table 8: Days off School/Work and Number of Infections of Any Kind or Seriousness

Parameter	ITT (N=58)	PP (N=51)
Days off school/work due to infections		
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][c]	2.28 [1.96; 2064]	2.29 [1.96; 2.66]
Infections of any kind or seriousness[a]	(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][c]	3.70 [3.28; 4.15]	3.70 [3.27; 4.16]
Confirmed[b] infections of any kind or seriousness	(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][c]	2.61 [2.26; 2.99]	2.58 [2.23; 2.97]

Source: Sponsor's BLA submission, nabi-7101-report-body.pdf, page 64 of 141.
SD = standard deviation; CI = confidence interval.
[a]Total number of infections as recorded in the subject's diary. Both "Yes" to the question "Was this an infection?", and problem/complaint without "No" were both counted as an infection.
[b]To be confirmed, the patient diary had to have "yes" to the question "Was this an infection?"
[c]The 90% CI was obtained using the generalized linear model procedure for a Poisson distribution.

Table 9: Confirmed and Unconfirmed Infections – ITT Population

Infections	No. of Subjects (%)	
	Confirmed	Unconfirmed
Acute sinusitis	36 (25.9%)	4 (6.9%)
Other respiratory infections	30 (21.6%)	18 (31.0%)
Other	23 (16.5%)	33 (56.9%)
Otitis media/ ear infections	15 (10.8%)	0
Bronchitis	14 (10.1%)	0
Acute exacerbation of chronic sinusitis	7 (5.0%)	0
GI-Infection	7 (5.0%)	3 (5.2%)
Urinary tract infection	4 (2.9%)	0
Pneumonia	2 (1.4%)	0
Conjunctivitis	1 (0.7%)	0
Total	**139 (100%)**	**58 (100%)**

Source: Sponsor's BLA submission, nabi-7101-report-body.pdf, page 65 of 141.

Table 10 provides the breakdown of days off school/work and infections of any kind/seriousness between adult and pediatric subjects. Table 11 provides the breakdown of the types of infections recorded among these two populations.

Table 10: Days off School/Work and Number of Infections of Any Kind or Seriousness: in Pediatric and Adult Subjects – ITT Population

Parameters	**Pediatric (N=7)**	**Adult (N=51)**
Days off school/work due to infections		
Total days	7	115
Mean (SD) per subject	1.0 (2.24)	2.3 (5.09)
Median (range) per subject	0.0 (0 – 6)	0.0 (0 - 24)
Days per subject per year [90% CI][c]	1.11 [0.56; 1.95]	2.43 [2.08; 2.83]
Infections of any kind or seriousness[a]	(n=6)	(n=51)
Total infections	16	181
Mean (SD) per subject	2.7 (2.94)	3.5 (3.61)
Median (range) per subject	2.5 (0 – 6)	3.0 (0 - 14)
Infections per subject per year [90% CI][c]	2.64 [1.70; 3.88]	3.83 [3.38; 4.32]
Confirmed[b] infections of any kind or seriousness	(n=6)	(n=51)
Total infections	12	127
Mean (SD) per subject	2.0 (2.28)	2.5 (2.72)
Median (range) per subject	1.5 (0 - 5)	2.0 (0 - 14)
Infections per subject per year [90% CI][c]	1.98 [1.18; 3.07]	2.69 [2.31; 3.10]

Source: Sponsor's BLA submission, nabi-7101-report-body.pdf, page 66 of 141.
SD = standard deviation; CI = confidence interval.
[a]Total number of infections as recorded in the subject's diary. Both "Yes" to the question "Was this an infection?", and problem/complaint without "No" were both counted as an infection.
[b]To be confirmed, the patient diary had to have "yes" to the question "Was this an infection?"
[c]The 90% CI was obtained using the generalized linear model procedure for a Poisson distribution.

Table 11: Comparison Total Pediatric versus Adult Infections (Confirmed + Unconfirmed*)

Parameter	Pediatric (N=7)	Adult (N=51)	Total (N=58/ITT)
Acute sinusitis	2 (8.3%)	38 (18.5%)	40 (20.3%)
Other respiratory infections	6 (25.0%)	42 (20.5%)	48 (24.4%)
Other	4 (16.7%)	52 (25.4%)	56 (28.4%)
Otitis media/ ear infections	2 (8.3%)	13 (6.3%)	15 (7.6%)
Bronchitis	0 (0.0%)	14 (6.8%)	14 (7.1%)
Acute exacerbation of chronic sinusitis	0 (0.0%)	7 (3.4%)	7 (3.6%)
GI-Infection	2 (8.3%)	8 (3.9%)	10 (5.1%)
Urinary tract infection	0 (0.0%)	4 (2.0%)	4 (2.0%)
Pneumonia	0 (0.0%)	2 (1.0%)	2 (1.0%)
Conjunctivitis	0 (0.0%)	1 (0.5%)	1 (0.5%)
Total	**16 (66.7%)**	**181 (88.3%)**	**197 (100%)**

Source: Sponsor's BLA submission, nabi-7101-report-body.pdf, Table 14.2.2.4.3.1.1.
*There were 4 unconfirmed infections in the pediatric population

The sponsor has presented data relating the number of infections to trough IgG levels. Table 12 is a compilation of that data.

Table 12: 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: Sponsor's BLA submission, nabi-7101-report-body.pdf, page 66 of 141.
[a]1 subject with low trough values was missing the number of infections data

Table 13 presents data describing days on antibiotics for subjects in the study. Eight subjects were on antibiotics throughout the study either prophylactically or for ongoing/recurrent infections, and the data is also presented with the exclusion of these 8 subjects. The sponsor has stated that when the primary efficacy analysis is performed to

the exclusion of these 8 subjects, the result remain < 1.0 SBI per person-year; Table 14 presents the same data but with a breakdown of pediatrics and adult subjects.

Table 13: Days on Antibiotics

Parameter	ITT	PP
All subjects[a]		
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]
Subjects excluding those with antibiotics all year		
No. of subjects	(n=50)	(n=44)
Total days on antibotics[a]	1812	1714
Mean (SD) per subject	36.2 (52.66)	39.0 (54.96)
Median (range) per subject	24.0 (0 – 306)	27.0 (0 – 306)
Days per subject per year [90% CI] [b]	39.07 [37.58; 40.60]	38.85 [37.33; 40.42]

Source: Sponsor's BLA submission, nabi-7101-report-body.pdf, page 67 of 141.
SD = standard deviation; CI = confidence interval.
[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.

Table 14: Days on Antibiotics in Pediatric and Adult Subjects – ITT Population

Parameter	Pediatric	Adult
All subjects[a]		
No. of subjects	(n=7)	(n=51)
Total days on antibotics[a]	437	3992
Mean (SD) per subject	62.4 (135.13)	78.3 (117.12)
Median (range) per subject	8.0 (0 – 367)	32.0 (0 – 372)
Days per subject per year [90% CI] [b]	69.37 [64.05; 74.97]	84.51 [82.33; 86.73]
Subjects excluding those with antibiotics all year		
No. of subjects	(n=6)	(n=44)
Total days on antibotics[a]	70	1742
Mean (SD) per subject	11.7 (16.32)	39.6 (55.08)
Median (range) per subject	4.0 (0 – 40)	27.0 (0 – 306)
Days per subject per year [90% CI] [b]	13.22 [10.79; 15.99]	42.41 [40.76; 44.10]

Source: Sponsor's BLA submission, nabi-7101-report-body.pdf, page 68 of 141.
SD = standard deviation; CI = confidence interval.
[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.

Table 15 presents the data regarding subject hospitalization due to infection. The narratives of the 2 subjects hospitalized follow the table.

Table 15: 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: Sponsor's BLA submission, nabi-7101-report-body.pdf, page 68 of 141.
SD = standard deviation.

Subject ----(b)(6)----: a 20-year old man had severe bacterial pneumonia.

The subject was treated in the study for almost 1 year. 16 days after the last study drug application (Infusion 13) and 4 days after worsening of symptoms, the subject presented to his primary care physician and was diagnosed with moderate bronchitis. Treatment with a 5-day course of azithromycin was initiated for bronchitis; no action was taken with

study drug. After another 4 days, the subject was admitted to the hospital for chest pain and difficulty breathing symptoms. Results of a computed axial tomography scan of the chest revealed left lower lobe pneumonia with reactive mediastinal and hilar lymphadenopathy and splenomegaly and the subjects was diagnosed with severe bacterial pneumonia. He received salbutamol, enoxaparin, ketorolac, ibuprofen, potassium chloride, and Culturelle (Lactobacillus) but no action was taken with study drug. The fever and bronchitis resolved the next day and 5 days later the bacterial pneumonia was considered resolved.

The investigator considered the bacterial pneumonia, fever, and bronchitis to be probably not related to the study drug. This bacterial infection was considered an SBI for the efficacy analysis.

Subject ----(b)(6)----: a 48-year old woman had a severe acute exacerbation of bronchitis and an acute respiratory failure secondary to pneumonia.

Four days after Infusion 6 (4-week cycle), the subject was hospitalized for 5 days for an acute exacerbation of severe chronic obstructive bronchitis. The subject had had symptoms of increased cough, congestion, and dyspnea for the previous 1 – 2 months. The subject was treated with Levaquin, prednisone, and IV gamma globulin (not study drug) but the symptoms did not resolve and she was diagnosed with moderate bronchiectasis. 6 days later, she was admitted to the hospital due to a severe acute exacerbation of obstructive chronic bronchitis. Results of a chest x-ray showed no acute pulmonary infiltrates and results of a chest computed tomography with and without contrast showed no manifestation of chronic interstitial fibrosis. Treatment with IV vancomycin and Duoneb with breathing treatments was initiated for chronic bronchitis. No action was taken with study drug. 4 days later, the bronchiectasis was considered resolved and the subject was discharged from the hospital in stable condition followed by resolution of the obstructive chronic bronchitis. The subject continued in the study and received 5 subsequent infusions of study drug.

About 3 weeks after Infusion 12, the subject was admitted to the hospital due to severe acute respiratory failure considered life threatening and treated with antibiotics, steroids, and breathing treatments. No action was taken with study drug. The subject’s condition worsened and she was moved to the critical care unit where she was intubated. There she experienced hypokalemia and anemia, which were treated with potassium and a blood transfusion. The next day, the subject had diagnostic bronchoscopy with bronchoalveolar lavage and material for bacterial cultures taken which resulted in improvement as shown by x-ray. According to the discharge summary the x-ray initially presented with bilateral interstitial infiltrates. About a week after the bronchoscopy and lavage there was much further improvement (x-ray) and cultures were negative so the acute respiratory failure was considered resolved and the subject was discharged from the hospital. The subject continued in the study and received 1 subsequent infusion of study drug.

The investigator considered acute exacerbation of obstructive chronic bronchitis, acute respiratory failure, and bronchiectasis to be probably not related to the study drug. This was not considered to be an SBI by the investigator.

Reviewer's Comments: ***Based upon the narrative and the complete subject information file, Subject ----(b)(6)---- should be categorized as having an SBI during the study period. The sponsor will be requested to recalculate all parameters that are affected by the addition of this subject to the other determined to have an SBI during the study period, bringing the total to two. The secondary efficacy endpoint data is supportive of the primary efficacy endpoint.***

Pharmacokinetic Evaluation
See mid-cycle review of Dr. Harold Boxenbaum.

Safety Evaluation
Table 16 presents the treatment exposure in the safety population. Fifty-two subjects had their highest doses > 400 mg/kg, 13 subjects had highest doses > 600 mg/kg and 5 subjects had highest doses > 800 mg/kg.

Table 16: 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: Sponsor's BLA submission, nabi-7101-report-body.pdf, page 78 of 141.

Table 17 presents the data on infusion rates and pre-infusion trough levels. The highest recorded infusion rate was 6.4 mL/kg/h. IgG trough levels were similar after all infusions throughout the study.

Table 17: Treatment Exposure: Infusion Rates and IgG Trough Level – Safety Set

Assessment	Mean (SD)
Infusion rate (mL/kg/h)	
Highest rate during first infusion	3.18 (0.547)
Lowest rate from other than first infusion	0.19 (0.068)
Highest rate from other than first infusion	3.34 (0.657)
Number (%) of infusions reaching highest infusion rate	
Highest infusion 1.0 - <1.5 mL/kg/h	17 (2.3%)
Highest infusion 1.5 - <2.0 mL/kg/h	20 (2.7%)
Highest infusion 2.0 - <2.5 mL/kg/h	62 (8.3%)
Highest infusion 2.5 - <3.0 mL/kg/h	31 (4.2%)
Highest infusion 3.0 - <3.5 mL/kg/h	246 (33%)
Highest infusion ≥3.5 mL/kg/h	370 (49.6%)
Total	746 (100%)
IgG trough levels (mg/dL at pre-infusion)	
Infusion 1	1017.6 (273.3)
Infusion 2	980.8 (199.0)
Infusion 3	999.3 (231.3)
Infusion 4	960.8 (192.7)
Infusion 6	959.7 (262.4)
Infusion 8	992.7 (262.3)
Infusion 10	960.8 (222.2)
Infusion 12	970.9 (229.5)

Source: Sponsor's BLA submission, nabi-7101-report-body.pdf, page 79 of 141.

Table 18 summarizes the AEs among the safety population and Table 19 presents the most frequent (> 5%) treatment-emergent AEs (TEAEs).

Table 18: 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[a]	2 (3.2%)
Total number of TEAEs leading to withdrawal[a]	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

Source: Sponsor's BLA submission, nabi-7101-report-body.pdf, page 80 of 141.
[a]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 19: Most Frequent (> 5%) TEAEs

TEAE by MedDRA Preferred Term	3-Week Cycle (N=17)	4-Week Cycle (N=46)	Total (N=63)
Headache	8 (47.1%)	24 (52.2%)	32 (50.8%)
Sinusitis	5 (29.4%)	19 (41.3%)	24 (38.1%)
Fatigue	4 (23.5%)	14 (30.4%)	18 (28.6%)
Upper respiratory tract infection	4 (23.5%)	12 (26.1%)	16 (25.4%)
Pharyngolaryngeal pain	0	13 (28.3%)	13 (20.6%)
Diarrhea	4 (23.5%)	9 (19.6%)	13 (20.6%)
Cough	1 (5.9%)	13 (28.3%)	14 (22.2%)
Bronchitis	3 (17.6%)	9 (19.6%)	12 (19.0%)
Pyrexia	2 (11.8%)	10 (21.7%)	12 (19.0%)
Nausea	1 (5.9%)	8 (17.4%)	9 (14.3%)
Acute sinusitis	0	7 (15.2%)	7 (11.1%)
Back pain	1 (5.9%)	6 (13.0%)	7 (11.1%)
Pharyngitis	2 (11.8%)	5 (10.9%)	7 (11.1%)
Pain	0	7 (15.2%)	7 (11.1%)
Dizziness	1 (5.9%)	5 (10.9%)	6 (9.5%)
Vomiting	2 (11.8%)	4 (8.7%)	6 (9.5%)
Viral upper respiratory tract infection	2 (11.8%)	4 (8.7%)	6 (9.5%)
Infusion site reaction	1 (5.9%)	4 (8.7%)	5 (7.9%)
Nasopharyngitis	0	5 (10.9%)	5 (7.9%)
Urinary tract infection	3 (17.6%)	2 (4.3%)	5 (7.9%)
Lethargy	1 (5.9%)	4 (8.7%)	5 (7.9%)
Asthma	0	5 (10.9%)	5 (7.9%)
Nasal congestion	0	5 (10.9%)	5 (7.9%)
Gastroenteritis viral	0	5 (10.9%)	5 (7.9%)
Blood pressure increased	1 (5.9%)	3 (6.5%)	4 (6.3%)
Malaise	1 (5.9%)	3 (6.5%)	4 (6.3%)
Myalgia	1 (5.9%)	3 (6.5%)	4 (6.3%)
Otitis media	0	4 (8.7%)	4 (6.3%)
Influenza	1 (5.9%)	3 (6.5%)	4 (6.3%)
Migraine	0	4 (8.7%)	4 (6.3%)
Ear Pain	1 (5.9%)	3 (6.5%)	4 (6.3%)
Sinus congestion	0	4 (8.7%)	4 (6.3%)
Hypertension	1 (5.9%)	3 (6.5%)	4 (6.3%)
Hypotension	2 (11.8%)	2 (4.3%)	4 (6.3%)

Source: Sponsor's BLA submission, nabi-7101-report-body.pdf, Table 14.3.2.3.1.

AEs temporally associated with infusions (TAAEs) are defined as those occurring between the start of Nabi-IGIV 10% infusion and up to 72 h following the infusion completion, regardless of other factors that may have impacted a possible causal association with product administration. Tables 20 and 21 list the most frequent (> 5%) TAAEs.

Table 20: Most Frequent (>5%) TAAEs by System Organ Class (SOC) and Preferred Term – Safety Population

TAAE	No. of Subjects (%)	
	All TAAEs	Related TAAEs
Gastrointestinal disorders		
Diarrhea	4 (6.3%)	1 (1.6%)
Nausea	5 (7.9%)	3 (4.8%)
General disorders and administration site conditions		
Fatigue	15 (23.8%)	13 (20.6%)
Infusion site reaction	5 (7.9%)	0
Infections and infestations		
Sinusitis	5 (7.9%)	0
Investigations		
Blood pressure increased	4 (6.3%)	3 (4.8%)
Nervous system disorders		
Dizziness	4 (6.3%)	1 (1.6%)
Headache	27 (42.9%)	24 (38.1%)
Lethargy	4 (6.3%)	3 (4.8%)

Source: Sponsor's BLA submission, nabi-7101-report-body.pdf, page 82 of 141.
Subjects reporting >1 TAAE are counted only once in each level (SOC or preferred term).
Related TAAEs included 'probably related', 'unknown', or missing.

Table 21: Most Frequent (≥5%) TAAEs by Frequency – Safety Population

TAAE	No. of Subjects (%)	No. of AEs per infusion (%)
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: Sponsor's BLA submission, nabi-7101-report-body.pdf, page 82 of 141.
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.

Severe TAAEs occurred in 23.8% of subjects with the most common being headache (6.3%, 4 subjects), however migraines accounted for 3.2%, 2 subjects, as well. The remainder of severe TAAEs occurred in 1 or 2 subjects only. There were 8 (12.7%) TAAEs related to Nabi-IGIV. The most common were headache 3 (4.8%), and migraine and fatigue each occurring in 2 (3.2%) subjects. The remainder occurred in single subjects only and included blurred vision, cellulitis, back pain, fibromyalgia, lethargy, nystagmus and pruritis.

There were a total of 431 TAAEs that occurred among 47 (74.6%) of subjects. The timing of TAAEs surrounding the infusions, the number of infusions/subject with TAAEs and the number of TAAEs per infusion is presented in Table 22.

Table 22: 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: Sponsor's BLA submission, nabi-7101-report-body.pdf, page 83 of 141.

Table 23 presents a temporal analysis of TAAEs by weighted mean percentages of infusions with ≥1 TAAEs. The 1-sided upper confidence interval (CI) for all time periods evaluated was < 40%.

Table 23: 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: Sponsor's BLA submission, nabi-7101-report-body.pdf, page 84 of 141.

Infusions with >1 TAAE are only counted once.

Table 24 presents the data for the number of subjects experiencing all TAAEs and related TAAEs by infusion.

Table 24: TAAEs by Infusion – Safety Population

Infusion	N	No. of Subjects (%)	
		All TAAEs	Related TAAEs
1	63	32 (50.8%)	24 (38.1%)
2	62	19 (30.6%)	14 (22.6%)
3	61	20 (32.8%)	14 (23.0%)
4	59	16 (27.1%)	11 (18.6%)
5	54	15 (27.8%)	10 (18.5%)
6	52	11 (21.2%)	8 (15.4%)
7	52	9 (17.3%)	8 (15.4%)
8	52	13 (25.0%)	11 (21.2%)
9	52	15 (28.8%)	10 (19.2%)
10	52	11 (21.2%)	9 (17.3%)
11	52	14 (26.9%)	10 (19.2%)
12	52	10 (19.2%)	9 (17.3%)
13	51	12 (23.5%)	6 (11.8%)
14	8	2 (25.0%)	2 (25.0%)
15	8	2 (25.0%)	2 (25.0%)
16	8	3 (37.5%)	2 (25.0%)
17	8	3 (37.5%)	1 (12.5%)

Source: Sponsor's BLA submission, nabi-7101-report-body.pdf, page 85 of 141.

There was 1 TAAE that resulted in a dose change. This involved a subject on a 3-week cycle that developed oral pruritis 7 minutes after the first infusion. The event was moderate in severity and considered related to Nabi-IGIV infusion. A total of 4 subjects had 8 TAAEs that resulted in interruption of the infusion. The events included 2 (3.2%) due to infusion site reactions, as well as blurred vision, nystagmus, hypertension, increased blood pressure and headache. Table 25 the TAAEs by dose.

Table 25: TAAEs by Dose – Safety Population

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: Sponsor's BLA submission, nabi-7101-report-body.pdf, page 86 of 141.

Table 26 breaks down the demographic data of subjects in relation to the number of TAAEs.

Table 26: Demographic and Baseline Characteristics of Subjects According to TAAEs –Safety Population

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: Sponsor's BLA submission, nabi-7101-report-body.pdf, page 86 of 141.

Table 27 presents the number and percentages of TEAEs with break down by severity, as well as relatedness.

Table 27: Summary of TEAEs – Safety Population

Parameter	No. of Subjects (%) (N=63)
Subjects with ≥ TEAE	59 (93.7%)
Severity: Mild	6 (9.5%)
Moderate	20 (31.7%)
Severe	33 (52.4%)
Subjects with ≥ TEAE considered related to the study treatment by the investigator	40 (63.5%)
Severity: Mild	11 (17.5%)
Moderate	21 (33.3%)
Severe	8 (12.7%)

Source: Sponsor's BLA submission, nabi-7101-report-body.pdf, page 89 of 141.
Subjects reporting TEAEs with >1 severity classification are counted only once (at the worst severity classification).

Table 28 summarizes the most frequent TEAEs (occurring with ≥ 5% frequency), with a break down by cycle and severity. Table 29 presents related TEAEs which occur in > 1 subject, with a break down by cycle and severity.

Table 28: TEAEs – Summary of Incidence (≥ 5%) by Cycle and Severity

	3-Week Cycle (N=17)			4-Week Cycle (N=46)			Total (N=63)		
TEAE by MedDRA Preferred Term	**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Headache	2(11.8%)	3(17.6%)	3(17.6%)	7(15.2%)	13(28.3%)	4(8.7%)	9(14.3%)	16(25.4%)	7(11.1%)
Sinusitis	0	4(23.5%)	1(5.9%)	4(8.7%)	10(21.7%)	5(10.9%)	4(6.3%)	14(22.2%)	6(9.5%)
Fatigue	0	2(11.8%)	2(11.8%)	7(15.2%)	6(13.0%)	1(2.2%)	7(11.1%)	8(12.7%)	3(4.8%)
Upper respiratory tract infection	2(11.8%)	2(11.8%)	0	4(8.7%)	8(17.4%)	0	6(9.5%)	10(15.9%)	0
Pharyngolaryngeal pain	0	0	0	7(15.2%)	4(8.7%)	2(4.3%)	7(11.1%)	4(6.3%)	2(3.2%)
Diarrhea	1(5.9%)	2(11.8%)	1(5.9%)	3(6.5%)	5(10.9%)	1(2.2%)	4(6.3%)	7(11.1%)	2(3.2%)
Cough	0	1(5.9%)	0	4(8.7%)	8(17.4%)	1(2.2%)	4(6.3%)	9(14.3%)	1(1.6%)
Bronchitis	0	1(5.9%)	2(11.8%)	1(2.2%)	6(13.0%)	2(4.3%)	1(1.6%)	7(11.1%)	4(6.3%)
Pyrexia	1(5.9%)	1(5.9%)	0	3(6.5%)	6(13.0%)	1(2.2%)	4(6.3%)	7(11.1%)	1(1.6%)
Nausea	0	1(5.9%)	0	2(4.3%)	4(8.7%)	2(4.3%)	2(3.2%)	5(7.9%)	2(3.2%)
Acute sinusitis	0	0	0	1(2.2%)	6(13.0%)	0	1(1.6%)	6(9.5%)	0
Back pain	0	0	1(5.9%)	2(4.3%)	3(6.5%)	1(2.2%)	2(3.2%)	3(4.8%)	2(3.2%)
Pharyngitis	0	2(11.8%)	0	3(6.5%)	1(2.2%)	1(2.2%)	3(4.8%)	3(4.8%)	1(1.6%)
Pain	0	0	0	3(6.5%)	3(6.5%)	1(2.2%)	3(4.8%)	3(4.8%)	1(1.6%)
Dizziness	1(5.9%)	0	0	3(6.5%)	2(4.3%)	0	4(6.3%)	2(3.2%)	0
Vomiting	0	1(5.9%)	1(5.9%)	3(6.5%)	1(2.2%)	0	3(4.8%)	2(3.2%)	1(1.6%)
Viral upper respiratory tract infection	0	1(5.9%)	1(5.9%)	1(2.2%)	3(6.5%)	0	1(1.6%)	4(6.3%)	1(1.6%)
Infusion site reaction	0	1(5.9%)	0	3(6.5%)	1(2.2%)	0	3(4.8%)	2(3.2%)	0
Nasopharyngitis	0	0	0	1(2.2%)	4(8.7%)	0	1(1.6%)	4(6.3%)	0
Urinary tract infection	2(11.8%)	0	1(5.9%)	1(2.2%)	1(2.2%)	0	3(4.8%)	1(1.6%)	1(1.6%)
Lethargy	0	0	1(5.9%)	2(4.3%)	2(4.3%)	0	2(3.2%)	2(3.2%)	1(1.6%)
Asthma	0	0	0	1(2.2%)	4(8.7%)	0	1(1.6%)	4(6.3%)	0
Nasal congestion	0	0	0	4(8.7%)	1(2.2%)	0	4(6.3%)	1(1.6%)	0
Gastroenteritis viral	0	0	0	2(4.3%)	3(6.5%)	0	2(3.2%)	3(4.8%)	0
Blood pressure increased	1(5.9%)	0	0	3(6.5%)	0	0	4(6.3%)	0	0
Malaise	0	0	1(5.9%)	0	2(4.3%)	1(2.2%)	0	2(3.2%)	2(3.2%)
Myalgia	0	1(5.9%)	0	2(4.3%)	1(2.2%)	0	2(3.2%)	2(3.2%)	0
Otitis media	0	0	0	1(2.2%)	3(6.5%)	0	1(1.6%)	3(4.8%)	0
Influenza	1(5.9%)	0	0	2(4.3%)	0	1(2.2%)	3(4.8%)	0	1(1.6%)
Migraine	0	0	0	0	0	4(8.7%)	0	0	4(6.3%)
Ear Pain	0	1(5.9%)	0	2(4.3%)	0	1(2.2%)	2(3.2%)	1(1.6%)	1(1.6%)
Sinus congestion	0	0	0	2(4.3%)	2(4.3%)	0	2(3.2%)	2(3.2%)	0
Hypertension	0	1(5.9%)	0	0	3(6.5%)	0	0	4(6.3%)	0
Hypotension	0	0	2(11.8%)	1(2.2%)	0	1(2.2%)	1(1.6%)	0	3(4.8%)

Source: Sponsor's BLA submission, nabi-7101-report-body.pdf, Table 14.3.2.5.1. Subjects reporting TEAEs with >1 severity classification are counted only once (at the worst severity classification). Severe = 'severe', blank or 'unknown' in CRF.

Table 29: Related TEAEs – Summary of Incidence (total > 1) by Cycle and Severity

	3-Week Cycle (N=17)			4-Week Cycle (N=46)			Total (N=63)		
TEAE by MedDRA Preferred Term	**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Headache	2(11.8%)	2(11.8%)	2(11.8%)	5(10.9%)	12(26.1%)	1(2.2%)	7(11.1%)	14(22.2%)	3(4.8%)
Fatigue	0	1(5.9%)	2(11.8%)	5(10.9%)	5(10.9%)	0	5(7.9%)	6(9.5%)	2(3.2%)
Pyrexia	1(5.9%)	0	0	1(2.2%)	0	0	2(3.2%)	0	0
Cough	0	0	0	2(4.3%)	0	0	2(3.2%)	0	0
Nausea	0	1(5.9%)	0	2(4.3%)	0	0	2(3.2%)	1(1.6%)	0
Back pain	0	0	0	0	2(4.3%)	1(2.2%)	0	2(3.2%)	1(1.6%)
Migraine	0	0	0	0	1(2.2%)	2(4.3%)	0	1(1.6%)	2(3.2%)
Fibromyalgia	0	0	0	0	2(4.3%)	1(2.2%)	0	2(3.2%)	1(1.6%)
Lethargy	0	0	1(5.9%)	1(2.2%)	1(2.2%)	0	1(1.6%)	1(1.6%)	1(1.6%)
Abdominal discomfort	0	0	0	1(2.2%)	1(2.2%)	0	1(1.6%)	1(1.6%)	0
Chest discomfort	0	0	0	0	2(4.3%)	0	0	2(3.2%)	0
Gastroenteritis	0	0	0	1(2.2%)	1(2.2%)	0	1(1.6%)	1(1.6%)	0
Dizziness	0	0	0	1(2.2%)	1(2.2%)	0	1(1.6%)	1(1.6%)	0
Blood pressure diastolic decreased	3(17.6%)	0	0	0	0	0	3(4.8%)	0	0
Blood pressure increased	0	0	0	3(6.5%)	0	0	3(4.8%)	0	0
Blood pressure systolic increased	0	0	0	1(2.2%)	1(2.2%)	0	1(1.6%)	1(1.6%)	0
Hypertension	0	1(5.9%)	0	0	1(2.2%)	0	0	2(3.2%)	0

Source: Sponsor's BLA submission, nabi-7101-report-body.pdf, Table 14.3.2.6.1. Subjects reporting TEAEs with >1 severity classification are counted only once (at the worst severity classification). Related = 'probably related', blank or 'unknown' in CRF. Severe = 'severe', blank or 'unknown' in CRF.

<u>Hypotension Related AEs</u>

Nabi-IGIV 10% contains Polysorbate 80 (PS80) in higher concentration than other licensed IGIV products, see Table 30.

Table 30: 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 the sponsor 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 sponsor's response was that they would assess this cardiovascular effect based on safety data from their ongoing clinical trial. In their BLA submission, the sponsor has noted 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."

The sponsor 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 Nabi-IGIV 10%. The sponsor 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."

Reviewer's Comments: ***While it appears from the submitted vital sign data that the reported drops in systolic blood pressure (SBP) were transient and thereby may not have clinical significance, it is apparent that there were more subjects with recorded drops in SBP than were reported. It will be requested of the sponsor to tabulate the vital signs from all subjects whose SBP dropped more than 20 mmHg during any infusion(s).***