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Applicant	Octapharma
Established Name	Immune Globulin Intravenous (HUMAN) 10%
(Proposed) Trade Name	Panzyga
Pharmacologic Class	Immunoglobulins
Formulation(s), including Adjuvants, etc	Immune Globulin Infusion (Human) 10%
Dosage Form(s) and Route(s) of Administration	Liquid solution containing 10% IgG (100 mg/mL), for intravenous use only
Dosing Regimen	For Primary Humoral Immunodeficiency, 300 to 600 mg/kg every 3 to 4 weeks For Chronic Immune Thrombocytopenic Purpura, a total dose 2 g/kg, divided into two daily dose of 1 g/kg, given on two consecutive days

<p>Indication(s) and Intended Population(s)</p>	<p>For treatment of :</p> <ol style="list-style-type: none">1) Primary humoral immunodeficiency (PID) in adults and children aged ≥ 2 years.2) Chronic immune thrombocytopenic purpura (ITP) in adults
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Table of Contents

Glossary 5

1. EXECUTIVE SUMMARY 6

2. CLINICAL AND REGULATORY BACKGROUND..... 6

 2.1 Disease or Health-Related Condition(s) Studied 6

 2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the
 Proposed Indication(s) 7

 2.4 Previous Human Experience with the Product (Including Foreign Experience)..... 7

 2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission 7

3. Submission Quality and Good Clinical Practices 8

 3.1 Submission Quality and Completeness..... 8

5. Sources of Clinical Data and Other Information Considered in the Review 8

 5.1 Review Strategy 8

 5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review..... 8

 5.3 Table of Studies/Clinical Trials..... 8

6. Discussion of Individual Studies/Clinical Trials 9

6.1 Trial #1: NGAM-01 9

 6.1.1 Objectives..... 9

 6.1.2 Design Overview..... 9

 6.1.3 Population10

 6.1.4 Study Treatments or Agents Mandated by the Protocol11

 6.1.6 Sites and Centers11

 6.1.7 Surveillance/Monitoring.....11

 6.1.8 Endpoints and Criteria for Study Success12

 6.1.9 Statistical Considerations & Statistical Analysis Plan13

 6.1.10 Study Population and Disposition14

 6.1.11 Efficacy Analyses.....18

 6.1.12 Safety Analyses22

6.2 Trial #2: NGAM-0523

 6.2.1 Objectives.....23

 6.2.2 Design Overview.....23

 6.2.4 Study Treatments or Agents Mandated by the Protocol23

 6.2.6 Sites and Centers24

 6.2.7 Surveillance/Monitoring.....24

 6.2.8 Endpoints and Criteria for Study Success24

 6.2.9 Statistical Considerations & Statistical Analysis Plan24

 6.2.10 Study Population and Disposition25

 6.2.11 Efficacy Analyses.....27

 6.2.12 Safety Analyses28

6.3 Trial #3: NGAM-0228

 6.3.1 Objectives.....28

 6.3.2 Design Overview.....28

 6.3.3 Population29

 6.3.4 Study Treatments or Agents Mandated by the Protocol30

 6.3.6 Sites and Centers30

 6.3.7 Surveillance/Monitoring.....30

 6.3.8 Endpoints and Criteria for Study Success31

 6.3.9 Statistical Considerations & Statistical Analysis Plan32

 6.3.10 Study Population and Disposition33

6.3.11 Efficacy Analyses.....	36
6.3.12 Safety Analyses	37
10. Conclusions.....	38
10.1 Statistical Issues and Collective Evidence	38
10.2 Conclusions and Recommendations.....	38

GLOSSARY

AE	Adverse Event
AESI	Adverse Event Special Interest
AR	Alternative Response
CHMP	Committee for Medicinal Products for Human Use
CHQ-PF50	Child Health Questionnaire-Parent Form
CI	Confidence Interval
(b) (4)	
CMV	Cytomegalovirus
CR	Complete Response
CVID	Common Variable Immunodeficiency
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
hCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
IDMC	Independent Data Monitoring Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IMP	Investigational Medical Product
IND	Investigational New Drug
IVIG	Intravenous Immunoglobulin
IRB	Institutional Review Board
ITP	Immune Thrombocytopenia
ITT	Intention to Treat
MedDRA	Medical Dictionary for Regulatory Activities
NYHA	New York Heart Association
PID	Primary Immunodeficiency
PK	Pharmacokinetic
PP	Per Protocol
QoL	Quality of Life
RBC	Red Blood Cell
SBI	Serious bacterial infections
SAE	Serious Adverse Event
TEAE	Treatment-emergent adverse event
VZV	Varicella-Zoster Virus
WBC	White Blood Cell
XLA	X-linked agammaglobulinaemia

1. EXECUTIVE SUMMARY

This original BLA submission seeks market authorization for Newgam, a 10% (100 mg/mL) human normal immunoglobulin G (IgG) for intravenous administration (IGIV), as replacement therapy (primary (b) (4) [REDACTED], i.e., PID (b) (4) [REDACTED]) in adults and children aged ≥ 2 years and immunomodulating therapy (idiopathic thrombocytopenia, ITP) in adults. The proposed name of Newgam is Panzyga.

Three clinical studies were included in this submission: studies NGAM-01 and NGAM-05 were conducted in subjects with PID syndromes, and study NGAM-02 was conducted in subjects with ITP. All three studies are prospective, open-label, phase III studies without control arms.

The applicant investigated Newgam's efficacy and safety for the PID indication in study NAGM-01 with 51 subjects and NAGM-05 with 21 subjects. The primary efficacy endpoint of NGAM-01 was serious bacterial infections (SBIs) per person-year. The upper limit of the one-sided 99% confidence interval (CI) of SBIs for all subjects in NGAM-01 was 0.5033, which is less than 1.0. Therefore, the pre-specified efficacy acceptance criterion was met. NGAM-05 was an extension study of NGAM-01 to test a higher infusion rate with safety analyses only. Safety analyses for both NGAM-01 and NGAM-05 were verified to support the approval of Newgam for PID indication. For the ITP indication, both efficacy and safety of Newgam were demonstrated through NGAM-02 with 40 subjects. The lower limit of the one-sided 97.5% CI for the response rate (an increase in platelets to at least $50 \times 10^9/L$ within 7 days after the first infusion) of ITP subjects was 63.98%, which exceeds the pre-specified reference value of 0.60. Subgroup analyses were also conducted in all three studies and the results were consistent with the primary results in most subgroups.

The statistical results from the three studies support the proposed indications in the BLA submission.

2. CLINICAL AND REGULATORY BACKGROUND

The investigated medical product, Newgam, is a 10% (100 mg/mL) human normal immunoglobulin G for intravenous administration, formulated in a liquid presentation. It is a newly developed IVIG to optimize the immunoglobulin G yield obtainable from each plasma donation and provides viral safety through two dedicated virus inactivation/removal steps (solvent/detergent (S/D) treatment and nanofiltration).

Newgam has been developed as a solution with 10% protein content, which has the advantage of shorter individual infusion times due to the higher concentration and thus lower volume to be infused compared with 5% solutions.

2.1 Disease or Health-Related Condition(s) Studied

Primary Immunodeficiency Diseases (PID) is a heterogeneous group of disorders with an intrinsic defect of the tissues, cells, or proteins of the immune system resulting in immune deficiency. Many of these disorders are characterized by hypogammaglobulinaemia with

or without defective antibody production. Children and adults with PID have an increased risk of getting recurrent bacterial and viral infections that typically attack the respiratory tract (sinusitis, bronchitis and pneumonia) but can also affect the gastrointestinal tract (gastroenteritis). They can be severe and can lead to substantial morbidity. At present, most primary immune deficiencies are not curable, but intravenous preparations of immunoglobulin G have been shown to decrease the total number of severe infections and the duration of hospitalization.

Primary immune thrombocytopenia is an immune-mediated disorder characterized by increased platelet destruction. First-line treatment options for ITP subjects include corticosteroids, intravenous immunoglobulins and intravenous anti-Rh0.

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

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

(b) (4) Investigational New Drug applications (INDs) for Newgam for the indications PID (IND #14001), ITP (IND #14121) (b) (4) were submitted.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

The correspondence history between the applicant and FDA includes the following items:

- A pre-IND meeting was held with FDA on February 22, 2008 and the written meeting memorandum was issued by FDA on March 21, 2008 (CRMTS #6508).
- FDA reviewed the applicant's IND application (IND 14001, NGAM-01 & NGAM-05) submitted on April 6, 2009 and provided comments within an IND advice letter, dated May 4, 2009. No statistical comments were included in this letter.
- FDA reviewed the applicant's IND application (IND 14121, NGAM-02) submitted on August 6, 2009 and provided comments within IND advice letter, dated September 10, 2009, October 9, 2009 and April 6, 2010. No statistical concerns were included in these letters.
- FDA provided a written response to a clinical question addressed in a pre-BLA meeting request on December 12, 2013 (CRMTS #9173). The applicant explained that IND 14121 had been put on temporary hold from the end of May 2013 because the investigational product was unavailable. The transfer of the production from Vienna, Austria to Lingolsheim, France caused manufacture delays. FDA agreed to consider a licensure of the ITP indication based on available interim data in IND 14121 given the data provides evidence of both safety and efficacy.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

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

5.1 Review Strategy

Three clinical studies were included in this submission: studies NGAM-01 (IND14001) and NGAM-05 (IND (b) (4)) were conducted in subjects with PID syndromes, and study NGAM-02 (IND 14121) was conducted in subjects with ITP. The efficacy and safety of Newgam for PID subjects was investigated in NGAM-01 and the safety of Newgam for PID subjects was studied in NGAM-05, an extension of NGAM-01. Both efficacy and safety of Newgam for ITP subjects were established in NGAM-02. All three studies are reviewed in this memo.

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

The following documents in the BLA submission were reviewed:

- 1.14 Labeling
- 2.2 Introduction
- 2.5 Clinical Overview
- 2.7 Clinical Summary
- 5.3.5.2 Study Report of Uncontrolled Clinical Studies for ITP (NGAM-02)
- 5.3.5.2 Study Report of Uncontrolled Clinical Studies for PID (NGAM-01, NGAM-05)

All data sources are included in the applicant's eCTD submission located in the FDA/CBER Electronic Document Room (EDR).

5.3 Table of Studies/Clinical Trials

Table 1 summarizes clinical studies included in this BLA submission.

Table 1: Descriptive of Clinical Efficacy and Safety Studies

Study ID	Number of Study Centres Location(s) Study Period	Design	# Subjects by Arm	Study Drug, Route and Dose	Study Objective	Sex M/F Mean Age	Diagnosis	Primary Endpoints
NGAM-01	11 centers in Germany, Poland, USA Jan 2010 – Jun 2012	Phase III, prospective, open-label, non-controlled, nonrandomized, multicenter	51 PID subjects were enrolled in each of the following age groups: N=13: ≥2 to <12 years N=12: ≥12 to <16 years N=26: ≥16 to ≤75 years	Newgam 10% IV infusion 200 – 800 mg/kg body weight every 21 (±3) or 28 (±3) days or as required for maintenance of minimum trough levels of serum IgG above 5 g/L	Efficacy, Safety and Pharmacokinetics	33 males, 18 females; mean ages 6.5, 13.7 and 43.0 years in age groups	PID	Efficacy: rate of serious bacterial infections per person-year on treatment
NGAM-02	20 centres in Germany, Poland, France, Ukraine, Russia, India, Czech Republic, Romania, Bulgaria Oct 2011 – Jul 2013	Phase III, prospective, open-label, non-controlled, multicenter	40 subjects with chronic primary ITP were enrolled: Age between ≥18 and ≤65 years (at study start: between ≥18 and ≤80 years)	Newgam 10% IV infusion Daily dose of 1 g/kg given for two consecutive days, for a total of 2 g/kg	Efficacy and Safety	23 males, 17 females; mean age 36.7 years	ITP	Efficacy: increase in platelets to at least 50x10 ⁹ /L within 7 days after the first infusion, i.e., by study Day 8
NGAM-05	6 centres in USA May 2011 – Sep 2012	Phase III, Prospective, open-label, non-controlled, nonrandomized, multicenter	A total of 21 subjects was enrolled LPLV was on 26-Sep-2012 N=8: ≥2 to <12 years N=3: ≥12 to <16 years N=10: ≥16 to ≤75 years	Newgam 10% IV infusion 200 – 800 mg/kg body weight every 21 (± 3) or 28 (± 3) days or as required for maintenance of minimum trough levels of serum IgG above 5 g/L	Efficacy and Safety in plasma exchange therapy	13 males, 8 females mean ages 8.0, 14.0 and 39.4 years in age groups	PID	Safety: AEs, short term tolerance, lab parameters

Source: Original BLA, Module 2.7: Summary-clin-efficacy-iii.pdf, Appendix Table 2.7.3.6, page 26.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: NGAM-01

This study was conducted to investigate the efficacy, safety and PK of Newgam in subjects with PID in order to apply for market authorization of Newgam worldwide, including the United States and the European Union.

6.1.1 Objectives

The primary objective was to assess the efficacy of Newgam in preventing SBIs compared to historical control data in subjects with PID.

Secondary objectives included:

- To evaluate the safety of Newgam.
- To determine the PK profile of Newgam.
- To assess the effect of Newgam on quality of life (QoL) measures.

6.1.2 Design Overview

This was a prospective, open-label, non-controlled, non-randomized multicenter phase III study of two multiple dose intravenous Newgam regimens (every 3 weeks or every 4 weeks, continuing the subject's pre-study infusion interval) for 1 year.

The total study duration per subject was approximately 13 months (including the screening period). The subjects received the study treatment over a period of 12 months:

every 3 or every 4 weeks (± 3 days) following the same dosing interval as the previous commercial IVIG infusions. Therefore, each subject received either 17 (at 3-week intervals) or 13 (at 4-week intervals) infusions of Newgam.

Initially, it was planned to have a descriptive interim analysis after 15 subjects (out of 42 evaluable subjects) completed a Newgam treatment period of 6 months with the sole purpose of applying for a marketing authorization in European countries. Protocol Amendment 4 dated August 19, 2010 deleted the planned interim analysis, without any consequence for the study proceedings. The change was due to the adoption of a new Committee for Medicinal Products for Human Use (CHMP) guideline on the clinical investigation of IVIG, stating that an interim analysis after 6 months of treatment in 15 subjects is not sufficient to apply for marketing authorization in Europe.

6.1.3 Population

Male or female subjects well known to the study site who had a confirmed diagnosis of common variable immunodeficiency (CVID) or X-linked Agammaglobulinaemia (XLA) were eligible for inclusion and constituted the study population base.

Subjects had to meet all the following criteria in order to be included in the study:

1. Age of ≥ 2 years and ≤ 75 years old.
2. Minor subjects had to be above a minimum weight based on the amount of blood required for testing: per individual, the trial-related blood loss (including any losses in the maneuver) should not exceed 3% of the total blood volume during a period of 4 weeks and should not exceed 1% at any single time (the total volume of blood is estimated at 80 mL/kg body weight).
3. Confirmed diagnosis of CVID or XLA.
4. Previously treated with a commercial IVIG a) every 21–28 days for at least six infusion intervals (± 3 days for the last three infusions and ± 7 days for the three infusions before the last three infusions) b) at a constant dose between 200 and 800 mg/kg body weight ($\pm 20\%$ of the mean dose for the last 6 infusions).
5. Availability of the IgG trough levels of the two previous infusions before enrolment, and maintenance of at least 5.5 g/L in the trough levels of these two infusions.
6. Negative result on a pregnancy test (hCG-based assay in urine) for women of childbearing potential and use of a reliable method of contraception for the duration of the study.
7. For adult subjects: freely given written informed consent. For minor subjects: freely given written informed consent from parents/legal guardians and written informed assent from the child/adolescent in accordance with the applicable approvals.
8. Willingness to comply with all aspects of the protocol, including blood sampling, for the duration of the study.

Subjects were not eligible for inclusion in this study if any of the following criteria would have applied:

1. Acute infection requiring intravenous antibiotic treatment within 2 weeks prior to and during the screening period.
2. Known history of adverse reactions to IgA in other products.
3. Exposure to blood or any blood product or derivative, other than commercially available IVIG, within the past 3 months prior to enrolment.
4. Ongoing history of hypersensitivity or persistent reactions to blood or plasma derived products, or any component of the investigational product.
5. Requirement of any routine premedication for IVIG infusion.
6. History of congenital impairment of pulmonary function.
7. Severe liver function impairment (ALAT 3x > upper limit of normal).
8. Presence of renal function impairment (creatinine >120 µmol/L), or predisposition for acute renal failure (e.g., any degree of pre-existing renal insufficiency or routine treatment with known nephritic drugs).
9. History of autoimmune hemolytic anemia.
10. History of diabetes mellitus except for type II in subjects aged <16 years.
11. Congestive heart failure NYHA class III or IV.
12. Non-controlled arterial hypertension (systolic blood pressure >160 mmHg or diastolic blood pressure >90 mmHg).
13. History of deep vein thrombosis or thrombotic complications of IVIG therapy.
14. A positive result at screening on any of the following viral markers: HIV, HCV and HBV.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Infusions were administered with a consistent dose throughout the study. The dose to be infused was 200 to 800 mg/kg body weight every 21 (± 3) or 28 (± 3) days, with individual doses and intervals being dependent on the subject's previous IVIG dose and interval before entry into the study. If the body weight changed by more than 5% during the study, the dose was to be adjusted to keep the dose constant on a milligram per kilogram body weight basis. As long as minimum trough levels of serum IgG were maintained above 5 g/L, this treatment regimen remained the same throughout the study. If serum IgG trough levels dropped to 5 g/L or less, the dose was to be adapted at the investigator's discretion.

The subjects received IVIG by using an infusion pump for precise infusion rates. All Newgam infusions started at a rate of 0.01 mL/kg/min (60 mg/kg/h) for the first 30 minutes, followed by 0.02 mL/kg/min (120 mg/kg/h) for the second 30 minutes; if tolerated, further increments were made.

6.1.6 Sites and Centers

This study was actively conducted in 11 centers in Germany (one center), Poland (three centers) and the US (seven centers).

6.1.7 Surveillance/Monitoring

An Independent Data Monitoring Committee (IDMC) was constituted by the applicant to ensure subject safety within the study. During the study, the IDMC was responsible for

the periodic review of the relevant data and to give advice on the continuation, modification or termination of the study. The IDMC always recommended continuation of the study.

6.1.8 Endpoints and Criteria for Study Success

The primary endpoint is the rate of SBIs (defined as bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess) per person-year on treatment.

The null hypothesis to be tested is that the SBI rate is greater than or equal to 1.0 per person-year, tested at the 1% level of significance. The null hypothesis will be rejected if the upper one-sided 99% confidence limit is less than 1.0.

Secondary endpoints for efficacy are the following:

- Trough levels of serum total IgG (measured centrally and locally from serum samples taken before each infusion)
- Trough levels of specific antibodies against *Haemophilus influenzae*, *Streptococcus pneumoniae* (types 4, 6B, 9V, 14, 18C, 19F, 23F), CMV, VZV, tetanus, measles.
- The occurrence of all infections of any kind or seriousness.
- Non-serious infections (total and by category).
- Time to resolution of infections.
- Use of antibiotics.
- Hospitalizations due to infection.
- Episodes of fever.
- Days missed from school or work due to infections and their treatment.
- QoL assessments using the CHQ-PF50 from parent or guardian of subjects < 14 years of age and the SF-36 Health Survey in subjects \geq 14 years of age.

Safety endpoints follow:

- Occurrence of AEs.
- Occurrence of temporally associated AEs (An AE will be considered to be temporally associated with the infusion if it starts during or within 72 hours of the end of the infusion).
- Proportion of infusions with one or more temporally associated AEs.
- AEs by infusion rate.
- Short term tolerance parameters including vital signs (blood pressure, heart rate, temperature, respiratory rate).
- Laboratory parameters: hematology (complete blood count with WBC differential, hematocrit, hemoglobin, haptoglobin, plasma-free hemoglobin and platelets), clinical chemistry, direct Coombs' test, urinalysis, and tests for viral safety.
- Physical examination to detect relevant somatic or neurological diseases.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample Size

It is known that the observed serious infection frequency is less than 0.5 per year during periods of regular (generally every 3 to 4 weeks) administration of IVIG (Guidance for Industry - Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency, 2008). The applicant calculated that 42 evaluable patients followed up for 1 year would enable the null hypothesis that the SBI rate is greater than or equal to 1.0 per person-year to be tested at the 1% level of significance with 90% power (STPLAN v4.3 software). Therefore it was planned that at least 42 evaluable subjects were required in this study. In addition, the subjects were planned to be enrolled in three age groups:

- At least 12 subjects and at most 14 subjects at least 2 years of age and less than 12 years of age enrolled to achieve at least 10 subjects completed,
- At least 12 subjects and at most 14 subjects at least 12 years of age and less than 16 years of age enrolled to achieve at least 10 subjects completed, and
At least 24 subjects and at most 26 subjects at least 16 years of age and no greater than 75 years of age enrolled to achieve at least 20 subjects completed.

To account for an overall drop-out rate of about 15%, it was planned to enroll approximately 50 PID patients in the study.

Analysis Populations

The safety analysis set consists of all subjects who received at least part of one treatment with Newgam.

The full analysis set (FAS) consists of all subjects who received at least one complete treatment with Newgam and for whom data on infections are available from at least one post-treatment diary entry.

The per-protocol set (PP), being a subset of the FAS, consists of those subjects in the FAS who complete the study without major protocol violations.

Efficacy endpoints were analyzed on the basis of both the FAS and the PP analysis sets, to allow for an assessment of the robustness of the results with respect to protocol violations. Analysis of the safety endpoints was based on the safety set.

Efficacy Analyses

Point estimates of the primary endpoint along with a one-sided 99% CI were presented. Calculation of this CI accounts for intra-subject correlation in incidents following a compound Poisson process model (Kegler, 2007). The null hypothesis (tested at the 1% level of significance) is that the serious infection rate is greater than or equal to 1.0 per person-year. Therefore the null hypothesis is rejected if the upper one-sided 99% CI is less than 1.0.

For secondary efficacy analyses, summaries were completed for all subjects overall and by age group. The time to resolution of each infection was calculated and summarized.

The rate of other infections was analyzed and presented using the same methods as for the SBI rate, with a 95% CI and summarized by infusion schedule and age groups.

Descriptive summaries were provided where appropriate for each of the primary and secondary variables. Continuous, quantitative, variable summaries included the number of subjects (N) (with non-missing values), mean, standard deviation, median, minimum and maximum, 1st and 3rd quartile. Categorical, qualitative, variable summaries included the frequency and percentage of subjects who are in the particular category.

Safety Analyses

Descriptive summaries were provided for safety variables. All safety evaluations were presented separately for age groups ≥ 2 years and < 12 years, ≥ 12 years and < 16 years, and ≥ 16 years and < 75 years to facilitate the comparison of children, adolescent and adult safety data.

Three different time periods were used to define an infusional AE: 1 hour, 24 hours and 72 hours. An Adverse Event (AE) is defined as an infusional AE if, and only if, the onset or worsening is after start of first infusion of trial medication and it has an onset either during the infusion or within 1, 24 or 72 hours of the end of the infusion.

Subgroup Analyses

Primary and secondary endpoints were evaluated by treatment schedule groups, age groups and overall. No further subgroups, including site or country, were examined in this study by the applicant. I examined the subgroup analysis by race and sex.

Other Statistical Issues

No adjustments for covariates or for multiple comparisons were planned.

In general, missing data was not imputed: calculations pertaining to person-year computations were based on observed values only.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The numbers of subjects per treatment schedule and age group included in each analysis set are provided in Table 2. A total of 51 subjects (13 children, 12 adolescents and 26 adults) were enrolled and comprise the safety and FAS analysis sets. The first subject signed the informed consent on January 15, 2010 and the last subject's last visit was on June 7, 2012.

Table 2: Number of Subjects per Analysis Set (NGAM-01)

	≥ 2 - <12 Years	≥ 12 - <16 Years	≥ 16 - ≤ 75 Years	3-week schedule	4-week schedule	Total all subjects
Enrolled (Total)	13	12	26	21	30	51
Treated (Safety) Full Analysis Set (FAS)	13	12	26	21	30	51
Per-protocol Set (PP)	12	12	26	21	29	50

Source: Adapted from original BLA. Module 5.3.5.2/NGAM-01: report-dbody.pdf, Table 7, page 71.

Subject (b) (6) (4-week treatment schedule; ≥ 2 - <12 years age group) was excluded from the PP analysis population. This subject missed two infusion visits (third and eighth infusions) and was late for other visits, including the follow-up visit which was completed more than 25 days out of the window frame. As a consequence of the missed infusions, the subject had IgG trough levels lower than 5 g/L at the fourth, ninth and tenth infusion visits and no dose adjustment was done.

6.1.10.1.1 Demographics

Demographic characteristics of the enrolled population can be found in Table 3. More males (65%) than females were enrolled, the difference being in the children and adolescent age groups. All subjects were white, and the mean age was 26.8 years (± 19.25 yrs).

Table 3: Demographic Data (NGAM-01)

	≥ 2 - < 12 Years N=13	≥ 12 - < 16 Years N=12	≥ 16 - ≤ 75 Years N=26	3-week schedule N=21	4-week schedule N=30	Total all subjects N=51
Sex						
Male	10	10	13	14	19	33
Female	3	2	13	7	11	18
Age (years)						
Mean	6.5	13.7	43.0	26.2	27.2	26.8
SD	1.76	0.98	12.94	21.16	18.16	19.25
Median	7	14	41	15	28	17
Range	2, 9	12, 15	17, 65	2, 65	5, 63	2, 65
Race						
White	13	12	26	21	30	51
Ethnicity						
Hispanic/Latino	3	1	3	3	4	7
Non-Hispanic	9	11	23	18	25	43
Not Reported	1	0	0	0	1	1
Height (cm)						
Mean	120.7	162.3	171.8	156.3	156.7	156.5
SD	13.91	12.20	8.63	25.29	23.63	24.08
Median	122	159	173	163	165	163
Range	90, 142	139, 182	158, 191	90, 191	108, 186	90, 191
Weight (kg)						
Mean	24.3	57.3	76.5	59.7	57.9	58.7
SD	6.58	10.84	19.72	31.43	23.00	26.51
Median	23	58	74	56	64	61
Range	13, 36	40, 76	50, 145	13, 145	18, 100	13, 145
BMI(kg/m ²)						
Mean	16.4	21.9	25.8	22.8	22.3	22.5
SD	1.55	4.37	6.55	8.56	4.63	6.47
Median	16	21	25	20	22	22
Range	15, 19	16, 31	19, 52	15, 52	15, 32	15, 52

Source: Original BLA. Module 5.3.5.2/NGAM-01: report-dbody.pdf, Table 8, pages 72-73.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The medical history at screening is summarized in Table 4.

Table 4: Medical Characteristics and History of PID at Screening (NGAM-01)

Number of patients with...	Children ≥2 Years <12 Years N = 13 N (%)	Adolescents ≥12 Years <16 Years N = 12 N (%)	Adults ≥16 Years ≤75 Years N = 26 N (%)	3-week schedule N = 21 N (%)	4-week schedule N = 30 N (%)	Total All Patients N = 51 N (%)
CVID	10 (76.9)	10 (83.3)	23 (88.5)	17 (81.0)	26 (86.7)	43 (84.3)
XLA	3 (23.1)	2 (16.7)	3 (11.5)	4 (19.0)	4 (13.3)	8 (15.7)
Any medical history apart PID	13 (100.0)	12 (100.0)	26 (100.0)	21 (100.0)	30 (100.0)	51 (100.0)
Any prior medication	13 (100.0)	12 (100.0)	20 (76.9)	21 (100.0)	24 (80.0)	45 (88.2)
Any prior non-drug therapy						
Yes	1 (7.7)	0 (0.0)	1 (3.8)	2 (9.5)	0 (0.0)	2 (3.9)
No	12 (92.3)	12 (100.0)	25 (96.2)	19 (90.5)	30 (100.0)	49 (96.1)
Physical examination (all body systems)						
Normal	9 (69.2)	10 (83.3)	17 (65.4)	16 (76.2)	20 (66.7)	36 (70.6)
Abnormal	4 (30.8)	2 (16.7)	9 (34.6)	5 (23.8)	10 (33.3)	15 (29.4)
Chest x-ray						
Normal	10 (76.9)	7 (58.3)	20 (76.9)	14 (66.7)	23 (76.7)	37 (72.5)
Abnormal	1 (7.7)	4 (33.3)	6 (23.1)	5 (23.8)	6 (20.0)	11 (21.6)
NCS						
Abnormal CS	2 (15.4)	1 (8.3)	0 (0.0)	2 (9.5)	1 (3.3)	3 (5.9)
Smoking history						
Non-smoker	13 (100.0)	11 (91.7)	22 (84.6)	19 (90.5)	27 (90.0)	46 (90.2)
Ex-smoker	0 (0.0)	1 (8.3)	4 (15.4)	2 (9.5)	3 (10.0)	5 (9.8)
Smoker	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Original BLA. Module 5.3.5.2/NGAM-01: report-dbody.pdf, Table 9, page 73.

6.1.10.1.3 Subject Disposition

Table 5 summarizes the disposition of subjects. Fifty of the 51 (98%) subjects completed the study (Subject (b) (6), on the 4-week schedule, did not). After having received nine infusions, Subject (b) (6) terminated the study early due to the investigator's judgment to increase the IVIG dose up to 800 mg/kg following an episode of bronchiectasis.

Table 5: Number of Subjects by Age and Treatment Group (NGAM-01)

Population set	2 - 12 Years	12 - 16 Years	16 - 75 Years	3-week schedule	4-week schedule	Total all subjects
Enrolled (Total)	13	12	26	21	30	51
Treated (Safety)	13	12	26	21	30	51
Completed	13	11	26	21	29	50
Early- terminated	0	1	0	0	1	1

Source: Adapted from original BLA. Module 5.3.5.2/NGAM-01: report-dbody.pdf, Table 7, page 71.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint

The rate of SBIs per person-year during the treatment period with Newgam is summarized in Table 6 by treatment schedule and by age group as well as overall.

Table 6: The rate of SBIs per person-year (FAS) (NGAM-01)

SBIs	2 - 12 Years N=13	12 - 16 Years N=12	16 - 75 Years N=26	3-week schedule N=21	4-week schedule N=30	Total all subjects N=51
# serious bacterial infections	1	0	3	0	4	4
Bacterial pneumonia	1	0	3	0	4	4
# subjects with SBI	1	0	1	0	2	2
Bacterial pneumonia	1	0	1	0	2	2
# person years exposure	12.96	11.51	25.77	20.52	29.71	50.24
Rate of SBI	0.077	0	0.116	0	0.135	0.080
One sided 99% CI – upper limit	0.7885	N/A	1.1878	N/A	0.8493	0.5033

Source: Adapted from original BLA. Module 5.3.5.2/NGAM-01: report-dbody.pdf, Table 11, page 77.

The upper limit of the one-sided 99% CI for all subjects was 0.5033, which is less than 1.0. Therefore the null hypothesis is rejected, and the acceptance criterion is met.

The results for the PP population support the primary analysis: the upper limit of the one-sided 99% CI is 0.6246 which is also less than 1.0. In addition, the upper limit is less than 1.0 for the 4-week treatment schedule (0.8493) and the children group (0.7885). However, an upper limit of the one-sided 99% CI greater than 1.0 was observed in the adult group (1.1878). Upper limits of the CIs greater than 1.0 were also observed for children in the 4-week schedule (1.2698) and for adults in the 4-week schedule (1.7101).

6.1.11.2 Analyses of Secondary Endpoints

The applicant analyzed the following secondary efficacy variables.

Trough levels of serum IgG and some specific antibodies

The serum IgG trough levels were nearly constant for both treatment schedules during the course of the study. The values calculated for subjects with a 4-week schedule (median values between 8.1 g/L and 8.65 g/L) were lower compared with the values calculated for the 3-week schedule (median values between 11.0 g/L and 12.2 g/L).

Occurrence of all infections of any kind or seriousness

A total of four serious bacterial infections (all bacterial pneumonia) and 185 other infections were observed. Regarding the other infections, most frequently observed infections belonged to the category upper respiratory tract infections (90 infections), infections of the gastrointestinal tract (28 infections) and lower respiratory tract infections (16 infections). The applicant provided a frequency table for all infections in the study report (Table 13, page 84).

Non-serious infections

During the course of the study, 39 of the 51 subjects (76.5%) had 185 cases of other infections. The highest percentages of subjects with infections were observed for infections in the categories upper respiratory tract infections (28 subjects [54.9%]), infections of the gastrointestinal tract (17 subjects [33.3%]) and lower respiratory tract infections (13 subjects [25.5%]).

Time to resolution of infections

The mean time to resolution was 14.3 days (sd: 7.63 days) for SBIs and 18.4 days for other infections (sd: 34.82 days). The median time to resolution was 16 days for SBIs and 8 days for other infections.

Use of antibiotics

During the course of the study, 42 of the 51 subjects (82.4%) used antibiotics. Therapeutic use of antibiotics was higher (86%) than prophylactic use (14%) in all treatment schedules and age groups. The percentages of subjects using antibiotics were similar in both treatment schedules. The rate of treatment episodes requiring use of antibiotics and number of days on antibiotics per person-year were higher in the 3-week schedule than in the 4-week schedule: 3.5 and 126.6 *versus* 2.8 and 60.2, respectively. Regarding the age groups distributions, a smaller percentage of adult subjects (19 subjects, 73.1%) than children (92.3%) and adolescents (91.7%) used antibiotics.

Absences from work or school due to infections

Overall, half of the subjects (25 subjects, 49.0%) had 68 absences from work or school due to infections; the percentage of subjects and the number of absences were higher in the 3-week treatment schedule (13 subjects [61.9%] and 37 absences). The rates of absences from work/school per person-year and of number of days absent from work/school per person-year were higher in the 3-week treatment schedule: 4.094 *versus* 3.331.

Regarding the different age groups, the frequency of absences from school due to infections was higher in the children and adolescent age groups (10 subjects [76.9%] and

9 subjects [75.0%], respectively, had 27 and 28 absences from school, with a total of 54 and 77 days missed). The highest rate of absences from work/school per person-year is 6.69 for adolescents, compared with 4.167 for children and 2.018 for adults. No major differences to the results presented for FAS were noted in the PP population.

Hospitalizations due to infections

During the course of the study, only one subject (Subject (b) (6), an adult enrolled in the 4-week treatment schedule) was hospitalized for 4 days due to a SBI (pneumonia) (overall rate of days in hospital per person-year: 0.080).

Episodes of fever

The episodes of fever have been presented descriptively. The number of patients with at least one episode of fever during the course of the clinical study and the number of episodes per person-year were summarized in Table 7. All episodes of fever were listed in the appendix of study report.

Table 7: Total Number of Episodes of Fever. Sample Characteristics by Age Group and Treatment Schedule (FAS, N = 51)

Episodes of Fever	2 - 12 Years N=13	12 - 16 Years N=12	16 - 75 Years N=26	3-week schedule N=21	4-week schedule N=30	Total all subjects N=51
# subjects with fever N(%)	5 (38.5)	1 (8.3)	5 (19.2)	3 (14.3)	8 (26.7)	11 (21.6)
Total # of episode of fever	6	2	6	4	10	14
# of episodes of fever per person-year	0.463	0.174	0.233	0.195	0.336	0.279

Source: Original from original BLA. Module 5.3.5.2/NGAM-01: report-dbody.pdf, Table 18, page 90.

6.1.11.3 Subpopulation Analyses

For subgroup analyses by age, see section 6.1.11.1. An upper-sided 99% CI greater than 1.0 was observed in the adult group, children on the 4-week schedule, as well as adults on the 4-week schedule.

Since all enrolled subjects were White, no subgroup analysis by race is necessary.

The comparison of rate of SBIs between male and female is summarized in Table 8. Both subjects who experienced SBIs were male. Some female subgroups did not meet the overall pre-specified criteria of being below an upper one-sided 99% CI of 1.0 because of the low sample size. Overall, the results between male and female groups are comparable.

Table 8: Subgroup analysis of the rate of SBIs by Sex (FAS) (NGAM-01)

SBIs	2 - 12 Years N=13	12 - 16 Years N=12	16 - 75 Years N=26	3-week schedule N=21	4-week schedule N=30	Total all subjects N=51
Male	10	10	13	14	19	33
# subjects with SBI	1	0	1	0	2	2
# SBI events	1	0	3	0	4	4
Rate of SBI	0.1	0	0.0769	0	0.2105	0.1212
One sided 99% CI – upper limit*	0.6638	0.4605	0.5106	0.3289	0.6108	0.3517
Female	3	2	13	7	11	18
# subjects with SBI	0	0	0	0	0	0
# SBI events	0	0	0	0	0	0
Rate of SBI	0	0	0	0	0	0
One sided 99% CI – upper limit*	1.5351	2.3026	0.3542	0.6579	0.4187	0.2558

*: The one-sided 99% CIs in this table were calculated with exact method for Poisson distribution with R.

The primary difference between the US and European results is that the 2 subjects who reported the 4 SBIs were among the 38 US subjects and no SBIs were reported in the 13 European subjects. Table 9 summarizes the subgroup analysis by region.

Table 9: Subgroup analysis of the rate of SBIs by Region (FAS) (NGAM-01)

SBIs	2 - 12 Years N=13	12 - 16 Years N=12	16 - 75 Years N=26	3-week schedule N=21	4-week schedule N=30	Total all subjects N=51
US	11	11	16	20	18	38
# subjects with SBI	1	0	1	0	2	2
# SBI events	1	0	3	0	4	4
Rate of SBI	0.091	0	0.188	0	0.222	0.105
One sided 99% CI – upper limit*	0.6035	0.4187	0.6278	0.2303	0.644	0.3054
Europe	2	1	10	1	12	13
# subjects with SBI	0	0	0	0	0	0
# SBI events	0	0	0	0	0	0
Rate of SBI	0	0	0	0	0	0
One sided 99% CI – upper limit*	2.3026	4.602	0.4605	4.602	0.3838	0.3542

*: The one-sided 99% CIs in this table were calculated with exact method for Poisson distribution with R.

6.1.11.4 Dropouts and/or Discontinuations

The full analysis set includes all 51 enrolled subjects.

6.1.11.5 Exploratory and Post Hoc Analyses

Not applicable.

6.1.12 Safety Analyses

Overall, enrolled subjects received 740 infusions. Mean duration of exposure overall was 359.78 days and was similar among treatment schedules and for all age groups.

6.1.12.1 Methods

All safety evaluations were presented separately for age groups ≥ 2 through < 12 years, ≥ 12 through < 16 years, and ≥ 16 through < 75 years to facilitate the comparison of children, adolescent and adult safety data.

6.1.12.3 Deaths

There were no deaths.

6.1.12.4 Nonfatal Serious Adverse Events

Five of the 51 subjects (9.8%) experienced seven SAEs. No children experienced an SAE. Four of the 26 adult subjects (15.4%) and one adolescent subject (1/12, 8.3%) had at least one SAE. Four (4/30, 13.3%) of the subjects were enrolled in the 4-week treatment schedule and one subject (1/21, 4.8%) was enrolled in the 3-week schedule. Table 10 summarizes all seven SAEs.

Table 10: Serious Adverse Events (Safety set) (NGAM-01)

<i>Subject</i>	<i>Age group</i>	<i>Treatment group</i>	<i>MedDRA term</i>	<i>Intensity</i>	<i>Relationship with study medication</i>	<i>Outcome</i>
(b) (6)	Adults	3-week	Gout	Severe	Not related	Recovered/resolved
	Adults	4-week	Pneumonia	Moderate	Not related	Recovered/resolved
	Adolescents	4-week	Bronchiectasis	Moderate	Not related	Recovered/resolved
	Adolescents	4-week	Bronchiectasis	Moderate	Not related	Recovered/resolved
	Adolescents	4-week	Bronchiectasis	Moderate	Unlikely	Recovered/resolved
	Adults	4-week	Septoplasty	Mild	Not related	Recovered/resolved
	Adults	4-week	Thrombocytopenia	Moderate	Not related	Recovered/resolved

Source: Adapted from original BLA. Module 5.3.5.2/NGAM-01: report-dbody.pdf, Table 29, page 121.

No SAE was considered to be related (probable or possible relationship) with Newgam. All SAEs were resolved at the end of the study. For all SAEs no action was taken with regard to the study medication.

6.1.12.5 Adverse Events of Special Interest (AESI)

Infusional AEs (within 72 hours after the end of infusion) were reported in 16 of 21 subjects (76.2%) enrolled in the 3-week treatment schedule and in 22 of 30 subjects (73.3%) in the 4-week treatment schedule.

A higher infusional AEs rate was noticed in the adolescents group (11 of 12 subjects [91.7%]) compared with 10 of 13 subjects in children group (76.9%) and 17 of 26 subjects (65.4%) in adult group.

6.1.12.6 Clinical Test Results

Not applicable.

6.1.12.7 Dropouts and/or Discontinuations

Not applicable.

6.2 Trial #2: NGAM-05

This study is an extension of study NGAM-01.

6.2.1 Objectives

The primary objective is to assess the safety and tolerability of Newgam when administered at infusion rates from 0.08 mL/kg/min (the maximum rate in the NGAM-01 study) to 0.14 mL/kg/min in PID subjects.

The secondary objective is to obtain a continued assessment of the effect of Newgam on quality of life (QoL) measures (see section 6.2.8 for further information).

6.2.2 Design Overview

This was a prospective, open-label, non-controlled, non-randomized, multicenter, phase 3 study of two multiple-dose intravenous Newgam regimens (every 3 weeks or every 4 weeks, continuing the subject's infusion interval from the main study NGAM-01) for 3 months. Subjects received a total of five or four infusions of Newgam depending on whether their regular treatment intervals were every 3 or 4 weeks, respectively.

There were 21 subjects enrolled in this study, taken exclusively from the cohort of subjects who had completed the main study NGAM-01 and had received Newgam at the maximum infusion rate of 0.08 mL/kg/min. The eligible subjects were screened during the follow-up visit of the main study NGAM-01.

6.2.3 Population

All subjects who completed the NGAM-01 study in the US following the study protocol were considered for inclusion in the extension study NGAM-05.

6.2.4 Study Treatments or Agents Mandated by the Protocol

All subjects received Newgam in this study. All Newgam infusions started at a rate of 0.01 mL/kg/min (60 mg/kg/h) for the first 30 minutes, followed by 0.03 mL/kg/min (180 mg/kg/h) for the next 15 minutes; if tolerated, further increments were made at predefined patterns with the following maximum rates:

- 0.10 mL/kg/min (600 mg/kg/h) in the first infusion; if this was tolerated,
- 0.12 mL/kg/min (720 mg/kg/h) in the second infusion; if this was tolerated,
- 0.14 mL/kg/min (840 mg/kg/h) in all subsequent infusions.

6.2.6 Sites and Centers

The study was conducted at six centers in the United States, selected on the basis of previous participation in study NGAM-01.

6.2.7 Surveillance/Monitoring

An IDMC was established by the applicant during the main study NGAM-01 to ensure the safety of the subjects in the study. For the study NGAM-01, the IDMC remained constituted and continued to carry out the same tasks.

6.2.8 Endpoints and Criteria for Study Success

There was no assessment of efficacy in the NGAM-05 study, because it focused upon the safety and tolerability of Newgam at higher infusion rates.

A single assessment of QoL was planned, based on the completion of the questionnaires, at the follow-up examination. The QoL performed at the follow-up visit for the NGAM-01 study served as baseline. The Child Health Questionnaire-Parent Form (CHQ-PF50) was to be completed by a parent or guardian of subjects less than 14 years of age, or the Short Form-36 (SF-36) Health Survey was to be completed by subjects aged at least 14 years, as determined at the start of the main Study NGAM-01. These questionnaires were the same standard, validated QoL questionnaires used in the main study NGAM-01.

Immunoglobulin G trough levels were to be recorded before each infusion.

The following safety parameters were assessed: type and frequency of AEs, laboratory parameters (hematology, biochemistry, urinalysis, viral markers and direct Coombs' test), vital signs and physical examinations.

The primary safety variable is the occurrences of adverse events that are causally and/or temporally related to the administration of Newgam. An AE will be considered to be temporally associated with the infusion if it starts during or within 72 hours of the end of the infusion.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Sample Size

The planned number of subjects enrolled in this study was a minimum of 20 and a maximum of 35 subjects. The sample size was determined exclusively by the number of subjects from US study sites, who completed study NGAM-01 without meeting any exclusion criteria for the extension study. Therefore, no statistical power considerations or sample-size calculations were performed for this extension study.

Analysis Population

The safety analysis set is the only population that was considered in the statistical analysis. It is defined as all subjects who received at least one dose of Newgam in the context of this study. Subjects who dropped out before their first treatment were not included in the analysis of NGAM-05.

Analyses

Descriptive summaries will be provided where appropriate for each variable.

Missing Data

In general, missing data were not imputed.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

In total, 21 subjects (10 adults, 3 adolescents and 8 children) were enrolled in six centers in this study in two treatment groups (3-week or 4-week schedule. The age of the subjects which determined the stratification in the age groups, was the age at the start of the NGAM-05 study.

During the course of the study, no major protocol violations or deviations were reported and no subject was excluded from analysis.

6.2.10.1.1 Demographics

An overview of selected demographic characteristics can be found in Table 11. Eight female subjects and 13 male subjects participated in this study. The youngest subject was 6 years old and the oldest was 62 years of age. Two subjects that were in the adolescent age group in Study NGAM-01 were assigned to the adult age group in Study NGAM-05. High standard deviation in weight among subjects were observed as expected within the children and adolescents age groups due to ongoing growth. In adults, a high standard deviation of weight among subjects was also observed. All subjects were white, with four subjects reporting a Hispanic or Latino background.

Table 11: Demographic Data (Safety Set, N = 21) (NGAM-05)

	2 - 12 Years N=8	12 - 16 Years N=3	16 - 75 Years N=10	3-week schedule N=12	4-week schedule N=9	Total all subjects N=21
Sex						
Male	6	1	6	8	5	13
Female	2	2	4	4	4	8
Age (years)						
Mean	8.0	14.0	39.4	22.6	25.4	23.8
SD	1.2	1.0	18.54	19.89	20.70	19.78
Median	8	14	40	15	18	15
Range	6,10	13, 15	16, 62	7, 62	6, 61	6, 62
Race						
White	8	3	10	12	9	21
Ethnicity						
Hispanic/Latino	2	0	2	2	2	4
Non-Hispanic	5	3	8	10	6	16
Not Reported	1	0	0	0	1	1
Weight (kg)						
Mean	26.3	53.6	74.5	53.8	52.3	53.2
SD	5.30	10.90	14.07	24.75	26.93	25.05
Median	24	51	72	53	63	56
Range	20, 36	44, 66	56, 99	24, 99	20, 91	20, 99

Source: Original BLA. Module 5.3.5.2/NGAM-05: report-dbody.pdf, Table 6, page 49.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Baseline characteristics, type of PID and medical history are summarized in Table 12. Medical history and diagnosis of type of PID were taken from Study NGAM-01 and descriptively analyzed for the NGAM-01 sub-population participating in extension study NGAM-05.

Table 12: Baseline Patient Characteristics and History of PID Screening (NGAM-05)

Population set	2 - 12 Years N=8	12 - 16 Years N=3	16 - 75 Years N=10	3-week schedule N=12	4-week schedule N=9	Total all subjects N=21
CVID	6	3	7	9	7	16
XLA	2	0	3	3	2	5
Any medical history apart PID	8	3	10	12	9	21
Newly diagnosed/worsened physical examination abnormality (all body systems)						
Yes	1	0	2	2	1	3
No	7	3	8	10	8	18

Source: Original BLA. Module 5.3.5.2/NGAM-05: report-dbody.pdf, Table 7, page 50.

6.2.10.1.3 Subject Disposition

Subjects who dropped out before their first treatment were considered in the analysis of NGAM-05. Table 13 summarizes the subject disposition of this study.

Table 13: Number of subjects by treatment group (Safety set, N=21) (NGAM-05)

Population set	2 - 12 Years N=8	12 - 16 Years N=3	16 - 75 Years N=10	3-week schedule N=12	4-week schedule N=9	Total all subjects N=21
Enrolled (Total)	8	3	10	12	9	21
Treated (Safety)	8	3	10	12	9	21
Completed	8	3	10	12	9	21
Early- terminated	0	0	0	0	0	0

Source: Original BLA. Module 5.3.5.2/NGAM-05: report-dbody.pdf, Table 5, page 47.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

No assessment of efficacy was planned.

6.2.11.2 Analyses of Secondary Endpoints

No statistical analyses were performed for CHQ-PF50 and SF-36. The applicant presented some observations of these two scores in the study report. These results are descriptive and the interpretation is left to the clinical reviewer.

For CHQ-PF50, comparing the baseline mean scores in both treatment schedules, high differences between scores of more than 10 were observed for the global behavior item and general health perceptions (mean scores at baseline greater in the 3-week schedule) and for role/social limitations (higher mean scores at baseline in 4-week treatment schedule).

A deterioration of the scores from baseline to end of study in the 3-week treatment schedule compared with the 4-week treatment schedule was noticed especially for role/social limitations/emotional/behavioral (a decrease of mean score of -12.96 versus an increase of 2.78 in 4-week treatment schedule), role/social limitations - physical (-11.11 versus no change in 4-week treatment schedule), global behavior item (change of -5.00 versus increase of mean score with 6.25 points in 4-week schedule) and self-esteem. In the 4-week treatment schedule, a notable difference in the changes from baseline to end of treatment compared with the 3-week treatment schedule was noticed for mental health score and for bodily pain/discomfort (change of -11.39 versus mean score increase of 2.08).

For SF-36, a deterioration of the scores from baseline to end of study in the 3-week treatment schedule compared with the 4-week treatment schedule was noticed especially for norm based component score – physical, norm-based component – mental, vitality bodily pain and role emotional. In the 4-week treatment schedule, a slight increase in the mean scores from baseline for social functioning and physical functioning compared with 3-week treatment schedule was observed.

6.2.11.3 Subpopulation Analyses

6.2.11.4 Dropouts and/or Discontinuations

There were no dropouts.

6.2.11.5 Exploratory and Post Hoc Analyses

6.2.12 Safety Analyses

All 21 subjects attended all visits and received all planned Newgam infusions (five infusions for the subjects in the 3-week schedule and four infusions for the subjects enrolled in the 4-week treatment schedule). No deaths occurred and no nonfatal SAEs were recorded during the course of this study.

During the course of this study, infusional AEs were reported in 8 subjects (38.1%). Overall, the infusional AEs were associated mainly for MedDRA SOC gastrointestinal disorders (4 subjects, 19.0%). Infusional AEs for all other SOCs were reported in 1-2 subjects.

A higher rate of subjects with infusional AEs was noticed in the 3-week schedule (6 subjects, 50.0%) compared with the 4-week schedule (2 subjects, 22.2%). A similar difference between the two treatment schedules was observed for the infusional AEs that were considered related to the study medication: 13 episodes (27.7%) in the 3-week and 3 episodes (13.6%) in the 4-week schedule. However, the number of infusions in subjects on the 3-week schedule was about double the one of those in the 4-week schedule (60 versus 36 infusions).

A higher percentage of children (4, 50.0%) compared with adults (3 subjects, 30.0%) and adolescents (1 subject, 33.3%) had at least one infusional AE. The most frequently reported preferred terms within 72 hours were nausea and headache in 2 subjects (9.5%), each.

6.3 Trial #3: NGAM-02

6.3.1 Objectives

The primary objective of the study was to assess the efficacy of Newgam in correcting the platelet count in subjects with ITP.

The secondary objective of the study was to evaluate the safety of Newgam.

6.3.2 Design Overview

This was a prospective, open-label, non-controlled, multi-center phase 3 study investigating the efficacy and safety of Newgam in subjects with primary ITP.

Originally the study was planned to be conducted at approximately 40 study sites in Europe and India, with an expected average of 3 subjects enrolled per site.

Approximately 95 eligible subjects were planned to be enrolled in one active treatment group. After 40 subjects were enrolled, the study was put on hold due to delayed availability of study medication. It was decided that rather than performing an interim analysis and final analysis, a single final analysis would be done at this stage including the data from all 40 subjects, using the originally defined primary and secondary endpoints.

Prior to treatment initiation, baseline investigations were to be completed. The first investigational medicinal product (IMP) administration took place within 24 hours of Baseline and was administered for 2 consecutive days.

There was no randomization in the study. The overall study participation for an individual subject was 2 months, including a viral safety follow-up (63 days).

6.3.3 Population

Male or female subjects at least 18 years and not older than 65 years of age with clinically diagnosed chronic primary ITP were eligible for study inclusion and constituted the study population base.

Subjects who met the following criteria were included:

- Age ≥ 18 years and ≤ 65 years.
- Confirmed diagnosis of chronic primary ITP (threshold platelet count less than $100 \times 10^9/L$) of at least 12 months duration and fulfilling the following criteria:
 - a) history and physical examination excluding other causes of thrombocytopenia
 - b) pattern of bleeding associated with platelet disorders using the verbal rating scale according to Buchanan (2002)
 - c) isolated thrombocytopenia in the blood count; apart from thrombocytopenia, the blood count is normal for the subject's age, or if abnormal, readily explained
 - d) peripheral blood smear consistent with ITP: thrombocytopenia with platelets of normal size or slightly larger than normal, with absence of platelet clumps and giant platelets; normal red blood cell and white blood cell morphology
 - e) when any abnormal finding is present, additional diagnostic evaluation exclude other causes of thrombocytopenia.
- Platelet count of $\leq 20 \times 10^9/L$ with or without bleeding manifestations.
- Freely given written informed consent from subject.
- Women of childbearing potential must have a negative result on a pregnancy test (HCG-based assay) and need to practice contraception using a method of proven reliability for the duration of the study.

Subjects who met any of the following criteria were excluded from the study:

- Thrombocytopenia secondary to other diseases (such as AIDS or SLE) or drug-related thrombocytopenia.

- Administration of IGIV, anti-D, thrombopoetin receptor agonists or other platelet enhancing drugs (including immunosuppressive or other immunomodulatory drugs) within 3 weeks before enrollment, except for:
 - a) long-term corticosteroid therapy when the dose has been stable during the preceding 3 weeks and no dosage change is planned until study Day 22
 - b) long-term azathioprine, cyclophosphamide or attenuated androgen therapy when the dose has been stable during the preceding 3 months and no dosage change is planned until study Day 22
- Unresponsive to previous treatment with IGIV or anti-D immunoglobulin.
- Experimental treatment (e.g. Rituximab) within 3 months before enrollment.
- Splenectomy in the previous 4 weeks or planned splenectomy throughout the study period.
- Subject with Evans syndrome (autoimmune thrombocytopenia and autoimmune hemolysis).
- Known or suspected HIV or HCV infection.
- Live viral vaccination within the last two months before study entry.
- Emergency operation.
- Severe liver or kidney disease (ALAT 3x > upper limit of normal, creatinine > 120 μ mol/L).
- Congestive heart failure, New York Heart Association (NYHA) class III or IV.
- Non-controlled arterial hypertension (systolic blood pressure >160 mmHg diastolic blood pressure >90 mmHg).
- History of hypersensitivity to blood or plasma derived products, or any component of the investigational product.
- Known IgA deficiency and antibodies against IgA.
- History of, or suspected alcohol or drug abuse.
- Pregnant or nursing women.
- Unable or unwilling to comply with the study protocol.
- Participating in another interventional clinical study and receiving investigational medicinal product within three months before study entry.

6.3.4 Study Treatments or Agents Mandated by the Protocol

Each subject enrolled in the study was to receive Newgam, with a daily dose of 1 g/kg body weight given for 2 consecutive days for a total of 2 g/kg.

6.3.6 Sites and Centers

The study was planned to be conducted at approximately 40 study sites in Europe and India, but at the time the study was stopped only 20 sites had enrolled subjects: 1 center in Germany, 4 centers in Czech Republic, 5 centers in Russia, and 2 centers in each of these countries: Bulgaria, India, Poland, Romania and Ukraine.

6.3.7 Surveillance/Monitoring

An Independent Data Monitoring Committee (IDMC) was constituted by the Sponsor to ensure the safety of the subjects. The IDMC acted as an independent advisor to the

applicant, providing guidance to help ensure the protection of subjects participating in the study and the ongoing scientific validity, integrity and scientific relevance of the study. During the study, the IDMC periodically reviewed relevant data and provided recommendations about continuing, modifying, stopping the study or other similar procedures according to considerations of subject safety.

6.3.8 Endpoints and Criteria for Study Success

The primary efficacy endpoint is the response rate p , where a successful response for a subject is defined as an increase in platelets to at least $50 \times 10^9/L$ within 7 days after the first infusion (i.e., by study Day 8).

The analysis of the primary endpoint aims at demonstrating that the lower limit of the one-sided 97.5% CI for the response rate p is above the pre-defined value of 0.60.

The following secondary endpoints were analyzed:

- Additional response rates, calculated on the basis of an alternative definition for response and for additionally defined criteria for complete response and loss of response:
 - Alternative definition (AR), defined as an increase in platelet count to $\geq 30 \times 10^9/L$ and to at least double the baseline platelet count, confirmed on at least 2 separate occasions at least 7 days apart, and absence of bleeding
 - Complete Response (CR), defined as an increase in platelet count to $\geq 100 \times 10^9/L$, confirmed on at least 2 separate occasions at least 7 days apart, and absence of bleeding
 - Loss of AR/CR = Criteria for AR/CR fulfilled (including the confirming platelet count), but deteriorated afterwards in the following sense:
 - Decrease in platelet count to $< 30 \times 10^9/L$ / $< 100 \times 10^9/L$ or
 - Decrease in platelet count to less than double the baseline count or
 - Occurrence of bleeding
- Platelet measurements
- Number and proportion of responders with platelets reaching normal levels (according to the individual laboratory's reference ranges)
- Time to reach an increase in platelet count to $\geq 50 \times 10^9/L$
- Time to reach AR/CR
- Maximum platelet count
- Duration of platelet response
- Duration of AR and CR
- Regression of hemorrhages
- Relationship of any new hemorrhages to platelet count

For safety, the following study endpoints were assessed: type and frequency of AEs, post study related safety reports, pregnancies, drug overdose, drug interaction, drug misuse, medication error, laboratory parameters (hematology, biochemistry, urinalysis, viral markers and direct Coombs' test), vital signs and physical examinations.

6.3.9 Statistical Considerations & Statistical Analysis Plan

Sample Size

The hypothesis to be tested was $H_0: p \leq 0.6$ vs $H_a: p > 0.6$. This threshold was obtained from a historical control response rate of 0.75 and a region of indifference of $\delta=0.15$. The hypothesis will be tested at a one-sided significance level of $\alpha = 0.025$.

The original sample size estimation resulted in a required minimum of 86 subjects to achieve a power of at least 80% to show that the lower limit of the one-sided 97.5% CI for the response rate p exceeds the prespecified reference value of 0.60. Therefore it was planned to enroll a total of 95 subjects into the trial, allowing for a dropout rate of approximately 10%.

Analysis Population

The total set consists of all subjects enrolled in the trial including drop-outs. For the statistical analyses the following four sets were defined: safety set, full analysis set (FAS), and two per protocol sets (PP1, PP2).

Safety Set consists of all subjects enrolled in the trial who received at least part of one dose of Newgam. This is the set of subjects exposed to treatment and includes drop-outs unless they did not receive a single dose of Newgam; these cases will be accounted for in the report, but are excluded from all analyses.

Full Analysis Set (FAS) consists of all subjects of the safety set who satisfy all major eligibility criteria and for whom at least one post-baseline measurement of platelet concentration data is available.

Reviewer's comment: Please note that this FAS does not include all enrolled subjects, but is only a set of eligible subjects with treatment effects measured.

The first Per Protocol (PP1) Set consists of all subjects of the FAS excluding those who showed major protocol violations before the primary efficacy endpoint (Day 8) is reached. This is the set of subjects who participated in the trial as intended until the primary efficacy evaluation. This definition ensures that protocol violations at a later time point do not result in unjustified exclusions from the primary PP efficacy analysis.

The second Per Protocol (PP2) Set consists of all subjects of the FAS excluding those who showed major protocol violations potentially affecting the (secondary) efficacy evaluation. This set of subjects was used to assess AR/CR and related secondary endpoints; in particular the exclusion of subjects who took prohibited co-medication will ensure that no treatment effects are erroneously attributed to the study drug.

Partial analysis sets were defined for the PP populations to exclude efficacy data after use of ITP medication.

In this study, all efficacy analyses were performed on the FAS.

Primary Efficacy Analysis

The Clopper-Pearson method for calculating the confidence interval for the binomial proportion was used.

Secondary Efficacy Analyses

Additional response rates were calculated on the basis of AR, CR and loss of response, and were examined by exploratory and descriptive analyses. The overall response rates and the mean duration of response were presented descriptively. The individual platelet counts of each subject during the course of the trial were presented graphically and the mean, standard deviation, median, minimum and maximum were provided for the time period from Day 2 to Day 8 as well for the complete study period.

The initial presence, severity and the regression of hemorrhages were listed individually and summarized in tables. The relationship of any new hemorrhages to platelet count was assessed by an exploratory data analysis listing all occurrences of new hemorrhages together with all platelet counts available for the subject. If the total number of new hemorrhages exceeded five episodes, summary statistics for the platelet counts associated with these bleeding episodes were presented, and an exploratory logistic regression conducted.

Interim Analysis

An interim analysis was planned to be conducted after 30 subjects completed the study, in order to apply for marketing authorization in the EU. No formal testing would be performed on the interim data and no adaptation of the trial design or premature stop was planned. No interim analysis data would be reported to the FDA. Recruitment of subjects would continue without interruption until the total number of subjects has been achieved. Therefore no adjustment to the p-value was necessary.

However, after data for 40 subjects were available, the study was put on temporary hold from the end of May 2013 because Newgam was not available. At that time the observed response rate was above 80% and the goal to achieve a lower one-sided 97.5% confidence limit greater than 0.6 was already achieved. With the agreement of the FDA (CRMTS 9173), this study was terminated early and a single final analysis was performed based on all 40 subjects.

Other Statistical/Analytical issues

No adjustments for covariates were planned. No replacement of missing data values was planned and only observed cases would be evaluated.

6.3.10 Study Population and Disposition

6.3.10.1 Populations Enrolled/Analyzed

The number of subjects in each analysis set is summarized in Table 14. The first subject was screened and included in the study on October 27, 2011 (Subject (b) (6)) and the last subject (Subject (b) (6)) completed the study on July 22, 2013.

Table 14: Number of subjects per Analysis Set (NGAM-02)

Analysis Set	Number of Subjects (N=40)
Enrolled (Total set)	40 (100.0%)
Treated (Safety set)	40 (100.0%)
FAS	36 (90.0%)
PP1 population	33 (82.5%)
PP1 partial population	11 (27.5%)
PP2 population	32 (80.0%)
PP2 partial population	10 (25.0%)

Source: Original BLA. Module 5.3.5.2/NGAM-02: report-dbody.pdf, Table 9, page 61.

All 40 enrolled subjects received at least 1 dose of Newgam and are therefore included in the Safety Set. Four subjects (Subjects (b) (6)) were excluded from the FAS as they were not eligible to take part in the study:

- Subject (b) (6) had two major protocol violations, one regarding an inclusion criterion (platelet count was too high) and the other regarding IMP administration (Day 2 infusion was not administered due to AE)
- Subject (b) (6) had two major protocol violations regarding exclusion criteria (the subject had Evans syndrome and was taking forbidden medication – mycophenolate mofetil)
- Subject (b) (6) had two major protocol violations regarding exclusion criteria (the subject was (b) (6) and was taking dapson, a prohibited medication)
- Subject (b) (6) had a major protocol violation regarding an exclusion criteria (the subject was (b) (6))

Three subjects (Subjects (b) (6)) were excluded from the PP1 population:

- Subjects (b) (6) had a major violation regarding IMP administration in that the Day 2 infusion was not administered due to an AE
- Subject (b) (6) had a major violation regarding IMP administration in that she only received 21 mL of Newgam instead of 520 mL on Day 2

Two subjects (Subjects (b) (6)) had a protocol violation that resulted in the exclusion of their data from the PP2 population as neither subject attended the confirmatory assessment. Subject (b) (6) also had a major violation regarding an exclusion criterion ((b) (6)).

Eleven subjects were included in the PP1 Partial Set, and 10 were in the PP2 Partial Set (Subject (b) (6) who was in the PP1 Partial Set was excluded entirely from the PP2 Set as the confirmatory assessment was not done).

6.3.10.1.1 Demographics

Demographic characteristics were similar across analysis populations. There were 23 male subjects (57.5%) versus 17 female subjects (42.5%) enrolled in the study. The majority of subjects were white (36 subjects; 90.0%) and 4 subjects (10.0%) were Asian. Other demographic and baseline characteristics of the study population are displayed in Table 15.

Table 15: Selected Demographic and Baseline Characteristics (Safety Set, N=40)
(NGAM-02)

	Mean	S.D.	Median	Range
Age (years)	36.7	15.34	32	18 -72
Height (cm)	172.7	8.88	173	154-192
Weight (kg)	73.8	14.81	72	52-110
BMI (kg/m ²)	24.6	3.87	24	19-33

Source: Original BLA. Module 5.3.5.2/NGAM-02: report-dbody.pdf, Table 10, page 61.

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Medical history (including surgical history) apart from ITP was recorded for 31 subjects (77.5%) The most common conditions were petechiae (6 subjects, 15.0%), ecchymosis (5 subjects, 12.5%), and caesarean section and hypertension (both in 4 subjects, 10.0%).

6.3.10.1.3 Subject Disposition

Out of all 40 enrolled subjects, no subject withdrew prior to first administration of study medication, 9 subjects (22.5%) withdrew prematurely after at least 1 administration of study medication and 31 subjects (77.5%) completed the study. Table 16 and Table 17 summarize the disposition of subjects and reasons of withdrawal.

Table 16: Disposition of Subjects (All Subjects, N=40) (NGAM-02)

Population	Number of Subjects (N=40)
Enrolled (Total set)	40 (100.0%)
Treated (Safety set)	40 (100.0%)
Completed	31 (77.5%)
Terminated early	9 (22.5%)

Source: Original BLA. Module 5.3.5.2/NGAM-02: report-dbody.pdf, Table 6, page 57.

Table 17: Subject withdrawal (All Subjects, N=40) (NGAM-02)

Reason for withdrawal	Number of Subjects (N=40)
No withdrawal	31 (77.5%)
Investigator judgment	3 (7.5%)
Death	2 (5.0%)
Withdrawal by subject	2 (5.0%)
Adverse event	1 (2.5%)
Lost to follow-up	1 (2.5%)

Source: Original BLA. Module 5.3.5.2/NGAM-02: report-dbody.pdf, Table 7, page 57.

6.3.11 Efficacy Analyses

6.3.11.1 Analyses of Primary Endpoint(s)

A successful response was observed for 29 of the 36 subjects in the FAS (80.6%), resulting in a lower limit of the one-sided 97.5% CI of 63.98%. Since the lower limit of the one-sided 97.5% CI for the proportion of responders is above the pre-defined reference value of 0.6, the null hypothesis is rejected, and the acceptance criterion is met.

A similar result was obtained with the PP1 set, with 27 of the 33 subjects (81.8%) having a successful response, resulting in the lower limit of one-sided 97.5% CI as 64.54%.

Reviewer's Comment: I verified the CI calculations with R. This interim data, analyzed as the final dataset, supports the efficacy of ITP indication for Newgam.

6.3.11.2 Analyses of Secondary Endpoints

Descriptive statistics were provided by the applicant in the study report. No further statistical analyses were performed.

6.3.11.3 Subpopulation Analyses

No subgroup analyses were planned or provided by the applicant. I conducted subgroup analyses by sex, age, and race. It is observed that the response rate is higher in the female group and the younger group. The estimation of response rate of Asian group might be biased because of small sample size.

Table 18: Subgroup analyses of response rate (FAS) (NGAM-02)

<i>Subgroup</i>	<i>Sample size</i>	<i>Successful responses</i>	<i>Response rate</i>	<i>95% Confidence interval</i>
FAS	36	29	80.56%	(63.98%, 91.81%)
Sex				
Male	19	14	73.68%	(48.80%, 90.85%)
Female	17	15	88.24%	(63.56%, 98.54%)
Age				
18 - 39	25	22	88.0%	(68.78%, 97.45%)
40 or higher	11	7	63.64%	(30.79%, 89.07%)
Race				
White	33	28	84.85%	(68.10%, 94.89%)
Asian	3	1	33.33%	(0.84%, 90.57%)

6.3.11.4 Dropouts and/or Discontinuations

Nine subjects terminated early among the 40 enrolled subjects. Two of these early termination subjects were not included in the FAS (subjects (b) (6) for reasons stated in Section 6.2.10.1). The other seven early termination subjects were included in the FAS; all seven of these subjects had platelet lab results such that success or failure could be determined (i.e., either they reached the threshold of $50 \times 10^9/L$ within the 7 days for a success or they had lab results through Day 7 showing the threshold was not met and thus indicating a failure).

Although two of the four subjects enrolled but not included in the FAS discontinued the study early (Subjects (b) (6) as noted above), these four subjects were excluded from the primary analysis according to the pre-specified definition for the FAS (did not meet eligibility criteria).

6.3.12 Safety Analyses

6.3.12.1 Methods

6.3.12.3 Deaths

Two subjects (5.0%) died during the study.

Subject (b) (6) died on (b) (6), 6 days after the first infusion, because of severe intraparenchymal cerebral bleeding. The 25-year-old male subject received his first and second infusion on (b) (6), respectively.

Subject (b) (6) died on (b) (6) (during the safety follow-up period) because of severe sepsis. The 57-year-old male subject received his first and second infusion on (b) (6), respectively. The date of Day 22/ET was recorded as (b) (6).

The causality of both fatal events was assessed as not related to infusion of Newgam.

6.3.12.4 Nonfatal Serious Adverse Events

Six subjects (15.0%) experienced 10 SAEs; in 2 subjects (5.0%) these were fatal. One of the SAEs was treatment related: Subject (b) (6) experienced moderate aseptic meningitis which was considered to be possibly related (recorded within the 72-hour period); the outcome was resolved. Five subjects (12.5%) reported eight non-fatal SAE episodes.

6.3.12.5 Adverse Events of Special Interest (AESI)

Overall, 24 subjects (60.0%) experienced 71 infusional AEs. Regarding the number of infusional events experienced by the individual subjects, 13 subjects (32.5%) experienced 1 or 2 infusional AEs, and just under 30% (11 subjects; 27.5%) experienced between 3 and 7 infusional AEs. Sixteen subjects (40.0%) did not experience an infusional AE. The most common infusional AEs at all time points were headache and pyrexia. Gastrointestinal disorders were also common. A higher percentage of subjects experienced infusional AEs at 24 and 72 hours than at 1 hour, but there was no marked increase between 24 and 72 hours.

6.3.12.7 Dropouts and/or Discontinuations

All enrolled subjects were included in the safety set.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

This BLA submission proposes treatment of PID and ITP with Immune Globulin Intravenous (Human) 10%. Three clinical studies were conducted by the applicant to support the licensure: NGAM-01 and NGAM-05 for the PID indication and NGAM-02 for the ITP indication. All three studies are prospective, open-label, uncontrolled, phase III studies with 51, 21, and 40 subjects, respectively.

The primary efficacy endpoint of NGAM-01, the SBI annual rate, achieved 0.5033 as the upper one-sided 99% confidence limit and was less than the pre-specified reference value of 1.0. Therefore the efficacy of PID treatment is supported. It is noted the 99% upper confidence limit is higher than 1.0 for the adult subgroup. For safety, no statistical concerns were triggered in both NGAM-01 and NGAM-05.

For the ITP indication, a successful response, defined as an increase in platelets to at least $50 \times 10^9/L$ within 7 days, was observed for 29 of the 36 subjects (80.6%) with an exact Clopper-Pearson 95% CI of 63.98% to 91.81%. The lower limit of the one-sided 97.5% confidence interval for the proportion of responders is therefore above the pre-defined reference value of 0.6, supporting the Newgam's efficacy. For safety, no statistical issues were detected.

10.2 Conclusions and Recommendations

Both the efficacy analysis and safety analysis in this original BLA were verified to support the claim for the use of Immune Globulin Intravenous (Human) 10% in subjects with PID and ITP.