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Application Type	Original Application
STN	125587/0
CBER Received Date	April 15, 2015
PDUFA Goal Date	April 14, 2016
Division / Office	DHRR /OBRR
Priority Review	No
Reviewer Name(s)	Laurence Landow
Review Completion Date / Stamped Date	
Supervisory Concurrence	
Applicant	Octapharma Pharmazeutika Prod.Ges.m.b.
Established Name	Immune Globulin Intravenous (Human)
(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	Solution, Intravenous
Dosing Regimen	Primary humoral immunodeficiency: 300 - 600 mg/kg body weight (3-6 mL/kg) administered every 3 - 4 weeks. Chronic immune thrombocytopenic purpura: two daily doses of 1 g/kg (10mL/kg) given on two consecutive days.
Indication(s) and Intended Population(s)	Primary humoral immunodeficiency in adults and children aged ≥2 years. Chronic immune thrombocytopenic purpura in adults.
Orphan Designated (Yes/No)	No

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GLOSSARY

AESI: adverse event of special interest
AE: adverse event (an untoward medical occurrence associated with use of a drug whether or not considered drug related)
AR: adverse reaction (adverse event known to be caused by a drug)
AR: alternate response (in Study NGAM-02: elevation in platelet count to $\geq 30 \times 10^9$/L and at least double the baseline platelet count, confirmed on at least 2 separate occasions at least 7 days apart, and absence of bleeding)
CI: confidence interval
CR: complete response (in study NGAM-02: elevation 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)
CSR: clinical study report
CVID: common variable immunodeficiency
FA: full analysis set (enrolled subjects meeting all inclusion and exclusion criteria)
IG: immunoglobulin G
IGIV: Immune Globulin Infusion (Human) administered intravenously
ITP: immune thrombocytopenia (also known as immune thrombocytopenic purpura)
Newgam: previous trade name for Panzyga®
PI: primary immunodeficiency disease
PT: MedDRA preferred term
QoL: quality of life
SAR: serious adverse reaction
SBI: serious bacterial infection
SOC: MedDRA system organ class
TEAE: treatment emergent adverse event (untoward medical occurrence not necessarily considered drug related)
XLA: X-linked agammaglobulinemia

1. Executive Summary

BLA 125587 is intended to support the use of Octapharma's investigational product, Panzyga® (Immune Globulin Intravenous (Human) 10% Liquid Preparation), for two indications: (1) treatment of primary immunodeficiency (PI) in adults and children aged ≥2 years (studied under Investigational New Drug application [IND] 14001) and (2) chronic immune thrombocytopenia (ITP) in adults (studied under IND 14121). The three clinical studies included in the submission, NGAM-01, NGAM-05 and NGAM-02, followed the same general design: prospective, open-label, single-arm, historical controlled, multicenter, multinational. Duration of exposure to Panzyga varied according to indication: every 3 or 4 weeks for 12 months (NGAM-01) or for 4 months (NGAM-05) for the PI indication, and daily for 2 consecutive days (NGAM-02) for the chronic ITP indication.

1. NGAM-01 was a phase 3 efficacy study in adults and children with PI aged ≥2 years (N=51). The primary endpoint was the number of serious bacterial infections (SBI, as defined in FDA's Guidance for Industry)[1] experienced by subjects over 12 months of exposure to Panzyga. Secondary endpoints included: (a) infection of any kind or seriousness; (b) time to resolution of infection; (c) use of antibiotics; (d) number of days of work/school missed; (e) number and days of hospitalizations; and (f) number of episodes of fever.
2. NGAM-05 was an extension study comprising a subcohort of subjects (N=21) previously enrolled in study NGAM-01. NGAM-05 did not assess efficacy but did evaluate safety, tolerability and quality of life (QoL) when Panzyga was administered at rates of 0.08 to 0.14 mL/kg/min every 3 or 4 weeks for 4 months. The primary endpoint was the number of causally and/or temporally related treatment emergent adverse events (TEAE). Only descriptive statistics were reported.
3. NGAM-02 was a phase 3 efficacy study in adults aged ≥16 years (N=40) with chronic ITP. A daily dose of Panzyga was administered over two consecutive days and followed-up for safety through Day 63. The primary endpoint was platelet response rate, defined as the proportion of enrolled subjects meeting the eligibility criteria (Full Analysis population) who demonstrated an increase in platelet count to ≥50 x 10^9/L within 7 days after the first infusion. Secondary endpoints included maximum platelet count; time to reach a platelet count of ≥50 x 10^9/L within the first 7 days; duration of response, i.e., number of days the platelet count remained ≥50 x 10^9/L; and bleeding outcome in subjects who were bleeding at baseline.

Efficacy

NGAM-01 and NGAM-02 both met their primary efficacy endpoint.

- In NGAM-01, the null hypothesis (SBI rate ≥1.0 per person-year at the 1% level of significance) was rejected for all age cohorts and treatment schedules with an upper bound of the 99% confidence interval (CI) of 0.5033.

[1] "Safety, efficacy, and pharmacokinetic studies to support marketing of Immune Globulin Intravenous (Human) as replacement therapy for primary humoral immunodeficiency"

- In NGAM-02, the null hypothesis (increase in platelet count to ≥50 x 10^9/L within 7 days after the first infusion) was rejected for the 29/36 enrolled subjects who met the prespecified enrollment criteria (point estimate: 80.6%; 95% CI: 63.98% to 91.81%).

Safety

NGAM-01 and NGAM-05

- Seven SAEs were reported in five NGAM-01 subjects. These included a 39 year old Caucasian male who experienced pneumonia (moderate intensity), a 14 year old Caucasian male who experienced bronchiectasis and bronchospasm (moderate), a 59 year old Caucasian male experienced gout (severe), a 41 year old Caucasian female who was admitted to hospital for a septoplasty under general anesthesia, and a 41 year old Caucasian female who was admitted to hospital after noticing a petechiae on her lower extremity and was found to have a platelet count of 11 x 19^9/L. No SAEs were reported in NGAM-05.
- Clinical laboratory TEAEs included leukopenia in the 39 year old Caucasian male mentioned previously, thrombocytopenia in the 41 year old Caucasian female mentioned previously, and non-serious anemia ((b) (6)).
- The most common adverse reactions reported were headache (11 subjects, 21.6%), pyrexia (7 subjects, 13.7%), nausea (5 subjects, 9.8%) and upper abdominal pain (5 subjects, 9.8%).

NGAM-02

- Ten SAEs were reported in six NGAM-02 subjects, only one of which, aseptic meningitis in a 28 year old Caucasian male, was considered related to study medication and has been reported with other IGIV products. The remaining five included a 25 year old Caucasian male with a past medical history of Evans Syndrome whose enrollment was a protocol violation (exclusion criterion) and who experienced a cerebral hematoma and subsequently died; a 57 year old Caucasian male who experienced sepsis, pneumonia, and respiratory failure (severe); and two male Caucasian subjects aged 48 and 64 years, who experienced worsening autoimmune thrombocytopenia.
- Clinical laboratory TEAEs included hemolysis in the 25 year old Caucasian male with a history of Evans Syndrome mentioned previously and a 22 year old female who did not receive any treatment for the hemolysis.
- The most common adverse reactions reported were headache (17 subjects, 42.5%), pyrexia (8 subjects, 20.0%), and nausea (6 subjects, 15%).

No case of thrombosis, renal dysfunction/acute renal failure, or TRALI was reported. The QoL physical component showed a slight worsening whereas the QoL mental component showed a slight improvement.

Risk-Benefit Assessment

Clinical benefits conferred by administration of Panzyga, reduction in SBI (PI) and elevation of platelet count (chronic ITP), outweigh potential risks (thromboembolic events, hemolysis, aseptic meningitis).

RECOMMENDATION
I recommend an approval action be taken for this BLA. I also recommend that a Waiver be granted for pediatric subjects with ITP.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Demographic characteristics of both populations are summarized as follows:
(a) The PI population was younger than the chronic ITP population, primarily because NGAM-02 excluded enrollment of children
(b) Males greatly outnumbered females in the PI cohort; the imbalance was smaller in the chronic ITP cohort
(c) Race and ethnicity were highly skewed: White subjects comprised 100% of the PI cohort and 90% of the chronic ITP cohort, while Hispanic/Latino subjects comprised 13.7% of the PI cohort and 2.5% of the chronic ITP cohort.

Table 1 presents this information in tabular format. It should be noted that sample sizes were too small to provide meaningful analyses of potential product-demographic interactions.

Table 1: Demographic Data: Age, Gender, Race and Ethnicity (Safety Population, N=91)

Parameter	PI N=51 (56%)	ITP N=40 (44%)	All Subjects N=91 (100%)
Age (years)			
Mean	26.8	36.7	31.1
Median	17	32	30
Min, Max	2, 65	18, 72	2, 72
Gender (n, %)			
Male	33 (64.7%)	23 (57.5%)	56 (61.5%)
Female	18 (35.3%)	17 (42.5%)	35 (38.5%)
Race (n, %)			
White	51 (100.0%)	36 (90.0%)	87 (95.6%)
Asian	0	4 (10.0%)	4 (4.4%)
Ethnicity (n, %)			
Hispanic/Latino	7 (17.7%)	1 (2.5%)	8 (8.8%)
Not Hispanic/Latino	43 (84.3%)	38 (95.0%	81 (89.0%)
Not reported	1 (2.0%)	1 (2.5%)	2 (2.2%)

Adapted from Table 14.1.2.1, Integrated Summary of Safety, 19 MAR 2015, page 5 of 298

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

- Primary Immunodeficiency
  PI comprises a heterogeneous population of disorders characterized by hypogammaglobulinemia with or without defective antibody production. Children and adults with PI are at increased risk for recurrent bacterial and viral infections that typically affect the respiratory tract (sinusitis, bronchitis and pneumonia) but can also affect the gastrointestinal tract (gastroenteritis). Symptoms can be severe and can lead to substantial morbidity. Responses to antibacterial therapy are often

poor. At present, most primary immune deficiencies are not curable, but IgG products have been shown to decrease the number of severe infections and duration of hospitalization. The primary therapeutic use of IgG is to provide antibodies to prevent viral and bacterial diseases (replacement therapy). Use of IgG replacement therapy to reduce the incidence of viral and bacterial diseases has been applied in three therapeutic domains: (a) replacement for subjects with PI syndromes who have significant defects in antibody formation (humoral immunity); (b) provision of antibody to subjects with immunodeficiency secondary to a disease, immunosuppressive therapy or losses of IgG; and (c) as adjuvant therapy in the treatment of infectious diseases.

IgG products are currently licensed for the following indications: (i) treatment of primary immunodeficiencies; (ii) prevention of bacterial infections in subjects with hypogammaglobulinemia and recurrent bacterial infection caused by B-cell chronic lymphocytic leukemia; (iii) prevention of coronary artery aneurysms in Kawasaki disease; (iv) prevention of infections, pneumonitis, and acute graft-*versus*-host disease after bone marrow transplantation; (v) reduction of serious bacterial infection in children with human immunodeficiency virus (HIV); (vi) increase of platelet count in idiopathic thrombocytopenic purpura (ITP) to prevent or control bleeding; (vii) lymphocytic leukemia; and (viii) CIDP and multifocal motor neuropathy.

- Immune Thrombocytopenia

  Evidence of clinical benefit using immunoglobulin therapy was first documented in a patient with ITP (*Lancet* 1981 Jun 6. 1(8232):1228-31). Chronic ITP, often referred to as immune thrombocytopenic purpura, is an immune-mediated disorder characterized by increased platelet destruction due to development of auto-antibodies against platelet-membrane antigens. These antibodies are produced in the spleen, which is also the major site of platelet destruction. The diagnosis of chronic ITP remains one of exclusion and is based principally on history, physical examination, complete blood count and examination of the peripheral smear, which should exclude other causes of thrombocytopenia, e.g., HIV infection, systemic lupus erythematosus, and thyroid disorders. First-line treatment options for chronic ITP patients include corticosteroids, IGIV and intravenous anti-Rho.

  According to recent guidelines, IGIV is recommended for patients with platelet counts <20 to 30 x 10^9/L in case of severe bleeding and/or mucous membrane bleeding. In subjects suffering from chronic ITP, IGIV increases platelet count and reduces/controls bleeding.

  Reviewer Comment

  The most accepted mechanism of action of IGIV in ITP is blockade of Fcγ receptors on macrophages, which prevents destruction of immunoglobulin G (IgG) sensitized platelets by the reticuloendothelial system. The mechanism of action for Rho(D) is believed to result from formation of anti-Rho(D) (anti-D)-

coated RBC complexes resulting in Fc receptor blockade, thus sparing antibody-coated platelets.

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

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

- Chronic ITP: corticosteroids, intravenous anti-Rho

2.3 Safety and Efficacy of Pharmacologically Related Products

IGIV

- PI: available literature suggests IGIV therapy is associated with an observed SBI frequency of <0.5 per year during periods of regular (every 3 to 4 weeks) administration of IGIV, 200 to 600 mg/kg per infusion.

  The incidence of adverse reactions (AR) reported in IGIV clinical trials varies by product, maximal infusion rate, and subject population/indication being studied. Because of these differences, the safety profile of each IGIV product is determined independently. As an example, the most common adverse reactions using GAMMAPLEX® reported in >5% of clinical trial subjects were headache, pyrexia, nasal congestion/edema, fatigue, nausea, hypertension, rash, hypotension, infusion site reaction, vomiting, myalgia, chills, tachycardia, chest pain/discomfort, pain, dizziness, malaise, dysuria, and dry skin.

- ITP: in a clinical trial using GAMMAPLEX®, response to treatment on or before Day 9 was achieved by 29 of 35 subjects (82.9%). The one-sided 97.5% lower confidence limit of the response rate was 66.4%, which met the *a priori* success criterion of >60%.

  The most common ARs reported in clinical trials in >5% of subjects were headache, vomiting, nausea, pyrexia, pruritus, dehydration, and arthralgia. In a clinical trial using Octagam®, the most common ARs reported in >5% of subjects during a clinical trial were headache, fever and increased heart rate. In a clinical trial using Privigen®, the most common ARs observed in >5% of study subjects, were headache, pyrexia, positive direct antiglobulin test, anemia, vomiting, nausea, bilirubin and blood lactate dehydrogenase increased. A serious AR, aseptic meningitis, was reported.

Rho(D) IGIV

— ITP: in a clinical trial of adult chronic ITP, 21/24 subjects responded (increase ≥ 20,000/mm^3) during the first two courses of therapy for an overall response rate of 88%; mean peak platelet count was 92,300/mm^3 (range: 8,000 to 229,000).

The most common ARs reported in ≤2% of doses administered were headache, chills, fever, asthenia, pallor, diarrhea, nausea, vomiting, arthralgia, myalgia, dizziness, hyperkinesia, abdominal or back pain, hypotension, hypertension, increased LDH, somnolence, vasodilation, pruritus, rash and sweating.

Corticosteroids

— ITP: hydrocortisone and related products such as Solu-Cortef are indicated for ITP in adults.

The most common ARs reported affect the musculoskeletal (impaired wound healing, muscle atrophy), gastrointestinal (gastritis), dermatologic (ecchymosis), neurologic (paranoia), endocrine (glucose resistance), ophthalmic (cataracts), metabolic (truncal obesity), infectious (infection), and cardiovascular systems (hypertension)

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

Panzyga is a new 10% IGIV product developed by Octapharma. The applicant is applying for licensure in the United States and the European Union.

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

<u>NGAM-01</u>

— Enrollment under IND 14001 was initiated on 15-JAN-2010 and completed on 7-JUN-2012. Five amendments to the original protocol were made prior to study completion and submission to FDA.
— Amendments 1-3 had no substantial effect on trial conduct.
— Amendment 4 (19-AUG-2010)
    - Increased the number of sites and prolonged the recruitment period
    - Permitted subjects <16 years of age with a history of diabetes mellitus type II to be enrolled
    - Permitted flu vaccination, including H1N1 strain, during the study
    - Measles was to be reported as an SAE
    - Only TEAEs classified as at least possibly related to the Panzyga were to be assessed as to their expectedness by the applicant
    - An interim analysis after 6 months of treatment in 15 subjects was deleted to conform to adoption of a new CHMP guideline on the clinical investigation of IGIV (EMA/CHMP/BPWP/94033/2007 rev 2).
— Amendment 5 (16-FEB-2012)
    - Clarified that subjects were to be evaluated in the age cohort assigned at the time when they had signed the informed consent/assent
    - Secondary endpoints and safety evaluations were updated upon request of the EMA Pediatric Committee (PDCO)
    - A clarification was added that discrepancies between diary entries and eCRF entries were to be explained by investigator in source records

- Information was added that therapeutic efficacy parameters were to be evaluated per person-year on treatment

NGAM-02

— Enrollment under IND 14121 was initiated on 27-OCT-2011 and completed on 22-JUL-2013. Three amendments were made to the original protocol prior to study completion and submission to FDA.
— Amendment 28 (7-JUN-2013) indicated subject recruitment was on hold due to a shortage of Panzyga (Octapharma's response to a 30-SEP-2015 IR indicates that the company became aware of the shortage in Q4 2012).
— Amendment 29 (18-OCT-2013) was a pre-BLA Meeting Request filed to obtain advice over whether FDA would insist on completion of study NGAM-02 before granting licensure. FDA informed Octapharma (12-DEC-2013) that a review of interim data could suffice, provided there was adequate evidence of safety and efficacy.
— Amendment 32 (3-FEB-2013) notified FDA that study NGAM-02 had been terminated.

2.6 Other Relevant Background Information

Post-dose peak levels of IgG are reached immediately following infusion of IGIV. Post-infusion, exogenous IgG is distributed between plasma and extravascular fluid compartments until approximately half is partitioned in the extravascular space, i.e., a rapid initial drop in serum IgG is to be expected. Endogenous production rate, actual catabolism rate, underlying disease and inter-subject variability help to explain the wide range observed for terminal half-lives.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The clinical portion of the submission included clinical study reports (CSR) from 3 clinical trials. The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review.

3.2 Compliance With Good Clinical Practices And Submission Integrity

The applicant indicates the 3 studies were conducted in compliance with Good Clinical Practices, and principles set forth in Title 21 CFR parts 50, 54, 56, 312 and 314, International Conference on Harmonization Guidelines for Good Clinical Practice, and local and national regulatory requirements.

3.3 Financial Disclosures

Covered clinical study (name and/or number): NGAM-01, NGAM-05, NGAM-2		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 31 NGAM-01/NGAM-05 (N=11); NGAM-02 (N=20)		

Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

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

4.1 Chemistry, Manufacturing, and Controls

- Stability

Octapharma needs to commit to providing stability updates for the consistency lots manufactured in 2014 annually as a PMC annual report. The final stability report will be submitted as a PMC Final Study Report by November 4, 2016. This issue will not prevent approval.

- Manufacturing Process

A routine measurement of (b) (4) remaining in the product after (b) (4) step should be added. A justification on why the range will be changed after only one lot is out-of-range is necessary. This issue will not prevent approval.

- Facilities

Based on the findings from the Pre-License Inspection, there is no assurance that the firm is manufacturing under GMP conditions. Furthermore, the firm's 483 responses were not comprehensive and failed to address the underlying issues (such as lack of QA oversight). **A CR is proposed with a follow-up inspection.**

4.2 Assay Validation
Not applicable.

4.3 Nonclinical Pharmacology/Toxicology
No pharmacology/toxicology issues were identified.

4.4 Clinical Pharmacology
No clinical pharmacology issues were identified.

4.4.1 Mechanism of Action
The most accepted mechanism of action of IGIV in ITP is blockade of Fcγ receptors on macrophages, which prevents destruction of immunoglobulin G (IgG) sensitized platelets by the reticuloendothelial system.

4.4.2 Human Pharmacodynamics (PD)
No PD issues were identified.

4.4.3 Human Pharmacokinetics (PK)
Re-analysis of PK data will be needed.

4.5 Statistical
No significant statistical issues were identified.

4.6 Pharmacovigilance
The risk management plan submitted with this application includes a pharmacovigilance plan outlining routine pharmacovigilance practices and labeling. At this time, routine pharmacovigilance is adequate to monitor the important identified and potential risks, and missing information as described in the proposed pharmacovigilance plan.

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

5.1 Review Strategy
The package insert was reviewed first, followed by clinical study reports (CSR) for the PI (NGAM-01, NGAM-05) and chronic ITP indications (NGAM-02).

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review
This review is based on material that includes labeling claims in the package insert, research on similar submissions on human immune globulin products, and the following Guidances for Industry:

a) *Providing Regulatory Submissions to the Center for Biologics Evaluation and Research (CBER) in Electronic Format — Biologics Marketing Applications*

b) *Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency*

Three study reports were submitted to support the application.[2]

- Clinical Study Report NGAM-01: "Clinical study to evaluate the efficacy, pharmacokinetics and safety of immunoglobulin intravenous (human) 10% (NewGam) in patients with Primary Immunodeficiency Diseases". This is the major efficacy study for the PI indication.
- Clinical Study Report NGAM-05: "Clinical study to evaluate the safety and tolerability of immunoglobulin intravenous (human) 10% (NewGam) administered at high infusion rates to patients with Primary Immunodeficiency Diseases (extension of study NGAM-01)". This is a supportive trial for the PI indication.
- Clinical Study Report NGAM-02: "Prospective, open-label, non-controlled, multicenter, phase III clinical study to evaluate the efficacy and safety of immunoglobulin intravenous (human) 10% (NewGam) in primary immune thrombocytopenia". This is the major efficacy study for the chronic ITP indication.
- Integrated summaries of safety and efficacy were not submitted but standalone analyses of clinical safety and clinical efficacy stratified by clinical trial were submitted.

[2] The updated product trade name for NewGam is Panzyga

5.3 Table of Studies/Clinical Trials

Study ID	Population	Design	Test Product/Dosage	Evaluation Criteria	Endpoints
NGAM-01	PI and IgG titer ≥5.5 g/L in the trough levels of 2 previous IGIV infusions before enrollment Age ≥2 and ≤75 years Children: N=13 Adolescent: N=12 Adult: N=26 N=51 M=33 F=18	Prospective, open-label, single-arm Multicenter: 11 sites in Germany, Poland and U.S. First Subject In: 15-JAN-2010 Last Subject Out: 07-JUN-2012	Panzyga 10% intravenous 200-800 mg/kg body weight every 21 days or 28 days over 12 months, i.e., either 17 (at 3-week intervals) or 13 (at 4-week intervals) infusions of Panzyga	Efficacy, Safety, PK	<u>Primary Endpoint</u> Rate of SBI per person-year on treatment when administered at up to 0.08 mL/kg/min. <u>Secondary Endpoints</u> Trough levels of serum total IgG, specific antibodies against *H. influenzae*, *S. pneumonia*, CMV, VZV, tetanus and measles. 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 PK plasma profile for serum total IgG, IgG subclasses and specific antibodies against *H. influenzae*, *S. pneumonia*, CMV, VZV, tetanus and measles. Safety and tolerability, viral safety, effect of passive transmission of isoagglutinins (anti-A/anti-B) and anti-D.

NGAM-05	PI and completed NGAM-01 at the maximum infusion rate of 0.08 mL/kg/min without need for premedication at each of the last three infusions Age ≥2 and ≤75 years Children: N=8 Adolescent: N=3 Adult: N=10 N=21 M=13 F=8	Prospective, open-label, single-arm Multicenter: 6 sites in U.S.	Panzyga 10% intravenous 200-800 mg/kg body weight every 21 or 28 days for 5 infusions or 4 infusions, respectively	Safety, QoL	<u>Primary Endpoint</u> Safety and tolerability when Panzyga administered at infusion rates from 0.08 mL/kg/min up to 0.14 mL/kg/min. TEAEs, physical exam, hematological and chemistry variables, urinalysis, Coombs' test, vital signs and viral markers <u>Secondary Endpoints</u> QoL questionnaires
NGAM-02	Chronic ITP Age 16-72 years N=40 M=23 F=17	Prospective, open-label, single-arm Multicenter: 20 sites in Germany, Bulgaria, Czech Republic, Russia, India, Poland, Romania and Ukraine FPI: 27-OCT-2011 LPLV following study hold decision: 22-JUL-2013	Panzyga 10% intravenous 1 g/kg/day for 2 consecutive days, for a total of 2 g/kg	Efficacy, Safety	<u>Primary Endpoints</u> Proportion of enrolled subjects who met the eligibility criteria and showed an increase in platelet count to ≥50 x 10^9/L within 7 days after 1st infusion, i.e., by study Day 8, with a response rate >0.60. <u>Secondary Endpoints</u> Additional response rates based on alternative criteria. Alternative Response (AR): Increase in platelet count to ≥30 x 10^9/L and 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): Increase in platelet count to ≥100 x 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 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 ≥50 x 10^9/L Maximum platelet count Duration of platelet response of AR and CR Regression of hemorrhages Relationship of any new hemorrhages to platelet count Safety and tolerability: monitoring of vital signs, TEAEs, laboratory chemistry and hematology. Viral markers

Adapted from Module 5.2, Tabular Listings of All Clinical Studies, August 2014

5.4 Consultations
Not applicable.

5.4.1 Advisory Committee Meeting (if applicable)
Not applicable.

5.4.2 External Consults/Collaborations
Not applicable.

5.5 Literature Reviewed (if applicable)
Not applicable.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Indication #1: Primary Immunodeficiency

Study NGAM-01: "Clinical study to evaluate the efficacy, pharmacokinetics and safety of immunoglobulin intravenous (human) 10% in subjects with Primary Immunodeficiency Diseases"

6.1.1 Objectives

The primary objective was to assess the efficacy of Panzyga in preventing SBI compared with historical control data.

Secondary objectives included evaluation of safety, PK profile and effect on QoL measures.

6.1.2 Design Overview

Prospective, open-label, single-arm, historical-controlled, non-randomized, multicenter, multinational, phase 3 trial

6.1.3 Population

Inclusion criteria

- Age ≥2 years to ≤75 years
- Confirmed diagnosis of common variable immunodeficiency (CVID) or X-linked agammaglobulinemia (XLA)
- Previously treated with a commercial IGIV (human) every 21 to 28 days for at least 6 infusion intervals at a constant dose of 200-800 mg/kg body weight
- Availability of IgG trough levels from the two previous infusions before enrollment and maintenance of trough levels of ≥5.5 g/L for these two infusions
- For minor subjects above a minimum weight based on the amount of blood required for testing: per individual, trial-related blood loss is ≤3% of total blood volume during a period of 4 weeks and ≤1% at any single time
- Negative result on a pregnancy test (urine hCG-based assay) for women of childbearing potential and use of a reliable method of contraception for the duration of the study
- Willingness to comply with all aspects of the protocol, including blood sampling, for the duration of the study

Exclusion criteria

- Acute infection requiring intravenous antibiotic treatment within 2 weeks before screening
- Known history of ARs to IgA found in other products
- Exposure to blood or any blood product or derivative, other than commercially available IGIV within the past 3 months
- Ongoing history of hypersensitivity or persistent reactions to blood or plasma derived products or to any component of Panzyga
- Requirement of any routine premedication for IGIV infusion

- Congenital impairment of pulmonary function, severe liver impairment (ALT 3x ULN), renal function impairment (serum creatinine >120 umol/L), congestive heart failure, uncontrolled arterial hypertension or positive result from the following viral markers: human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV)
- Presence of any clinically relevant disease or unstable condition at screening, other than PI, which in the opinion of the investigator could interfere with the conduct of the study
- Treatment with steroids (oral or parenteral, long-term, i.e., 30 days or more, not intermittent or burst, daily ≥0.15 mg of prednisone or equivalent/kg/day), immunosuppressive or immunomodulatory drugs
- Planned vaccination during the study period (except for "killed" influenza vaccines, including H1N1) or live or attenuated vaccinations of any type.
- Treatment with any investigational agent within 3 months prior to enrollment
- Known or suspected abuse of alcohol, drugs, psychotropic agents, or other chemicals within the past 12 months prior to enrollment
- Pregnant or nursing women

6.1.4 Study Treatments or Agents Mandated by the Protocol

The dose regimen of Panzyga selected — once every 3 weeks or once every 4 weeks — was consistent with the subject's previous dosage regimen, i.e., subjects received a total of 17 or 13 intravenous infusions of Panzyga over the 12 month study period. The Panzyga dose (mg/kg) was administered based on body weight. Treatment intervals between administrations were the same throughout the study as long as minimum serum IgG trough levels were >5 g/L. If serum IgG trough levels decreased to ≤5 g/L, the dose was modified at investigator discretion. If body weight changed by >5%, the dose was adjusted to keep the dose constant on a mg/kg body weight basis.

6.1.5 Directions for Use

Routine premedication to alleviate potential tolerability problems was not allowed. Subjects who experienced two consecutive infusion-related ARs likely to be prevented by premedication were permitted to receive antiemetics, antihistamines, or antiemetic drugs.

Each subject received Panzyga via infusion pump. All 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 at pre-defined patterns, with the maximum rate increased to 0.08 mL/kg/min (480 mg/kg/h) following the 7th infusion. The infusion rate was increased only if tolerated by the subject. If an AR occurred during infusion, the rate was reduced to half the rate at which the event occurred or the infusion was interrupted until symptoms subsided. The infusion was resumed at a rate tolerated by the subject.

6.1.6 Sites and Centers

A total of 11 sites participated in the study:

Site 01 – James N. Moy MD (U.S.)
Site 02 – Alan P. Knutsen, MD (U.S.)

Site 03 – Isaac R. Melamed, MD (U.S.)
Site 05 – Sudhir Gupta, MD (U.S.)
Site 06 – Dr. Anna Pituch-Noworolska (Poland)
Site 08 – Dr. Magdalena Strach (Poland)
Site 09 – Dr. Grazyna Pulka (Poland)
Site 10 – Prof. Dr. Michael Borte (Germany)
Site 14 – Hans D. Ochs, MD (U.S.)
Site 15 – Ai Lan Kobayashi, MD (U.S.)
Site 17 – William Smits, MD (U.S.)

6.1.7 Surveillance/Monitoring

Subjects had to visit the study site for each planned infusion. Clinical examinations for safety and efficacy evaluations were performed during these visits. Subject diaries were evaluated at each visit by the investigator. Blood samples for PK evaluation were collected on the 9th Panzyga infusion day for subjects on the 3-week schedule, or on the 7th Panzyga infusion day for subjects on the 4-week schedule. At the 10th or 12th infusion visit for subjects on the 4-week or 3-week schedule, respectively, an additional sample was taken for measles antibody trough titer testing by bioassay. An end of study visit was performed for each subject 3 to 4 weeks (according to the treatment schedule) after the last infusion, or sooner if subject withdrew from the study.

An Independent Data Monitoring Committee (IDMC) was constituted to oversee subject safety. The IDMC was sought for review every 12 weeks during the study and at any time in response to serious adverse events (SAEs) or other subject experience and to give advice on the continuation, modification or termination of the study.

6.1.8 Endpoints and Criteria for Study Success

Primary endpoint

The primary endpoint was the point estimate for the rate of SBI (predefined as bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia and visceral abscess) per person-year. Substantial evidence of efficacy was prespecified as rejection of the null hypothesis and defined as an SBI rate per person-year <1.0 (upper 1-sided 99% confidence limit) at a 1% level of significance.

Secondary efficacy endpoints included

- Trough levels of serum total IgG and of specific antibodies against *Haemophilus influenzae*, *Streptococcus pneumoniae* (types 4, 6B, 9V, 14, 18C, 19F and 23F), cytomegalovirus (CMV), varicella-zoster virus (VZV), tetanus and measles
- 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 Child Health Questionnaire-Parent Form (CHQ-PF50) from parent or guardian of subjects <14 years of age and the Short Form-36 (SF-36) Health Survey in subjects ≥14 years of age

6.1.9 Statistical Considerations & Statistical Analysis Plan

SBI frequency was estimated at <0.5 per year. The applicant calculated that 42 evaluable subjects followed for 1 year would enable testing of the null hypothesis of an SBI rate ≥1.0 per person-year at the 1% level of significance with 90% power. To account for an overall drop-out rate of 15% and three age strata, approximately 50 PI subjects would need to be enrolled in the study. The SBI incidence was presented as the point estimate of mean rate per person-year and associated CIs. Based on historical data, a statistical demonstration of SBI rate per person-year <1.0 is considered adequate to provide substantial evidence of efficacy. The rate of other infections (any kind of seriousness) was analyzed and presented by using the same method as for SBI but using a 95% CI.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed (see Table 2)

- Enrolled (Total Set): subjects enrolled in the study whether or not they received Panzyga[3]
- Safety Set: subjects who received at least some Panzyga
- Full Analysis Set (FAS): subjects who received at least one complete treatment with Panzyga and for whom data on infections were available from at least one post-treatment diary. The FAS was used for the primary endpoint analysis.
- Per Protocol Set (PP): subjects in the FAS who completed the study without major protocol violations
- Pharmacokinetic Set: subjects who had concentration data for at least one of the pre-infusion trough levels

Table 2: Number of Subjects per Analysis Set

Analysis Sets	Children ≥2 to <12 N=13 N (%)	Adolescents ≥12 to <16 N=12 N (%)	Adults ≥16 to ≤75 N=26 N (%)	3-week schedule N=21 N (%)	4-week schedule N=30 N (%)	All Subjects N=51 N (%)
Enrolled (Total)	13 (100.0)	12 (100.0)	26 (100.0)	21 (100.0)	30 (100.0)	51 (100.0)
Safety (Treated)	13 (100.0)	12 (100.0)	26 (100.0)	21 (100.0)	30 (100.0)	51 (100.0)
Full Analysis (FAS)	13 (100.0)	12 (100.0)	26 (100.0)	21 (100.0)	30 (100.0)	51 (100.0)
Per-Protocol (PP)	12 (92.3)	12 (100.0)	26 (100.0)	21 (100.0)	29 (96.7)	50 (98.0)
Pharmacokinetic (PK)	13 (100.0)	12 (100.0)	26 (100.0)	21 (100.0)	30 (100.0)	51 (100.0)

Adapted from Table 14.1.1.1, CSR NGAM-01, 29 JUL 2013, page 162 of 11678

6.1.10.1.1 Demographics

As indicated in Table 3, 18 female subjects and 33 male subjects participated in study NGAM-01. Distribution across the two treatment schedules by gender was balanced.

[3] All enrolled subjects received at least one administration of Panzyga

Males predominated in the pediatric and adolescent subcohorts but were equally represented among adults. The youngest subject was 2 years of age and the oldest 65 years of age.

Table 3: Demographic Data (Total Set, N=51)

Parameter	Children ≥2 to <12 N=13 N (%)	Adolescents ≥12 to <16 N=12 N (%)	Adults ≥16 to ≤75 N=26 N (%)	3-week schedule N=21 N (%)	4-week schedule N=30 N (%)	All Subjects N=51 N (%)
Gender [N (%)]						
Female	3 (23.1)	2 (16.7)	13 (50.0)	7 (33.3)	11 (36.7)	18 (35.3)
Male	10 (76.9)	10 (83.3)	13 (50.0)	14 (66.7)	19 (63.3)	33 (64.7)
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
Min, Max	2, 9	12,15	17, 65	2,65	5, 63	2, 65
Race [N (%)] White	13 (100.0)	12 (100.0)	26 (100.0)	21 (100.0)	30 (100.0)	51 (100.0)
Ethnicity [N (%)]						
Hispanic/Latino	3 (23.1)	1 (8.3)	3 (11.5)	3 (14.3)	4 (13.3)	7 (13.7)
Not Hispanic/Latino	9 (69.2)	11 (91.7)	23 (88.5)	18 (85.7)	25 (83.3)	43 (84.3)
Hispanic/Latino Not Reported	1 (7.7)	0	0	0	1 (3.3)	1 (2.0)

Adapted from Table 14.1.1.1, CSR NGAM-01, 29 JUL 2013, pages 7 to 164 of 11678
N=number of subjects

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Of the 51 enrolled subjects, 43 (84.3%) were diagnosed with CVID and 8 (15.7%) were diagnosed with XLA; 45 (88.2%) were taking medication prior to entering the study and 2 (3.9%) had received non-drug therapies.

Infections and infestations, particularly chronic sinusitis, pneumonia and sinusitis, were the most frequently reported events by medical history (49 subjects or 96.1%). Distribution frequency was similar across age cohorts except for increased prevalence of (a) respiratory, thoracic and mediastinal disorders in adults: 16/26 or 61.5%; (b) surgical and medical procedures in children: 10/13 or 76.9%; and (c) immune system disorders in adolescents: 5/12 subjects or 41.7%.

On physical examination, 15/51 or 29.4% showed abnormalities, with a slight preponderance of abnormalities in the 4-week schedule (10/30 subjects or 33.3% compared with 5/21 subjects or 23.8% in the 3-week schedule). Abnormalities were greater in adults (9/26 or 34.6%) and in children aged <12 years (4/13 or 30.8%). The most frequently observed abnormal findings occurred in the Head, Eyes, Ears, Nose, and Throat SOC and included conjunctivitis, post-nasal drip, edematous nasal turbinates, and tympanic membrane scarring/perforation among 11/51 subjects or 21.6%, with similar percentages for both treatment schedules (4/21 or 19.0% in the 3-week schedule and 7/30 or 23.3% in the 4-week schedule).

The chest x-ray examination at screening was normal in 37/51 subjects (72.5%); 3/51 subjects (5.9%) — 2 pediatric subjects in the 3-week schedule and 1 adolescent subject in 4-week schedule — showed abnormal, clinically significant findings, e.g., acute bronchitis and bronchiectasis. None of the subjects had pneumonia or TB. All subjects were either non-smokers (46 subjects, 90.2%) or ex-smokers (5 subjects, 9.8%). All viral markers (HIV, HBV and HCV) were negative at screening. All urine pregnancy tests done at screening for female subjects of childbearing potential were negative.

6.1.10.1.3 Subject Disposition

A total of 51 subjects (13 children, 12 adolescents and 26 adults) were enrolled into a 3-week or 4-week schedule as per pre-enrollment dosing schedule. All enrolled subjects were eligible for inclusion in the safety, FAS and PK populations. Of these 51 subjects, 50 completed the trial. Adolescent subject #(b) (6), who was on a 4-week schedule, was withdrawn prematurely by the investigator after receiving 9 doses of Panzyga due to recurrent episodes of bronchiectasis despite therapy, i.e., treatment failure.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint

Table 4 lists data for the primary efficacy endpoint: rate of SBI per person-year. The null hypothesis (SBI rate ≥1.0 per person-year at the 1% level of significance) was tested and rejected for all age cohorts and treatment schedules with an upper bound of the 99% CI of 0.5033.

Table 4: SBI Rate per Person-Year by Age and Treatment Schedule (FAS, N=51)

Serious Bacterial Infections	Children ≥2 to <12 N=13 N (%)	Adolescents ≥12 to <16 N=12 N (%)	Adults ≥16 to ≤75 N=26 N (%)	3-week schedule N=21 N (%)	4-week schedule N=30 N (%)	All Subjects N=51 N (%)
Total number of SBI [n (%)]	1	0	3	0	4	4
Bacterial pneumonia	1	0	3	0	4	4
Total number of subjects with SBI	1 (2)	0	1 (4)	0	2 (7)	2 (4)
Bacterial pneumonia	1 (2)	0	1 (4)	0	2 (7)	2 (4)
Number of person-years exposure	12.96	NA	25.77	20.52	29.72	50.24
Total number (rate) of SBI per person-year	0.08	NA	0.12	NA	0.14	0.08
One-sided 99% CI – upper limit	0.79	NA	1.19	NA	0.85	0.50

Adapted from Table 14.2.1.1, CSR NGAM-01, 29 JUL 2013, page 319 of 11678
N=number of subjects; n=number of infections

For the PP set, the corresponding value for SBI per person-year was 0.63. An upper-bound 99% CI <1.0 was observed for the 4-week schedule cohort (0.85) and in the pediatric cohort (0.80); an upper-bound 99% CI >1.0 was observed in the adult cohort

(1.19), in the pediatric 4-week schedule cohort (1.27) and in the adult 4-week schedule cohort (1.71).

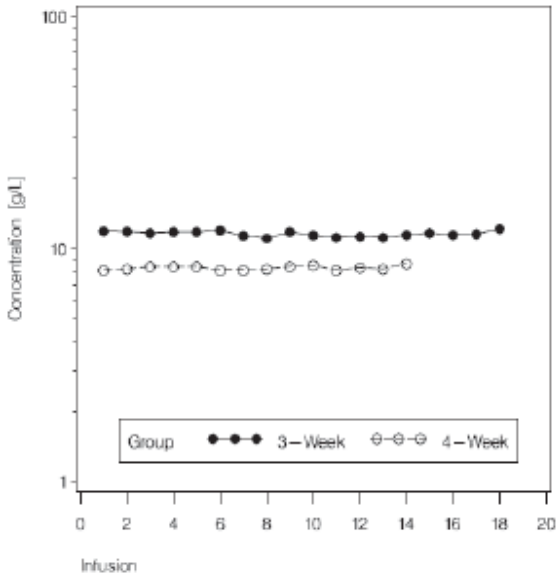
Four SBIs (bacterial pneumonia) were observed in 2 subjects (4%), one adult and one child. Both subjects were in the 4-week schedule. No SBI occurred in adolescent subjects or in subjects enrolled in the 3-week treatment schedule. Subject #(b) (6), who experienced an SBI, was excluded from the PP set because of having missed two infusion visits; low IgG levels caused by the missed infusions possibly explain the occurrence of the SBI.

6.1.11.2 Analyses of Secondary Endpoints

— Trough levels of serum IgG and specific antibodies

Serum IgG trough levels were nearly constant for both treatment schedules during the course of the study. Median values calculated for subjects in the 4-week treatment schedule (8.1 g/L to 8.65 g/L) were lower compared with values calculated for subjects in the 3-week schedule (11.0 g/L to 12.2 g/L).

Figure 1: Median IgG Trough Level Concentration (Central Determination) by Infusion (Pharmacokinetic Set, N = 51)



Source: Figure 14.2.3, CSR NGAM-01, 31 JUL 2013, page 79 of 11678

Trough concentrations for other specific antibodies (against *H. influenza*, CMV, VZV, tetanus, measles and *S. pneumonia* [types 4, 6B, 9V, 14, 18C, 19F and 23F]) were higher in subjects enrolled in 3-week schedule compared with subjects enrolled in the 4-week schedule. An increase in antibody concentration from 1st infusion until after treatment end was apparent for most of the parameters investigated, irrespective of treatment schedule. This increase over time was most prominent for measles (both treatment schedules), *H. influenzae* (both treatment schedules), *S. pneumonia* serotype 6B (both treatment schedules), serotype 4 (3-week schedule), serotype 23F (3-week schedule), serotype 14 (4-week schedule) and serotype 18C (4-week schedule). Assuming a protective measles antibody concentration of 120 mIU/mL being associated with

protection in healthy vaccinated children, all 50 subjects investigated for measles in this study were sufficiently protected against measles infection.

— Occurrence of non-serious (other) infections

Non-serious infections were observed in 39 subjects (76.5%). In general, non-serious infections were experienced by a higher percentage of 3-week schedule subjects than 4-week schedule subjects: 18 of 21 subjects (85.7%) in the 3-week schedule *versus* 21 of 30 subjects (70.0%) in the 4-week schedule. The rate of non-serious infections per person-year was highest in children (4.5) and lowest in adults (3.2).

Table 5 presents reported non-serious infections (n=185). Upper respiratory tract (n=90) and gastrointestinal tract (n=28) infections accounted for almost two-thirds (n=118) of the total. The incidence of both events was higher in the 3-week schedule than in the 4-week schedule. The number of person-years exposure was highest in adults and lowest in adolescents.

Table 5: Number of Non-Serious Infections (FAS, N=51)

	Children ≥2 to <12 N=13	**Adolescents ≥12 to <16 N=12**	**Adults ≥16 to ≤75 N=26**	**3-week schedule N=21**	**4-week schedule N=30**	**All Subjects N=51**
Other infections	58	43	84	86	99	185
Ear	8	3	2	6	7	13
Eye	1	0	3	1	3	4
GI tract	12	5	11	15	13	28
GU tract	0	0	14	3	11	14
Upper Respiratory Tract	23	27	40	47	43	90
Lower Respiratory Tract	6	3	7	5	11	16
Skin	4	0	1	3	2	5
Not otherwise classified	4	5	5	6	8	14
Number of person-years exposure	12.96	11.51	25.77	20.52	29.72	50.24
One sided 95% CI — upper limit	7.6760	7.9908	5.3002	6.8911	5.1651	5.1188

Adapted from Table 14.2.2.1, CSR NGAM-01, 29 JUL 2013, page 361 of 11678

— Time to resolution of infections

Mean resolution time was 14.3 days for SBI and 18.4 days for other infections. Mean time to resolution of other infections was longer in the 4-week treatment schedule than in the 3-week schedule: 21.4 days *versus* 14.9 days. Children showed the shortest mean resolution time and adults the longest: 12.4 days *versus* 22.2 days.

— Use of antibiotics

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. The rate of treatment episodes requiring antibiotics and number of days on antibiotics were highest in adolescents and lowest in adults: 4.3 and 151.8 *versus* 2.5 and 52.7, respectively.

— Absence from work or school due to infections

Half of the subjects experienced absence from work or school due to infections, with the highest percentage of subjects in the 3-week schedule and in children: 13 subjects (61.9%) and 10 subjects (76.9%), respectively. The rate of absence from work/school per person-year and number of days absent from work/school per person-year were similar between treatment schedules. The rate of absence from work/school per person-year and number of days absent from work/school per person-year were higher in the adolescent cohort than in the pediatric or adult cohorts: 2.433 and 6.690 *versus* 2.083 and 4.167 *versus* 0.504 and 2.018, respectively.

— Hospitalizations due to infections and fever

During the study, one 4-week schedule adult subject was hospitalized for 4 days (rate of days in hospital per person-year = 0.080) due to an SBI (pneumonia). Overall, fever was observed in 11 subjects (21.6%). Subjects on the 4-week schedule had a higher rate of fever per person-year than those on the 3-week schedule: 0.336 vs 0.195. Children experienced the highest rate of fever (0.463 per person-year) among the three age cohorts.

Reviewer Comment

It is not readily apparent why higher IGIV trough levels and shorter times to resolution of infections in the 3-week schedule cohort compared with the 4-week schedule cohort were also associated with a higher number of non-serious infections, greater use of antibiotics, and increased absence from school/work. Random variation due to small sample size is one possible explanation.

— QoL

The 36-Item Short Form Health Survey (SF-36) questionnaire was developed by the Boston Health Research Institute. It has become the most widely-used QoL evaluation tool in the world (*Int J Med Sci* 2009;6: 160-167). The reliability and validity of the SF-36 questionnaire have been demonstrated in a number of specific populations world-wide (*Qual Manag Health Care* 2000;8:72-81). The CHQ-PF50 is similar to the SF-36 but is used for children aged <14 years. Reliability and validity have been demonstrated in diverse settings (*Qual Life Res* 2005;14: 719-34; *Arthritis Care & Research* 2011;63: S420-S430).

Data from QoL questionnaires were analyzed at first infusion and follow-up or termination visits, and at intervals of 3 months (i.e., at the 5th, 10th and 14th infusion days for patients on the 3-week schedule, or on the 4th, 8th and 11th infusion days for patients on the 4-week schedule). Assessments were made using the Child Health Questionnaire-Parent Form (CHQ-PF50) completed by the parent or guardian of subjects aged <14 years and the SF-36 Health Survey in subjects aged ≥14 years.[4]

[4]The SF-36 Health Survey consists of 8 scales: physical function, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health. The items and scales of the SF-36 questionnaire are scored so that a higher score indicates a better health state. After data entry, the items and scales were scored according to the scoring manual by transforming raw scales scores to a 0 to 100 scales (transformed scale scores) and by transforming the 0 to 100 scale scores to have a mean of 50 and standard deviation of 10 in the general US population (norm-based scale scores).

- *CHQ-PF50 questionnaire*

The transformed score for the physical component summary for all subjects showed a slight improvement (mean change: 2.77) from baseline to follow-up visit: 45.90 versus 49.27. Baseline and follow-up values for the psychosocial component summary were similar with a mean change of 0.26: 51.72 and 51.33 (not significant). Scores at the follow-up visit for the physical and psychosocial component were similar: 51.33 versus 49.27. Summary values (mean) for the physical component at the follow-up visit were similar for the 4-week schedule and 3-week schedule: 49.96 versus 48.50.

- *SF-36*

The norm-based score for the physical component summary for all subjects showed a slight worsening (mean change of –2.23), with a decrease of the mean value from baseline to follow-up visit: 45.39 versus 43.16. In contrast, the norm-based score for the mental component summary showed a slight increase (mean change: 2.59) of the mean value: 45.60 versus 48.19. Comparing both components, the mental component score at the follow-up visit was higher than the score of the physical component: 48.19 versus 43.16.

Pharmacokinetic Results

For both the 3-week and 4-week schedules, IgG median concentration showed a steep decline from its peak just after the end of infusion, followed by a slower terminal elimination phase. Maximum concentration of IgG was 21.82 g/L for the 3-week schedule and 17.42 g/L for the 4-week treatment schedule; the minimum concentration of IgG was >6.8 g/L for both treatment intervals. The maximum concentration of IgG was typically reached at infusion end (median Tmax for 3-week treatment schedule: 2.98 hours and median Tmax for 4-week treatment schedule: 2.47 hours). Mean estimates of the AUC_{tau} parameter for IgG were very similar between the two treatment schedules (7580.6h*g/L in 3-week treatment schedule and 7578.0 h*g/L in 4-week treatment schedule), with similar coefficients of variability. Median IgG half-life values were lower than the means but similar in both treatment schedules, ranging from 26.23 to 38.55 days across both treatment intervals.

6.1.11.3 Subpopulation Analyses

No subpopulation analyses except as described in Section 6.1.10.1 were conducted.

6.1.11.4 Dropouts and/or Discontinuations

One major protocol violation leading to exclusion from the PP analysis population was reported in pediatric subject (b) (6) (4-week schedule), who missed the 3rd and 8th infusions and was late for other visits, including the follow-up visit. As a consequence of missed

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The CHQ-PF50 questionnaire consists of 50 items organized into 15 sub-scales: global health, physical functioning, role/social limitations due to emotional or behavioral difficulties, role/social limitations due to physical health, bodily pain and discomfort, behavior, global behavior, mental health, self-esteem, general health perceptions, change in health, emotional impact on parent, time impact on parent, family activities and family cohesion. Two summary scores can be derived: physical and psychosocial. In accord with the scoring manual, computed scores were transformed giving each scale a possible range from 0 to 100. For all CHQ-PF50 scales, higher scores indicate more positive functioning or better health status.

infusions, the subject had IgG trough levels <5 g/L at the 4th, 9th and 10th infusion visits and no dose adjustment was done.

6.1.11.5 Exploratory and Post Hoc Analyses

Endpoints were evaluated by treatment schedule cohorts, age cohorts and overall.

6.1.12 Safety Analyses

— Exposure

As presented in Table 6, 740 infusions were infused for a mean duration of 360 days; exposure was similar among treatment schedules and age cohorts. The average duration of infusion was 2.2 hours.

Table 6: Number of Infusions, Exposure Days and Dosage by Age (Total Set, N=51)

Study Medication Exposure	**Children ≥2 to <12 N=13**	**Adolescents ≥12 to <16 N=12**	**Adults ≥16 to ≤75 N=26**	**Total N=51**
Number of infusions (n)	186	184	370	740
Percent of infusions administered at maximum rate (0.08 mL/kg/min) post 7th infusion	91.74	91.96	88.32	90.11
Average duration of each infusion (hours), mean	2.239	2.177	2.195	2.201
Duration of treatment (days)				
Mean	364.00	350.42	362.00	359.78
SD	9.35	31.43	5.76	16.82
Median	364	358	363.50	362
Min, Max (rounded-off)	356, 392	252, 371	352, 379	252, 392
Number of subjects premedicated [n (%)]	0	0	2 (7.7)	2 (3.9)
Number of infusions premedicated	0	0	3 (0.8)	3 (0.4)

Adapted from Table 14.1.6, CSR NGAM-01, 29 JUL 2013, page 294 of 11678
N=number of subjects
n=number of infusions

6.1.12.1 Methods

TEAE rates were calculated with respect to intensity (mild, moderate, severe) and relationship to Panzyga (temporally associated and based on medical judgment by the investigator) and infusion speed. Infusional TEAEs were defined as those occurring within 72 hours after end of infusion. For infusional TEAEs, the onset time in relation to the infusion and infusion rate at the start of the event (if applicable) was captured. The ratio of infusions with temporally associated TEAEs over total infusions was presented.

Vital sign parameters (blood pressure, heart rate, temperature, respiratory rate) and safety laboratory parameters (hematology, clinical chemistry, direct Coombs test, urinalysis and viral safety) were evaluated and presented descriptively. For categorical parameters frequency tables were presented, whereas appropriate sampling statistics was presented for continuous parameters.

6.1.12.2 Overview of Adverse Events

— Overall Safety

Table 7 indicates that 51 subjects received 740 infusions and experienced 476 TEAEs. No TEAE led to discontinuation of Panzyga and no subject was withdrawn from the study due to a TEAE. Overall, 48/51 (94%) subjects experienced a TEAE, 5 experienced an SAE and 7 experienced a severe intensity TEAE. The incidence of TEAEs was similar among children, adolescents and adults, although the adult cohort was twice as large as for children and adolescents.

Table 7: Number of TEAEs (n) by Age and Treatment Schedule (Safety Set, N=51)

Severity of Infections	Children ≥2 to <12 N=13	Adolescents ≥12 to <16 N=12	Adults ≥16 to ≤75 N=26	3-week schedule N=21	4-week schedule N=30	All Subjects N=51
Number of TEAEs (n)	146	107	223	213	263	476
Number of related TEAEs**	9	5	45	27	33	60
Number of SAEs	0	3	4	1	6	7
Number of subjects with [N (%)]						
Any TEAEs	12 (92.3)	12 (100.0)	24 (92.3)	19 (90.5)	29 (96.7)	48 (94.1)
Related TEAEs**	2 (15.4)	3 (25.0)	11 (42.3)	6 (28.6)	10 (33.3)	16 (31.4)
SAEs	0	1 (8.3)	4 (15.4)	1 (4.8)	4 (13.3)	5 (9.8)
Related SAEs	0	0	0	0	0	0
Significant TEAE*	12 (92.3)	12 (100.0)	24 (92.3)	19 (90.5)	29 (96.7)	48 (94.1)
Severe TEAEs	0	2 (16.7)	5 (19.2)	5 (23.8)	2 (6.7)	7 (13.7)
TEAEs leading to withdrawal	0	0	0	0	0	0
TEAEs leading to death	0	0	0	0	0	0

Adapted from Tables 14.3.1.1 to 14.3.1.9, CSR NGAM-01, 29 JUL 2013, pages 1427 to 1679 of 11678
N=number of subjects
n=number of safety events
**Non-serious and dose changed or product withdrawn or other action taken or drug therapy started*
***Possibly or probably related*

As presented in Table 8, in decreasing order of frequency, reported TEAEs included upper respiratory tract infection (15/21 subjects or 29.4%), headache (14 or 27.5%), nasopharyngitis (13 or 25.5%), sinusitis (13 or 25.5%), and pyrexia (11 or 21.6%).

Table 8: Number of Subjects with TEAEs (Frequency >20.0%) Stratified by SOC, PT and Age (Safety Set, N=51)

Number of subjects with	Children ≥2 years to <12 years N=13 N (%)	Adolescents ≥ 12 years to <16 years N=12 N (%)	Adults ≥ 16 years to ≤ 75 years N=26 N (%)	Total All Subjects N=21 N (%)
Infections	12 (92.3)	10 (83.3)	18 (69.2)	40 (78.4)
Upper respiratory tract infection	4 (30.8)	4 (33.3)	7 (26.9)	15 (29.4)
Nasopharyngitis	3 (23.1)	3 (25.0)	7 (26.9)	13 (25.5)
Sinusitis	5 (38.5)	4 (33.3)	4 (15.4)	13 (25.5)
Gastrointestinal disorders	9 (69.2)	7 (58.3)	11 (42.3)	27 (52.9)
General disorders	6 (46.2)	9 (75.0)	12 (46.2)	27 (52.9)
Pyrexia	5 (38.5)	1 (8.3)	5 (19.2)	11 (21.6)
Nervous system disorders	4 (30.8)	6 (50.0)	10 (38.5)	20 (39.2)
Headache	4 (30.8)	2 (16.7)	8 (30.8)	14 (27.5)

Respiratory, thoracic and mediastinal disorders	6 (46.2)	4 (33.3)	10 (38.5)	20 (39.2)
Musculoskeletal and connective tissue disorders	2 (15.4)	1 (8.3)	11 (42.3)	14 (27.5)

Adapted from Table 14.3.1.2, CSR NGAM-01, 29 JUL 2013, page 1441 of 11678

6.1.12.3 Deaths

No deaths were reported.

6.1.12.4 Nonfatal Serious Adverse Events

As shown in Table 9, 7 SAEs were experienced by 1 adolescent subject and 4 adult subjects (no subject aged ≤12 years experienced an SAE). All SAEs required hospitalization but were considered by the investigator to be unrelated to study medication.

Table 9: Listing of Serious Adverse Events (Safety Set, N=51)

Schedule	ID #	Age Cohort	MedDRA Preferred Term	Intensity	Relationship	Outcome
3-week	(b) (6)	Adult	Gout	Severe	Not related	Resolved
4-week		Adult	Pneumonia	Moderate	Not related	Resolved
		Adolescent	Bronchiectasis	Moderate	Not related	Resolved
			Bronchospasm	Moderate	Not related	Resolved
			Bronchiectasis	Moderate	Unlikely	Resolved
		Adult	Septoplasty	Mild	Not related	Resolved
		Adult	Thrombocytopenia	Moderate	Not related	Resolved

Adapted from Listing 16.2.7.2.1, Appendix 16.2.7, CSR NGAM-01, 6 MAR 2013, page 5 of 1766

Brief narratives of subjects who experienced an SAE are as follows.

- Subject #(b) (6) was a 39 y/o Caucasian male enrolled in the 4-week treatment schedule on (b) (6). PMH was notable for CVID since 2004 and multiple instances of pneumonia since 2003. He presented to the study site on (b) (6) for infusion of Panzyga and reported to have a one week history of cough with yellow sputum, fever, weight loss, malaise and night sweats. He was admitted to the hospital with a diagnosis of bacterial pneumonia and treated with levofloxacin for 14 days. By (b) (6), he was afebrile and discharged from the hospital. This is one of the four reported SBIs.

- Subject #(b) (6) was a 14 y/o Caucasian male enrolled in the 4-week treatment schedule on (b) (6). PMH was notable for CVID and asthma since July 1997, idiopathic thrombocytopenia (date unknown) and bronchiectasis since November 2007. During the regular infusion visit on (b) (6), he had worsening pulmonary function tests (PFTs) and was treated with intravenous cefuroxime for 14 days. At the time of the next infusion visit ((b) (6)), no improvement was seen and he was admitted to the hospital. On (b) (6), while undergoing replacement of venous access port in the operating room, he experienced bronchospasm and was treated with subcutaneous epinephrine and intravenous ketamine. Nebulized albuterol was administered in the post-anesthesia care unit and the subject transferred to the pediatric intensive care unit with a diagnosis of bronchiectasis. On (b) (6) he was transferred to the

general care ward. The subject's PFTs slowly improved and he was discharged on (b) (6). The bronchiectasis was considered resolved at the time of discharge. On (b) (6) upon arrival to the study site for his fifth infusion visit, he was again noted to have worsening PFTs and complained of shortness of breath and dizziness. The subject was admitted to the hospital for treatment and further evaluation of worsening bronchiectasis. Chest therapy with continued albuterol therapy was ordered. Eventually he was discharged from the hospital and instructed to complete a 30 day course of ciprofloxacin. Previous home medications were continued.

- Subject #(b) (6) was a 59 y/o Caucasian male enrolled in the 3-week treatment schedule and began his first infusion on (b) (6). PMH was positive for gout since 1990, COPD since 2008, CVID, GERD and chronic sinusitis since 2008. He was seen at study site on (b) (6) for his 10th infusion visit when he reported having a gout flare-up, which began 4 days earlier. His right ankle was swollen and required walking with crutches. The subject returned to the hospital the following day and administered intravenously 1 g of Rocephin. When he returned to clinic on (b) (6) to receive a second dose of Rocephin, there was concern about osteomyelitis and he was sent to the emergency room and admitted that evening for further testing and evaluation. Right ankle x-rays showed diffuse arthritic changes. The subject was discharged on (b) (6). Antibiotics were discontinued and prednisone was tapered over 10 days. The event was considered resolved on (b) (6).

- Subject #(b) (6) was a 41 y/o Caucasian female enrolled in the 4-week treatment schedule on (b) (6). PMH included CVID since 2000, COPD since 2005, chronic sinusitis and chronic conjunctivitis since 2007 and UTI since 2008. On (b) (6), she was admitted to the hospital due to chronic sinusitis for which she underwent a planned correction of nasal septum deviation. On (b) (6), a septoplasty under general anesthesia was performed. No complications were reported during the surgery and post-surgical period. The subject was discharged from the hospital on (b) (6) in a good clinical condition.

- Subject #(b) (6) was a 41 year old Caucasian female who was enrolled in the 4-week treatment schedule on (b) (6). She had previously experienced thrombocytopenia from September 2008 to February 2009. On (b) (6) a small petechiae was observed on the lower extremity. Platelet count performed during this time showed a value of 11 x 10^9/L and she was hospitalized with a diagnosis of thrombocytopenia. The subject was treated with prednisone and the platelet counts increased to 91.2 x 10^9/L. The subject was discharged from the hospital on (b) (6) with a recommendation of prednisone dose reduction.

Reviewer Comment

I concur with the investigators' attribution, i.e., these SAEs were unrelated to Panzyga, for the following reasons.

1. Subject #(b) (6) had a PMH of gout. Gout was not reported in any other member of the safety population and has not been reported previously with IGIV products.
2. Subject #(b) (6) and #(b) (6) had a PMH of respiratory disease. It is unlikely that treatment with immunotherapy (Panzyga) triggered these respiratory SAEs absent additional signs/symptoms of hypersensitivity, e.g., hypotension.
3. Subject #(b) (6) had a PMH of chronic sinusitis. Exacerbation of this infection despite Panzyga therapy likely accounted for the decision to undergo elective septoplasty.
4. Subject #(b) (6) had a PMH of thrombocytopenia and experienced a recurrence of this condition approximately one month after initiating treatment. It is unlikely that Panzyga led to this event, since study NGAM-02 showed the product substantially elevates platelet count.

6.1.12.5 Adverse Events of Special Interest

— One case of hemolysis (mild; resolved) was reported.
— No cases of thromboembolism, renal dysfunction, TRALI, or aseptic meningitis were reported.
— Infusional TEAEs

Overall, 38/51 subjects (74.5%) experienced an infusional TEAE: 16 (76.2%) in the 3-week schedule and 22 (73.3%) in the 4-week schedule. The most commonly reported TEAEs were headache (9 or 17.6%), pyrexia (7 or 13.7%), sinusitis (4 or 7.8%), and cough (4 or 7.8%). Adolescents (11 subjects or 91.7%) outnumbered children (10 subjects or 76.9%) and adults (17 subjects or 65.4%).

Table 10 shows that infusional TEAEs represented 12% (89/740) of administered infusions and 71.2% (89/125) of reported TEAEs. Infusional TEAEs were slightly more frequent in the 4-week (52/384 or 13.5%) than in the 3-week schedule (37/356 or 10.4%) cohort, and more numerous in children (26/186 or 14.0%) than in adults (44/370 or 11.9%) or adolescents (19/184 or 10.3%).

Table 10: Number of Infusions with Infusional TEAEs by Age Group (Safety Set, N=51)

Number of infusions with infusional AEs within 72 hours after end of infusion by MedDRA SOC and PT	Children ≥2 Years <12 Years n = 186		Adolescents ≥12 Years <16 Years n = 184		Adults ≥16 Years ≤75 Years n = 370		Total All Patients n=740	
	Related* n (%)	Overall n (%)	Related* n (%)	Overall n (%)	Related* n (%)	Overall n (%)	Related* n (%)	Overall n (%)
All infusions with at least one infusional AE	**5 (2.7)**	**26 (14.0)**	**4 (2.2)**	**19 (10.3)**	**26 (7.0)**	**44 (11.9)**	**35 (4.7)**	**89 (12.0)**
Nervous system disorders	**1 (0.5)**	**3 (1.6)**	**1 (0.5)**	**1 (0.5)**	**19 (5.1)**	**22 (5.9)**	**21 (2.8)**	**26 (3.5)**
Headache	1 (0.5)	2 (1.1)	1 (0.5)	1 (0.5)	19 (5.1)	22 (5.9)	21 (2.8)	25 (3.4)
General disorders and administration site conditions	**3 (1.6)**	**7 (3.8)**	**3 (1.6)**	**7 (3.8)**	**8 (2.2%)**	**9 (2.4)**	**14 (1.9)**	**23 (3.1)**
Pyrexia	0 (0.0)	4 (2.2)	1 (0.5)	1 (0.5)	3 (0.8)	3 (0.8)	4 (0.5)	8 (1.1)
Chills	3 (1.6)	3 (1.6)	2 (1.1)	2 (1.1)	0 (0.0)	0 (0.0)	5 (0.7)	5 (0.7)
Infections and infestations	**0 (0.0)**	**6 (3.2)**	**0 (0.0)**	**7 (3.8)**	**0 (0.0)**	**8 (2.2)**	**0 (0.0)**	**21 (2.8)**
Sinusitis	0 (0.0)	1 (0.5)	0 (0.0)	4 (2.2)	0 (0.0)	1 (0.3)	0 (0.0)	6 (0.8)
Gastrointestinal disorders	**3 (1.6)**	**4 (2.2)**	**0 (0.0)**	**2 (1.1)**	**8 (2.2)**	**8 (2.2)**	**11 (1.5)**	**14 (1.9)**
Nausea	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)	5 (1.4)	5 (1.4)	6 (0.8)	6 (0.8)
Skin and subcutaneous tissue disorders	**0 (0.0)**	**8 (4.3)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.3)**	**0 (0.0)**	**9 (1.2)**
Dermatitis contact	0 (0.0)	7 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (0.9)
Musculoskeletal and connective tissue disorders	**0 (0.0)**	**2 (1.1)**	**0 (0.0)**	**1 (0.5)**	**1 (0.3)**	**3 (0.8)**	**1 (0.1)**	**6 (0.8)**
Respiratory, thoracic and mediastinal disorders	**0 (0.0)**	**1 (0.5)**	**0 (0.0)**	**1 (0.5)**	**1 (0.3)**	**2 (0.5)**	**1 (0.1)**	**4 (0.5)**

Source: 14.3, Table 14.3.1.11.4.1, CSR NGAM-01, 29 JUL 2013, page 1758 of 11678
N=number of infusions

Reviewer Comment

The incidence of infusional TEAEs reported in ≥5% of Panzyga PI subjects (irrespective of causality) was compared with the incidence of the same verbatim term in the package insert of other marketed IGIV 10% products at the

≥5% cut-off) by this reviewer and the results listed in Table 11. In general, Panzyga was associated with a lower-to-average incidence of TEAEs than expected when compared with other IGIV products.

Table 11: Infusional TEAEs Reported in in ≥5% of Panzyga PI Subjects Compared With Compared with Other Licensed IGIV Products

TEAE	Number (%) of Subjects	IGIV 10% Product
Headache		
	24 (52.2)	Flebogamma
	35 (43.8)	Privigen
	36 (32.0)	Gamunex-C
	35 (30.0)	Octagam
	12 (24.5)	Hizentra
	11 (21.6)	**Panzyga**
	94 (5.2)	GAMMAGARD LIQUID
Migraine	**1 (2.0)**	**Panzyga**
	12 (0.7)	GAMMAGARD LIQUID
Pain		
	20 (25.0)	Privigen
	7 (13.7)	**Panzyga**
	4 (8.7)	Flebogamma
	9 (8.0)	GAMUNEX-C
Extremity pain	**2 (3.9)**	**Panzyga**
	13 (0.7)	GAMMAGARD LIQUID
Infusion site	**2 (3.9)**	**Panzyga**
Back pain	**1 (2.0)**	**Panzyga**
	8 (17.4)	Flebogamma
Arthralgia	8 (7.0)	GAMUNEX-C
	1 (2.0)	**Panzyga**
	5 (0.3)	GAMMAGARD LIQUID
Myalgia	**1 (2.0)**	**Panzyga**
	5 (0.3)	GAMMAGARD LIQUID
Musculoskeletal chest pain	6 (13.0)	Flebogamma
	1 (2.0)	**Panzyga**
Chills (Rigors)		
	17 (37.0)	Flebogamma
	9 (11.3)	Privigen
	9 (8.0)	GAMUNEX-C
	2 (3.9)	**Panzyga**
	14 (0.8)	GAMMAGARD LIQUID
Fatigue/Asthenia		
	13 (16.3)	Privigen
	4 (8.2)	Hizentra
	9 (8.0)	GAMUNEX-C
	4 (7.8)	**Panzyga**
	33 (1.8)	GAMMAGARD LIQUID
Pyrexia		
	19 (41.3)	Flebogamma
	20 (17.0)	Octagam
	7 (13.7)	**Panzyga**
	15 (13.0)	GAMUNEX-C
	6 (7.5)	Privigen
	28 (1.5)	GAMMAGARD LIQUID

Nausea		
	10 (12.5)	Privigen
	5 (9.8)	**Panzyga**
	7 (6.0)	GAMUNEX-C
	4 (5.0)	Flebogamma
	17 (0.9)	GAMMAGARD LIQUID
Vomiting		
	7 (8.8)	Privigen
	2 (3.9)	**Panzyga**
	11 (0.6)	GAMMAGARD LIQUID
Tachycardia		
	11 (23.9)	Flebogamma
	25 (22)	Octagam
	1 (2.0)	**Panzyga**
Cough		
	5 (6.3)	Privigen
	2 (3.9)	**Panzyga**
	9 (0.5)	GAMMAGARD LIQUID
Pharyngitis		
	4 (5)	Gamunex-C
	2 (3.9)	**Panzyga**
Dizziness		
	7 (6.9)	GAMUNEX-C
	1 (2.0)	**Panzyga**
	11 (0.6)	GAMMAGARD LIQUID
Bronchospasm		
	1 (2.0)	**Panzyga**
	7 (0.4)	GAMMAGARD LIQUID
Influenza		
	6 (5)	GAMUNEX-C
	1 (2.0)	**Panzyga**

Adapted from Prescriber Information for approved IgG products

6.1.12.6 Clinical Test Results

Chemistry/Hematology

There were no clinically important changes in any chemistry or hematology test results. More abnormal hematology values at screening and treatment end (but not clinically significant) were observed in the 4-week treatment schedule cohort. See also paragraph 6.1.12.4.

— Direct Coombs' test

Two adolescent subjects tested direct Coombs' positive at Screening:

- Subject #(b) (6) (3-week treatment schedule) showed negative results in all subsequent direct Coombs' tests
- Subject #(b) (6) (4-week treatment schedule) had positive results at the 1st, 2nd, and 3rd infusions and negative results in all subsequent tests.

No subject became direct Coombs' positive during the trial.

— Viral Markers

No positive result to HBV, HCV, or HIV was observed for any subject during the study.

— Assessment of Tolerance in Children

As requested by the EMA Pediatric Committee (PDCO), special safety assessments were conducted among pediatric subjects enrolled in the study (children and adolescents). No signs or specific concerns were identified in any of the evaluations carried on (vital signs, infusional TEAEs, physical examination findings, laboratory parameters).

6.1.12.7 Dropouts and/or Discontinuations

See paragraph 6.1.11.4.

6.1.13 Study Summary and Conclusions

The study met its primary endpoint in the four prespecified datasets (total, safety, FAS, PP). No deaths were reported but one adolescent and four adult subjects experienced a total of 7 SAEs, all considered by the investigator to be unrelated to Panzyga. No child aged ≤12 years experienced an SAE. Within 72 hours of infusion end, 89 (12%) infusions (out of 740 infusions in the study) were associated with at least one infusional TEAE.

6.2 Indication #1: Primary Immunodeficiency

Study NGAM-05: "Clinical study to evaluate the safety and tolerability of immunoglobulin intravenous (human) 10% (NewGam) administered at high infusion rates to patients with Primary Immunodeficiency Diseases (extension of study NGAM-01)

6.2.1 Objectives
Primary: to assess the safety and tolerability of Panzyga when administered at infusion rates from 0.08 mL/kg/min (the maximum rate in NGAM-01) to 0.14 mL/kg/min.
Secondary: to assess Panzyga's effect on QoL.

6.2.2 Design Overview
Prospective, open-label, uncontrolled, nonrandomized, multicenter phase 3 study

6.2.3 Population
NGAM-01 subjects who had tolerated Panzyga at the maximum infusion rate of 0.08 mL/kg/min without need for premedication for at least the last three infusions, without restrictions in terms of age or treatment regimen.

Inclusion Criteria
1. Completed study NGAM-01
2. At each of the last three infusions in the main study NGAM-01, administration of Panzyga at the maximum infusion rate of 0.08 mL/kg/min and without the need for premedication
3. For adult subjects: freely given written informed consent. For subjects below the legal age of majority: freely given written informed consent from parents or legal guardians and written informed assent from the child or adolescent in accordance with the applicable approvals.
4. For female subjects of child-bearing potential: a negative result in a urine pregnancy test conducted at the screening visit.
5. Willingness to comply with all aspects of the protocol, including blood sampling, for the duration of the study

Exclusion Criteria
1. Any condition or circumstance that would have led to the exclusion of the subject from the NGAM-01 study.
2. Administration of any immunoglobulin infusion other than Panzyga between the conclusion of the NGAM-01 study and the beginning of the present study.
3. A deviation of the subject's treatment interval of more than 7 days between the last infusion of Panzyga in the NGAM-01 study and the first infusion of Panzyga in the present study.

6.2.4 Study Treatments or Agents Mandated by the Protocol

The protocol mandated two multiple-dose intravenous Panzyga regimens, i.e., every 3 weeks or every 4 weeks, as scheduled in NGAM-01, for 4 months. Therefore, each subject received either five infusions (at 3-week intervals) or four infusions (at 4-week intervals) of Panzyga. Infusions were administered with a consistent dose throughout the study. The infused dose 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 IGIV dose and interval. If body weight changed by >5% during the study, the dose was 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 >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 modified at investigator discretion.

6.2.5 Directions for Use

All 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

Six study sites in the United States were selected on the basis of their previous successful participation in study NGAM-01.

6.2.7 Surveillance/Monitoring

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

6.2.8 Endpoints and Criteria for Study Success

Efficacy

— Efficacy was not assessed in this study. IgG trough levels were recorded for dosing. QoL was assessed as a secondary endpoint.

The CHQ-PF50 questionnaire was used for all subjects <14 years of age at inclusion in the main study NGAM-01. Overall, for all individual scales, apart from general health and bodily pain/discomfort, a deterioration of the scores was noticed from baseline to study end. No notable increase in mean scores was observed from baseline to treatment end. For more individual scores a decrease of mean scores was observed between baseline and end of study when comparing the 3-week with the 4-week treatment schedule.

In the SF-36 questionnaire used for subjects aged ≥14 years or older, the norm based scores for the physical component summary and mental component summary remained almost constant during the study.

In the SF-36 questionnaire used for subjects aged ≥14 years or older, the norm based scores for the physical component summary and mental component summary remained almost constant during the study.

Safety

— Safety endpoints included (a) occurrence of TEAEs; (b) occurrence of TEAEs temporally associated with the study treatment; (c) proportion of infusions with one or more temporally associated TEAEs; (d) TEAEs by infusion rate; (e) Vital signs (blood pressure, heart rate, temperature, and respiratory rate); and (f) Laboratory parameters (hematology, clinical chemistry, direct Coombs' test, urinalysis and test for viral safety)

6.2.10 Study Population and Disposition

NGAM-01 subjects (N=21) aged ≥2 to <12 years, ≥12 to <16 years, and ≥16 to 75 years.

6.2.10.1 Demographic Characteristics

Overall, 21 subjects (8 female and 13 male) participated in this study. The youngest enrolled subject was 6 years old and the oldest was 62 years old. Two adolescent NGAM-01 subjects were assigned to the adult cohort in NGAM-05. All subjects were Caucasian (4 subjects were of Hispanic or Latino background and one did not list their ethnicity).

6.2.11 Efficacy Analyses

Not applicable.

6.2.12 Safety Analyses

— Exposure

Table 12 indicates that 21 subjects were enrolled. Note: all adolescent subjects were in the 3-week schedule treatment cohort.

Table 12: Number of Subjects Enrolled

No. of Subjects	**Children ≥2 years to <12 years (N=8) N (%)**	**Adolescents ≥ 12 years to <16 years (N=3) N (%)**	**Adults ≥ 16 years to ≤ 75 years (N=10) N (%)**	**3-week schedule N=12 N (%)**	**4-week Schedule N=9 N (%)**	**Total All Subjects N=21 N (%)**
Enrolled (Total Set)	8 (100)	3 (100)	10 (100)	12 (100)	9 (100)	21 (100)
Treated (Safety Set)	8 (100)	3 (100)	10 (100)	12 (100)	9 (100)	21 (100)
Completed	8 (100)	3 (100)	10 (100)	12 (100)	9 (100)	21 (100)
Early-terminated	0	0	0	0	0	0

Adapted from Table 14.1.1.1, CSR NGAM-05, 29 JUL 2013, page 89 of 2996

6.2.12.1 Methods

Each subject received Panzyga over a 4-month period for a total of five or four Panzyga infusions, depending on whether their regular treatment intervals were every 3 or 4 weeks, respectively. The administered dose on a milligram per kg body weight and the treatment intervals between administrations remained the same throughout the study, as long as minimum IgG trough levels were maintained above 5 g/L. If serum IgG trough levels dropped to 5 g/L or less, the dose was adapted at the investigator's discretion.

Subjects visited the study site for each planned infusion. At every visit, blood samples were collected for trough total IgG levels and subjects were weighed. Throughout the study, subjects were asked to document adverse events (TEAEs) and any changes in concomitant therapy between visits on a diary. During infusion visits, clinical examinations and laboratory tests for safety evaluations were performed. Females of childbearing potential had a urine pregnancy test at screening, at each visit if clinically indicated and at the end of the study. QoL was assessed using the CHQ-PF50 and SF-36 validated questionnaires at the end of the study. An end of study visit was performed for each subject 3 to 4 weeks (according to the treatment schedule) after the last infusion.

All subjects received concomitant medication. Overall, in both treatment arms and in the children and adults groups, the most common concomitant medication was systemic antibiotics, received by 13 subjects (61.9%). A higher frequency of use for drugs for obstructive airways disease, analgesics and anti-inflammatory products (2 subjects, 66.7%, each) was noticed in adolescent subjects compared with other age groups. Apart from systemic antibiotics, half of the children (4 patients, 5.0%) received antihistamines for systemic use and nasal preparations. Half of the adults (5 patients, 50.0%) took drugs for obstructive airway diseases. Corticosteroids for systemic use were administered in 3 subjects (14.3%), but in none of the subjects were they used as premedication to alleviate infusion symptoms, i.e., no subject took premedication for any of the infusions received in the study).

6.2.12.2 Overview of Adverse Events

Table 13 shows that TEAEs (n=69) were experienced by 17 subjects; most were mild or moderate in intensity, although a severe intensity TEAE was reported in 1 adult subject. The frequency of TEAEs was noticeably higher in the 3-week than in the 4-week treatment schedule and slightly higher in children than adults. All 3 adolescent subjects experienced TEAEs.

Table 13: Number of TEAEs by Age Cohort and Treatment Schedule (Safety Set, N=21)

	Children ≥2 years to <12 years (N=8) N (%)	**Adolescents ≥ 12 years to <16 years (N=3) N (%)**	**Adults ≥ 16 years to ≤ 75 years (N=10) N (%)**	**3-week schedule N=12 N (%)**	**4-week Schedule N=9 N (%)**	**Total All Subjects N=21 N (%)**
Number of TEAEs	33	6	30	47	22	69
Number of subjects (%) with						
Any TEAEs	7 (87.5)	3 (100.0)	7 (70.0)	11 (91.7)	6 (66.7)	17 (81.0)
Related* TEAEs	2 (25.0)	0	2 (20.0)	3 (25.0)	1 (11.1)	4 (19.0)
Serious TEAEs	0	0	0	0	0	0
Significant TEAEs**	5 (62.5)	1 (33.3)	6 (60.0)	7 (58.3)	5 (55.6)	12 (57.1)
Severe TEAEs†	0	0	1 (10.0)	1 (8.3)	0	1 (4.8)
TEAEs leading to withdrawal	0	0	0	0	0	0
TEAEs leading to death	0	0	0	0	0	0

Adapted from Tables 14.3.1.1.1, 14.3.1.1.3 and 14.3.1.7, CSR NGAM-05, 29 JUL 2013, pages 224, 232 and 326 of 2996

N=Number of subjects
n=number of events
* Related = probably or possibly, as assessed by the investigator
** = Non-serious and intervention required, i.e., dose reduced/increased or product withdrawn or drug therapy started
† = severe intensity and non-serious, irrespective of whether intervention was required

As presented in Table 14, in decreasing order of frequency, sinusitis (4/21 subjects or 19%), nausea (3 or 14.3%), and vomiting (3 or 14.3%) were the most commonly reported events.

Table 14: Number of Subjects with TEAEs (Frequency ≥5.0% of Subjects; Safety Set, N=21)

Number of subjects with	**Children N=8 N (%)**	**Adolescents N=3 N (%)**	**Adults N=10 N (%)**	**3-week schedule N=12 N (%)**	**4-week Schedule N=9 N (%)**	**Total All Subjects N=21 N (%)**
Any TEAE	7 (87.5)	3 (100.0)	7 (70.0)	11 (91.7)	6 (66.7)	17 (81.0)
Infections and infestations	3 (37.5)	1 (33.3)	5 (50.0)	5 (41.7)	4 (44.4)	9 (42.9)
Sinusitis	2 (25.0)	1 (33.3)	1 (10.0)	1 (8.3)	3 (33.3)	4 (19.0)
Nasopharyngitis	1 (12.5)	0	1 (10.0)	1 (8.3)	1 (11.1)	2 (9.5)
Gastrointestinal disorders	4 (50.0)	1 (33.3)	2 (20.0)	5 (41.7)	2 (22.2)	7 (33.3)
Nausea	1 (12.5)	0	2 (20.0)	3 (25.0)	0	3 (14.3)
Vomiting	2 (25.0)	1 (33.3)	0	2 (16.7)	1 (11.1)	3 (14.3)
Abdominal pain	2 (25.0)	0	0	0	2 (22.2)	2 (9.5)
Diarrhea	1 (12.5)	0	1 (10.0)	1 (8.3)	1 (11.1)	2 (9.5)
Injury, poisoning, procedural complications	4 (50.0)	0	2 (20.0)	4 (33.3)	2 (22.2)	6 (28.6)
Confusion	1 (12.5)	0	1 (10.0)	2 (16.7)	0	2 (9.5)

Adapted from Table 14.3.1.2, CSR NGAM-05, 29 JUL 2013, page 236 of 2996
N=Number of subjects

Reviewer Comment

Duration of exposure was 4 months longer in NGAM-05 than in NGAM-01. TEAEs were experienced by 81% of NGAM-01 subjects versus 94% of NGAM-05 subjects. In addition, sinusitis was the leading TEAE reported in NGAM-05 (19.0% of subjects), whereas the leading TEAE reported in NGAM-01 was upper respiratory tract infection (29.4% of subjects). Similarly, nasopharyngitis was reported in 9.5% of NGAM-05 subjects and 25.5% of NGAM-01 subjects. Possible explanations for this observation include self-selection bias (willingness to enroll in an extension study) and/or random variation due to small sample size.

6.2.12.3 Deaths
No subjects died during the study.

6.2.12.4 Non-fatal Serious Adverse Events
No SAEs were reported for any subject.

6.2.12.5 Adverse Events of Special Interest (AESI)

— One case of aseptic meningitis was reported. No cases of hemolysis, thromboembolism, renal dysfunction or TRALI were reported

— Infusional TEAEs

Infusional TEAEs were observed in 8 subjects (38.1%). They occurred more frequently in the 3-week schedule (6 subjects, 50.0%) than in the 4-week schedule (2 subjects, 22.2%), and in children (4 subjects, 50.0%) more than in adults (3 subjects, 30.0%) or adolescents (1 subject, 33.3%).

Overall, 6 infusions (6.3%) were associated with 16 related infusional TEAEs. Distribution was similar across treatment schedules and age cohorts (no adolescent experienced a related TEAE). Headache was the most common infusional TEAE by MedDRA PT, occurring with three infusions (3.1%].

Reviewer Comment

It is unclear why the incidence of infusional TEAEs was noticeably lower in NGAM-05 subjects (38.1%) than in NGAM-01 subjects (74.5%), especially since the maximum allowable target infusion rate in NGAM-05 was higher (0.14 mL/kg/min) than in NGAM-01 (0.08 mL/kg/min). Self-selection bias by enrollees and/or random variation due to small sample size may have played a role.

6.2.12.6 Clinical Test Results

There were no clinically significant changes in any of the laboratory results (hematology, chemistry, Coombs' test, viral safety and urinalysis). In general, subjects showed normal values of vital signs during the study and no major changes in physical examination were observed. Overall, evaluation of TEAEs, routine laboratory examination, vital signs and physical examination showed that administration of study medication was generally well tolerated and safe in both treatment schedules and all age cohorts.

6.2.12.6.1 Hematology laboratory data

No abnormal or clinically significant values or changes from baseline to end of treatment were noted in any subject.

6.2.12.6.2 Chemistry, Urinalysis, Viral Markers and Direct Coombs'

No abnormal or clinically significant values or changes from baseline to end of treatment were noted in any subject except for direct Coombs' where all subjects had negative results at all visits, except one adult in the 4-week schedule who presented a positive Coombs' test at the end of the study, and another adult in whom the test was missing at Infusion 2 and at Follow-up but was negative on all other occasions.

6.2.12.6.3 Vital Signs, Physical Findings, and Other Observations Related to Safety

No abnormal or clinically significant values or changes from baseline to end of treatment were noted in any subject.

6.2.12.7 Dropouts and/or Discontinuations

No subject dropped-out or was discontinued.

6.2.13 Study Summary and Conclusions

Panzyga was well tolerated by all 21 subjects and all subjects completed the study as planned, receiving a total of 96 infusions (60 in 3-week schedule and 36 in 4-week schedule). No subject died, experienced a non-lethal SAE or a TEAE that led to study withdrawal.

Over the entire study, 17/21 subjects (81.0%) had at least 1 TEAE (majority were mild and moderate in intensity). Three severe intensity TEAEs (paronychia, chest pain and musculoskeletal pain) were reported in 1 adult subject (4.8%); the latter 2 TEAEs were considered related to the Panzyga infusion. Related TEAEs were reported in 2 children (25.0%) and 2 adults (20.0%) (4 subjects overall, 19.0%), with nausea and headache as the most commonly reported related TEAEs.

A total of 11/96 infusions (11.5%) were associated with 22 temporally associated infusional TEAEs, of which 16 TEAEs in 6 infusions were considered related to Panzyga. Headache was the most commonly related infusional TEAE. The proportion of infusions with infusional TEAEs for all subjects was 0.1146 (upper limit of 95% CI: 0.1877), i.e., below the upper one-sided 95% CI of 40% for TEAEs, thereby meeting the target parameter recommended by the FDA Guidance.

Overall, the evaluation of TEAEs, routine laboratory examination, vital signs and physical examination showed that administration of Panzyga up to a maximum infusion rate of 0.14 mL/kg/min was generally well tolerated and safe in both treatment schedules and all age cohorts.

6.3 Indication #2: platelet response rate in adult subjects with chronic ITP

NGAM-02: “Prospective, open-label, non-controlled, multicenter, phase III clinical study to evaluate the efficacy and safety of immunoglobulin intravenous (human) 10% in primary immune thrombocytopenia”

6.3.1 Objectives

Primary: to assess the efficacy of Panzyga in elevating the platelet count.
Secondary: to assess safety.

6.3.2 Design Overview

Prospective, open-label, uncontrolled, multicenter phase 3 study

6.3.3 Population

Adult subjects with chronic primary ITP.

Inclusion criteria

1. Age of ≥18 years and ≤65 years.

2. Confirmed diagnosis of chronic primary ITP (diagnosed as a platelet count <100 x 10^9/L) of ≥12 months duration and fulfilling the following criteria:
    a) History and physical examination excludes other causes of thrombocytopenia.
    b) Pattern of bleeding associated with platelet disorders using the verbal rating scale according to Buchanan (*J Pediatr* 2002;141:683-688).
    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 chronic ITP: thrombocytopenia with platelets of normal size or slightly larger than normal, with absence of platelet clumps and giant platelets in the presence of normal red and white blood cell morphology.
    e) Additional diagnostic evaluation excludes other causes of thrombocytopenia when any abnormal finding is present
3. Platelet count of ≤20 x 10^9/L with or without bleeding manifestations.
4. Written informed consent from subject.
5. Women of childbearing potential must have had a negative result on a pregnancy test (human chorionic gonadotropin [HCG]-based assay) and need to practice contraception using a method of proven reliability for the duration of the study.

<u>Exclusion criteria</u>

1. Thrombocytopenia secondary to other diseases (such as Acquired Immunodeficiency Syndrome or systemic lupus erythematosus or drug-related.
2. Administration of intravenous immunoglobulin (IGIV), anti-D or thrombopoetin receptor agonists or other platelet enhancing drugs (incl. immunosuppressive or other immunomodulatory drugs) within 3 weeks before enrollment, except for:
    a) Long-term corticosteroid therapy when the dose had been stable during the preceding 3 weeks and no dosage change was planned until study Day 22.
    b) Long-term azathioprine, cyclophosphamide or attenuated androgen therapy when the dose had been stable during the preceding 3 months, and no dosage change was planned until study Day 22.
3. Unresponsive to previous treatment with IGIV or anti-D immunoglobulin.
4. Experimental treatment within 3 months before enrollment.
5. Rituximab within 4 months before enrollment.
6. Splenectomy in the previous 4 weeks or planned splenectomy throughout the study period.
7. Evans syndrome (autoimmune thrombocytopenia and autoimmune hemolysis).
8. HIV or hepatitis C virus infection.
9. Live viral vaccination within the last 2 months before study entry.
10. Emergency operation.
11. Severe liver or kidney disease (alanine aminotransferase 3x > upper limit of normal, creatinine >120 umol/L.
12. Congestive heart failure New York Heart Association class III or IV.

13. Non-controlled arterial hypertension (systolic blood pressure >160 mmHg or diastolic blood pressure >90 mmHg).
14. History of hypersensitivity to blood or plasma derived products, or any component of the investigational product.
15. Immunoglobulin A (IgA) deficiency and antibodies against IgA.
16. History of or suspected alcohol or drug abuse.
17. Pregnant or nursing women.
18. Unable or unwilling to comply with the study protocol.
19. Participating in another interventional clinical study and receiving investigational medicinal product within 3 months before study entry.
20. Body mass index ≥30 kg/m^2.
21. Subjects with risk factors for thromboembolic events in whom the risks outweigh the potential benefit of Panzyga treatment.
22. Risk factors such as obesity, advanced age, hypertension, diabetes, a history of atherosclerosis/vascular disease or thrombotic events, hyperlipidemia, multiple cardiovascular risk factors, acquired or inherited thrombophilic disorders, prolonged periods of immobilization, severe hypovolemia, central venous catheterization, active malignancy and/or known or suspected hyperviscosity.

6.3.4 Study Treatments or Agents Mandated by the Protocol

A total of 86 subjects with clinically diagnosed primary immune thrombocytopenia aged ≥18 to 65 years meeting the enrollment criteria were planned for recruitment. However, a**fter 40 subjects had been enrolled, the study was put on hold due to delayed availability of study medication**. The sponsor decided that rather than performing an interim analysis and a final analysis subsequently, a single final analysis would be completed at this stage, using the originally defined primary and secondary endpoints.

Reviewer Comment

Additional details surrounding termination of the trial were requested from the sponsor in an IR emailed 30-SEP-2015.

Study NGAM-02 began enrollment on 27-OCT-2011 and ended on 22-JUL-2013. Octapharma's response to the IR indicates that the company became aware of a shortage of Panzyga in Q4 2012. However, this was not communicated to the DMC until March 2013 and Octapharma indicates no discussion took place with the DMC over this matter. Later that year (October 2013), a pre-BLA Meeting Request (Amendment #0027 to IND 14121) was filed to obtain advice over whether FDA would insist on completion of Study NGAM-02 before granting licensure. FDA informed Octapharma on 12-DEC-2013 that a review of interim data could suffice, provided there was evidence of safety and efficacy. FDA was notified on 3-FEB-2014 that the study had been terminated (#0030, IND 14121).

Table 15 lists laboratory tests completed during the study. Prior to Panzyga administration, the following information was obtained: demographic data; medical and surgical history; record of all previous drug and nondrug therapy during the last 4 months; full physical examination; assessment of bleeding and blood sampling for laboratory parameters. The first dose of Panzyga was administered within 24 hours from

Baseline. A daily dose of 1 g/kg was infused for 2 consecutive days, for a total of 2 g/kg. During Panzyga administration, vital signs were monitored at start of infusion, every 30 minutes during infusion and 1 hour post-infusion. Prior to the second dose on Day 2, clinical laboratory parameters were tested. If a clinically significant change (defined as "out of the reference range", page 99, CSR) warranting termination of product administration was observed, the subject was withdrawn from the study and followed for safety.

Table 15: Laboratory Tests Completed During the Study

Hematology Test	Details	Timing
Lab Panel 1	- CBC with WBC differential - H/H	Baseline*, Day 2 to Day 8 Day 15 and Day 22
Lab Panel 2	- Reticulocyte count - Total, direct/indirect bilirubin - Serum haptoglobin - Plasma free hemoglobin - Urine sample for hemosiderin	Baseline*, Day 1 to Day 3, Day 8 and Day 22
Lab Panel 3	- Creatinine - AST and ALT - Sodium and potassium - BUN	Baseline*, Day 3, Day 5, Day 7, Day 15 and Day 22
Immunology	- Direct Coombs' test (with specificity if positive)	Baseline*, Day 2, Day 3 and Day 8
LDH		Baseline*, Day 1 to Day 3, Day 5, Day 7, Day 8, Day 15 and Day 22
Platelet Count		Baseline*, Day 2 to Day 8, Day 15, Day 22 and confirmatory assessments

Adapted from Table 4, Section 9.5.1.3, CSR NGAM-02, 10 MAR 2015, page 47 of 1244
**Baseline samples were collected within 24 hours prior to the first infusion*

Clinical assessment of bleeding was performed <u>each day</u> from Day 2 through Day 8, on Day 15 and on Day 22. Platelet counts were measured daily from Day 2 through Day 8.

- If no bleeding was evident and the platelet count reached or exceeded the threshold level of $\geq 30x10^9$/L and was at least double the Baseline value, a confirmatory assessment was performed 7 days after this threshold had been reached or exceeded.[5]
- If no bleeding was evident and the platelet count reached or exceeded the threshold level of $\geq 100x10^9$/L and was at least double the Baseline value, a <u>second</u> confirmatory assessment was performed 7 days after this threshold had been reached or exceeded.
- If bleeding was evident, bleeding severity was assessed by the treating investigator using a 6-point verbal rating scale.[6] If a subject had an unscheduled

[5] Confirmatory assessments were performed between Day 9 and Day 14 and consisted of platelet count, brief physical examination and bleeding assessment.
[6] Buchanan GR, Adix L: Grading of hemorrhage in children with idiopathic thrombocytopenic purpura. *J.Pediatrics* 2002;141:683-688

visit between study days due to occurrence of any new or altered bleeding, an additional platelet count was performed and severity of bleeding assessed.

Monitoring of TEAEs was performed until Day 63. Viral marker samples were assessed at Baseline, Day 22, and Day 63 as indicated in Table 15.

6.3.5 Directions for Use
The infusion was initiated at a rate 0.01 mL/kg/min (60 mg/kg/h) for the first 30 minutes, 0.02 mL/kg/min (120 mg/kg/h) for the second 30 minutes, 0.04 mL/kg/min (240 mg/kg/h) for the third 30 minutes, and 0.08 mL/kg/min (480 mg/kg/h) for the remainder of the infusion, as tolerated.

6.3.6 Sites and Centers
A total of 41 sites were initiated but subjects were enrolled at only 20 of these sites. .
Site 01 – Prof. Dr. Abdulgabar Salama (Germany)
Site 03 – Assoc. Prof. Dr. Evgeniy Hadjiev (Bulgaria)
Site 06 – Assoc. Prof. Nikolay Tzvetkov (Bulgaria)
Site 07 – Dr. Jan Straub (Czech Republic)
Site 08 – Prof. Jiri Mayer (Czech Republic)
Site 09 – Dr. Hani Hlusi (Czech Republic)
Site 10 – Dr. Daniel Lysak Czech Republic)
Site 19 – Dr. Shashikant Janardan Apte (India)
Site 20 – Dr. Shailesh R. Singi (India)
Site 23 – Prof. Andrzej Hellmann (Poland)
Site 25 – Dr. Wojeiech Homenda (Poland)
Site 28 – Dr. Gabriela Borsaru (Romania)
Site 30 – Dr. Emanuil Gheorghita (Romania)
Site 35 – Dr. Igor L. Davydkin (Russia)
Site 36 – Dr. Valentina Ivanova (Russia)
Site 37 – Dr. Natalia Glushko (Ukraine)
Site 40 – Prof. Svitlana Sivkovych (Ukraine)
Site 42 – Prof. Tatiana Pospelova (Russia)
Site 44 – Dr. Olga Bugrova (Russia)
Site 45 – Dr. Vadim Tyrenko (Russia)

6.3.7 Surveillance/Monitoring
The assessments were adequate for the purposes of the study.

6.3.8 Endpoints and Criteria for Study Success
Primary endpoint

- Response Rate, i.e., proportion of eligible subjects (i.e., subjects meeting the enrollment criteria) demonstrating a platelet count elevation $\geq 50 \times 10^9$/L within 7 days after the 1st infusion (lower bound of 97.5% CI: ≥ 0.6) in the FA set and for the PP1 set (PP analysis). Analysis populations are described below in section 6.3.10.1

Secondary endpoints (Additional Response Rates)

- Alternative Response (AR): increase in platelet count to **≥30 x 10^9/L** and 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): increase in platelet count to **≥100 x 10^9/L**, confirmed on at least 2 separate occasions at least 7 days apart, and **absence of bleeding**
- Loss of AR/CR: AR/CR fulfilled (including the confirming platelet count), but deteriorated afterwards
- 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 ≥50x10^9/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

6.3.9 Statistical Considerations & Statistical Analysis Plan

The *a priori* responder threshold of 0.60 (proportion of responders with a platelet count ≥50 x 10^9/L within 7 days after the 1st infusion) was calculated from an historic control value of p_0=0.75 and a region of indifference of δ=0.015. The null hypothesis (H_0: p ≤p_0−δ) was tested at a 1-sided significance level of α=0.025.

6.3.10 Study Population and Disposition

6.3.10.1 Populations Enrolled/Analyzed

Four populations were studied:

- Enrolled Population (Total Population): all subjects enrolled in the trial
- Treated Population (Safety Population): subjects receiving any PANZYGA
- Completed Population: subjects not withdrawn from the study
- Terminated Early Population

Four datasets were analyzed:

- Safety Set: subjects receiving any Panzyga
- Full Analysis (FA) Set: all subjects in the Safety Set who satisfied all major eligibility criteria and for whom at least 1 post-baseline measurement of platelet concentration data was available. This dataset was used for the primary endpoint.
- 1st Per Protocol (PP1) Set: all subjects in the FA set excluding those who showed major protocol violations before the primary efficacy endpoint (Day 8) was reached that potentially could affect evaluation of the primary endpoint. This definition ensured that protocol violations at a later time point did not result in unjustified exclusions from the primary analysis.
- 2nd Per Protocol (PP2) Set: all subjects in the FA set excluding those who showed major protocol violations, especially subjects who took prohibited co-

medications that potentially could affect evaluation of the secondary endpoints.

6.3.10.1.1 Demographics
Males slightly outnumbered females 23 *versus* 17. Their mean and median age was 36.7 and 32 years, respectively. All subjects were Caucasian (except for 4 Asians) and not Hispanic/Latino (except for one non-reported).

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
N/A

6.3.10.1.3 Subject Disposition
A total of 40 subjects were enrolled at 20 study sites. The first subject was screened and enrolled in the study on (b) (6) (Subject (b) (6)) and the last subject (Subject (b) (6)) completed the study on (b) (6).

Table 16 indicates that of the 40 enrollees, none withdrew prior to first administration of Panzyga. However, 9 subjects (22.5%) withdrew prematurely after one or more doses. Overall, 31 subjects (77.5%) completed the study.

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

Disposition	Number of Subjects	
	N	%
Enrolled (Total Set)	40	100.0%
Treated (Safety Set)	40	100.0%
Completed	31	77.5%
Terminated Early	9	22.5%

Adapted from Table 14.1.1.1, CSR NGAM-02, 5 MAR 2015, page 133 of 1244

Reasons for withdrawal included the following:

- Required other chronic ITP drug treatment: 3 subjects (7.5%) (#(b) (6))
- Death: 2 subjects (5.0%) (#(b) (6))
- Withdrawal of consent: 2 subjects (5.0%) (Subjects (b) (6))
- Worsening autoimmune thrombocytopenia TEAE assessed as not related and occurring 13 days after the first infusion: Subject (b) (6) (2.5%)
- Lost to follow-up following Day 22 visit: Subject (b) (6) (2.5%)

6.3.11 Efficacy Analyses
6.3.11.1 Analyses of Primary Endpoint
The primary endpoint, increased platelet count ≥50 x 10^9 /L within 7 days after the 1st infusion, was met in 29/36 (80.6%; 95% CI: 63.98% to 91.81%) FA set subjects. Since the lower limit of the one-sided 97.5% CI for the proportion of responders was above the prespecified reference value (0.6), the null hypothesis was rejected and efficacy confirmed. A similar result was obtained using the PP1 set: 27/33 subjects (81.8%; 95% CI: 64.54% to 93.02%) were responders.

Reviewer Comment

As prespecified in the original protocol, the FA set (subjects who met the eligibility criteria and for whom at least 1 post-baseline measurement of platelet concentration data was available), was the population to be used for the primary endpoint analysis. Use of a quasi-per protocol population instead of an intent-to-treat population for the primary analysis was discussed with the OBE reviewer and Team Leader and determined to be acceptable in a single-arm, open label study.

A *post hoc* analysis conducted by the applicant and confirmed by FDA discovered that 4/40 treated but ineligible subjects had been enrolled: subject #(b) (6) (platelet count of >20 x 10^9/L); subject #(b) (6) (Evans syndrome; receiving mycophenolate mofetil, a prohibited medication); subject #(b) (6) ((b) (6) positive; receiving dapsone, a prohibited medication); subject #(b) (6) ((b) (6) positive). Overall, 29 ("responders") of the 36 eligible subjects met the statistical criterion for success, i.e., lower bound of the one-sided 97.5% CI ≥0.6.

6.3.11.2 Analyses of Secondary Endpoints

Analyses of AR and CR, non-response (platelet count failed to increase to ≥50 x 10^9/L within 7 days after the 1st infusion), and loss of AR/CR were performed for the FA set (N=36) and the PP2 set (N=32).

- In the FA set (Table 17a), an AR was observed in 24/36 subjects (66.7%) and a CR in 18/36 subjects (50%). Fifteen subjects (41.7%) met the non-response criterion.
- In the PP2 set (Table 17b), an AR was observed in 22/32 subjects (68.8%) and a CR in 16/32 subjects (50%).

Table 17a: Alternative Response (AR), Complete Response (CR), Non-Response and Loss of Alternative Response/Complete Response in the Full Analysis Set (N=36)

Secondary Endpoint	Subjects (N) Included	Subjects (N) Meeting Prespecified Definition	Percent	95% CI	
				Lower	Upper
Alternative Response (AR)	36	24	66.7	49.03	81.44
Complete Response (CR)	36	18	50.0	32.92	67.08
Non-response	36	15	41.7	25.51	59.24
Loss of AR	24	11	45.8	22.55	67.18
Loss of CR	18	14	77.8	52.36	93.59

Table 17b: Alternative Response (AR), Complete Response (CR), Non-Response and Loss of Alternative Response/Complete Response in the Per-Protocol 2 Set (N=32)

Secondary Endpoint	Subjects (N) Included	Subjects (N) Meeting Prespecified Definition	Percent	95% CI	
				Lower	Upper
Alternative Response (AR)	32	22	68.6	49.99	83.88
Complete Response (CR)	32	16	50.0	31.89	68.11
Non-response	32	12	37.5	21.10	56.31
Loss of AR	22	11	50.0	28.22	71.78
Loss of CR	16	13	81.3	54.35	95.95

Adapted from Table 14.2.1.1.2.1, CSR NGAM-02, 5 MAR 2015, page 247 of 1244

Alternative Response (AR): increase in platelet count to ***≥30 x 10^9/L*** *and 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): increase in platelet count to ***≥100 x 10^9/L****, confirmed on at least 2 separate occasions at least 7 days apart, and absence of bleeding;*
Loss of AR/CR: AR/CR fulfilled (including the confirming platelet count), but deteriorated afterwards
Non-response: platelet count failed to increase to ≥50 x 10^9/L within 7 days after the 1st infusion

In the FA set, 11/24 subjects (45.8%) who initially met the AR criterion had loss of AR, while 14/18 subjects (77.8%) who initially met the CR criterion had loss of CR. In some cases, a subject satisfied more than 1 category of response or the clinical picture did not tally precisely with the respective category. Specifically, subject #(b) (6) fulfilled the definition of both AR and nonresponse; thus, the sum of subjects with an AR and a non-response was 39, although there were only 36 subjects in the FA set; Subject #(b) (6) fulfilled the definition of AR and a non-response, so the sum of subjects with an AR and non-response was 34, even though there were only 32 subjects in the PP2 set.

Subject #(b) (6)
Subject #(b) (6) reached the platelet count threshold for an AR on Day 3 and for CR on Day 5 and remained above the thresholds until Day 8, but at the confirmatory assessment the platelet count was below both thresholds and the subject fulfilled the definition of non-response. However, on Day 15 the subject started treatment with methylprednisolone and on Day 22 the platelet count was again above both thresholds, i.e., the subject also fulfilled the definition of AR and CR. In the PP2 Set, the subject met the criterion for non-response.

Subject #(b) (6)
Subject #(b) (6) reached the platelet count threshold for an AR on Day 2, but by Day 8 and at the confirmatory assessment 2 days later, platelet count had decreased again to <30x10^9/L, i.e., the subject met the criterion for non-response. At the Day 15 visit, however, the platelet count increased again and the subject met the criterion for an AR. The investigator confirmed that no measures had been taken or concomitant medication given that might have affected the platelet count and the subject was, therefore, included in both the FA and PP2 set.

Subject #(b) (6)
Subject #(b) (6) reached the platelet count threshold for an AR on Day 2 and for CR on Day 3. Her platelet count remained above the threshold for AR until the confirmatory assessment when the platelet count was below both thresholds and the subject met the criterion for non-response. This subject had been on a stable dose of 5 mg prednisolone prior to the study and continued up to Day 4. However, the subject discontinued the medication temporarily and restarted on Day 9. They are listed as having a minor violation.

Figure 2 and Table 18 show that 29 subjects (80.6%) in the FA set (N=36) achieved a "response" (i.e., an increase in platelet count to ≥50x10^9/L). Mean and median values (95% confidence values) for time-to-response were 1.8 days (1.50 to 2.09) and 2.0 days (1.00 to 2.00), respectively.

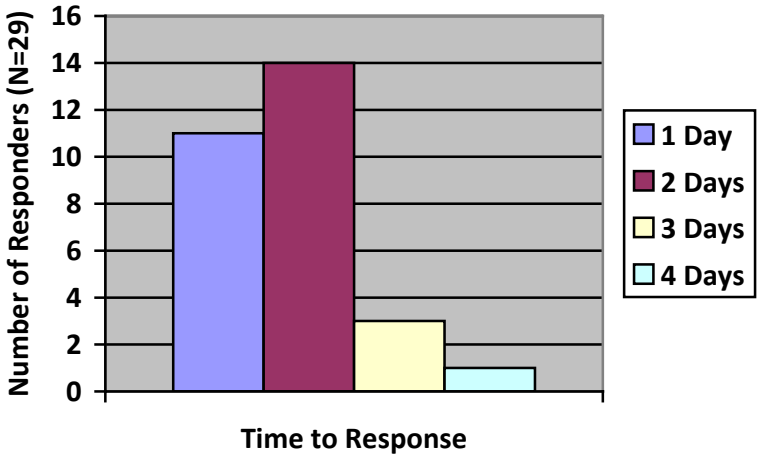

Figure 2: 29/36 subjects in the FA set "responded" to PANZYGAanzyga within 7 days of the 1st infusion. Most responders increased their platelet count to ≥50x10^9) on **Day 2** (14 subjects, 48.3%) or Day 1 (11 subjects, 37.9%).
Adapted from Table 14.2.1.2.1.1, CSR NGAM-02, 5 MAR 2015, page 247 of 1244

Table 18: Time to Response, Alternative and Complete Response (Responders only) (FA Set, N=36)

Parameter	No. of Subjects (Responders Only) (N[%])	Median Time to Response (Days)	95% CI	
			Lower	Upper
Time to response	29 (80.6%)	2.0	1.00	2.00
Time to AR	24 (66.7%)	1.0	1.00	2.00
Time to CR	18 (50.0%)	2.0	2.00	2.00

Adapted from Tables 14.2.1.2.1.1 and 14.2.1.2.2.1, CSR NGAM-02, 5 MAR 2015, pages 245 and 254 of 1244

The duration of response (days) among the 29/36 responders is depicted in Figure 3. Mean and median values (95% CI values) were 12.4 days (10.17 to 14.59) and 14.0 days (10.00 to 17.00), respectively. No bleeding episodes were observed in 13 subjects (36.1%) at Baseline; this number increased to 26 subjects (72.2%) at Day 22/ET. Subject (b) (6) developed new bleeding sites and a worsening of minor bleeding at Baseline to severe at Day 15 and Day 22/ET.

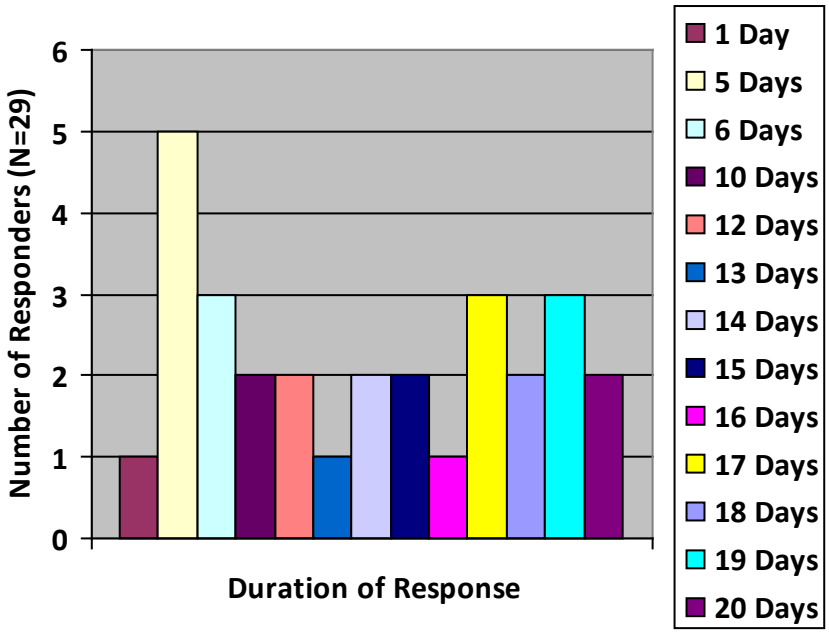

Figure 3: The platelet count threshold (≥50x10^9/L) in response to Panzyga was exceeded for >1 week in 20/29 responders and >2 weeks in 13/29 responders.
Adapted from Table 14.2.1.3.1.1, CSR NGAM-02, 5 MAR 2015, page 263 of 1244

6.3.11.3 Subpopulation Analyses
Not applicable.

6.3.11.4 Dropouts and/or Discontinuations
Three subjects (Subject (b) (6)) withdrew from the study as they required other drug treatment for chronic ITP. They were all from the same study site in India (Site 19). All 3 subjects were non-responders based on the secondary efficacy parameters (Subject (b) (6) was a responder for the primary efficacy criterion, but the response was too brief to fulfill the definition of AR).

6.3.11.5 Exploratory and Post Hoc Analyses
Not applicable.

6.3.12 Safety Analyses

- Exposure
  All 40 subjects received at least 1 dose of Panzyga. Duration (mean ± SD) of treatment was 1.93 days (± 0.27 days), ranging from 1 to 2 days. A total of 77 infusions were administered, with 37 subjects (92.5%) receiving 2 infusions and 3 subjects (7.5%) receiving 1 infusion. Almost all infusions were given according to the infusion rates defined in the protocol, with 76 of the 77 infusions (98.7%) given at the 0.01 and 0.02 mL/kg/min rate, 75 (97.4%) given at the 0.04 and 0.08 mL/kg/min rate, 1 (1.3%) given at a rate of 0.03 mL/kg/min, and 11 (14.3%) with interruptions. Virtually all enrolled subjects (N=39 or 97.5%) received at least 1 infusion at the maximum permissible rate of 0.08 mL/kg/min.

6.3.12.1 Methods

Baseline investigations were completed prior to infusion of Panzyga. These included demographic data, medical and surgical history, and a record of all previous drug and non-drug therapy during the last 4 months; a full physical examination; and assessment of bleeding and blood sampling for laboratory parameters. The first Panzyga administration occurred within 24 hours from Baseline. A daily dose of 1 g/kg (equivalent to 10 mL Panzyga/kg) was administered for 2 consecutive days, for a total of 2 g/kg.

During Panzyga administration, vital signs were monitored at the start of infusion, every 30 minutes during the infusion and about 1 hour after the end of the infusion. Before the second infusion, blood parameters were tested. If a clinically significant change (defined as out of the reference range, low or high) was noticed in the tested parameters and it was thus deemed not justifiable (for safety reasons) to administer the second infusion of study medication, the subject was withdrawn from the study and followed for safety.

During study visits, physical examinations were performed and blood parameters were assessed. Viral marker samples were assessed at Baseline, during Day 22 and during Day 63. A bleeding assessment was performed on each day from Day 2 through Day 8 and on Day 15 and Day 22. Confirmatory assessment visit(s), if applicable, took place and consisted of platelet count, brief physical examination and bleeding assessment. In case of bleeding, severity was assessed by the treating investigator using a 6-point verbal rating scale (see footnote 6 of this memo). If a subject had an unscheduled visit between study days due to occurrence of any new or altered bleeding, an additional platelet count was performed and the severity of bleeding assessed. Monitoring of TEAEs was performed until Day 63. A TEAE was defined as a treatment- emergent TEAE if onset or worsening occurred following the first infusion of Panzyga. Subjects who were non-responders or who needed emergent chronic ITP treatment, other than specified in this protocol, were followed for safety with all assessments until Day 63. If a subject withdrew prematurely, a study termination visit was performed with all assessments for the Day 22 study visit (except for Parvovirus B19).

6.3.12.2 Overview of Adverse Events

As depicted in Table 19 and 20 (below), of the 40 subjects in the Safety Set, 30 (75.0%) experienced ≥1 TEAE. The most frequently reported TEAEs were headache (17 subjects), pyrexia (9 subjects), autoimmune thrombocytopenia (6 subjects), and nausea (6 subjects). A significant TEAE (i.e., requiring intervention) was experienced by 13 (33%) subjects and a severe intensity TEAE by 5 (13%) subjects. A total of 58 TEAEs probably or possibly related to Panzyga were experienced by 23 subjects (57.5%). Most TEAEs were mild (85 TEAEs) or moderate (22 TEAEs) in intensity, but 5 subjects experienced 15 TEAEs that were severe in intensity:

- Subject #(b) (6) experienced severe headache, nausea and vomiting
- Subject #(b) (6) experienced severe headache, chills, nausea and vomiting
- Subject #(b) (6) experienced severe cerebral hematoma, muscle spasm, hypotension, and worsening of pre-existing autoimmune thrombocytopenia
- Subject #(b) (6) experienced worsening of pre-existing autoimmune thrombocytopenia

- Subject #(b) (6) experienced severe pneumonia, respiratory failure and sepsis

Reviewer Comment

Treatment failure was evident in 2 subjects. Subject #(b) (6) had a history of Evans syndrome (major protocol violation) which likely contributed to worsening thrombocytopenia and led to intracerebral hematoma and death. Subject #(b) (6) responded to study drug with a peak platelet count of 415 x 10^9/L which subsequently decreased to 9 x 10^9/L and necessitated laparoscopic splenectomy. She subsequently recovered and was discharged from the hospital.

Table 19: Summary of TEAEs (Safety Set, N=40)

	Number of Subjects N (%)	Number of Events (%) n (%)
TEAEs	30 (75.0%)	122 (100%)
Related TEAEs[2]	23 (57.5%	58 (47.5%)
SAEs	6 (15.0%)	10 (8.2%)
Related SAEs	1 (2.5%)	1 (0.8%)
Other significant TEAEs[1]	13 (32.5%)	43 (35.2%)
Severe intensity TEAEs	5 (12.5%)	15 (12.3%)
Nonserious TEAEs	28 (70.0%)	112 (91.8%)
TEAEs leading to withdrawal from study	1 (2.5%)	1 (0.8%)
TEAEs leading to withdrawal of Panzyga	3 (7.5%)	5 (4.1%)
Death	2 (5.0%)	2 (1.6%)
Infusional TEAEs	24 (60.0%)	71 (58.2%)

Adapted from Tables 14.3.1.1.1, 14.3.1.1.3, and 14.3.1.3, CSR NGAM-02, pages 535, 538 and 543 of 1244

1Nonserious and dose changed or product withdrawn or other action or drug therapy started

[2]Possibly or probably related

Table 20: Subjects with TEAEs (Frequency ≥5.0% of Subjects; Safety Set, N=40)

		No. of Subjects (%)	No. of Events
MedDRA SOC	**Preferred Term[1]**	**N (%)[2]**	**n**
Subjects with ≥1 TEAE		30 (75.0%)	122
Nervous system disorders		18 (45.0%)	34
	Headache	17 (42.5%)	22
	Dizziness	3 (7.5%)	4
General disorders & administration site conditions		14 (35.0%)	16
	Pyrexia	9 (22.5%)	9
	Asthenia	2 (5.0%)	3
	Chills	2 (5.0%)	3
Blood & lymphatic system disorders		11 (27.5%)	24
	Autoimmune thrombocytopenia	6 (15.0%) 5 (12.5%)	8 7
	Anemia	2 (5.0%)	2
	ITP (exacerbation)		
Gastrointestinal disorders		10 (25.0%)	17
	Nausea	6 (15.0%)	6
	Vomiting	4 (10.0%)	4
Infections & infestations		5 (12.5%)	7
Investigations		4 (10.0%)	5
Musculoskeletal and connective tissues disorders		3 (7.5%)	3
Skin and subcutaneous tissue disorders		3 (7.5%)	3

Metabolism and nutritional disorders	2 (5.0%)	3
Eye disorders	2 (5.0%)	2
Respiratory, thoracic & mediastinal disorders	2 (5.0%)	2
Vascular disorders	2 (5.0%	2

Adapted from Tables 14.3.1.2 and 14.3.1.5, CSR NGAM-02, 5 MAR 2015, pages 539 and 553 of 1244
[1]Only SOC shown if no preferred term incidence was ≥5% within a particular SOC
[2]Percent relates to number of subjects

6.3.12.3 Deaths

Two subjects died during the study, one from an unrelated cerebral hematoma (subject #(b) (6)) and the other from unrelated sepsis (subject #(b) (6)).

Subject #(b) (6): Cerebral Hematoma

A 25-year-old Caucasian male subject was enrolled on (b) (6) despite a PMH of Evans syndrome (since NOV-2009), an exclusion criterion. Medical history included chronic infection due to chronic immunosuppressive therapy, retinal hematoma, bronchitis, skin petechiae, and subfebrile body temperature. Previous treatment for chronic ITP included IGIV, dexamethasone, Solu-medrol, Mabthera, prednisone, and Sanimmun, with poor responses to therapy. Ongoing treatment included azathioprine and mycophenolate mofetil (also an exclusion criterion).

Physical examination showed cutaneous petechiae and hematomas. Skin bleeding was rated as severe, oral bleeding as minor, and overall bleeding severity as mild. Epistaxis was not present at Baseline.

On (b) (6), just prior to study enrollment, the subject was hospitalized due to acute worsening of chronic thrombocytopenia with progressive signs of bleeding (hematuria, petechiae). On admission, there were no signs of Evans syndrome and as the last relapse of Evans syndrome was in 2010, the subject was enrolled into clinical study NGAM-02. Platelet count at Baseline was 1 x 10^9/L and increased to 14 x 10^9/L on Day 4, then decreased to between 2 x 10^9/L and 4 x 10^9/L from Day 5 up to death. Panzyga was administered per protocol on (b) (6) and (b) (6), with a total daily dose of 107 g x 2, i.e., 214 g. From (b) (6) onward, the subject was somnolent. Bleeding at this time was assessed as mild and included minor oral bleeding and subcutaneous hematoma. A head CT performed on (b) (6) showed an intraparenchymal hematoma. A second CT showed hematoma expansion. Physical examination showed hypotension and severe nasal bleeding which required temporary frontal nasal tamponnade. The chest X-ray showed interstitial pulmonary edema and signs of pulmonary hypertension. On (b) (6), the subject became unconscious and experienced convulsions accompanied by hypoxemia. Seizures re-occurred and endotracheal intubation was performed. After early discontinuation of sedation, no improvement of consciousness status was noted and brain stem reflexes were not present. On the morning of (b) (6), transcranial Doppler showed cessation of perfusion in the cerebral artery bilaterally. Brain death was confirmed

by scintigraphy. The immediate cause of death was cerebral edema due to chronic ITP complicated by intracerebral bleeding.

Reviewer Comment
Enrollment of subject #(b) (6), who had a PMH of Evans syndrome, represented a major protocol violation because Evan syndrome was an exclusion criterion. Evans syndrome is an autoimmune disease characterized by direct Coombs'-positive autoimmune hemolytic anemia in conjunction with immune-mediated thrombocytopenia. The etiology is unknown. Since this subject had two conditions that can result in life-threatening coagulopathy, it is unlikely that Panzyga played a role in his demise.

Subject #(b) (6): Pneumonia, Respiratory Failure, Sepsis

A 57-year-old Caucasian male subject with primary ITP was enrolled on (b) (6). His PMH included a decreased platelet count of 120 x 10^9/L in 2011, identified during an episode of acute respiratory failure. A month prior to this event he had been vaccinated against the flu and experienced a prodrome of acute respiratory disease within 3 days of vaccination. Later in 2011, when his platelet count further decreased to 67 x 10^9/L, a diagnosis of chronic primary ITP of moderate severity subsequently was confirmed on (b) (6). A splenectomy was not performed.

Later that year, despite contraindications, he was re-vaccinated against the flu and again experienced prodromal symptoms within a few days. In 2012 he experienced hypothermia, rhinitis, weakness, sweating, chills and pain in muscles and joints, which he treated himself with non-steroidal anti-inflammatory drugs. After 1 week he developed a non-productive cough and pyrexia up to 40°C, and a week later he received symptomatic treatment as an outpatient.

On (b) (6), he was hospitalized with pneumonia, effusion pericarditis, thrombophlebitis, mild anemia and severe thrombocytopenia. He received treatment and recovered from the pneumonia, pericarditis and fever but severe thrombocytopenia (20-35x10^9/L) persisted. On (b) (6) he received treatment with corticosteroids and immunoglobulin for ITP. His condition improved but platelet count remained low.

Physical examination at Baseline showed minor skin bleeding, assessed as minor. Neither epistaxis nor oral bleeding were present. Except for low platelet count (18x10^9/L), none of the laboratory values was assessed as clinically significant.

Panzyga was administered uneventfully as per protocol on (b) (6) (Day 1) and (b) (6) (Day 2). Total daily dose was 61 g (122 g total). From (b) (6), the subject experienced non-serious acute bronchitis with fever. Laboratory tests showed an elevated WBC count with abnormally low neutrophils and abnormally high monocytes. On (b) (6), his platelet count decreased to 6 x 10^9/L accompanied by minor epistaxis. As a result, the dose of prednisolone was increased to 1000 mg QD IV. Skin hemorrhages improved and as of (b) (6)

(b) (6), the dose of prednisolone was reduced to 60 mg BID p.o. On (b) (6), severe bleeding with internal hemorrhage in muscles was detected. This was accompanied by anemia, fever, tachycardia, severe respiratory failure and rales. A CT scan confirmed pneumonia (SAE) due to *Achromobacter xylosoxidans*. He was treated with amikacin and supplemental oxygen therapy.

On (b) (6), a new suspected hemarthrosis of the right ankle was diagnosed. Laboratory tests showed a platelet count of 1 x 10^9/L. On (b) (6), following symptoms of pneumonia, the diagnosis was confirmed by CT scan. On (b) (6), he developed severe fever. *Stenotrophomonas maltophilia* was isolated from the sputum, although blood was sterile. Laboratory signs of systemic infection were positive. Diagnosis of sepsis (SAE) was made based on a procalcitonin test. Therapy included cephaperazone-sulbactam, pipacillin-tazobactam and levofloxacin.

On (b) (6), his fever worsened, a CT scan showed increased pulmonary infiltration, and signs of multi-organ failure became apparent (respiratory failure, hypotension). Tigecycline IV and dopamine were administered. On (b) (6), he developed pulmonary edema and shock, dying on the same day. Cause of death was sepsis with severe immune thrombocytopenia. An autopsy confirmed the presence of pneumonia. The investigator assessed the pneumonia, respiratory failure and sepsis as serious and not related to Panzyga.

Reviewer Comment

Subject #(b) (6) appears to have exhibited signs and symptoms of both ITP and immunodeficiency, since his PMH included episodes of acute respiratory failure after exposure to influenza vaccine as well as spontaneously. It is unlikely that Panzyga was causally related to his pneumonia, respiratory failure and sepsis. One possibility is that he suffered from immune-incompetence and that this condition led to his demise.

6.3.12.4 Non-fatal Serious Adverse Events

Table 21 shows that 5 subjects experienced 8 non-fatal SAEs. One SAE, aseptic meningitis, was possibly related to Panzyga (Subject (b) (6)) and ultimately resolved.

Table 21: Listing of Serious Adverse Events (Safety Set, N=40)

Subject #	Preferred Term	Intensity	Outcome	Causality
(b) (6)	Autoimmune thrombocytopenia	Mild	Resolved	Not related
	Pneumonia	Moderate	Resolved	Not related
	Dysphagia	Mild	Resolved	Not related
	Autoimmune thrombocytopenia	Mild	Resolved	Not related
	Cerebral hematoma	Severe	Fatal	Not related
	Autoimmune thrombocytopenia	Severe	Resolved	Not related
	Meningitis aseptic	Moderate	Resolved	Possible
	Pneumonia	Severe	Not resolved	Not related
	Respiratory failure	Severe	Not resolved	Not related
	Sepsis	Severe	Fatal	Not related

Adapted from Listings 16.2.7.1.2 and 16.2.7.2.1, Appendix 16.2.7, CSR NGAM-02, 24 FEB 2014, pages17 and 47 of 252

Below is a brief narrative of the Subject #(b) (6) whose aseptic meningitis was possibly related to treatment.

Subject #(b) (6) was a 28-year-old Caucasian male subject who had not undergone a splenectomy since chronic primary ITP was first diagnosed. He had no other relevant medical history and there were no abnormal findings on physical examination. Baseline platelet count was $7x10^9$/L and assessed as clinically significant. Panzyga was administered on (b) (6) (Day 1) and (b) (6) (Day 2). Total daily dose was 76 g. On Day 2, the subject developed a headache and fever (38.1°C). He was admitted to hospital and underwent lumbar puncture on the same day. Spinal fluid analysis showed cytosis with 3600 cells/uL, 3% lymphocytes and 97% neutrophils. The CSF was clear and colorless. Biochemical analysis revealed protein 1058 g/L, creatine phosphokinase 1.3 U/L and glucose 3.46 mmol/L. Spinal fluid analysis did not detect any bacteria; there were 7-10 neutrophils and 5-7 lymphocytes per field of vision. A CBC showed a WBC of $9.95x10^3$/uL, with 86.7% neutrophils. Aseptic meningitis was diagnosed and treated started with ceftriaxone, Amikacin and paracetamol. Results of a spinal fluid analysis on (b) (6) were normal (cytosis 7.2 cells/uL). The subject recovered and was discharged on (b) (6). No action was taken regarding Panzyga due to the SAE. The investigator assessed the event as serious with hospitalization required or prolonged as the reported criterion. The event was assessed to be of moderate severity and possibly related to Panzyga. Octapharma classified this serious case (hospitalization) as listed and possibly related to administration of Panzyga.

Reviewer Comment

I agree with the investigator's assessment of possible relatedness for aseptic meningitis. Aseptic meningitis has been reported following administration of IGIV products (*Ann Intern Med* 1994;121:259-62). Possible inciting factors include IgG itself, stabilizers found in each of the formulations, cytokine release triggered by the therapy, or cerebrovascular sensitivity.

6.3.12.5 Adverse Events of Special Interest (AESI)

- No cases of hemolysis, thromboembolism, renal dysfunction or TRALI were reported.
- Infusional TEAEs:

  As depicted in Table 22 and 23, the most commonly reported infusional TEAEs were headache, pyrexia, nausea and vomiting. Of the 40 enrolled subjects, 30 (75%) experienced at least 1 adverse event during the study; 23 (58%) subjects experienced 58 adverse events (48%) that were probably or possibly related. Of the 122 adverse events recorded overall, 71 (58%) were classified as infusional adverse events, of which 54 were probably or possibly related and occurred in 24 subjects (60%). The frequency of infusional TEAEs was lowest at the lowest 3 rates of 0.01, 0.02 and 0.04 mL/kg/min (between 1 and 3 TEAEs) and highest following the 0.08 mL/kg/min rate (29 of 77 infusions (37.7%), the final rate for 75 of 77 infusions.

Reviewer Comment

I tend to concur with the investigator's assessment of causality, since identical infusional TEAEs have been reported with other IGIV products. These events are rate-related and typically diminish with temporary cessation of the infusion or a reduction in the infusion rate.

Table 22: Number of Subjects with Infusional AEs (Frequency ≥5.0%) (Safety Set, N=40)

TEAE	Number of Subjects (%)/Number of Infusional TEAEs Within 72 hours of Infusion
Any TEAE	24 (60.0%)/71
Nervous system disorders	18 (45.0%/26
Headache	17 (42.5%)/21
Dizziness	3 (7.5%)/3
General disorders	12 (30%)/13
Pyrexia	8 (20.0%)/8
Asthenia	2 (5.0%)/2
Chills	2 (5.0%)/2
Blood disorders	4 (10%)/7
Anemia	3 (7.5%)/3
Gastrointestinal disorders	9 (22.5%)/14
Nausea	6 (15.0%)/6
Vomiting	4 (10%)/4
Infections	2 (5.0%)/2
Metabolism & nutritional disorders	2 (5.0%)/2
Skin & subcutaneous tissue disorders	2 (5.0%)/2

Adapted from Table 14.3.1.3, CSR NGAM-05, 5 MAR 2015, page 543 of 1244

Table 23: Number of Infusions with Infusional TEAEs (Frequency ≥5.0%) (Safety Set, N=40)

TEAE	All Infusions (N=77) Number of Infusions (%)
Infusions with at least 1 related infusional TEAE	25 (32.5%)
Nervous system disorders	15 (19.5%)
Headache	14 (18.2%)
General disorders	11 (14.3%
Pyrexia	8 (10.4%)
Gastrointestinal disorders	7 (9.1%)
Nausea	5 (6.5%)
Vomiting	4 (5.2%)

Adapted from Table 14.3.1.10.4, CSR NGAM-05, 5 MAR 2015, page 595 of 1244

Reviewer Comment

Headache was the most frequently reported TEAE (18.2%) among chronic ITP adult subjects in NGAM-02. This rate was somewhat lower than the rate reported in NGAM-01 subjects (27.5%) but much higher than the rate reported in NGAM-05 subjects (<5%). Differences in baseline characteristics, disease state and/or random variation due to small sample size likely account for these differences.

6.3.12.6 Clinical Test Results

6.3.12.6.1 Hematology laboratory data

From Baseline to Day 22/End-of-Treatment (ET), median platelet count (10^9/L) doubled in test subjects from 9.00 (range: 0 to 28.00) to 18.00 (range: 1.00 to 295.00), with a peak median value of 171.00 on Day 7.

Reviewer Comment

Although the primary endpoint was met in 29/36 subjects, median platelet count was only 18 x 10^9/L on Day 22/ET, consistent with a transient (1-2 week) response to Panzyga.

Over the same study period, the number of subjects with clinically significant, abnormally low values (outside the reference range) decreased from 29 to 11 whereas the number of subjects with non-clinically significant, abnormally low values increased from 11 to 26 (see Figure 4). Otherwise, no notable changes between Baseline and Day 22/ET in hematology test results were observed.

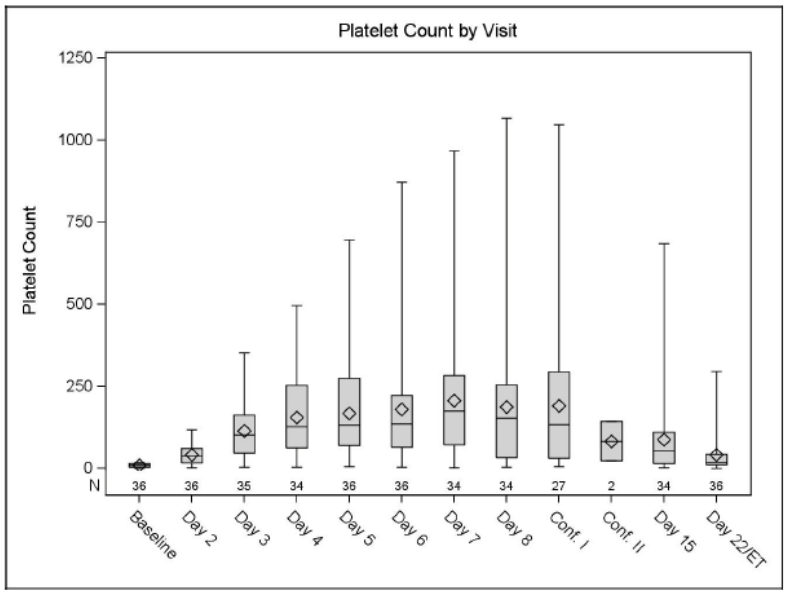

Figure 4: Summary of Platelet Count (x 10 ^{9}/L) By Visit (Safety Set, N=40)
Box plots showing median and interquartile range (band within box), mean (diamond), and minimum and maximum (whiskers). Conf= Confirmatory Assessment; ET=Early Termination; N=Number of subjects.
Source: Listing 16.2.6.1.1, Appendix 16.2.6, CSR NGAM-02, page 5 of 142

6.3.12.6.2 Chemistry, Urinalysis, Viral Markers and Direct Coombs'

- There were no notable changes in mean chemistry test results from Baseline until Day 22/ET
- Urinary hemosiderin was assessed on Day 1, Day 2, Day 3, Day 8 and Day 22. Hemosiderin was negative at all visits in all tested subjects (between 1 and 3 subjects did not have the test performed at each visit).
- HIV, HCV, HBV, HAV and parvovirus B19 were tested at Baseline, Day 22/ET and Day 63 (safety follow-up). If there was a change of the viral status from Baseline to Follow-up and a suspected seroconversion, the viral tests were repeated; if the result was confirmed, additional serological testing was performed. No changes in the viral status from Baseline to Day 22/ET or Day 63

were detected, suggesting that no suspected seroconversion occurred during this study.

- A direct Coombs' test was performed at Baseline and immediately prior to infusion on Days 2, 3 and 8. Negative results were reported at Baseline for all 39 subjects (100.0%) tested (Subject #(b) (6) had missing data at Baseline but tested positive on Day 2, Day 3 and Day 8). A total of 10 Baseline-negative subjects subsequently tested positive (#(b) (6)). As shown in Table 24, Subject #(b) (6) experienced clinically relevant hemolysis (mild), i.e., reported as a TEAE. This event was considered related to Panzyga but did not require treatment.

Table 24: Hemolysis-related Laboratory Parameters in Subject #(b) (6)

Parameter	Baseline	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day8
Hgb (g/dL)	12.1	11.3	10.9	10.2	10.1	10.2	10.8	9.9
Plasma-free Hb mg/L)	8.5	127.5	70.1	-	-	-	-	11
Serum Hp (g/L)	0.39	0.41	<0.25	-	-	-	-	<0.25
Serum LDH (U/L)	241	245	364	-	-	-	294	254
Coombs' test	Neg	Pos	Pos	-	-	-	-	Pos*
Platelet Count (x 0^9/L)	15	22	74	117	130	160	179	144

Adapted from Table 14.3.4.1, CSR NGAM-02, 5 MAR 2015, page 610 of 1244
Missing data between Days 3-8 were due to hemolysis according to the investigator.
*anti-A

Reviewer Comment
Hemolytic transfusion reactions have been reported with IGIV therapy. They result from passive transfer of anti-A (as in Subject #(b) (6)) and anti-B hemagglutinins.

6.3.12.6.3 Vital Signs, Physical Findings, and Other Observations Related to Safety
The following TEAEs were considered related to vital signs.

- Pyrexia

A total of 9 subjects experienced pyrexia. Investigator attribution was probable in one subject, unrelated in another, and possible in the remainder.

Reviewer Comment
Pyrexia is listed as an adverse reaction in the labeling of other IGIV products. Thus, I would agree that the etiology is possibly-probably related to the use of Panzyga.

- Tachycardia

Subject #(b) (6) experienced one episode of tachycardia 14 days after the first infusion; the event was mild and not related. The subject also had sepsis, pneumonia, respiratory failure and anemia.

- Hypotension

Subject #(b) (6) experienced one episode of hypotension 5 days after the first infusion; the event was severe and not related according to the investigator.

Reviewer Comment
Single episodes of tachycardia and hypotension occurring 5 days to 2 weeks after infusion of Panzyga are unlikely to be product-related.

6.3.12.7 Dropouts and/or Discontinuations
Subject #(b) (6) withdrew from the study after receiving 2 infusions due to a worsening autoimmune thrombocytopenia TEAE that was considered unrelated to study medication and required treatment with a different IGIV (other than Panzyga); he did not attend the Day 63 safety follow-up.

Subject #(b) (6) had study medication withdrawn due to TEAEs (chills and anemia in 1 subject each, and headache, pyrexia and nausea in 1 subject), all of which were considered related to study medication.

Reviewer Comment
When compared with the NGAM-02 study population as a whole, it seems unlikely that worsening autoimmune thrombocytopenia in subject #(b) (6) was related to Panzyga. The temporal relationship between Panzyga infusion and other TEAEs has been reported with other IGIV products and supports a causal relationship.

6.3.13 Study Summary and Conclusions

A total of 29/36 FA subjects (80.6%, exact Clopper-Pearson 95% CI of 63.98% to 91.81%) and 27/33 PP 1 subjects (81.8%, exact Clopper-Pearson 95% CI of 64.54% to 93.02%) had a positive response. The null hypothesis was rejected because the lower limit of the one-sided 97.5% CI for the proportion of responders was >0.6. Secondary endpoint analyses supported efficacy of Panzyga. Platelet counts increased within 1-2 days after infusion of the product and the response sustained for 14.0 days at >50 $x10^9$/L and 19.0 days at >20 $x10^9$/L.

Two subjects (5.0%) died during the study; both deaths were assessed as unrelated (see prior Reviewer Comments). A total of 6 subjects (15.0%) experienced SAEs, only one of which was considered as possibly-related (aseptic meningitis). One mild, probably-related hemolysis TEAE was reported but did not require treatment. No changes in viral status from Baseline to Day 22/ET or Day 63 were detected. Overall, Panzyga appears comparable to other IGIV preparations in terms of tolerability and safety.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1: Primary Immunodeficiency
7.1.1 Methods of Integration
Only the NGAM-01 population (N=51) was evaluated for efficacy since efficacy was not an endpoint in the NGAM-05 extension study (N=21).

7.1.2 Demographics and Baseline Characteristics
The NGAM-01 population consisted of Caucasian subjects on a 3-week schedule (N=21) and a 4-week schedule (N=30). The number of males (N=33) was twice the number of females (N=18); similar imbalances in sex were observed in subjects aged 2 to <12 years (10 males, 3 females) and 12 to ≤16 (10 males, 2 females). In the NGAM-05 extension study, there were 6 males and 3 females aged 2 to <12 years, and 1 male and 2 females aged 12 to <16 years. Most subjects (84%) were not Hispanic/Latino (14%) and their mean, median and age ranges were 27, 17, and 2 to 65 years, respectively.

7.1.3 Subject Disposition
Adolescent subject #(b) (6) (4-week schedule) was the only enrollee to drop-out or discontinue treatment. He was withdrawn prematurely by the investigator after receiving 9 doses Panzyga. This action was taken because in the investigator's judgment, a dose of 800 mg/kg would be needed to treat an episode of bronchiectasis

7.1.4 Analysis of Primary Endpoint(s)
Study NGAM-01 met its primary efficacy endpoint. Four SBIs (bacterial pneumonia) were observed in 2 subjects with an upper bound of the 99% CI of 0.5033, thus rejecting the null hypothesis of SBI rate ≥1.0 per person-year at the 1% level of significance.

7.1.5 Analysis of Secondary Endpoint(s)
Serum IgG trough levels were nearly constant for both treatment schedules during the course of the study. The percent of subjects experiencing infections was higher in the 3-week schedule cohort (86%) than in the 4-week schedule cohort (70%). The rate of infections per person-year was highest in children (4.475) and lowest in adults (3.260). Mean resolution time was 14.3 days for SBI and 18.4 days for other infections. 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. Half of the subjects experienced absence from work or school due to infections, with the highest percentage of subjects in the 3-week schedule and in children: 13 subjects (61.9%) and 10 subjects (76.9%), respectively.

7.1.6 Other Endpoints
See paragraph 7.1.5 with respect to treatment schedule cohorts, age cohorts, and overall

7.1.7 Persistence of Efficacy
The treatment effect persisted for the 12 month study period. Ongoing IGIV therapy must be continued for the lifetime of the patient.

7.1.8 Product-Product Interactions
Not applicable.

7.1.9 Additional Efficacy Issues/Analyses
Not applicable.

7.1.10 Efficacy Conclusions
When infused every 3 or 4 weeks, Panzyga is effective in reducing the number of SBIs.

7.2. Indication #2: Chronic ITP in Adults
7.2.1 Methods of Integration
Only study NGAM-02, a single, multicenter, uncontrolled trial, was conducted.

7.2.2 Demographics and Baseline Characteristics
Study NGAM-02 (N=40) enrolled 23 adult males and 17 adult females. The population was Caucasian except for 4 Asian (Indian) subjects. Mean (range) age was 37 (18 to 72) years.

7.2.3 Subject Disposition
No subject withdrew prior to the 1st Panzyga dose. However, 9 subjects (22.5%) withdrew prematurely after one or more doses for reasons that included other ITP drug treatment (N=3), death (N=2), withdrawal of consent (N=2), worsening autoimmune thrombocytopenia TEAE (not related) (N=1) and Lost to follow-up (N=1). Four subjects were dropped from the ITT analysis for major protocol violations.

7.2.4 Analysis of Primary Endpoint(s)
NGAM-02 met its prespecified primary efficacy endpoint in 29/36 eligible subjects (4 subjects with major protocol violations were from excluded from the analysis *per protocol*). The platelet count threshold ($\geq$50 x10^9/L) in response to Panzyga was exceeded for >1 week in 20/29 responders and >2 weeks in 13/29 responders

7.2.5 Analysis of Secondary Endpoint(s)
In the FA set, an AR was observed in 24/36 subjects (66.7%) and a CR was observed in 18/36 subjects (50%). Fifteen subjects (41.7%) met the non-response criterion.

7.2.6 Other Endpoints
Not applicable.

7.2.7 Subpopulations
Not applicable.

7.2.8 Persistence of Efficacy
The treatment effect persisted for approximately 14 days.

7.2.9 Product-Product Interactions
Not applicable.

7.2.10 Additional Efficacy Issues/Analyses
Not applicable.

7.2.11 Efficacy Conclusions
When infused for two consecutive days, Panzyga is effective in elevating platelet count to $\geq$50 x 10^9/L.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

NGAM-01, NGAM-05

Subjects had to visit the study site for each planned infusion. Clinical examinations for safety and efficacy evaluations were performed during these visits. Subjects documented the occurrence of infections, AEs, missed days from work or school, inpatient hospital stays and any changes in concomitant therapy between visits in a diary. AEs were assessed in terms of intensity (mild, moderate, severe) and relationship to Panzyga (temporally associated and based on medical judgment by the investigator) and infusion speed at each visit. Blood samples for PK evaluations were taken on the 9th Panzyga infusion day for subjects on the 3-week schedule, or on the 7th Panzyga infusion day for subjects on the 4-week schedule. At the 10th or 12th infusion visit for subjects on the 4-week or 3-week schedule respectively, an additional sample was taken for measles antibody trough titer testing by bioassay. An end of study visit was performed for each subject 3 to 4 weeks (according to the treatment schedule) after the last infusion, or sooner if subject withdrew from the study

NGAM-02

Baseline investigations were completed prior to infusion of Panzyga. The first administration occurred within 24 hours from Baseline. A daily dose of 1 g/kg (equivalent to 10 mL Panzyga/kg) was administered for 2 consecutive days, for a total of 2 g/kg. Vital signs were monitored at start of infusion, every 30 minutes during the infusion and about 1 hour after end of the infusion. Viral marker samples were assessed at Baseline, during Day 22 and during Day 63. A bleeding assessment was performed on each day from Day 2 through Day 8 and on Day 15 and Day 22. In case of bleeding, severity was assessed by the treating investigator using a 6-point verbal rating scale. If a subject had an unscheduled visit between study days due to occurrence of any new or altered bleeding, an additional platelet count was performed and the severity of bleeding assessed. Monitoring of TEAEs was performed until Day 63. If a subject withdrew prematurely, a study termination visit was performed with all assessments for the Day 22 study visit (except for Parvovirus B19).

8.2 Safety Database

Incidence by population (N=number of subjects)

TEAEs were experienced by 79/91 (49 PI and 30 ITP) or 86.8% of subjects and included:

- Death: N=2 (ITP)
- SAEs: N=11 (5 PI and 6 ITP)
- Significant TEAEs:[7] N=61 (48 PI and 13 ITP)

[7] Per protocol definition of a significant TEAE: non-serious and dose reduced/increased or product withdrawn or drug therapy started.
Significant TEAEs of severe and moderate intensity in PI subjects included: nasopharyngitis, gout, infected sebaceous cyst, conjunctivitis, pneumonia, bronchiectasis, asthma, abdominal pain, gastroenteritis, diarrhea, leucopenia, chest/musculoskeletal pain, nausea, headache, , sinusitis, URI, otitis externa/media, cystitis, influenza A, UTI, and vulvovaginal mycotic infection.
Significant TEAEs of severe and moderate intensity in ITP subjects included: pneumonia, sepsis,

- Severe intensity TEAEs: N=12 (7 PI and 5 ITP)
- Infusional TEAEs:[8] N=62 (38 PI and 24 ITP)

TEAEs classified by System Organ Class (SOC) with an incidence >40% in the three study populations (N=91) were reported for:

- Infections and Infestations: N=46 (50.5%)
- General Disorders and Administration Site Conditions: N=43 (47.3%)
- Gastrointestinal Disorders: N=39 (42.9%)
- Nervous System Disorder: N=39 (42.9%).

Infusional TEAEs classified by SOC with an incidence >15% included:

- General Disorders and Administration Site Conditions: N=29 (31.9%)
- Gastrointestinal Disorders: N=20 (22.0%)
- Infections and Infestations: N=16 (17.6%)

Incidence by event (n=number of events)

Total number of TEAEs: n=668 (PI: n=546; ITP: n=122) included:

- Deaths: n=2 (ITP) adjudicated as unrelated; attributed to sepsis and cerebral hemorrhage
- SAEs: n=17 (7 PI and 10 ITP)[9]
- Significant TEAEs: n=300 (257 PI and 43 ITP)

Severe intensity TEAEs: n=26 (11 PI and 15 ITP)

- Infusional TEAEs: n=218: (147 PI and 71 ITP)
- Infusional TEAEs treatment-related: n=128 (74 PI and 54 ITP)

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

NGAM-01 (N=51), NGAM-05 (N=21/51from NGAM-01); NGAM-02 (N=40).

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

For the PI indication, 51 subjects received 836 infusions totaling 24.1 kg of Panzyga.

For the chronic ITP indication, 40 subjects received 77 infusions totaling 5.7 kg of Panzyga. In the aggregate, 91 subjects received 913 infusions totaling 29.8 kg of Panzyga.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

Interpretation of safety data across NGAM-01, NGAM-05 and NGAM-02 is limited because of differences in underlying disease and immunological status (PI vs chronic

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autoimmune thrombocytopenia (worsening), cerebral hematoma, respiratory failure, muscle spasms, hypotension, headache, aseptic meningitis, nausea, pyrexia, chills, bronchitis, pneumonitis, loss of consciousness, and hypertension.

[8] Per protocol definition of an infusional TEAEs: TEAEs occurring within 72 hours of initiation of infusion.

[9] SAEs in PI subjects included thrombocytopenia, pneumonia, gout, bronchiectasis, bronchospasm, and septoplasty. SAEs in ITP subjects included thrombocytopenia, pneumonia, sepsis, dysphagia, aseptic meningitis, cerebral hematoma, pneumonitis, respiratory failure.

ITP), age (NGAM-02 only enrolled adults), and duration of exposure (12 months vs 2 days).

8.4 Safety Results

8.4.1 Deaths

No subject died in NGAM-01 and NGAM-05. Two unrelated deaths were reported in NGAM-02: subject #(b) (6) died of sepsis and subject #(b) (6) died of cerebral hemorrhage.

8.4.2 Nonfatal Serious Adverse Events

A total of 17 SAEs were reported in the three trials. In NGAM-01, 7 non-fatal, unrelated SAEs were reported in 5 PI subjects. In NGAM-05, no SAE was reported. In NGAM-02, 10 non-fatal SAEs were reported in 6 subjects, all unrelated except one possibly-related SAE of aseptic meningitis.

8.4.3 Study Dropouts/Discontinuations

In NGAM-01, 1 pediatric subject dropped out due to missed visits. In NGAM-02, 9 subjects dropped out because of death (N=2), requirement for other chronic ITP treatment (N=3), withdrawal of consent (N=2), worsening ITP (N=1) or loss to follow-up (N=1).

8.4.4 Common Adverse Events

In terms of individual TEAEs, the most frequently reported events in PI subjects were headache, pyrexia, nausea, and abdominal pain (upper). The most frequently reported TEAEs in ITP subjects were headache, pyrexia, and nausea.

Reviewer comment

Most likely because of their underlying disease, a higher number of non-serious infections were reported in PI subjects (78%) than in chronic ITP subjects (5%). ITP subjects, on the other hand, were more likely to experience headache (43% of subjects) than were PI subjects (22%).

8.4.5 Clinical Test Results

— Clinical Chemistry

In NGAM-01 and NGAM-05, no changes of clinical importance were noted between screening and end-of-treatment values for any of the biochemical parameters. In NGAM-02, Subject #(b) (6), who died from a cerebral hematoma SAE, had a clinically meaningful (i.e., outside the reference range) elevation in LDH on Day 5. Subject #(b) (6) experienced mild hemolysis and a slightly abnormal LDH value on Day 7; one week later, the subject had a mildly elevated AST and ALT TEAE.

— Viral Safety

In NGAM-01 and NGAM-05, no positive result to any of the viral markers was observed. In NGAM-02, no changes in viral status were detected. In 4 subjects, abnormal results in viral markers were reported that were already present at baseline.

8.4.6 Systemic Adverse Events

See paragraph 8.4.4 and 8.4.8.

8.4.7 Local Reactogenicity
Infusion site pain and infusion site pruritus occurred in ≤2 subjects.

8.4.8 Adverse Events of Special Interest
Infusional TEAEs were reported in two-thirds of subjects enrolled in the three studies, with a higher incidence in PI subjects than in ITP subjects.

One NGAM-1 subject experienced hemolysis (mild) and one NGAM-2 subject experienced aseptic meningitis. No cases of thromboembolism, renal dysfunction or TRALI were reported.

8.5 Additional Safety Evaluations
8.5.1 Dose Dependency for Adverse Events
Of the 91 enrolled subjects, all but one tolerated an infusion rate of 0.08 mL/kg/min, the maximum rate in NGAM-01 and NGAM-02. All subjects in NGAM-05 tolerated an infusion rate of 0.14 mL/kg/min, the maximal infusion rate per protocol.

8.5.2 Time Dependency for Adverse Events
See paragraph 8.4.8, Infusional TEAEs.

8.5.3 Product-Demographic Interactions
The reported rate of SBI per person-year was <1.0 in all both children and adults. Children showed the shortest mean resolution time and adults the longest. The incidence of TEAEs was higher in children than in adults. All 3 adolescent PI subjects experienced TEAEs compared with three-quarters of children and two-thirds of adults. Sample sizes were too small to provide meaningful analyses of product-demographic interactions.

8.5.4 Product-Disease Interactions
The efficacy and safety of IGIV has been well-studied in both in children and adults with immunological diseases.

8.5.5 Product-Product Interactions
Not applicable.

8.5.6 Human Carcinogenicity
Not applicable.

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound
Too rapid intravenous administration can lead to fluid overload and hyperviscosity syndrome. Patients at risk of complications include the elderly and those with cardiac or renal impairment.

8.5.8 Immunogenicity (Safety)
Not applicable.

8.5.9 Person-to-Person Transmission, Shedding
Not applicable.

8.6 Safety Conclusions
The safety profile of Panzyga is similar to that of other products in this class.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations
Not applicable.

9.1.1 Human Reproduction and Pregnancy Data
No pregnancy clinical or animal studies have been conducted.

9.1.2 Use During Lactation
No Pregnancy clinical or animal studies have been conducted.

9.1.3 Pediatric Use and PREA Considerations
Panzyga was evaluated in 25 pediatric PI subjects (age range: 2-15 years). Pharmacokinetics, efficacy and safety were similar to those in adults. No specific dose requirements were necessary to achieve the targeted serum IgG levels in pediatric subjects.

The safety and effectiveness of Panzyga has not been established in pediatric patients with ITP.

9.1.5 Geriatric Use
Clinical studies of Panzyga did not include sufficient numbers of subjects > 65 years to determine whether they respond differently from younger subjects. Geriatric patients > 65 years of age could be at increased risk for fluid overload or developing certain ARs such as thromboembolic events and acute renal failure.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered
QoL was assessed in NGAM-05. Assessments were made using the Child Health Questionnaire-Parent Form (CHQ-PF50) completed by the parent or guardian of subjects aged <14 years and the SF-36 Health Survey in subjects aged ≥14 years.

Overall, CHQ-PF50 questionnaire scores were similar from Baseline to Follow-up Visit.

10. CONCLUSIONS

Compared with other members of the product class, Panzyga is safe and effective for the conditions studied.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations
Compared with other licensed products in the class, risks and benefits are similar and acceptable.

Table 25: Benefit-Risk Assessment

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• PI: current treatment of PI using GIV is safe and effective. Administration is required every 3-4 weeks. • Chronic ITP: current treatment includes corticosteroids, IgG, and intravenous anti-Rho	• PI: the product is effective in reducing SBI • Chronic ITP: the product is effective in quickly (1-2 days) but transiently (1-2 weeks) raising platelet count to ≥50 x 10^9/L within 7 days after the first infusion
Unmet Medical Need	• PI: effective treatment already is available • Chronic ITP: effective treatment already is available	• Not an unmet medical need
Clinical Benefit	• PI: clinical benefit was investigated in subjects (N=51), including pediatric subjects 2-12 years of age (N=14) and 12-16 years of age (9), in an open-label, single-arm, phase 3 study at 14 centers in the US and one site in Canada. • Chronic ITP: clinical benefit was investigated in adult subjects (N=40) in an open-label, single-arm, phase 3 study at 20 ex-U.S. centers.	• PI: Panzyga was effective in reducing the number of SBI to <1% per year. • Chronic ITP: Panzyga was effective in raising the platelet count to ≥50 x 109/L within 7 days after the 1st infusion. The platelet count threshold (≥50x109/L) in response to Panzyga was exceeded for >1 week in 20/29 responders and >2 weeks in 13/29 responders. •
Risk	• Class effects associated with Panzyga appear to result primarily from the immunoglobulin component. Serious risks include thrombosis and renal dysfunction (including acute renal failure) and are listed in a Box Warning in the PI. Other risks include hypersensitivity (anaphylaxis) in patients with a history of anaphylaxis or those with antibodies against IgA (contraindication), fluid overload, aseptic meningitis, hemolysis, and, theoretically, CJD agent	• Clinical benefit exceeds risk. Risk is expected to be higher in PI patients than in chronic ITP patients because of repeated exposure to the product over the patient's lifetime.
Risk Management	• Patients should be made aware of potential signs/symptoms of hypersensitivity, renal failure, aseptic meningitis, hemolysis, TRALI, and thrombosis.	• Injections should be administered by infusion pump and patients monitored for signs of hypersensitivity and fluid overload.

11.2 Risk-Benefit Summary and Assessment
Panzyga is effective in reducing the number of SBI to <1% per year in PI and in elevating the platelet count in adults with chronic ITP. Risk of thrombosis and renal dysfunction appear to be low.

11.3 Discussion of Regulatory Options
Approval for the PI indication in adults and children aged ≥2 years and for the chronic ITP indication in adults.

11.4 Recommendations on Regulatory Actions
See 11.3.

11.5 Labeling Review and Recommendations
See amended PI.

11.6 Recommendations on Postmarketing Actions
I recommend a PMR in pediatric subjects with ITP that enrolls a population reflecting U.S. demographics characteristics.

*****Do Not Change Anything Below This Line*****