



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Epidemiology**

**Panzyga (Immune Globulin Intravenous, Human 10%) BLA 125587
Pharmacovigilance Plan Review Memorandum**

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Subject: Pharmacovigilance Plan Review Memorandum BLA 125587\0

Applicant: Octapharma Pharmazeutika Produktionsges.m.b.H

Product: Panzyga (Immune Globulin Intravenous, Human 10%)

BLA Submission: Original BLA 125587\0

Proposed indication: Primary humoral immunodeficiency (in adults and children) and chronic idiopathic thrombocytopenia (in adults).

Action Due Date: 14 April 2016

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1. INTRODUCTION

1.1 Product Description

Panzyga is a 10% liquid solution of human Immune Globulin (Ig) that contains the amino acid glycine as a (b) (4), and for the adjustment of iso-osmolality. The solution contains $\geq 96\%$ IgG while IgA content is (b) (4). Panzyga is administered intravenously (IV) and is indicated for the treatment of primary immunodeficiency (PID) in children and adults, and chronic immune thrombocytopenic purpura (ITP) in adults. During development, the working title for this product was NewGam 10%; however for the purposes of clarity in this memo the product will be called Panzyga, its proposed U.S. trade name¹.

1.2 Regulatory History

The pertinent regulatory history for Panzyga is summarized below in Table 1.

Table 1: Regulatory History

Event	Date
Pre-IND Meeting	22 February 2008
FDA Pre-IND Meeting Memorandum (CRMTS #6508)	21 March 2008
IND Application 14001, Indication PID	06 April 2009
FDA IND Advice Letter	04 May 2009
IND Application 14096, (b) (4)	15 July 2009
FDA IND Advice Letter	20 October 2009
IND Application 14121, Indication Primary ITP	06 Aug 2009
FDA IND Advice Letters	10 September 2009 09 October 2009 06 April 2010
FDA Response to Pre-BLA Meeting Request (CRMTS #9173)	12 December 2013
BLA 125587/0 submitted	15 April 2015
Mid-Cycle Review Meeting	30 September 2015
Mid-Cycle Communication with Applicant	13 October 2015
Internal Late-Cycle Meeting	07 December 2015
ADD	14 April 2016

IND = Investigational New Drug, BLA = Biologic License Application

On 15 Apr 2015 Octapharma Pharmazeutika submitted BLA 125587/0 for Panzyga Immune Globulin Intravenous (IGIV), Human 10%. Octapharma concurrently submitted Panzyga as a Marketing Authorization Application via the Decentralized Procedure (DCP) in Europe, and a New Drug Submission (NDS) in Canada.

1.3 Objectives and Scope

The Office of Biostatistics and Epidemiology, Division of Epidemiology (OBE/DE) has completed review of the pharmacovigilance plan for BLA 125587/0 seeking US licensure of Panzyga. The safety profile of IGIV has been well characterized and the class of products is considered safe for a variety of indications.

¹ Octapharma Pharmazeutika. Panzyga, Immune Globulin Intravenous (Human) 10% Liquid Preparation. U.S. Package Insert Draft: March 2015

Panzyga is a newly developed IGIV manufactured to optimize the IgG yield obtainable from each plasma donation resulting in a total protein content of 10%. In the BLA clinical overview the sponsor proposes that the higher protein concentration (10% vs. 5%) has the advantage of shorter infusion times and lower infusion volumes. The purpose of this memorandum is to identify potential safety issues that may need to be addressed through postmarketing surveillance or studies, should the BLA be approved. The comprehensive safety evaluation for this BLA included review of the Pharmacovigilance Plan (PVP), the Risk Management Plan (RMP) and supporting clinical study safety data. Panzyga is not currently licensed in any country and there is no post-licensure safety data available. The sponsor submitted a Periodic Safety Update Report (PSUR) covering the 120-day period from 04June2015 through 02October2015. The PSUR summarizes the previously submitted clinical studies and a new clinical trial evaluating the (b) (4).

2. MATERIALS REVIEWED

Materials reviewed in support of this safety assessment are listed in Table 2.

Table 2: Materials Reviewed

Source	Document
BLA 125587/0, Module 1.16	Risk Management Plan No. 01, Dated 23Mar2015
BLA 125587/0, Module 2.3.P	Drug Product
BLA 125587/0, Module 2.3.S	Drug Substance
BLA 125587/0, Module 2.5	Clinical Overview
BLA 125587/0, Module 2.7.4	Summary of Clinical Safety
BLA 125587/0, Module 5.3.5.2	NGAM-01 Clinical Study Report
	NGAM-02 Clinical Study Report
	NGAM-05 Clinical Study Report
BLA 125587/0.25, Module 5.3.6	Periodic Safety Update Report No. 01, Dated 27Oct2015

Pertinent published literature was also reviewed and is referenced in this memo.

3. CLINICAL STUDIES AND CLINICAL SAFETY DATABASE

The clinical data submitted in the BLA consists of three prospective, open label, single arm phase 3 clinical trials to evaluate the pharmacokinetics (PK), efficacy and safety of Panzyga: NGAM-01, NGAM-02 and NGAM-05. The sponsor proposes two distinct indications for Panzyga, and therefore the clinical studies encompass two patient populations:

- PID adult and children patient population
 - NGAM-01: N = 51 subjects
 - NGAM-05 (extension study of NGAM-01): N = 21 subjects who were previously enrolled in NGAM-01
- ITP adult patient population
 - NGAM-02: N = 40 subjects

(Note: As mentioned previously, Panzyga was known as NewGam during clinical trials.)

3.1 Clinical Studies in PID subjects: NGAM-01 and NGAM-05

3.1.1 NGAM-01 Clinical Study

The study evaluated two multiple dose intravenous regimens of Panzyga in 51 PID subjects (adult and children) for a period of 12 months. No clinically significant safety issues were identified in this study. Details of the study are described below.

Study Title: “Clinical study to evaluate the efficacy, pharmacokinetics and safety of immunoglobulin intravenous (human) 10% (NewGam) in patients with Primary Immunodeficiency Diseases (PID)”

Study Design: Phase 3 prospective, open- label, non- controlled, non-randomized multicenter study

Countries: Germany, Poland, USA

Study Population: adult and pediatric PID subjects (N = 51)

Total	N = 51
Gender	
Male	N = 33
Female	N = 18
Age groups	
≥2 to <12yo	N = 13
≥12 to <16yo	N = 12
≥16 to ≤75yo	N = 26

Study Duration: 15-Jan-2010 to 07-Jun-2012

Study Status: Completed. Final study report (31-July-2013)

Primary endpoint: Rate of serious bacterial infection (SBI) per person-year (e.g., bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, visceral abscess)

Safety related endpoints: Safety endpoints were secondary endpoints in NGAM-01. AE rates were assessed with respect to severity, relationship to the study product (based on medical judgment of investigator), and rate of infusion. Short-term tolerance parameters were presented descriptively as vital signs (e.g., blood pressure, heart rate, temperature, respiratory rate). Laboratory parameters of safety included hematology, clinical chemistry, direct Coombs’ test, urinalysis, and assessments for viral safety. Subjects were monitored for the occurrence of specific risks associated with IGIV including thromboembolic events (TEEs) and intravascular hemolysis.

Dosing Regimen: 200 – 800 mg/kg body weight every 21 or 28 days or as required for maintenance of serum IgG trough level above 5g/L

Patient Exposure:

- 3-week regimen: 21 subjects received 356 infusions; 520mg/kg IgG mean total dose per infusion
- 4-week regimen: 30 subjects received 384 infusions; 453mg/kg IgG mean total dose per infusion

Efficacy Study Results: While we defer to the OBRR clinical review of the efficacy endpoints, it should be noted here that lack of efficacy (i.e. bacterial infections) is closely associated with adverse events.

Overall, the efficacy endpoints were met and showed the following:

- Four serious bacterial infections (SBI) observed in 2/51 (3.9%) subjects
- The rate of SBI in NGAM-01 was less than 0.5 per person-year (total group 0.08), with an upper-sided 99% CI of 0.5033. Therefore, the null hypothesis H_0 : the rate of SBI is ≥ 1.0 per person-year at $\alpha = 0.01$ could be rejected.
- Serum IgG trough levels were nearly constant for both treatment schedules and met published guidelines for treatment standards. The sponsor concludes that Panzyga retains the same efficacy when administered at 21 or 28-day intervals. European guidance documents

recommend maintaining IGIV trough levels at or above 5-6 g/L for IGIV products². Trough levels in NGAM-01 were nearly constant and remained at or above 6.8 g/L for both treatment schedules. There were no trends in favor of one treatment schedule over another.

- Trough concentrations of specific antibodies were higher in the 3-week treatment schedule group than in the 4-week schedule group as expected

3.1.2 NGAM-01 Safety Dataset (N = 51)

Safety Study Results: There were 476 AEs observed in 48/51 (94.1%) subjects, with similar incidence among age groups and treatment schedules. The most frequently reported AEs per patient (related and unrelated) by MedDRA PT were upper respiratory infection, headache, nasopharyngitis and sinusitis. Table 3 categorizes all AEs by age group, treatment schedule, relatedness to Panzyga, and severity.

Table 3: NGAM-01 Summary of AEs by Age Group and Treatment Schedules (N = 51)

[Source: BLA submission NGAM-01 Table 21, Source: Section 14.3, [Tables 14.3.1.1.1 to 14.3.1.9](#)]

	Children ≥2 Years <12 Years N = 13	Adolescents ≥12 Years <16 Years N = 12	Adults ≥16 Years ≤75 Years N = 26	3-week schedule N = 21	4-week schedule N = 30	Total All Patients N = 51
Number of AEs [n]	146	107	223	213	263	476
Number of related** AEs [n]	9	5	45	27	33	60
Number of SAEs [n]	0	3	4	1	6	7
Number of patients with: [N (%)]						
Any AEs	12 (92.3)	12 (100.0)	24 (92.3)	19 (90.5)	29 (96.7)	48 (94.1)
Related** AEs	2 (15.4)	3 (25.0)	11 (42.3)	6 (28.6)	10 (33.3)	16 (31.4)
Serious AEs	0 (0.0)	1 (8.3)	4 (15.4)	1 (4.8)	4 (13.3)	5 (9.8)
Related** SAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Significant* AEs	12 (92.3)	12 (100.0)	24 (92.3)	19 (90.5)	29 (96.7)	48 (94.1)
Severe AEs	0 (0.0)	2 (16.7)	5 (19.2)	5 (23.8)	2 (6.7)	7 (13.7)
AEs leading to withdrawal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AEs leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

N = number of patients n = number of adverse events AE = adverse event

*Definition of significant AE: non-serious and dose changed or product withdrawn or other action/drug therapy started

** Possibly or probably related

Treatment related AEs: There were 16/51 (31.4%) subjects who experienced treatment-related AEs (AEs assessed as possibly or probably related to the medication) during 35/740 (2.8%) infusions (Table 4). The most frequently reported treatment-related PTs were headache (9/51, 17.6%), abdominal pain (4/51, 7.8%) and pyrexia (3/51 (5.9%).

² Guideline on Core SmPC for Human Normal Immunoglobulin for Intravenous Administration (IGIV) European Medicines Agency EMA/CHMP/BPWP/94038/2010 rev. 3.

Table 4: N G A M - 0 1 Treatment-Related*Adverse Events (N =51)[Source: BLA submission NGAM-01 Table 24, Source: Section 14.3, [Table 14.3.1.7](#)]

Number of patients with study medication-related* AEs	Total All Patients N = 51 N (%)	Children ≥2 Years <12 Years N = 13 N (%)	Adolescents ≥12 Years <16 Years N = 12 N (%)	Adults ≥16 Years ≤75 Years N = 26 N (%)
All patients with at least one related* AE	16 (31.4)	2 (15.4)	3 (25.0)	11 (42.3)
Nervous system disorders	9 (17.6)	1 (7.7)	1 (8.3)	7 (26.9)
Headache	9 (17.6)	1 (7.7)	1 (8.3)	7 (26.9)
Dizziness	1 (2.0)	0 (0.0)	0 (0.0)	1 (3.8)
Hypoaesthesia	1 (2.0)	0 (0.0)	0 (0.0)	1 (3.8)
General disorders and administration site conditions	8 (15.7)	1 (7.7)	2 (16.7)	5 (19.2)
Pyrexia	3 (5.9)	0 (0.0)	1 (8.3)	2 (7.7)
Fatigue	2 (3.9)	0 (0.0)	1 (8.3)	1 (3.8)
Chills	2 (3.9)	1 (7.7)	1 (8.3)	0 (0.0)
Pain	1 (2.0)	0 (0.0)	0 (0.0)	1 (3.8)
Asthenia	1 (2.0)	0 (0.0)	0 (0.0)	1 (3.8)
Feeling cold	1 (2.0)	0 (0.0)	0 (0.0)	1 (3.8)
Infusion site pruritus	1 (2.0)	0 (0.0)	0 (0.0)	1 (3.8)
Gastrointestinal disorders	7 (13.7)	2 (15.4)	0 (0.0)	5 (19.2)
Nausea	4 (7.8)	1 (7.7)	0 (0.0)	3 (11.5)
Abdominal pain	3 (5.9)	2 (15.4)	0 (0.0)	1 (3.8)
Abdominal pain upper	2 (3.9)	0 (0.0)	0 (0.0)	2 (7.7)
Vomiting	2 (3.9)	0 (0.0)	0 (0.0)	2 (7.7)
Blood and lymphatic system disorders	1 (2.0)	0 (0.0)	0 (0.0)	1 (3.8)
Leukopenia	1 (2.0)	0 (0.0)	0 (0.0)	1 (3.8)
Cardiac disorders	1 (2.0)	0 (0.0)	0 (0.0)	1 (3.8)
Tachycardia	1 (2.0)	0 (0.0)	0 (0.0)	1 (3.8)
Ear and labyrinth disorders	1 (2.0)	1 (7.7)	0 (0.0)	0 (0.0)
Ear pain	1 (2.0)	1 (7.7)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	1 (2.0)	0 (0.0)	0 (0.0)	1 (3.8)
Musculoskeletal stiffness	1 (2.0)	0 (0.0)	0 (0.0)	1 (3.8)
Respiratory, thoracic and mediastinal disorders	1 (2.0)	0 (0.0)	0 (0.0)	1 (3.8)
Cough	1 (2.0)	0 (0.0)	0 (0.0)	1 (3.8)

N = number of patients, AE = treatment-emergent adverse event, MedDRA = Medical Dictionary for Regulatory Activities
SOC = system organ class, PT = preferred term, *Related AEs: possible or probable (as assessed by investigator)

Infusional AEs: Infusional AEs were defined as occurring during the infusion and/or within 1 hour, 24 hours or 72 hours after the end of the infusion (regardless of the assessed relationship to treatment). Guidance for Industry recommends a one-sided 95% CI with an upper limit of < 40%, for proportion of infusions with AEs associated with IGIV³. Short term tolerance of the study medication was assessed through close monitoring of vital signs at specified time points during infusions. The sponsor notes that minor hemodynamic changes are not uncommon during IGIV, thus only those changes deemed clinically significant were reported as AEs. Of note, infusional AEs warrant careful evaluation because a temporal relationship to IGIV infusion is suggestive of an increased possibility of causality.

NGAM-01 reported 89/740 (0.1215) infusions that were associated with at least 1 infusional AE with a one-sided 95% CI upper limit of 0.1588. When analyzed by number of infusions, the most frequently observed PTs associated with infusional AEs (related and unrelated), were categorized as headache in 25/740 infusions (3.4%), pyrexia in 8/740 infusions (1.1%), and sinusitis and nausea with 6/740 infusions each (0.8%). Overall the most frequently observed MedDRA SOCs for infusional AEs, analyzed by subject were categorized as general disorders and administration site conditions (16/51 subjects, 31.4%). Infusional AEs classified as infections, gastrointestinal disorders and nervous system disorders were observed in 14/51(27.5%), 9/51 (17.6%) and 9/51 (17.6%) subjects respectively. Headache and pyrexia were the most frequently observed PTs in 9/51 (17.6%) and 7/51 (13.7%) subjects respectively during and within 72 hours of infusion.

Serious Adverse Events (SAEs): There were 7 SAEs in 5/51 (9.8%) subjects (table 5). These cases were reviewed in detail and are further described below. None of the SAEs were assessed to be treatment related AEs.

Table 5: NGAM-01 Listing of Serious Adverse Events (N = 51)

[Source: BLA submission NGAM-01 Table 29 Source: [Appendix 16.2.7, Listing 16.2.7.2.1](#)]

Treatment Group	Patient No.	Age Group	MedDRA PT	Intensity	Relationship With Study Medication	Outcome
3-week schedule	(b) (6)	Adults	Gout	Severe	Not related	Recovered / Resolved
4-week schedule		Adults	Pneumonia	Moderate	Not related	Recovered / Resolved
4-week schedule		Adolescents	Bronchiectasis	Moderate	Not related	Recovered / Resolved
4-week schedule		Adolescents	Bronchospasm	Moderate	Not related	Recovered / Resolved
4-week schedule		Adolescents	Bronchiectasis	Moderate	Unlikely	Recovered / Resolved
4-week schedule		Adults	Septoplasty	Mild	Not related	Recovered / Resolved

³ Guidance for Industry, Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency. U.S. Department of Health and Human Services, Food and Drug Administration. Center for Biologics Evaluation and Research, June 2008

4-week schedule	(b) (6)	Adults	Thrombocytopenia	Moderate	Not related	Recovered / Resolved
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MedDRA = Medical Dictionary for Regulatory Activities

NGAM-01 SAE Case summaries (N = 5)

- Patient (b) (6) was a 59 year-old male on a 3-week treatment schedule who experienced a flare of gout in his right ankle. The patient had a history of gout since 1990, and was taking anti-inflammatory medications at the time of the event. The flare seemed to have started prior to the 10th IGIV infusion but worsened during the 72 hours post infusion. An X-ray of the involved ankle showed diffuse arthritic changes and deep vein thrombosis was ruled out by venous doppler. The patient received empiric antibiotics, but cultures of blood and ankle aspirate were negative. The study investigator assessed the reaction as severe, not related to the treatment and recovered/resolved.

Reviewer comments: Given the presence of symptoms prior to the infusion, it is unlikely that this AE was related to the IGIV infusion. The investigator's assessment is appropriate.

- Patient (b) (6) was a 39 year-old male on a 4-week treatment schedule. His medical history included CVID and multiple past instances of pneumonia. He was taking no additional concomitant medications at the time of the AE. The patient received his last infusion of IGIV on (b) (6) he presented with a one week history of cough, yellow sputum, subjective fevers, weight loss, malaise and night sweats. Chest X-ray revealed pneumonia (SBI) of the RUL. Sputum cultures were negative for acid fast bacilli. The patient was hospitalized, treated empirically with levofloxacin and improved symptomatically. He was discharged on (b) (6). The investigator assessed the AE as moderate intensity, not related to the treatment and the event was reported as recovered/resolved.

Reviewer comments: Serious bacterial infections are events which could indicate a lack of efficacy of the study drug. Given that this AE occurred 3 weeks after the most recent IGIV infusion, it is likely that antibody levels in this patient were near trough and inadequate for immune protection. This infection was a complication of the underlying PID and the limitation of available treatment modalities. Unfortunately, patients with severe immune deficiencies are prone to SBI despite treatment with IGIV.

- Patient (b) (6) was a 14 year-old adolescent male on a 4-week treatment schedule. His medical history included CVID, asthma, ITP and bronchiectasis. His concomitant medications included albuterol, Symbicort inhaler, Zyrtec, Claritin, Flonase, Patanase and prednisone. He was also taking Pulmozyme for bronchiectasis. There were three separate SAEs reported for this patient during the study period. He experienced 2 episodes of moderately severe bronchiectasis which were assessed as unlikely and not related, and an episode of moderately severe bronchospasm assessed as not related, all of which recovered/resolved. The first adverse event was temporally associated with the fourth infusion of Panzyga. (b) (6) he had worsening PFTs prior to the start of IGIV infusion. He was subsequently treated with cefuroxime for 14 days. At his next visit (b) (6), PFTs were worse and cough increased. He was hospitalized and received albuterol, Rocephin and prednisone. He was also treated with chest physiotherapy. Sputum cultures were negative and chest X-ray and CT showed no significant changes. The subject was withdrawn from the study to allow for increased IGIV dosing to 800 mg/kg.

Reviewer comments: Based on the patient's extensive prior pulmonary history, the investigator assessment is appropriate that these AEs were unrelated to Panzyga.

- Patient (b) (6) was a 41 year-old female on a 4-week treatment schedule with a history of CVID, chronic sinusitis, COPD and chronic conjunctivitis. Her concomitant medications included fluticasone and salmeterol for COPD. The patient underwent a scheduled septoplasty 7 days after her last study infusion, to correct a deviated septum secondary to chronic sinusitis. The investigator assessed this AE as mild, not related, and recovered/resolved.

Reviewer comments: The patient's septoplasty was related to a condition that existed prior to enrollment in the study, and the investigator assessment is appropriate.

- Patient (b) (6) was a 41 year-old female on the 4-week treatment schedule. The patient had a history of CVID, chronic rhino-sinusitis, leucopenia and thrombocytopenia. The patient had experienced previous episodes of thrombocytopenia prior to enrollment requiring a 6-month course of steroids, with recovery of her platelet counts. One day prior to her scheduled Panzyga infusion, she developed petechiae and platelet count of $11 \times 10^9/L$. She was treated with a 5-day course of prednisone and her scheduled Panzyga. Her platelet count increased to $91 \times 10^9/L$ and she was discharged. The study investigator assessed this AE as moderate, not related to the study drug and recovered/resolved.

Reviewer comments: The patient's past medical history and chronology of the AE support the investigator's assessment.

Adverse Events of Special Interest: There were no TEEs or hemolysis during study.

Deaths: There were no deaths during study.

Conclusion: No clinically significant safety issues were identified.

3.1.3 NGAM-05 Clinical Study (extension of NGAM-01)

The primary objective of the study was to evaluate the safety and tolerability of Panzyga when administered at infusion rates from 0.08mL/Kg/min (the maximum rate in study NGAM-01) up to 0.14mL/Kg/min in subjects with PID. There were two multiple-dose IV Panzyga regimens (every 3 weeks or every 4 weeks, continuing the patient's infusion interval from the main study NGAM-01). No clinically significant safety issues were identified in this study. Details of the study are described below.

Study Title: "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)"

Study Design: Phase 3 prospective, open- label, non- controlled, non-randomized multicenter study

Countries: USA (There were 6 centers selected on the basis of previous participation in NGAM-01.)

Eligibility criteria: Subjects had to have completed NGAM-01 and received the last three infusions during NGAM-01 at the maximum infusion rate of 0.08 mL/Kg/min without needing premedication.

Study Population: adult and pediatric PID subjects (N = 21) Sample size calculation based on statistical power considerations was not performed. The sample size in NGAM-05 was determined exclusively by the number of subjects who completed NGAM-01 without meeting the exclusion criteria for NGAM-05.

Total	N = 21
Gender	
Male	N = 13
Female	N = 8
Age groups	
≥2 to <12yo	N = 8
≥12 to <16yo	N = 3
≥16 to ≤75yo	N = 10

Study Duration: 05-May-2011 – 26-Sep-2012

Study Status: Completed. Final study report (31-July-2013)

Objectives: NGAM-05 evaluated safety of Panzyga when administered at infusion rates from 0.08mL/Kg/min up to 0.14mL/Kg/min, and did not assess efficacy. Quality of life (though not an indicator of efficacy or safety) was assessed. IgG trough levels were recorded since they were required for dosing.

Safety related endpoints:

- Occurrence of AEs
- Occurrence of AEs temporally associated with the study treatment
- Proportion of infusions with one or more temporally associated AEs
- AEs by infusion rate
- Short term tolerance parameters including vital signs (blood pressure, heart rate, temperature and respiratory rate)
- Laboratory parameters (hematology, clinical chemistry, direct Coombs' test, urinalysis and viral safety tests)

Dosing Regimen: 200 – 800 mg/kg body weight every 21 or 28 days or as required for maintenance of serum IgG trough level above 5g/L. Each eligible patient received a total of five or four infusions depending on whether their regular treatment intervals were every 3 or four weeks, respectively. The study period did not exceed 4 months.

Patient Exposure:

- 3-week regimen: 12 subjects received 60 infusions; 567mg/kg IgG mean total dose per infusion
- 4-week regimen: 9 subjects received 36 infusions; 500mg/kg IgG mean total dose per infusion

3.1.4 NGAM-05 Safety Dataset (N = 21; subjects were previously enrolled in NGAM-01)

Safety Study Results: In the context of this study (as an extension of NGAM-01), an AE was defined as treatment-emergent (TE) if first onset or worsening occurred after the follow-up visit of the NGAM-01 study and not later than the follow-up visit of the NGAM-05 study. It should be noted that only TE AEs were analyzed in NGAM-05; non-TE AEs were not described in this report. The study reported 69 AEs in 17/21 (81%) of subjects (Table 6). Of those, 4/21 (19%) subjects had AEs assessed as related to the infusion. There were no serious AEs and 12/21 (57%) subjects experienced significant AEs, defined as non-serious (dose reduced/increased or product withdrawn or drug therapy started).

Table 6: NGAM-05 Subjects with AEs by Age Group and Treatment Schedule (Safety Set, N = 21)
[Source: BLA submission NGAM-05 Table 10 Source: Section 14.3, Tables 14.3.1.1.1, 14.3.1.1.3 and 14.3.1.7]

	Children ≥2 Years <12 Years N = 8	Adolescents ≥12 Years <16 Years N = 3	Adults ≥16 Years ≤75 Years N = 10	3-week schedule N = 12	4-week schedule N = 9	Total All Patients N = 21
Number of AEs [n]	33	6	30	47	22	69
Number of patients with: [N (%)]						
Any AEs	7 (87.5)	3 (100.0)	7 (70.0)	11 (91.7)	6 (66.7)	17 (81.0)
Related** AEs	2 (25.0)	0 (0.0)	2 (20.0)	3 (25.0)	1 (11.1)	4 (19.0)
Serious AEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Significant* AEs	5 (62.5)	1 (33.3)	6 (60.0)	7 (58.3)	5 (55.6)	12 (57.1)
Severe AEs	0 (0.0)	0 (0.0)	1 (10.0)	1 (8.3)	0 (0.0)	1 (4.8)
AEs leading to withdrawal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AEs leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

N = Number of patients, n = Number of events, AE = Adverse event

* Definition of significant AE: non-serious and dose reduced/increased or product withdrawn or drug therapy started

**Related = probably or possibly, as assessed by the investigator

Treatment-related AEs: There were 4/21 (19%) subjects with at least one AE assessed as related to Panzyga. The most frequently reported treatment-related AE (by MedDRA SOC) was gastrointestinal disorders in 3/21 (14.3%) subjects, followed by musculoskeletal and connective tissue disorders in 2/21 (9.5%), and nervous system disorders also in 2/21 (9.5%) subjects. The most frequently reported treatment-related AEs (by MedDRA PT) were nausea in 2/21 (9.5%) subjects, and headache also in 2/21 (9.5%) subjects, followed by abdominal pain, arthralgia, musculoskeletal pain, chest pain and vascular procedure complication, all in 1/21 (4.8%) subject. Table 7 presents the subjects with at least one treatment-related AE, categorized by MedDRA SOC, PT, age group and treatment schedule. Of note, there were no treatment-related AEs in the adolescent age group. There were more treatment-related AEs observed in the 3-week schedule 3/21 (25%) than in the 4-week schedule 1/21 (11%).

Table 7: NGAM-05 Treatment-related Adverse Events (Safety Set, N = 21)
[Source: BLA submission NGAM-05 Table 12 Source: Section 14.3, Table 14.3.1.7]

Number of patients with study medication-related* AEs by MedDRA SOC and PT	Children ≥2 Years <12 Years N = 8 N (%)	Adults ≥16 Years ≤75 Years N = 10 N (%)	3-week schedule N = 12 N (%)	4-week schedule N = 9 N (%)	Total All Patients N = 21 N (%)
All patients with at least one related** AE	2 (25.0)	2 (20.0)	3 (25.0)	1 (11.1)	4 (19.0)
Gastrointestinal disorders	1 (12.5)	2 (20.0)	2 (16.7)	1 (11.1)	3 (14.3)
Nausea	0 (0.0)	2 (20.0)	2 (16.7)	0 (0.0)	2 (9.5)
Abdominal pain	1 (12.5)	0 (0.0)	0 (0.0)	1 (11.1)	1 (4.8)

Table 7 (Cont.)					
Musculoskeletal and connective tissue disorders	0 (0.0)	2 (20.0)	2 (16.7)	0 (0.0)	2 (9.5)
Arthralgia	0 (0.0)	1 (10.0)	1 (8.3)	0 (0.0)	1 (4.8)
Musculoskeletal pain	0 (0.0)	1 (10.0)	1 (8.3)	0 (0.0)	1 (4.8)
Nervous system disorders	1 (12.5)	1 (10.0)	1 (8.3)	1 (11.1)	2 (9.5)
Headache	1 (12.5)	1 (10.0)	1 (8.3)	1 (11.1)	2 (9.5)
General disorders and administration site conditions	0 (0.0)	1 (10.0)	1 (8.3)	0 (0.0)	1 (4.8)
Chest pain	0 (0.0)	1 (10.0)	1 (8.3)	0 (0.0)	1 (4.8)
Injury, poisoning and procedural complications	1 (12.5)	0 (0.0)	1 (8.3)	0 (0.0)	1 (4.8)
Vascular procedure complication	1 (12.5)	0 (0.0)	1 (8.3)	0 (0.0)	1 (4.8)

N = Number of patients, AE = Treatment-emergent adverse event,
MedDRA = Medical Dictionary for Regulatory Activities, SOC = System Organ Class

*No treatment-related AE was observed in adolescent patients

** Related AEs = probably or possibly related, as assessed by investigator

Infusional AEs: The sponsor evaluated and analyzed all infusional AEs (related and unrelated), defined as an AE with onset or worsening during an infusion or within 72 hours after the end of the infusion. Infusional AEs were analyzed by time relative to infusion and by infusion rate. Each of these analyses was categorized by MedDRA SOC, PT, age group and treatment schedule. Table 8 presents an abbreviated summary of the number of subjects with infusional AEs. When analyzed by age group, the greatest proportion of infusional AEs 4/8 (50%) was seen in children ≥ 2 years and < 12 years. In terms of treatment schedule, the largest proportion of subjects with infusional AEs 6/12 (50%) was seen in the 3-week treatment group. As expected, the greatest number of infusional AEs overall was observed in the time period up to 72 hours after infusion, in 8/21 (38%) subjects. Gastrointestinal disorders were the most frequently reported SOCs across all three time periods, with nausea and headache as the most frequently reported PTs. Overall the proportion of infusions associated with infusional AEs was 0.1146 and upper limit of 95% CI was 0.1877, fulfilling the target parameter of $< 40\%$ recommended by FDA Guidance for Industry⁴.

Table 8: NGAM-05 Infusional AEs by Time Relative to Infusion, Age, Treatment Schedule (Safety Set, N=21) [Source: BLA submission NGAM-05 Table 13, Source: Section 14.3, Table 14.3.1.3]

Number of patients with Infusional AEs by time relative to infusion	Children ≥ 2 Years < 12 Years N = 8 N (%)	Adolescents ≥ 12 Years < 16 Years N = 3 N (%)	Adults ≥ 16 Years ≤ 75 Years N = 10 N (%)	3-week schedule N = 12 N (%)	4-week schedule N = 9 N (%)	Total All Patients N = 21 N (%)

⁴ Guidance for Industry, Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency. U.S. Department of Health and Human Services, Food and Drug Administration. Center for Biologics Evaluation and Research, June 2008

During the infusion and within 1 hour of the end of the infusion						
Any AE	2 (25.0)	0 (0.0)	2 (20.0)	3 (25.0)	1 (11.1)	4 (19.0)
During the infusion and within 24 hours after the end of infusion						
Any AE	2 (25.0)	0 (0.0)	3 (30.0)	4 (33.3)	1 (11.1)	5 (23.8)
During the infusion and within 72 hours after the end of infusion						
Any AE	4 (50.0)	1 (33.3)	3 (30.0)	6 (50.0)	2 (22.2)	8 (38.1)

N = Number of patients, AE = Adverse event, MedDRA = Medical Dictionary for Regulatory Activities

Three infusion rates were evaluated, 0.100, 0.120 and 0.140 mL/Kg/min

- There was one AE at 0.10 mL/Kg/min in 1/21 (4.8%) subjects
- There was one AE at 0.12 mL/Kg/min in 1/21 (4.8%) subjects
- There were four AEs at 0.14 mL/Kg/min in 4/19 (21%) subjects

Table 9 presents a summary of the number of subjects with TE infusional AEs occurring within one hour of infusion, categorized by infusion rate, MedDRA SOC and PT, age group and treatment schedule. The largest proportion of subjects 4/19(21%) with TE infusional AEs was observed at the infusion rate of 0.14 mL/Kg/min; 5 SOC and 6 individual PTs were reported. The most frequently reported SOC was gastrointestinal disorders in 2/19 (10.5%) subjects. TE infusional AEs at the slower infusion rates of 0.10 and 0.12 mL/Kg/min were observed in only 1/21 (4.8%) subjects in each of those groups. Nervous system disorders (SOC) and headache (PT) were reported for each subject.

Table 9: NGAM-05 Infusional Adverse Events (within 1 Hour) by Infusion Rate, MedDRA System Organ Class and Preferred Term, Age Group and Treatment Schedule (Safety Set, N = 21)

[Source: BLA submission NGAM-05 Table 14: Source: Section 14.3, [Table 14.3.1.4](#)]

Number of patients with TE Infusional AEs by infusion rate	Children ≥2 Years <12 Years N (%)	Adolescents ≥12 Years <16 Years N (%)	Adults ≥16 Years ≤75 Years N (%)	3-week schedule N (%)	4-week schedule N (%)	Total All Patients N (%)
Infusion rate = 0.100 [mL/kg/min]						
Any adverse event	N = 8 1 (12.5)	N = 3 0 (0.0)	N = 10 0 (0.0)	N = 12 0 (0.0)	N = 9 1 (11.1)	N = 21 1 (4.8)
Nervous system disorders	0 (0.0)	0 (0.0)	1 (10.0)	1 (8.3)	0 (0.0)	1 (4.8)
Headache	0 (0.0)	0 (0.0)	1 (10.0)	1 (8.3)	0 (0.0)	1 (4.8)
Infusion rate = 0.120 [mL/kg/min]						
Any adverse event	N=8 0 (0.0)	N=3 0 (0.0)	N=10 1 (10.0)	N=12 1 (8.3)	N=9 0 (0.0)	N=21 1 (4.8)
Nervous system disorders	0 (0.0)	0 (0.0)	1 (10.0)	1 (8.3)	0 (0.0)	1 (4.8)
Headache	0 (0.0)	0 (0.0)	1 (10.0)	1 (8.3)	0 (0.0)	1 (4.8)
Infusion rate = 0.14 [mL/kg/min]						
Any adverse event	N=6 2 (33.3)	N=3 0 (0.0)	N=10 2 (20.0)	N=11 3 (27.3)	N=8 1 (12.5)	N=19 4 (21.1)
Gastrointestinal Disorders	1 (16.7)	0 (0.0)	1 (10.0)	1 (9.1)	1 (12.5)	2(10.5)
Abdominal pain	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (5.3)
Nausea	0 (0.0)	0 (0.0)	1(1.0)	0 (0.0)	0 (0.0)	1 (5.3)

MedDRA = Medical Dictionary for Regulatory Activities; TE = Treatment-emergent; AE = Adverse event, N = number of subjects

The sponsor also evaluated the number of infusions with related infusional AEs. There were 6/96 (6.3%) infusions with at least one related AE (possibly or probably) within 72 hours of infusion (Table 10).

Table 10: NGAM-05 Infusions with Related Infusional Adverse Events (during Infusion or within 72 Hours after End of Infusion) (Safety Set, N = 21)

[Source: BLA submission NGAM-05 Table 15: Source: Section 14.3, Table 14.3.1.10.4.1]

Number of infusions with related** infusional AEs during infusion and within 72 hours after end of infusion by MedDRA SOC and PT	Children ≥2 Years <12 Years n = 36 n (%)	Adults ≥16 Years ≤75 Years n = 45 n (%)	3-week schedule n = 60 n (%)	4-week schedule n = 36 n (%)	Total All infusions n = 96 n (%)
All infusions with at least 1 related** infusional AE (within 72 hours)	3 (8.3)	3 (6.7)	4 (6.7)	2 (5.6)	6 (6.3)
Gastrointestinal disorders	1 (2.8)	2 (4.4)	2 (3.3)	1 (2.8)	3 (3.1)
Abdominal pain	1 (2.8)	0 (0.0)	0 (0.0)	1 (2.8)	1 (1.0)
Nausea	0 (0.0)	2 (4.4)	2 (3.3)	0 (0.0)	2 (2.1)
Nervous system disorders	1 (2.8)	2 (4.4)	2 (3.3)	1 (2.8)	3 (3.1)
Headache	1 (2.8)	2 (4.4)	2 (3.3)	1 (2.8)	3 (3.1)
Musculoskeletal and connective tissue disorders	0 (0.0)	2 (4.4)	2 (3.3)	0 (0.0)	2 (2.1)
Arthralgia	0 (0.0)	1 (2.2)	1 (1.7)	0 (0.0)	1 (1.0)
Musculoskeletal pain	0 (0.0)	1 (2.2)	1 (1.7)	0 (0.0)	1 (1.0)
General disorders and administration site conditions	0 (0.0)	1 (2.2)	1 (1.7)	0 (0.0)	1 (1.0)
Chest pain	0 (0.0)	1 (2.2)	1 (1.7)	0 (0.0)	1 (1.0)
Injury, poisoning and procedural complications	1 (2.8)	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.0)
Vascular procedure complication	1 (2.8)	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.0)

n = Total number of infusions, AE = Adverse event, MedDRA = Medical Dictionary for Regulatory Activities
SOC = System Organ Class, PT = Preferred term

*Adolescent patients had no AEs related to study medication

**Related = probably or possibly, as assessed by investigator

Serious Adverse Events (SAEs): There were no SAEs or AEs leading to withdrawal from the study.

Adverse Events of Special Interest: There were no TEEs or hemolysis during study.

Deaths: There were no deaths during study.

Conclusion: No clinically significant safety issues were identified.

3.2 Clinical Study in adult ITP subjects: NGAM-02

As per the sponsor, NGAM-02 is “the one pivotal clinical study that is relevant for gaining regulatory approval for the indication ITP”. The study evaluated two multiple dose IGIV regimens for a period of 21 months. Study details are described below.

3.2.1 NGAM-02 Clinical Study

Study Title: “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”

Study Design: Phase 3 prospective, open- label, non- controlled, non- randomized, multicenter study

Countries: Germany, Poland, Ukraine, Russia, India, Czech Republic, Romania, Bulgaria

Inclusion criteria relevant for this safety review included the following:

- Age ≥ 18 and ≤ 65 years
- Confirmed diagnosis of chronic primary ITP of ≥ 12 months duration (plt count $< 100K$)
 - History and physical excluding other causes of thrombocytopenia
 - pattern of bleeding associated with platelet disorders⁵
 - isolated thrombocytopenia
 - peripheral smear consistent with ITP
- Platelet count $\leq 20K$ with or without bleeding manifestation

Exclusion criteria were extensive but criteria with relevance specific to this safety review include:

- Thrombocytopenia secondary to other disease (i.e. AIDS, SLE, or drug-related)
- Unresponsive to previous treatment with IGIV or anti-D immunoglobulin
- Subject with Evans syndrome (autoimmune thrombocytopenia and autoimmune hemolysis)
- Live viral vaccination within the last 2 months before study entry
- Severe liver or kidney disease (alanine aminotransferase [ALAT] $3\times$ $>$ upper limit of normal, creatinine $>120 \mu\text{mol/L}$)
- Non-controlled arterial hypertension (systolic blood pressure >160 mmHg or diastolic blood pressure >90 mmHg)
- History of hypersensitivity to blood or plasma derived products, or any component of the investigational product

Study Population: 40 adult subjects with primary idiopathic thrombocytopenic purpura (ITP)

The study population was selected based on literature findings supporting the efficacy and safety of IGIV treatment in patients with clinically diagnosed ITP.^{6, 7} The study planned to enroll 86 adult subjects based on sample size calculations for statistical power, but enrollment was placed on hold after 40

⁵ Buchanan GR, Adix L: Grading of hemorrhage in children with idiopathic thrombocytopenic purpura. J.Pediatr. 2002; 141:683-688.

⁶ Imbach P: Immune thrombocytopenic purpura and intravenous immunoglobulin. Cancer 1991; 68 (6 Suppl):1422-1425.

⁷ Newland AC, Burton I, Cavenagh JD, et al: Vigam-S, a solvent/detergent-treated intravenous immunoglobulin, in idiopathic thrombocytopenic purpura. Transfus.Med. 2001; 11:37-44.

subjects due to delayed availability of the study medication. At that time, the observed treatment response rate was above 80%, and the goal to achieve a lower one-sided 97.5% confidence limit greater than 0.6 was already achieved. Consequently it was decided (in agreement with the FDA) to stop enrollment. There was no interim analysis performed, and a single final analysis was done using the originally defined primary and secondary endpoints.

Total	N = 40
Gender	
Male	N = 23
Female	N = 17

Study Duration: 27-Oct-2011 – 22-Jul-2013

Study Status: Completed. Final study report (10-Mar-2015)

Objectives: The primary objective of NGAM-02 was to assess the efficacy of Panzyga in correcting the platelet count.

Efficacy endpoint: Treatment response was defined as an increase in platelets to at least $50 \times 10^9/L$ within 7 days after the first infusion or at least once prior to Day 9. This definition of clinical response served as the basis for the primary endpoint, which was the response rate (i.e., the proportion of patients with an elevation of platelet count to $\geq 50 \times 10^9/L$ within 7 days after the first infusion). A pre-defined value of 0.60 was the threshold for treatment response rate based on a historical control value.

Safety related endpoints: The secondary objective of the study was to evaluate the safety of Panzyga. Safety endpoints were AEs, vital signs, physical examination, laboratory parameters and viral safety. Clinical assessments for safety were conducted according to the following protocol:

- Monitoring for type and frequency of AEs until day 63
- AEs defined as “Treatment emergent AE” (TEAE) if first onset or worsening occurred after the start of first Panzyga infusion
- Non-responders, or patients requiring emergent ITP treatment other than specified in the protocol were followed for safety with all assessments until day 63
- Bleeding severity assessments by treating investigator using 6-point verbal rating scale⁸
- If a patient withdrew prematurely, a study termination visit with all assessments scheduled for the day 22 study visit were to be performed (excluding Parvovirus B19)

Dosing Regimen: Daily dose of 1 g/kg given for two consecutive days, for a total of 2g/kg. Study participation for an individual patient lasted for approximately 2 months consisting of 11-14 visits to the study site. The treatment dose was the generally accepted dosage recommended by the Core Summary of Product Characteristics (SPC) for Human Normal Immunoglobulin for Intravenous Administration⁹.

Patient Exposure: Forty subjects received 77 infusions; mean total dose IgG 1.90g/kg with a mean total dose of 141.22g per infusion.

Efficacy Study Results: The efficacy of Panzyga in increasing platelet counts to $\geq 50 \times 10^9/L$ within 7 days of the first infusion was confirmed, with a response in over 80% of subjects, and the lower limit of one-sided 97.5% CI above the predefined reference value of 0.6, with the exact Clopper-Pearson 95% CI of 63.98% to 91.81%.

⁸ Buchanan GR, Adix L: Grading of hemorrhage in children with idiopathic thrombocytopenic purpura. J.Pediatr. 2002; 141:683-688.

⁹ Guideline on Core SmPC for Human Normal Immunoglobulin for Intravenous Administration (IGIV) European Medicines Agency EMA/CHMP/BPWP/94038/2010 rev. 3

While we defer to the OBRR clinical review of the efficacy endpoints, it should be noted here that lack of efficacy (i.e. persistent thrombocytopenia and clinically evident bleeding) is associated with adverse events and safety.

3.2.2 NGAM-02 Safety Dataset (N = 40)

Safety Study Results: All 40 of the enrolled subjects had exposure to Panzyga and were included in the safety set analysis. There were 77 infusions (5,649g Panzyga) administered over the course of the study. All except 3 subjects received two infusions. According to the protocol, all AEs occurring (or worsening) after initiation of study treatment (including events likely to be related to the underlying disease, a concomitant illness or medication) were defined as treatment-emergent AEs (TEAEs). Table 11 summarizes the TEAEs observed in the safety set. The most frequently reported TEAEs were non-serious (112 episodes in 28 subjects) and included the following:

- headache (17 subjects, 43%)
- pyrexia (9 subjects, 23%)
- autoimmune thrombocytopenia (6 subjects, 15%)
- nausea (6 subjects, 15%)

Table11: NGAM-02 Summary of Adverse Events (Safety Set, N=40)

[Source: BLA Submission NGAM-02 Table 20: Section 14.3, [Tables 14.3.1.1.1, 14.3.1.1.3, 14.3.1.3, Appendix 16.2.1](#), Listing]

	Number of patients (%) N (%)	Number of episodes (%) n (%)
TEAEs	30 (75.0%)	122 (100.0%)
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 AEs ¹	13 (32.5%)	43 (35.2%)
Severe AEs	5 (12.5%)	15 (12.3%)
Non-serious AEs	28 (70.0%)	112 (91.8%)
AEs leading to withdrawal from study	1 (2.5%)	1 (0.8%)
AEs leading to withdrawal of study drug	3 (7.5%)	5 (4.1%)
Death	2 (5.0%)	2 (1.6%)
Infusional AEs within 72 hours	24 (60.0%)	71 (58.2%)

AE=adverse event, SAE=serious AE, TEAE=treatment-emergent AE

¹ Definition of significant AE: non-serious and dose changed or product withdrawn or other action or drug therapy started.

² Possibly or probably related.

Treatment Emergent Adverse Events (TEAEs): There were 122 TEAEs in 30 subjects (75%) described in Table 12. The TEAEs were assessed based on relatedness to infusion, as well as timing and infusion rate (infusional AEs), and the following was observed:

- 58 probably or possibly related TEAEs in 23 subjects (57.5%)
 - 21 nervous system disorders in 15 subjects (headache and dizziness)
 - 12 general disorders and administration site conditions in 11 subjects (pyrexia and chills)
 - 7 blood and lymphatic disorders in 3 subjects (anemia)
- 8 infusional TEAEs within 1 hour in 12 subjects (20%)
- 52 infusional TEAEs within 24 hours in 22 subjects (55%)
- 71 infusional TEAEs within 72 hours in 24 subjects (60%)
- 31 infusional TEAEs observed in the total of 77 infusions (40.3%)

- 8 TEAEs at 0.080 mL/Kg/min in 7 subjects (compared to 1 TEAE in 1 subject at each of the lower infusion rates 0.010, 0.020 and 0.040 mL/Kg/min)
- 3 subjects (7.5%) had TEAEs leading to permanent withdrawal of study drug

Table 12: NGAM-02 Patients with Treatment-emergent Adverse Events
(Frequency ≥5.0% of the Patients) by MedDRA System Organ Class and Preferred Term (N=40)

[Source BLA Submission NGAM-02 Table 21: Source: Section 14.3, [Tables 14.3.1.2](#) and [14.3.1.5](#)]

MedDRA System Organ Class	Preferred Term ¹	Number of patients (%) N (%) ²	Number of events n
Patients with at least 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 and administration site conditions		14 (35.0%)	16
	Pyrexia	9 (22.5%)	9
	Asthenia	2 (5.0%)	3
	Chills	2 (5.0%)	3
Blood and lymphatic system disorders		11 (27.5%)	24
	Autoimmune thrombocytopenia	6 (15.0%)	8
	Anaemia	5 (12.5%)	7
	Idiopathic thrombocytopenic purpura	2 (5.0%)	2

MedDRA=Medical Dictionary for Regulatory Activities

¹ If there were no preferred terms with an incidence ≥5% within a particular System Organ Class, then only the System Organ Class is shown.

² Percentage relates to the number of patients.

Serious Adverse Events (SAEs) and Deaths: There were 10 SAEs (including two deaths) observed in 6 subjects (Table 13).

Table 13: NGAM-02 Listing of Serious Adverse Events (Safety Set, N=40)

[Source BLA Submission NGAM-02 Table 28, Source: [Appendix 16.2.7](#), Listings 16.2.7.2.1 and 16.2.7.1.2]

Patient Number	MedDRA Preferred Term	Intensity	Outcome	Causality
(b) (6)	Autoimmune thrombocytopenia	Mild	Resolved	Not related
	Pneumonitis	Moderate	Resolved	Not related
	Dysphagia	Mild	Resolved	Not related
	Autoimmune thrombocytopenia	Mild	Resolved	Not related
	Cerebral haematoma	Severe	Fatal	Not related
	Autoimmune thrombocytopenia	Severe	Resolved	Not related

(b) (6)	Meningitis aseptic	Moderate	Resolved	Possible
	Pneumonia	Severe	Not resolved	Not related
	Respiratory failure	Severe	Not resolved	Not related
	Sepsis	Severe	Fatal	Not related

MedDRA=Medical Dictionary for Regulatory Activities

Case summaries of SAEs (N = 4) and deaths (N = 2) are presented below.

- Subject (b) (6) was a 48 year-old man who experienced 3 SAEs including worsening of autoimmune thrombocytopenia (mild), pneumonitis (moderate), and dysphagia (mild). Five days after the first infusion he was hospitalized for severe thrombocytopenia (platelets = 11K). He had two subsequent hospitalizations during the safety follow-up period for pneumonitis and dysphagia. All SAEs reportedly resolved and were assessed as not-related to the study medication by the investigator.

Reviewer Comments: The SAEs observed in this subject do not appear to have been related to study medication, and are more likely confounding by indication and concomitant medications. Historical data has shown a response rate of ~ 75% in patients treated with IGIV for primary immune thrombocytopenia^{10,11,12}. The pneumonitis and dysphagia were likely complications of prolonged hospitalization and corticosteroid treatment.

- Subject (b) (6) was a 64 year-old man with a history of chronic primary ITP who had been treated with methylprednisolone for one month prior to enrollment. Seven days after the first infusion of study medication, he developed non-serious worsening of ITP with platelet count decreasing from 22K to 4K. He was treated with corticosteroids and a platelet growth factor. The SAE was assessed by the investigator as resolved, not related to the study medication.

Reviewer Comments: The SAE observed in this subject does not appear to have been related to study medication, and is likely confounding by indication due to his underlying disease. Historical data has shown a response rate of ~ 75% in patients treated with IGIV for primary immune thrombocytopenia.

- Subject (b) (6) was a 25 year-old woman with chronic primary ITP. The platelet count increased one day after the first infusion of study medication from 19K to 79K. By day 6, her platelet count peaked at 415K, but rapidly declined to 9K on day 24, with petechial bleeding. She was

¹⁰ Robak T, Mainau C, Pyringer B, et al.: Efficacy and safety of a new intravenous immunoglobulin 10% formulation (octagam® 10%) in patients with immune thrombocytopenia. Hematology 2010;15:351-359.

¹¹ Julia A, Kovaleva L, Loria S, et al.: Clinical efficacy and safety of Flebogammadif, a new high-purity human intravenous immunoglobulin, in adult patients with chronic idiopathic thrombocytopenic purpura. Transfus. Med. 2009;19:260-268.

¹² Robak T, Salama A, Kovaleva L, et al.: Efficacy and safety of Privigen, a novel liquid intravenous immunoglobulin formulation, in adolescent and adult patients with chronic immune thrombocytopenic purpura. Hematology 2009;14:227-236.

hospitalized treated with corticosteroids and underwent splenectomy. The SAE resolved and was assessed as not related to the study medication by the investigator.

Reviewer Comments: The SAE observed in this subject does not appear to have been related to study medication, and is likely confounding by indication. Historical data has shown a response rate of ~ 75% in patients treated with IGIV for primary immune thrombocytopenia.

- Subject (b) (6) was a 28-year-old man with a history of chronic primary ITP. He received two infusions of study medication as per protocol and approximately 12 hours after the second infusion developed headache and fever. Spinal fluid cell count was 3,600 cells/ μ L, with 97% neutrophils, with elevated protein and negative cultures. The subject was diagnosed with aseptic meningitis. He was hospitalized and treated with antibiotics, with resolution of the SAE. The investigator assessed this SAE as possibly related to the study medication.

Reviewer Comments: Aseptic meningitis is a rare complication that has been associated with all commercial preparations of IGIV at an estimated rate ranging from 0-1%¹³ of patients. The symptoms usually commence within 48 hours of infusion and can persist for 3-5 days.

Deaths

- Subject (b) (6) was a 57 year-old male with a long-standing history of respiratory disease and primary immune thrombocytopenia, who died of severe sepsis 45 days after the first infusion of the study medication during the safety follow-up period. He was initially hospitalized for pneumonia, pericarditis and thrombocytopenia. His course was complicated by recurrent bronchitis and pneumonia treated with antibiotics and steroids. Sputum culture grew *Achromobacter*. The subject eventually developed multi-organ failure. The death was assessed as unrelated by the investigator.

Reviewer Comments: This subject had a complicated medical history and hospital course. Given his pre-existing respiratory disease and prolonged hospitalization, the death of this subject is likely not related to Panzyga treatment.

- Subject (b) (6) was a 25 year-old male with Evans syndrome since 2009 on mycophenolate mofetil who died 6 days after the first infusion of study medication due to severe intraparenchymal cerebral hemorrhage. The subject had evidence of hemolysis likely due to Evans Syndrome.

Reviewer Comments: Due to the pre-existing diagnosis of Evans Syndrome, this patient should have been excluded from enrollment. Hemolysis was likely due to underlying Evans Syndrome. This death is appropriately assessed as unrelated to Panzyga treatment.

Adverse Events of Special Interest: There were no TEEs during study. The investigators reviewed data for any indication of potential intravascular hemolysis and reported 6/40 subjects (15%) with laboratory values consistent with hemolysis, however only 1/6 had clinically evident hemolysis (i.e. reported as an AE) which was described as mild with no treatment required, and was classified as probably related to Panzyga.

Conclusion: No clinically significant safety issues were identified.

¹³ Orbach O, Katz U, Sherer Y, et al: Intravenous immunoglobulin: adverse effects and safe administration. Clin Rev Allergy Immun. 2005; 29(3): 173-84

4. PHARMACOVIGILANCE PLAN (PVP)

Octapharma proposes routine pharmacovigilance (PV) and labeling for the identified and potential risks and missing information for Panzyga (Table 14). Routine PV will be conducted by the sponsor's Corporate Drug Safety Unit (CDSU) according to standard operating procedures (SOPs) of the company.

Table 14: Proposed PV actions for important identified and potential risks and missing information

Safety Concerns	Proposed Actions
Important Identified Risks: 1. Thromboembolic events (TEEs) 2. Aseptic meningitis 3. Hypersensitivity reactions, including anaphylactic reactions 4. Acute renal failure 5. Hemolysis	Routine PV and labeling
Important Potential Risks: Virus safety (viral transmission)	
Important Missing Information: 1. Safety in the elderly patients has not been studied in controlled clinical trials. 2. Safety in patients with impaired renal and hepatic function has not been studied in controlled clinical trials. 3. There is no experience using Panzyga in pregnant or breastfeeding women.	

Routine Pharmacovigilance Activities

Routine pharmacovigilance activities include adverse event reporting in accordance with 21 CFR 600.80 and quarterly periodic safety reports for 3 years (annual thereafter), as well as continuous monitoring of the safety profile including signal detection and evaluation. This will include 15-day expedited reports for serious, unlabeled (unexpected) AEs, and Periodic Benefit-Risk Evaluation Reports/Periodic Safety Update Reports (PBRERs/PSURs). Global literature searches for reports on suspected adverse drug reactions involving Octapharma products will be conducted weekly by the sponsor. As per the sponsor, procedures are in place to implement actions or risk management activities in response to a safety signal, as necessary.

5. INTEGRATED RISK ASSESSMENT

Final determination of the benefit/risk profile of Panzyga is pending the clinical, statistical and product reviews. Safety related data for Panzyga has been reviewed in detail.

5.1 Safety issues common to the IGIV class: *thromboembolic events; hemolysis; acute renal failure; hypersensitivity reactions; aseptic meningitis*

Thromboembolic events (TEE), hemolysis and acute renal failure are common to the IGIV class.^{14,15,16} No TEEs were identified in the clinical safety database. There was a single case of clinically evident mild hemolysis in NGAM-02 (adult ITP subject) that did not require treatment. . True hypersensitivity reactions associated with IGIV are rare¹⁷, but can occur in patients with anti-IgA antibodies. There were no hypersensitivity reactions identified in the clinical safety database. Aseptic meningitis is a rare complication that has been associated with all commercial preparations of IGIV at an estimated rate ranging from 0-1%¹⁸ of patients. In trial NGAM-02, one subject experienced aseptic meningitis and was treated with antibiotics; symptoms resolved.

Routine PV is planned for these important identified risks common to the IGIV class.

5.2 Viral safety

The potential risk of viral safety and transmission of infectious pathogens is common to products derived from donor plasma. The manufacturing process for Panzyga includes two viral inactivation/removal steps: solvent/detergent (S/D) treatment and nanofiltration. Measures to screen for infectious transmission included testing for Parvovirus B19, Hepatitis C virus, Hepatitis A virus, Human Immunodeficiency virus and Hepatitis B surface antigen. In cases of suspected seroconversion, viral tests were to be repeated and if confirmed additional serologic tests for specific viral antibodies (IgG and IgM) were to be performed. There were no cases of viral transmission in the clinical studies. Routine PV is planned for this important potential risk.

5.3 Limitations of small sample size and limited follow-up

Based on the rarity of both clinical indications, PID and chronic ITP, the clinical trials were small. The main limitation of the Panzyga safety dataset is the small sample size exposed in clinical trials. This makes the detection of rare adverse events unlikely; and there is no safety data on the use of Panzyga in select under-represented patient populations (pediatric patients with chronic ITP, and no safety data for either indication in elderly patients, patients with renal or hepatic impairment and pregnant or breastfeeding women). Therefore, the sponsor has listed the safety profile of Panzyga in these select populations as Important Missing Information in the proposed PVP, and proposes routine PV. Additionally, the clinical trials have limited follow-up and do not provide long term safety evaluation. PID and primary ITP are chronic conditions which require long term treatment.

¹⁴ FDA Safety Communication: Updated information on the risks of thrombosis and hemolysis potentially related to administration of intravenous, subcutaneous and intramuscular human immune globulin products. Available at <http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm327934.htm>

¹⁵ FDA. Immune Globulin Products (Human) intravenous, subcutaneous and intramuscular. Detailed View: Safety Labeling Changes Approved By FDA Center for Biologics Evaluation and Research (CBER) – June 2013. Available at <http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm360566.htm>

¹⁶ FDA. Adverse Event Report for an Immune Globulin: FDA Investigation and Actions. Available at <http://www.fda.gov/downloads/BiologicsBloodVaccines/InternationalActivities/UCM273193.pdf>

¹⁷ Guideline on Core SmPC for Human Normal Immunoglobulin for Intravenous Administration (IGIV) European Medicines Agency EMA/CHMP/BPWP/94038/2010 rev. 3.

¹⁸ Orbach O, Katz U, Sherer Y, et al: Intravenous immunoglobulin: adverse effects and safe administration. Clin Rev Allergy Immun. 2005; 29(3): 173-84

5.4 Clinical trial safety data

The data from the two clinical trials of adult and children subjects with PID (NGAM-01 and NGAM-05) support the safety and efficacy of Panzyga to treat adults and children with PID. The sponsor concludes that evaluation of AEs, laboratory results, vital signs and physical exams demonstrated that Panzyga was well tolerated and safe for children, adolescent and adult patients with PID. Review of the safety data in NGAM-01 and NGAM-05 did not identify additional safety concerns. There were no thromboembolic events, or cases of hemolysis reported during these studies. Though we note that the study size was small in the efficacy NGAM-01 trial (N = 51), it included more than the recommended minimum number of 30 subjects, and the recommended 40-50 subjects necessary to achieve at least 80% power with one-sided hypothesis testing and an alpha = 0.01.¹⁹ The safety analysis performed by the sponsor evaluates all infusional AEs (occurring during or within 72 hours of the end of infusion), whether or not the AE was assessed as being treatment-related. This provided a broad representation and decreased the risk of missing potential safety concerns in a small sample size of a rare clinical entity. The NGAM-05 trial (N=21) was an extension of NGAM-01, designed as a safety study of higher infusion rates, and presents evidence supporting the tolerability and safety of Panzyga with maximum infusion rates up to 0.14mL/Kg/min. The single pivotal phase 3 study NGAM-02 (N = 40) supports the safety and efficacy of Panzyga in adult ITP subjects. In this study, there were two deaths (both unrelated to treatment) and 1 case of clinically evident mild hemolysis with no treatment required. In conclusion, the AEs observed in the clinical safety dataset, were consistent with the well characterized safety profile of IGIVs and meet the standards outlined by regulatory guidance. The sponsor proposes labeling and routine pharmacovigilance for all of the identified and potential risks and missing information associated with Panzyga (Table 11).

5.5 Postlicensure Safety Data

There are no post-licensure materials for review, as the product has not been marketed in any country.

6.0 OBE/DE RECOMMENDATIONS

Based on review of the pre-licensure safety data and the sponsor's proposed pharmacovigilance plan for BLA 125587, should the product be licensed, routine pharmacovigilance is recommended to monitor the risks associated with Panzyga. Routine pharmacovigilance includes adverse event reporting in accordance with 21 CFR 600.80 and quarterly periodic safety reports for 3 years (annual thereafter). The available data do not suggest a safety signal that would trigger either a Risk Evaluation and Mitigation Strategy (REMS), a postmarketing commitment (PMC) or a required postmarketing (PMR) study that is specifically designed to evaluate safety as a primary endpoint.

¹⁹Guidance for Industry, Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency. U.S. Department of Health and Human Services, Food and Drug Administration. Center for Biologics Evaluation and Research, June 2008