

Summary Basis for Regulatory Action

Date: August 1, 2018

From: Michael Kennedy, PhD, Chair of the Review Committee

STN#: BL 125587

Applicant Name: Octapharma Pharmazeutika Produktionsges.m.b.H.

Date of Submission: April 15, 2015

Goal Date: August 2, 2018

Proprietary Name/Established Name: PANZYGA/immune globulin intravenous, human-ifas

Indications:

- 1. Primary humoral immunodeficiency (PI) in patients 2 years of age and older**
- 2. Chronic immune thrombocytopenic purpura (ITP) in adults**

Recommended Action:

The Review Committee recommends approval of this product.

Review Office(s) Signatory Authority: Wilson W. Bryan, MD, Director, Office of Tissues and Advanced Therapies

- I concur with the summary review.**
- I concur with the summary review and include a separate review to add further analysis.**
- I do not concur with the summary review and include a separate review.**

Document title	Reviewer name, Document date
CMC Review(s) <ul style="list-style-type: none">• <i>CMC (product office)</i>• <i>Facilities review (OCBQ/DMPQ)</i>• <i>Establishment Inspection Report (OCBQ/DMPQ)</i>	Lu Deng, PhD; Yonggang Wang, PhD; Pei Zhang, MD; Malgorzata Norton Christian Lynch, Randa Melhem, Silvia Wanis
Clinical Review(s) <ul style="list-style-type: none">• <i>Clinical (product office)</i>• <i>Postmarketing safety epidemiological review (OBE/DE)</i>• <i>BIMO</i>	Laurence Landow, MD; Rachel Witten, MD; Poornima Sharma, MD Wendy Paul, Wambui Chege, Erin McDowell

Statistical Review(s) <i>Clinical data</i> <i>Non-clinical data</i>	Jiang Hu, PhD
Pharmacology/Toxicology Review(s) <ul style="list-style-type: none"> • <i>Toxicology (product office)</i> • <i>Developmental toxicology (product office)</i> • <i>Animal pharmacology</i> 	Evi Struble, PhD
Clinical Pharmacology Review(s)	Carl-Michael Staschen, PhD; Iftekhar Mahmood, PhD
Labeling Review(s) <ul style="list-style-type: none"> • <i>APLB (OCBQ/APLB)</i> 	Alpita Popat, PharmD, MBA
Other Review(s) <ul style="list-style-type: none"> • <i>additional reviews not captured in above categories</i> • <i>consult reviews</i> 	OCBQ/DBSQC reviewer(s): Simleen Kaur; Hsiaoling Wang, PhD; Varsha Garnepudi, Ritu Agarwal, PhD
Advisory Committee summary	N/A

1. Introduction

Biologics License Application (BLA) 125587 is intended to support the use of Octapharma's product, Panzyga® (immune globulin intravenous, human-ifas), 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). Panzyga is a human immunoglobulin solution with 10% protein content for intravenous administration. It is made from a pool of at least 1000 donations of human (b) (4) plasma per batch. The manufacturing process has three virus inactivation/removal steps including solvent/detergent treatment, nanofiltration and ion exchange chromatography.

Study NGAM-01 provided evidence of efficacy for the indication of PI. A total of 51 subjects were enrolled in NGAM -01. Study NGAM -05, which was an extension study for NGAM-01, provided evidence of safety and tolerability collected in 21 subjects who were enrolled initially in NGAM-01. NGAM-02 evaluated efficacy of Panzyga for the treatment of ITP in 40 subjects. All three studies followed the same general design: prospective, open-label, single-arm, historical controlled, multicenter, and multinational. The duration of exposure to Panzyga (and dose) 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. This document summarizes the basis for approval of Panzyga for the indications of PI and ITP, and highlights the key review issues. The review team recommends approval of this BLA.

2. Background

Primary Immunodeficiency (PI)

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 frequency and duration of hospitalizations. 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.

Chronic Immune Thrombocytopenia (ITP)

Chronic ITP, often referred to as immune thrombocytopenic purpura, is an autoimmune disorder characterized by immunological destruction of otherwise normal platelets most commonly occurring in response to an unknown stimulus. ITP may occur in isolation (primary) or in association with other disorders (secondary). ITP has an annual incidence of 1-5 per 100,000 adults. ITP is a chronic disease in adults and thus the prevalence exceeds incidence. In the U.S., its prevalence is 8/100,000 in children and 12/100,000 in adults.

In general, clinicians use platelet threshold of $<30 \times 10^9/L$ as a trigger for treatment which is supported by clinical guidelines. Treatment for ITP is tailored to individual patients, based on presence and severity of bleeding, bleeding risk, the rapidity of desired platelet count rise and possible side effects of therapy. IGIV is used to increase platelet counts rapidly (24-48 hours), to reduce/control bleeding or to prepare patients for surgical intervention. The most accepted mechanism of action of IGIV in ITP is blockade of Fc γ receptors on macrophages, which prevents destruction of immunoglobulin G (IgG) sensitized platelets by the reticuloendothelial system. The recommended dose of IGIV is 1 gm/kg given on 2 consecutive days for a total dose of 2 gm/kg. An alternative dosing scheme is 0.4 gm/kg given daily for up to 5 days. The efficacy of both dosing schedules is comparable. The responses to IGIV are transient and generally last for 2-6 weeks. Therapy with IGIV is combined with a longer course of steroids to sustain improvement in platelet counts. Intravenous anti-RhD is a type of immune globulin that may be effective in patients with Rh positive blood type and an intact spleen. Refractory cases of ITP may require further treatment with splenectomy, rituximab, additional immunosuppression or therapy with thrombopoietin receptor agonists.

Several IGIV products are approved for management of ITP. Some recently approved IVIG products include Privigen and Gammalex. The response rates with these products in ITP are approximately 81% with duration of response ranging from 10-15 days. Most adverse reactions to IGIV are infusion-related, and these are generally transient. These

can be mitigated with premedication with histamine 1(H1) blockers and with slowing of infusion rate. Infusion reactions include headache, fever, chills, nausea, vomiting, hypertension or hypotension. Rare but serious side effects include: aseptic meningitis, hemolytic anemia, anaphylaxis, thrombosis and acute renal injury.

Panzyga is currently marketed in 30 countries worldwide, including the United Kingdom, France, Belgium, and Canada. The applicant recently submitted a summary of post-marketing safety reports in response to an information request which did not reveal any new or unexpected safety signals. The post-marketing safety reports included primarily infusion reactions of varying severity, aseptic meningitis and delayed hemolytic reaction.

PREA (Pediatric Review Committee)

Panzyga is subject to requirements under PREA (Pediatric Research Equity Act), as this is a new product for the indications of PI and ITP. A request for a waiver of pediatric studies for the indication of chronic ITP (age 0-18 years) was included in this submission. The basis for the waiver request was the anticipated lack of meaningful therapeutic benefit with Panzyga compared to other treatments. This BLA was presented to the Pediatric Review Committee (PeRC) on March 9, 2016. The PeRC did not agree to a full waiver in pediatric patients for the indication of chronic ITP. The basis for refusal was inclusion of subjects 1 year and older in a clinical trial supporting approval of Eltrombopag, (a thrombopoietin agonist) for the treatment of chronic ITP, indicating the feasibility of conducting studies in a pediatric population with ITP. Additionally, under Section 505B, to qualify for a waiver a product must not represent a meaningful therapeutic benefit over existing therapies AND is not likely to be used in a substantial number of patients. The latter requirement was not met by the waiver request. In children < 1 year of age with ITP, the clinical course can be variable with occurrence of spontaneous remissions limiting the feasibility of conducting clinical studies. Therefore, the PeRC granted a waiver for studies in children less than 1 year of age for chronic ITP. A deferral of studies for ages >1 to <18 years for the indication of chronic ITP was also granted. A partial waiver was granted for patients ages birth to less than 2 years for the indication of PI, on the basis that studies would be impossible or highly impracticable. No additional pediatric studies for PI are required because the pediatric study assessment has been fulfilled with the data submitted in the BLA.

Regulatory History

The original BLA was submitted on April 15, 2015. Based on unresolved issues related to facilities inspection and chemistry, manufacturing, and controls (CMC), a complete response (CR) letter was issued on February 10, 2016. The applicant resubmitted the BLA on January 31, 2018, which included CMC, clinical pharmacology, and labeling information. This resubmission was considered a Class 2 response to FDA's CR letter, and the action due date was designated as August 2, 2018.

3. CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC)

Panzyga is prepared from (b) (4) plasma donated by healthy qualified plasma donors. The plasma is processed to (b) (4) according to the (b) (4) fractionation process. The purification process includes (b) (4) steps. There are three virus inactivation/reduction steps in the Panzyga process: a solvent/detergent (SD) treatment step, a 20 nm nanofiltration, and an ion exchange (b) (4) chromatography step. The final product is formulated using glycine as the excipient and will be filled in configurations of 10 mL, 25 mL, 50 mL, 100 mL, 200 mL and 300 mL solutions. The product is supplied in (b) (4) glass vials with bromobutyl rubber stoppers and an aluminum flip-off cap. The manufacturing process until final bulk solution is performed at Lingolsheim, France (OSA). Filling of the bulk solution is performed at Vienna, Austria (OPG). Quality Control is performed at Lingolsheim (OSA) or Vienna (OPG). The proposed dating period of each material was evaluated based on the data from clinical lots, conformance lots, and process performance qualification lots, and summarized as follows:

Table 1. Proposed Dating Periods

Materials	Proposed by Sponsor	Recommended by Agency
(b) (4)	(b) (4)	Acceptable
(b) (4)	(b) (4)	Acceptable
Drug Substance (b) (4)	(b) (4)	Acceptable
Drug Product (Final Container)	Octapharma proposes a shelf life of 2 years at 2-8 °C, and within its shelf-life, the product may be stored at 25 °C for up to 9 months. After storage at ≤ 25 °C the product must be used or discarded.	Acceptable

a) Product Quality

The analytical methods and their qualifications and/or validations reviewed for the Immune Globulin Intravenous (Human) drug substance and drug product were found to be adequate for their intended use.

b) CBER Lot Release (only applicable for BLAs)

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

c) Facilities review/inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of Panzyga® (immune globulin intravenous, human-ifas) are listed in the table below. The activities and inspectional histories for each facility are noted in the table and further described in the paragraphs that follow:

Table 2. Manufacturing Facilities for Panzyga®

Name/Address	FEI Number	DUNS Number	Inspection / Waiver	Justification / Results
Drug Substance Manufacturing and in-process testing through (b) (4)			Pre-License Inspection	CBER Oct. 5 – 14, 2015 OAI
Octapharma OSA 72 rue du Maréchal Foch, 67380 Lingolsheim, France	3011099411	770748127	Pre-License Inspection (Re-inspection)	CBER May 21 – 25, 2018 VAI
Drug Product Fill/Finish, Visual Inspection, Labeling & Packaging, and QC Testing			Waived	Team Biologics January 9 – 17, 2017 VAI
Octapharma OPG, Oberlaaer Strasse 235, A-1100, Vienna, Austria	3002809097	301119178		
Drug Product Visual Inspection and Labeling & Packaging			Waived	Team Biologics February 15 – 18, 2016 VAI
Octapharma ODE, Otto-Reuter-Straße 3, Dessau-Roßlau, 06847 Germany	3008923644	N/A		

The initial CBER Pre-License Inspection (PLI) of the Octapharma S.A.S. Lingolsheim facility (OSA) was conducted from October 5-14, 2015. At the end of the inspection, a Form FDA 483 was issued to the firm. Following review of the firm's responses to the 483 Observations from the initial PLI, a Complete Response (CR) Letter was issued to the firm (dated February 10, 2016) for unresolved inspectional, review, and clinical pharmacology issues. The initial PLI was ultimately classified as Official Action Indicated (OAI).

The firm's complete response to the CR Letter was received on January 31, 2018. A second CBER PLI was conducted at the Octapharma OSA Lingolsheim facility from May 21-25, 2018. At the conclusion of the inspection, a Form FDA 483 was issued to the firm. The firm responded to the Form FDA 483, and all corrective actions were reviewed and found to be adequate. All inspectional issues are considered to be satisfactorily resolved.

Team Biologics performed a surveillance inspection of Octapharma OPG in January 2017. All 483 issues were resolved and the inspection was classified as voluntary action indicated (VAI).

The Octapharma ODE facility was inspected by Team Biologics in February 2016. All 483 issues were resolved, and the inspection was classified as VAI.

d) Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). FDA concluded that this request is justified as the manufacturing of this product will not alter significantly the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

e) Product Comparability

Octapharma provided adequate characterization to support comparability of all product lots (clinical, engineering, conformance). Octapharma has been producing Panzyga for the European and Canadian markets since 2016.

f) Container closure

Panzyga is a liquid formulation, and intended for intravenous injection. It is available in six different fill volumes: 10mL, 20mL, 50mL, 100mL, 200mL and 300mL. The final product is filled at the OPG Vienna facility. A description for the primary packaging (vial, stopper, and cap) is summarized in the following Table:

Table 3. Primary Packaging Description

Container closure system	Size
Vials: Glass (b) (4) (b) (4) supplied by (b) (4)	20mL (10mL fill volume)
	30mL (20mL fill volume)
	70mL (50mL fill volume)
	100mL (100mL fill volume)
	250mL (200mL fill volume)
	300mL (300mL fill volume)
Stopper: Bromobutyl rubber, (b) (4) supplied by (b) (4)	20 mm light grey ((b) (4) coating) – used for the 20-30mL vials.
	32mm light grey ((b) (4) coating) – used for the 70mL-300mL vials.
Cap: Aluminum flip off supplied by (b) (4)	20mm blue cap – used for the 20-30mL vials.
	32mm white cap – used for the 70mL-300mL vials

Container closure integrity testing (CCIT) was performed at the OPG Vienna facility by the (b) (4) method, using the (b) (4); all acceptance criteria were met.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

The animal toxicology program consisted of single-dose toxicity studies, one in mice and one in rats; safety pharmacology studies in rabbits, spontaneously hypertensive rats and guinea pigs; and a local toxicity study in rabbits. Most of the nonclinical studies were performed with a preclinical material with the same formulation as Panzyga but manufactured with an earlier process. There were no adverse effects attributed to the preparation administered to animals at doses multiple times higher than the human dose.

Panzyga contains TNBP and Triton X-100 (Octoxynol-9), two impurities that are process-related, deriving from the solvent detergent treatment. These impurities are present at levels equal to those in the approved product Octagam; thus, a safety database for human use of an IGIV product with a similar formulation exists. In the BLA, the applicant also submitted data from acute and sub-chronic toxicology and genotoxicity studies which show that exposure to these impurities at doses multiple times higher than the human dose was the no-observed-effect-level (NOEL).

Given the lack of toxicity of the preclinical material, and the comparability of Panzyga to the preclinical material, these nonclinical toxicology studies support the approval of the BLA.

5. CLINICAL PHARMACOLOGY

The pharmacokinetics (PK) of Panzyga in 50 pediatric and adult subjects with Primary Humoral Immunodeficiency were assessed in Study NGAM-01. Subjects received infusions of Panzyga (200 to 800 mg/kg body weight) every 3 or 4 weeks for 12 months. Blood samples for the PK study were collected between the 7th and 9th Panzyga infusion at 0.25, 1, 24, 72 hours, and Days 7, 14, 21 (for the 3-week schedule) and 28 (for the 4-week schedule) post-infusion. For the 3-week schedule, the half-life of IgG with baseline correction ranged from 116 to 141 hours across all age groups. The clearance of IgG was higher in 0<6, 6-<12, and 12 - <16 years of age by 47%, 7%, and 40 %, respectively. For the 4-week schedule, the half-life of IgG with baseline correction ranged from 148 to 185 hours across all age groups. The clearance of IgG was higher in 0<6, 6-<12, and 12 - <16 years of age by 19%, 19%, and 200%, respectively. The reason for substantially higher clearance of IgG in adolescents than adults is not known.

The PK profile of Panzyga was not studied in patients with chronic ITP.

6. CLINICAL/STATISTICAL/PHARMACOVIGILANCE

a) Clinical Program

Demographics:

Three clinical studies included in the submission are: NGAM-01 (indication: PI, n=51), NGAM-05 (extension study for NGAM-01, n=21) and NGAM-02 (indication: ITP, n=40) -- see Table 4.

Table 4. 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

Clinical Studies:

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) 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.

Subjects received Panzyga via IV infusion at a dose between 200 to 800 mg/kg body weight for one of two treatment intervals (i.e., every 3 or 4 weeks), consistent with the subject's previous dosage regimen. Subjects participated in the study for a mean of 360 days. Infusions were initiated at a rate of 1 mg/kg/min for the first 30 minutes, and, if tolerated, could be advanced to a maximum tolerated rate not exceeding 4 mg/kg/min. The mean age of subjects was 26.8 years (range: 2 to 65 years).

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, full analysis data set (FADS), and PK populations. Of these 51 subjects, 50 completed the trial. One subject, 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.

NGAM-01 met its primary efficacy endpoint (SBI rate). The observed rate was 0.08 serious bacterial infections per patient per year (4 infections over 50.2 patient-years; see Table 5). 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. Only 1 adult subject was hospitalized for 4 days due to an SBI (rate of days in hospital per person-year: 0.080). Approximately 50% of all patients missed at least 1 day of work or school due to infections, with an annual rate of less than 4 days/person-year. Episodes of fever were observed in less than 25% of all patients. The mean resolution time was 14 days for serious bacterial infections and 18 days for other infections.

Table 5. SBI Rate per Person-Year by Age and Treatment Schedule (FADS, 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

Throughout the entire study, the serum IgG trough levels were nearly constant for both treatment schedules and were above the required trough levels of about 5-6 g/L. The calculated pharmacokinetic parameters showed that the minimum concentration of IgG was at least 6.8 g/L for both treatment intervals.

No subject was pre-medicated prior to any infusion. The product was well tolerated and all patients completed the study as planned. 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%).

2. NGAM-05 was an extension study comprised of subjects (N=21) who were enrolled initially 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 higher rates (0.08 to 0.14 mL/kg/min) than in NGAM-01. Subjects in NGAM-05 received a dose of Panzyga every 3 or 4 weeks for 4 months. The primary endpoint was the number of causally and/or temporally related treatment emergent adverse events (TEAEs). Only descriptive statistics were reported (see safety data for study NGAM-05 under the Safety Section, below).
3. NGAM-02 was a Phase 3 study in adults aged ≥18 years (N=40) with chronic primary ITP. Subjects were enrolled if they had a history of chronic ITP with a platelet count of less than or equal to 20×10^9 /L with or without bleeding manifestations. Subjects on long-term steroids and immunosuppressive therapies were allowed if their dose had been stable (3 weeks for steroids and 3 months for other immunosuppressants) with no plan to change dose until study Day 22.

Subjects with risk factors for thrombosis, including obesity, advanced age, and history of thrombosis or atherosclerosis, were excluded.

The proposed sample size for the trial was 86; however due to a drug shortage, the study was terminated prematurely after 40 subjects completed enrollment. All 40 subjects treated on NGAM 02 were from sites outside the USA. FDA agreed to consider licensure of the ITP indication despite the smaller sample size, provided the data from 40 subjects met criteria for safety and efficacy.

In NGAM-02, Panzyga was administered at a dose of 1gm/kg/day for two consecutive days and subjects were followed-up for safety through Day 63. The primary endpoint was platelet response rate, defined as the proportion of enrolled subjects meeting eligibility criteria who demonstrated an increase in platelet count to $\geq 50 \times 10^9/L$ within 7 days after the first infusion. Key secondary endpoints included maximum platelet count, time to platelet response, duration of response, and hemostatic outcome in subjects who had bleeding at baseline. Response rate above 60% was prespecified as the study success criterion. This threshold was obtained from a historical control value of $p_0=0.75$ and a region of indifference of $\delta=0.15$. Sample size of 86 subjects was needed to achieve power of 80% for this trial with an alpha of 0.025.

Four subjects enrolled and treated in NGAM-02 trial were deemed to be ineligible and hence removed from the efficacy analysis. These four subjects met exclusionary criteria, including HIV positivity, history of Evan's syndrome and platelet count $>20 \times 10^9/L$ at enrollment. Hence, the primary efficacy analysis was based on 36 subjects that met the protocol-specified definition of full analysis set (FAS).

The NGAM-02 trial met its primary efficacy endpoint as 29/36 enrolled subjects (81%; 95% CI 64% to 92%) responded to Panzyga. Median time to response was 2 days and duration of response was 14 days. 80% (23/29) of subjects with a response attained a normal platelet count. For the 36 efficacy-evaluable subjects, mean maximum platelet count after the start of treatment was $237 \times 10^9 /L$.

Twenty-three subjects (23/36; 64%) had bleeding at baseline. 44 % (16/36) of the subjects had minor or mild bleeding and 19% (7/36) had moderate bleeding. Subjects had epistaxis, oral and skin bleeding at presentation. Improvement in platelets correlated with overall improvement in bleeding. On study Day 7, only 14% of subjects had bleeding, with resolution of 5/7 moderate bleeds. One subject experienced new bleeding during the course of the study. This bleeding event involved muscles and joint and was graded as severe. This subject was a non-responder. Two study deaths were not related to Panzyga.

All enrolled and treated subjects (n=40) were included in the safety analysis. The most common adverse events were infusion-related and included headache (50%), fever (23%), nausea (18%), emesis (10%) and dizziness (10%). One subject developed aseptic meningitis on Day two after receiving a second infusion of

Panzyga. He was treated with antibiotics and supportive care with resolution of symptoms. 26% (10/39) of subjects converted from negative direct antiglobulin test (DAT) at baseline to positive test after receiving Panzyga. One subject did not undergo baseline coombs test but tested positive on all three subsequent tests. Five subjects (13%) developed hemolytic anemia that resolved spontaneously without any intervention.

Overall a primary efficacy of 81% compares favorably with response rates reported with approved IGIV products that range between 70%-82% (Julia A et al; *Transfusion Medicine* 2009, Robak T et al, *Hematology* 2009, Robak T et al, *Hematology* 2010).

Post-Marketing Data:

In supplement 125587/3.0 (dated February 15, 2018), the applicant provided a periodic safety update report for the time interval from September 22, 2017 to January 19, 2018. The post-marketing safety data contained in this report were compiled from individual case safety reports (ICSRs) that were received by the applicant from worldwide reporting sources during the reporting period. Clinical review of the post-marketing safety information contained in this report did not reveal any additional safety issues for Panzyga compared to known safety issues for products in this class.

b) Statistical Summary:

Statistical review of NGAM-01 efficacy data concurs with the clinical review. The primary efficacy endpoint of NGAM-01 was serious bacterial infections (SBIs) per person-year. The upper limit of the one-sided 99% confidence interval (CI) of SBIs for all subjects (n=51) in NGAM-01 was 0.5033, which is less than 1.0. Therefore, the pre-specified efficacy acceptance criterion was met.

NGAM-05 was an extension study of NGAM-01 to test a higher infusion rate with safety analyses only.

Statistical review of NGAM-02 concurs with the clinical review. As prespecified in the study protocol, the primary efficacy analysis was conducted in 36 subjects, which was the FAS. This was defined as subjects that satisfied eligibility criteria, were exposed to Panzyga and had one post-baseline platelet count available. Four subjects were excluded from the FAS as they were enrolled despite meeting exclusion criteria. A response rate above 60% was prespecified as a study success criterion. A response rate of 81% (29/36) resulted in a lower limit of the one-sided 97.5% CI of 63.98%. Since the lower limit of the one-sided 97.5% CI for the proportion of responders was above the pre-defined reference value of 0.6, the null hypothesis was rejected, and the study success criterion was met.

c) Pharmacovigilance:

Key identified risks of Panzyga include infusional reactions including anaphylaxis, especially in IgA-deficient patients, thrombosis, renal insufficiency, aseptic meningitis

and Coombs-positive hemolytic anemia. Other possible adverse events include volume overload, TRALI (transfusion related acute lung injury), hypertension and potential risk for transmitting infectious agents e.g. viruses, variant Creutzfeldt Jakob disease and Creutzfeldt Jakob agent. Based on the review of safety data from the three completed studies and post-licensure safety data, a post-marketing safety study is not indicated. FDA recommends routine pharmacovigilance for this product. This includes adverse event reporting under 21 CFR 600.80 and quarterly periodic safety reports for 3 years and then annually thereafter. The available data do not suggest a safety signal that would trigger Risk Evaluation and Mitigation Strategy (REMS) or a post-marketing commitment (PMC) study that is specifically designed to evaluate safety as a primary endpoint. A PREA (Pediatric Research and Equity Act)-mandated PMR study is required to assess efficacy and safety of Panzyga in the pediatric population (ages >1 year to <18 years).

Results of CBER Bioresearch Monitoring (BIMO):

Bioresearch Monitoring (BIMO) inspections were issued for two foreign clinical study sites that participated in the conduct of Study NGAM-02 and three domestic clinical study sites that participated in the conduct of Studies NGAM-01 and NGAM-05. The BIMO inspections did not reveal substantive problems that impact the data submitted in this BLA.

d) Pediatrics

A partial waiver was granted for patients ages birth to less than 2 years for the indication of PI on the basis that studies would be impossible or highly impracticable. 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.

For details regarding pediatric waiver submission under PREA for indication of ITP, please refer to Section 2; Background.

e) Other Special Populations

Not applicable.

SAFETY

Safety of Panzyga was evaluated in 51 unique subjects treated in NGAM-01 and NGAM-05 for the indication of PI and 40 subjects treated in NGAM-02 for the indication of immune thrombocytopenia. Integration of safety data across these two indications is problematic, because of significant differences in demographics (adults and pediatrics versus adults), duration of exposure (12 months versus 2 days), dose and frequency (300-600 mg/kg every 3-4 weeks versus 1gm/kg x 2 doses), indication (primary

immunodeficiency versus ITP). Hence the safety data for both indications was analyzed separately.

NGAM-01 (Primary Immunodeficiency)

Seven Serious Adverse Events (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 who experienced gout (severe), a 41-year-old Caucasian female who was admitted to hospital for a septoplasty under general anesthesia, and another 41-year-old Caucasian female who was admitted to hospital after noticing petechiae on her lower extremity and was found to have a platelet count of $11 \times 10^9/L$.

Among NGAM-01 subjects, clinical laboratory TEAEs included leukopenia in the 39-year-old Caucasian male mentioned previously, and thrombocytopenia in the 41-year-old Caucasian female mentioned previously who developed petechia on her lower extremity.

The incidence of infusional TEAEs was 74.5% (38/51 subjects) in NGAM-01. Out of 740 infusions administered in the study, 89 (12%) infusions were associated with at least one infusional TEAE. The most common adverse reactions reported in NGAM-01 (n=51 subjects) were headache (11 subjects, 21.6%), pyrexia (7 subjects, 13.7%), nausea (5 subjects, 9.8%) and upper abdominal pain (5 subjects, 9.8%). No subject had an AE that resulted in discontinuation from the study.

NGAM-05 (Primary Immunodeficiency)

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 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.

NGAM-02 (Chronic ITP)

Study NGAM-02: The key safety issues identified included infusion-related adverse events, Coombs positive hemolytic anemia and a single case of aseptic meningitis. This is outlined in detail under section 6a; Clinical Program. Overall the adverse events observed in this study are consistent with the well characterized safety profile of IGIVs.

Study NGAM-02: The key safety issues identified included infusion related adverse events, Coombs positive hemolytic anemia and a single case of aseptic meningitis. This is outlined in detail under section 6a; Clinical Program. Overall the adverse events observed in this study are consistent with the well characterized safety profile of IGIVs.

7. ADVISORY COMMITTEE MEETING

An Advisory Committee Meeting was not convened for the discussion of this submission as other products in the same class have been approved for same indications and no significant issues of safety or efficacy were encountered during the course of the review.

8. OTHER RELEVANT REGULATORY ISSUES

None.

9. LABELING

The proposed proprietary name, PANZYGA, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on June 3, 2015 and June 6, 2018, and was found acceptable.

CBER communicated the acceptability of the proprietary name to the applicant on July 2, 2015. The four-letter suffix to the proper name (ifas) was accepted by APLB on July 20, 2018. The APLB found the package insert (PI) and package/container labels acceptable from a promotional and comprehension perspective.

The review committee negotiated revisions to the PI, including the warning and precautions section and clinical trials experience. The following highlights the key labeling issues that were addressed.

- Section 5, Warnings and Precautions: Volume overload and hypertension are added under this section as they are adverse events associated with this class of products and included in label for other approved IGIV products.

- Section 6.1, Clinical trials experience: Safety data for treatment of chronic ITP in adults was updated to reflect the analysis of the FDA review team. Based on additional adverse reactions identified, Table 2 under Section 6.1 was updated. This resulted in identification of additional subjects with headache, nausea, dizziness, and anemia that occurred as a result of Panzyga administration. The risk-benefit analysis of Panzyga remains unchanged despite this updated safety analysis.

All issues were acceptably resolved after exchange of information and discussions with the applicant.

10. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

The review committee recommends approval of this resubmitted BLA. The clinical data from Studies NBAM-01, NGAM-02 and NGAM-05 provide substantial evidence of effectiveness and supports a favorable benefit/risk determination for the use of Panzyga in the management of PI (Primary humoral immunodeficiency) and ITP (Chronic Immune Thrombocytopenia). The review committee recommends approval of this original BLA. The clinical data from studies NBAM-01, NGAM-02 and NGAM-05 provide substantial evidence of effectiveness and supports a favorable benefit/risk determination for the use of Panzyga in the management of PI and ITP.

b) Risk/Benefit Assessment

Panzyga is effective in reducing the number of serious bacterial infections (SBI) to <1 per patient year in PI and in elevating the platelet count in adults with chronic ITP. Risk of thrombosis and renal dysfunction appear to be low.

Panzyga has demonstrated efficacy in the management of ITP based on the results of the study and has an acceptable safety profile. Unlike 5% IGIV, 10% IGIV products like Panzyga require shorter infusion times and have lower infusion volumes minimizing risk of fluid overload. The most common risks of Panzyga include infusion-related adverse events. These can be mitigated by lowering the rate of infusion and pre-medicating with H1 blockers. Other adverse events seen with Panzyga included aseptic meningitis (1/40 subjects) and hemolytic anemia. These adverse events are anticipated with this class of products and were self-limited with Panzyga. Overall, the benefits described above outweigh the risks related to Panzyga for the proposed indications of PI and chronic ITP.

c) Recommendation for Post-Marketing Activities

FDA recommends routine pharmacovigilance for this product. This includes adverse event reporting under 21CFR 600.80 and quarterly periodic safety reports for 3 years and then annually thereafter. The available data do not suggest a safety signal that would trigger either a Risk Evaluation and Mitigation Strategy (REMS) or a post-marketing commitment (PMC) that is specifically designed to evaluate safety as a primary endpoint. However, since PREA is triggered, a post-marketing requirement trial evaluating Panzyga in pediatric subjects aged >1 year to less than 18 years is required for the chronic ITP indication.