Application Type	Efficacy Supplement
STN	125587/70
CBER Received Date	April 21, 2020
PDUFA Goal Date	February 19, 2021
Division / Office	DCEPT /OTAT
Priority Review	No
Reviewer Name(s)	Ekaterini Tsilou, MD
Review Completion Date / Stamped Date	
Supervisory Concurrence	Lei Xu, MD, PhD Ilan Irony, MD
Applicant	Octapharma Pharmazeutika Produktionsges.m.b.H.
Established Name	Immune Globulin Intravenous (Human) – ifas
Trade Name	Panzyga
Pharmacologic Class	Immunoglobulins
Formulation(s), including Adjuvants, etc.	Liquid Solution Containing 10% IgG
Dosage Form(s) and Route(s) of Administration	Liquid Solution for Intravenous (IV) Administration
Dosing Regimen	Loading dose: 2 g/kg (20 mL/kg), divided into 2 daily doses of 1 g/kg (10 mL/kg) given on 2 consecutive days, Maintenance dose: 1-2 g/kg (10-20 mL/kg) every 3 weeks divided in 2 doses given over 2 consecutive days
Indication(s) and Intended Population(s)	Treatment of adults with chronic inflammatory demyelinating polyneuropathy (CIDP) to improve neuromuscular disability and impairment
Orphan Designated	No

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GLOSSARY

AE	adverse event
AR	adverse reaction
BLA	Biologics License Application
CAs	Competent Authorities
CIDP	Chronic Inflammatory Demyelinating Polyneuropathy
CFR	Code of Federal Regulations
CMC	Chemistry, Manufacturing, and Controls
CR	complete response
CSR	Clinical Study Report
ES	Executive Summary
FAS	full analysis set
GCP	Good Clinical Practice
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
INCAT	Inflammatory Neuropathy Cause and Treatment Disability Score
IRB	Institutional Review Board
I-RODS	Inflammatory Rasch-built Overall Disability Scale
ISE	integrated summary of efficacy
ITP	Immune Thrombocytopenic purpura
ITT	intent-to-treat
IGIV	Intravenous Immune Globulins
MADSAM	Multifocal Acquired Demyelinating Sensory And Motor Neuropathy
MedDRA	Medical Dictionary for Regulatory Activities
MRC Sum Score	Medical Research Council (MRC) Sum Score
NDA	New Drug Application
OBE	Office of Biostatistics and Epidemiology
OCOD	Office of Communication Outreach and Development (CBER)
OSE	Office of Surveillance and Epidemiology
PD	pharmacodynamics
PE	Plasma Exchange
PeRC	Pediatric Review Committee
PI	package insert
PID	primary humoral immunodeficiency
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
REMS	risk evaluation and mitigation strategy
RMS/BLA	regulatory management system for the biologics license application
SAE	serious adverse event
SAF	safety set
SD	standard deviation
TEAE	Treatment emergent adverse event

1. Executive Summary

Panzyga is a 10% liquid preparation of immune globulin intravenous (IGIV) (human) for intravenous administration. Panzyga was licensed in the United States in 2018. Panzyga is approved in the United States and the European Union (EU) for the treatment of primary humoral immunodeficiency (PI) and chronic immune thrombocytopenic purpura (ITP). It is also approved in the EU for the treatment of secondary immunodeficiencies (SID), Guillain-Barré syndrome (GBS), Kawasaki disease, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and multifocal motor neuropathy (MMN).

The indication originally proposed by the applicant for Panzyga under this Biological License Application (BLA) efficacy supplement was for "treatment of adults with chronic inflammatory demyelinating polyneuropathy (CIDP) to improve neuromuscular disability and impairment (b) (4) ." FDA requested the applicant to revise the indication to "treatment of adults with chronic inflammatory demyelinating polyneuropathy (CIDP) to improve neuromuscular disability and impairment." This request was made because the applicant did not submit data from any studies using a randomized withdrawal design to establish efficacy for (b) (4) (b) (4)

In the United States, Gamunex-C and Privigen brands of IGIV are currently the only intravenous Immune globulin products approved for CIDP treatment to improve neuromuscular disability and impairment. Gamunex-C is also approved for maintenance therapy in CIDP to prevent relapse.

The efficacy and safety of Panzyga in adults with CIDP was evaluated in a prospective, double-blind, randomized, dose controlled multicenter Phase 3 study (Study NGAM-08). The study was conducted in 25 study sites in Canada and Europe (Russia, Bulgaria, Hungary, Ukraine, Romania, Czech Republic, Poland, and Germany). The study included a screening period, a wash-out period and a dose evaluation period. One hundred seventy-one (171) patients with CIDP were screened and there were 21 screen failures. One hundred fifty (150) subjects entered the wash-out period, during which the current medication (immune globulins or corticosteroids) was reduced stepwise until the subject deteriorated. One hundred forty-two (142) subjects (18 to 83 years of age) deteriorated and were randomized 1:2:1 to receive first a loading dose of 2 g/kg, and then to 0.5 g/kg, 1.0 g/kg or 2.0 g/kg Panzyga for 7 maintenance infusions at 3-week intervals during the dose evaluation period. There were 35, 69 and 38 subjects in 0.5 g/kg, 1.0 g/kg or 2.0 g/kg Panzyga dose groups, respectively.

The primary efficacy endpoint was the proportion of responders in the 1.0 g/kg Panzyga arm at Week 24 (End of Study Visit) relative to Baseline (Week 0). A pre-defined threshold of 0.42 for the proportion of responders in the 1 g/kg dose group was set by the applicant based on the lower limit of the 95% Wilson-Score confidence interval (CI) for the proportion of responders of the treated arm in the PRIMA study that supported the approval of Privigen brands of IGIV for the treatment of CIDP in adults. A responder was defined as a subject with a decrease of at least 1 point on the adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) disability score (a scale from 0 to 10, from healthy to unable to make any purposeful movements with arms and/or legs) relative to Baseline. Other efficacy assessments included grip strength, Inflammatory Rasch-built Overall Disability Scale (I-RODS) score and Medical Research Council (MRC) sum score. The proportion of responders in the 0.5 g/kg and 2.0 g/kg Panzyga

arms at Week 24 relative to baseline was also compared to the 1.0 g/kg arm, based on the adjusted INCAT disability score, the grip strength and I-RODS scores.

The proportion of responders assessed by the adjusted INCAT disability score was 79.7% (95% CI: 68.8, 87.5) in the 1.0 g/kg group, with 55 out of 69 subjects classified as responders. The lower limit of the 95% Wilson-Score CI for the proportion of responders exceeded the predefined threshold of 42%, and the primary endpoint of the study was met. The primary endpoint result was supported by consistent improvements in all secondary efficacy endpoints (IRODS score, maximum grip strength and MRC sum score) from baseline to completion. In the secondary analysis of the proportion of responders based on adjusted INCAT disability score, grip strength and I-RODS score across the three dose arms, there was evidence of a dose response with higher proportions of responders with increasing dose in all these outcomes.

All 142 subjects received at least 1 dose of Panzyga. Seventy-three out of the 142 subjects experienced a total of 209 adverse reactions (AR). The most frequent ARs that occurred in more than 5% of subjects include headache (14.8%), fever (14.1%), dermatitis (9.9%), and blood pressure increased (7.7%). Generally, the incidence of ARs was similar across the three dose arms; the only AR where a dose effect was evident was for headache, with an incidence of 2.9% in the 0.5 g/kg arm, 14.5% in the 1.0 g/kg arm and 23.7% in the 2.0 g/kg arm. Two serious ARs (headache and vomiting) were reported in one subject but did not lead to study discontinuation.

The applicant requested a partial waiver for Panyzyga for pediatric studies in patients from birth to less than 2 years of age because necessary studies are impossible or highly impracticable due to low prevalence. The applicant also requested a deferral of pediatric studies in patients two to less than 17 years of age. The FDA Pediatric Review Committee (PeRC) agreed with granting partial pediatric waiver in pediatric patients birth to less than 2 years of age and a deferral of studies for pediatric patients 2 to less than 17 years of age.

Clinical Reviewer's Recommendations on Regulatory Action:

Based upon review of safety and efficacy information in this BLA efficacy supplement, this reviewer recommends that BLA efficacy supplement, 125587/70, be approved with a PREA Post-marketing Requirement (PMR) to conduct a pediatric study in subjects with CIDP aged 2 years to less than 17 years. A partial waiver is recommended for pediatric studies in subjects with CIDP under age 2 years.

Unlike the clinical development program for Gamunex-C, the applicant has not conducted a randomized withdrawal design study to support the effectiveness of Panzyga for (b) (4) . Therefore, we requested the applicant to modify the indication to "for the treatment of adults with chronic inflammatory demyelinating polyneuropathy (CIDP) to improve neuromuscular disability and impairment." The applicant has accepted this change in the requested indication.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Demographics of the 142 subjects enrolled in the *NGAM-08* Study are presented in Table 1.

Demographic characteristics are summarized as follows:

a. Subjects between 18 and 83 years of age were enrolled in the study.
b. There were more male subjects than female subjects.
c. All subjects were white.

Table 1: Demographic Data by Dose Group (N=142)

Treatment Arm	**0.5g/kg N=35**	**1.0g/kg N=69**	**2.0g/kg N=38**	**Total N=142**
Age (years)				
Mean (SD)	52.4 (14.4)	56.3 (14.6)	58.0 (13.8)	55.8 (14.4)
Median	56.00	59.00	62.50	59.00
Min, Max	26, 73	18, 83	30, 83	18, 83
Sex (n (%))				
Male	22 (62.9%)	38 (55.1%)	24 (63.2)	84 (59.2%)
Female	13 (37.1%)	31 (44.9 %)	14 (36.8%)	58 (40.8%)
Race (n (%))				
White	35 (100%)	69 (100%)	38 (100%)	142 (100%)
Weight (Kg)				
Mean (SD)	84.1 (16.5)	81.7 (16.3)	77.7 (16.9)	81.2 (16.6)
Median	83	80	75.5	79
Min, Max	56, 120	49, 122	48, 122	48, 122
Height (cm)				
Mean (SD)	173.5 (9.5)	172.8 (8.3)	171.6 (9.0)	172.7 (8.8)
Median	172	172	171.50	172
Min, Max	153, 191	155, 191	154, 200	153, 200
BMI (kg/m^2)				
Mean (SD)	27.9 (4.9)	27.3 (4.6)	26.3 (5.2)	27.2 (4.8)
Median	27.2	27.4	25.1	26.9
Min, Max	18.7, 39.9	16.6, 39.4	18.7, 39.6	16.6, 39.9

Source: Modified from sBLA 125587/70.0, Module 5.3.5.1; CSR, Table 14.1.2.1.2, p146.

Reviewer's Comment:
Demographics in NGAM-08 study were similar to ICE and PRIMA studies in regard to age, and sex and race distribution. The overwhelming percentages of White in ICE, PRIMA, and NGAM-08 studies are consistent with the results of a 2010 United States CIDP patient survey which found that whites/Caucasians comprised 94% of CIDP patients.

1.2 Patient Experience Data

Clinician-reported outcomes were used as primary, and secondary efficacy endpoints in Study NGAM-08 (Table 2).

Table 2 Patient Experience Data Relevant to this Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☒	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) is an acquired immune-mediated neurological disorder characterized by progressive weakness and impaired sensory function in the legs and arms. The disorder is caused by damage to the myelin sheath of peripheral nerves. The precise pathophysiology of CIDP remains uncertain although B and T cell mechanisms have been implicated.

CIDP can occur at any age from childhood to beyond the eighth decade of life. Prevalence increases with advancing age with a peak incidence of 40 to 60 years of age; men are more likely to be affected than women. A recent meta-analysis showed a crude incidence rate of 0.33 per 100,000 [Broers MC et al. Neuroepidemiology. 2019;52(3-4):161-172] with overall prevalence reported around 0.8 to 8.9 per 100,000. It often presents with symptoms that include tingling or numbness beginning in the toes and fingers, weakness of the arms and legs, loss of deep tendon reflexes, fatigue, and abnormal sensations. CIDP is considered closely related to Guillain-Barre syndrome and in some, but not all respects, appears to be the chronic counterpart of that acute disease.

Long-term prognosis of CIDP has been correlated to age at onset, response to treatment, and time from symptom onset to the start of treatment. Younger patients with acute onset are more likely to respond than elderly patients. Proximal impairment has been linked to better prognosis than distal weakness [Ripellino P, et al. Autoimmune Diseases 2014:1-11].

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

Treatment of CIDP includes Intravenous Immune Globulin (Human) (IGIV), plasma exchange (PE), and corticosteroids. Based on the most recent Cochrane Database of Systematic Reviews [Oaklander AL, et al. 2019. Neuro Rehabilitation. 2019;44(4):609-612.]:

- Plasma Exchange (PE): Moderate-quality evidence (2 trials; 59 participants) showed that twice-weekly exchanges produced short-term improvement in neurological examination and probably improved disability. Three through 17% of procedures had AEs including difficult venous access and hemodynamic changes.

- Corticosteroids: It was uncertain whether daily oral prednisone improved impairment in CIDP versus no treatment because of the very low quality of evidence (1 trial, 28 participants). For high-dose monthly oral dexamethasone compared to oral prednisolone, moderate-quality evidence (1 trial, 41 participants) indicated that 6-month use of high-dose monthly oral dexamethasone did not improve disability more than daily oral prednisolone. IV methylprednisolone was also no better than oral prednisolone. AEs were poorly reported but clinical use and other research has established multiple serious effects of prolonged corticosteroid use.

According to the National Institute of Neurological Disorders and Stroke's website [https://www.ninds.nih.gov/Disorders/All-Disorders/Chronic-Inflammatory-Demyelinating-Polyneuropathy-CIDP-Information-Page], "Physiotherapy may improve muscle strength, function and mobility, and minimize the shrinkage of muscles and tendons and distortions of the joints [in CIDP]."

2.3 Safety and Efficacy of Pharmacologically Related Products

Other IGIV products: According to five randomized controlled trials (RCTs) (269 subjects), IGIV showed more short-term improvement than placebo. Adverse events were more common with IGIV than placebo, but serious adverse events were not. One RCT with 19 subjects showed little or no difference in short-term improvement of impairment with plasma exchange when compared with IGIV. There was little or no difference in short-term improvement of disability with IGIV in comparison to oral prednisolone (1 RCT with 29 subjects) or intravenous methylprednisolone (1 RCT with 45 subjects).

Gamunex-C (Immune Globulin Intravenous (Human), 10% solution) was the first IGIV approved by FDA for treatment of CIDP in adults (licensed in 2008). The current CIDP indications include 1) treatment to improve neuromuscular disability and impairment, and 2) maintenance therapy to prevent relapse. The approval is based on results of the ICE Study (Immune Globulin Intravenous (Human), 10% Caprylate/Chromatography Purified CIDP Efficacy), a multicenter, randomized, double-blind, placebo-controlled study. The ICE Study included two separately randomized periods to assess whether Gamunex-C was more effective than placebo for the treatment of CIDP to improve neuromuscular disability and impairment (assessed in the 24-week Efficacy Period), and for maintenance therapy to prevent relapse (assessed in the 24-week Randomized Withdrawal Period) [Gamunex-C Package Insert, https://www.fda.gov/media/70738/download; Hughs AC 2009. Expert Rev. Neurother 9(6):789–795].

- In the 24-week Efficacy Period of the Gamunex-C ICE study, 117 subjects with CIDP were randomized in a 1:1 ratio to either Gamunex-C or placebo group. Gamunex-C or placebo was given every 3 weeks for up to 24 weeks, and subjects who did not show an improvement in adjusted INCAT disability score of one point or more at week 6 received the alternate treatment in a crossover period. The primary outcome was the percentage of subjects who had maintained an improvement from baseline in adjusted INCAT disability score of one point or more through to week 24. The INCAT scale is used to assess functional disability of both upper and lower extremities in demyelinating polyneuropathy. The INCAT scale has upper and lower extremity components (maximum of 5 points for upper (arm disability) and maximum of 5 points for lower (leg disability)) that add up to a maximum of 10-points (0 is normal and 10 is severely incapacitated). The adjusted INCAT score excludes a change from one to zero solely due to upper limb score. More subjects with CIDP responded to Gamunex-C: 28 of 59 subjects (47.5%) responded to GAMUNEX-C compared with 13 of 58 subjects (22.4%) administered Placebo (25% difference; 95% CI 7%-43%; p=0.006).

- In the Randomized Withdrawal Period of the ICE trial, time to relapse was evaluated in 57 subjects who previously responded to Gamunex-C: 31 were randomly reassigned to continue to receive Gamunex-C and 26 subjects were randomly reassigned to Placebo. Subjects who continued to receive Gamunex-C experienced a longer time to relapse versus subjects treated with Placebo (p=0.011). The probability of relapse was 13% with GAMUNEX-C versus 45% with Placebo (hazard ratio, 0.19; 95% confidence interval, 0.05, 0.70).

  Maintenance therapy in CIDP patients who respond to IGIV may not need to be continued indefinitely. In the ICE study randomized withdrawal phase, 55% of subjects who responded during the initial phase of the study and who were re-randomized to placebo did not relapse after 24 more weeks. Similar results were observed after 6 months on placebo in the randomized portion of the PATH study. In a recent Spanish retrospective CIDP study in which IGIV dose was individualized, approximately 25% of patients remained stable at six months following their last IGIV infusion [Querol R et al. Muscle Nerve 2013; 48:870-876].

Privigen is the other IGIV product to receive a CIDP indication in the United States and is indicated for the treatment of adults with chronic inflammatory demyelinating polyneuropathy (CIDP) to improve neuromuscular disability and impairment. Approval of Privigen was based on PRIMA and PATH studies.

- PRIMA study, a prospective, open-label, single-arm, historical-controlled, multicenter clinical trial, enrolled 28 subjects with CIDP (13 IGIV-pretreated and 15 IGIV-naive) to receive a Privigen loading dose of 2 g/kg followed by Privigen maintenance doses of 1 g/kg every 3 weeks for up to 21 weeks with a 3 week follow up.

  Efficacy was based on the responder rate of Privigen in comparison to an historical control (the placebo group in the Efficacy Period of the ICE Study) in the adjusted 10-point INCAT score. The responder rate was defined as the proportion of subjects who demonstrated clinically meaningful improvement (at least 1-point decrease on adjusted INCAT score except for a change from one to zero solely due to upper limb

score) between baseline and Week 25, with a pre-specified threshold of 35% in the lower limit of the 2-sided 95% Wilson-Score confidence interval (CI). The overall percentage of responders in PRIMA was 61% (95% CI: 42.4% to 76.4%). Response rates were 47% in IGIV-untreated and 77% in IGIV-pretreated subject subgroups. In a post-hoc analysis, the overall percentage of subjects in PRIMA who responded by week 10 and maintained the response through week 25 and lacked confounding changes in glucocorticoid/immunosuppressant dosage was 53.6% (95% CI: 35.8% to 70.5%).

- In PATH study with the same Privigen dosing regimen, all 207 subjects were IGIV-pretreated and had relapsed following withdrawal of IGIV prior to being administered with Privigen. The response rate in the adjusted 10-point INCAT score was 73%. Among the subset of 151 subjects in the PATH study who had deteriorated by one or more points in adjusted INCAT score following withdrawal of IGIV, 137 subjects (90.7%) responded during the Privigen "re-stabilization" period with an increase of one or more adjusted INCAT score points.

- The overall median time to first adjusted INCAT response in PRIMA was 7.5 weeks (18 weeks in IGIV-untreated and 3 weeks in IGIV-pretreated). The median time to first adjusted INCAT response in PATH (all IGIV-pretreated) was 3.7 weeks (95% CI: 3.4 to 5.9 weeks). Mean INCAT score in PRIMA showed a clinically meaningful improvement by 1.4 points (1.1 points for IGIV-untreated, and 1.8 points for IGIV-pretreated [1.2 points in PATH]).

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

Panzyga was licensed in the United States in 2018. Panzyga is approved in the United States and the European Union (EU) for the treatment of primary humoral immunodeficiency (PI) and chronic immune thrombocytopenic purpura (ITP). It is also approved in the EU for the treatment of secondary immunodeficiencies (SID), Guillain-Barré syndrome (GBS), Kawasaki disease, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and multifocal motor neuropathy (MMN).

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

Study NGAM-08 was conducted under IND 14096.

The original BLA was submitted to the FDA on April 15, 2015 and the approval letter from CBER was issued on August 2, 2018 for the treatment of primary humoral immunodeficiency (PI) in patients 2 years of age and older and chronic immune thrombocytopenic purpura (ITP) in adults.

There was no pre-sBLA meeting for this submission. The applicant submitted this efficacy supplement (STN 125587/70) on April 21, 2020 to expand the clinical indication of Panzyga for the treatment of adult patients with CIDP.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty.

3.2 Compliance With Good Clinical Practices And Submission Integrity

The study was conducted in accordance with 21 CFR 312, the ethical principles of the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP) (E6), the European Directive 2001/20/EC, as well as the valid national laws of the participating countries.

The protocol and the subsequent substantial amendments, as well as samples of the patient information sheet and informed consent form and any other materials provided to the patients, were submitted to the Competent Authorities (CAs) and properly constituted IECs and IRBs for formal approval of the study conduct in accordance with local regulations. The study did not begin until the protocol had received written approval from the CAs and IECs and IRBs in accordance with local requirements.

3.3 Financial Disclosures

Covered clinical study (name and/or number): NGAM-08		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 26		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)

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

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

4.1 Chemistry, Manufacturing, and Controls

No chemistry, manufacturing and controls (CMC) data were included in the BLA efficacy supplement. For CMC information on Panzyga please see original BLA 125587 CMC review: https://www.fda.gov/media/115246/download.

4.2 Assay Validation

Octapharma commits to developing and validating an [redacted] assay as a lot release test, such as [redacted], and to propose a specification. This will be done as a CMC postmarketing commitment (PMC).

4.3 Nonclinical Pharmacology/Toxicology

No nonclinical pharmacology/toxicology updates were included in the BLA efficacy supplement.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The mechanisms of action of immunoglobulins in the treatment of CIDP in adults have not been fully elucidated.

4.4.2 Human Pharmacodynamics (PD)

Not applicable.

4.4.3 Human Pharmacokinetics (PK)

There was the option of rescue treatment with two consecutive blinded infusions of 2.0 g/kg Panzyga at 3-week intervals (±4 days) for all subjects in the 0.5 and 1.0 g/kg Panzyga arms who were either stable at Week 6 or deteriorated after Week 3 and before Week 18. The actual administered dose for the three dose groups was: 0.91 ± 0.4 (n=35), 1.24 ± 0.2 (n=69) and 1.97 ± 0.2 (n=38) g/kg for 0.5, 1 and 2g/kg, respectively. Serum immunoglobulin G (IgG) levels were accessed prior to infusion (week 0) and at weeks 3, 6, 9, 12, 15, 18, 21, 24. The % change in mean IgG from baseline to the end of study (EOS) assessment was 46% in the 0.5 g/kg group, 57% in the 1.0 g/kg group and 88% in the 2.0 g/kg group. Overall, the % change in IgG level at EOS assessment was increased by 57% and 88% from the baseline values following maintenance dose of 1 g/kg and 2 g/kg, respectively. The IgG trough level and efficacy data for the 0.5 g/kg should be interpreted carefully since the actual administered dose was almost 1 g/kg.

The Clinical Pharmacology reviewer recommended removing the statement that “dose should be individualized” for CIDP from the draft PI, as the applicant has not established a dose individualization method.

Pease see Clinical Pharmacology review memo for more details.

4.5 Statistical

Please see Biostatistical review memo.

4.6 Pharmacovigilance

Original post-marketing pharmacovigilance plan was submitted with the original BLA application. An updated post-marketing pharmacovigilance plan, Version 0.4, was submitted with this supplement. Review of post-market safety data did not reveal any unexpected safety concerns. The Pharmacovigilance review team from Division of Epidemiology (DE), Office of Biostatistics and Epidemiology (OBE) agreed with the applicant’s plan for routine pharmacovigilance (PV).

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

5.1 Review Strategy

This reviewer focused on efficacy and safety data from Study NGAM-08 to assess whether PANZYGA could be approved for the treatment of adults with CIDP to improve neuromuscular disability and (b) (4)

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

The clinical review emphasized review of the final Clinical study report (CSR) and protocol for study NGAM-08.

5.3 Table of Studies/Clinical Trials

There is only one study, NGAM-08, in the BLA efficacy supplement (Table 3).

Table 3 List of Study

Population	**Design**	**Test Product/Dose**	**Endpoints**
Male or female patients of ≥18 to <80 years of age with a documented diagnosis of CIDP by a neurologist First Subject In: 09-Aug-2017 Last Subject Out: 05-Sep-2019	Prospective, double-blind, randomized, multicenter (25 sites in Europe and Canada) Phase III Study The study consisted of: -a Screening Period, -wash-out Period, and -a Dose-evaluation Phase	Panzyga 10% Intravenous Loading Dose: 2 g/kg (20 mL/kg), divided into a daily dose of 1 g/kg (10 mL/kg) given on two consecutive days Maintenance dose: 1 – 2 g/kg (10 - 20 mL/kg) given every 3 weeks, over two consecutive days.	**Primary:** • To provide confirmatory data on the effect of 1.0 g/kg Panzyga every three weeks in patients with active CIDP based on the percentage of responders at Week 24, which should corroborate the existing evidence on efficacy of IGIV in CIDP as known from published literature. **Secondary:** • To assess the effect of 0.5 g/kg and 2.0 g/kg Panzyga every three weeks in patients with active CIDP based on the percentage of responders at Week 24 compared to patients on 1.0 g/kg Panzyga every three weeks • To evaluate the safety of Panzyga administration using various dosages in patients with CIDP • To further evaluate the beneficial effect of three Panzyga dosages in patients with CIDP by assessing different parameters/scores/scales

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

No Advisory Committee meeting was held because initial review of information submitted in the BLA did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

5.4.2 External Consults/Collaborations

No external consultation was requested for the BLA efficacy supplement.

5.5 Literature Reviewed (if applicable)

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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

Study NGAM-08: Prospective, Double-blind, Randomized, Multicenter Phase III Study Evaluating Efficacy and Safety of Three Different Dosages of NewGam in Patients With Chronic Inflammatory Demyelinating Poly(radiculo)neuropathy (“ProCID trial”)

6.1.1 Objectives (Primary, Secondary, etc.)

Primary Objective
To provide confirmatory data on the effect of 1.0 g/kg Panzyga (NewGam) every three weeks in patients with active CIDP based on the percentage of responders at Week 24, which should support the existing evidence on efficacy of IGIV in CIDP.

Reviewer comment:
The proprietary name for Immune globulin intravenous (IGIV) - human-ifas 10% was changed from NewGam to Panzyga.

Secondary Objectives

- To assess the efficacy of 0.5 g/kg and 2.0 g/kg Panzyga (NewGam) every three weeks in patients with active CIDP based on the percentage of responders at Week 24 compared to patients on 1.0 g/kg Panzyga (NewGam) every three weeks
- To evaluate the safety of Panzyga (NewGam) NewGam administration using various dosages in patients with CIDP
- To further evaluate the beneficial effect of three Panzyga (NewGam) dosages in patients with CIDP by assessing different parameters/scores/scales

Exploratory Objectives

- To assess the primary and secondary objectives at three weeks after end of rescue medication (if applicable)
- To further evaluate the beneficial effect of Panzyga (NewGam) administration in patients with CIDP by additional assessments/scores including quality of life (QoL) measures

6.1.2 Design Overview

This was a prospective, parallel group, double-blind, randomized, dose controlled multicenter phase 3 efficacy study. Subjects were enrolled from 25 study sites in Canada and Europe. The study planned to enroll a minimum of 140 adult subjects with definite or probable CIDP according to the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) criteria.

The study consisted of three periods:

a. Screening Period
   Subjects were screened based on study Eligibility Criteria.

b. Wash-out Period (up to 12 week)

   Eligible subjects' medication (immunoglobulins or corticosteroid) was reduced in a predefined manner for a maximum of 12 weeks:
   - Immunoglobulins: 25% at each sequential infusion;
   - Corticosteroids: Per the discretion of the investigator at a rate to expect study entry within 6-12 weeks

   Definition of deterioration:
   - a worsening of their overall status according to the Patients' Global Impression of Change (PGIC) scale,

   AND ONE of the following:
   - an increase in modified Inflammatory Neuropathy Cause and Treatment (INCAT) by at least 1 point, OR
   - a decrease of at least 8 kPa on grip strength in one hand OR
     reached the Inflammatory Rasch-built Overall Disability Scale (I-RODS) minimum clinically important difference related to the varying standard errors (MCID-SE) cut-off of -1.96 or less.

c. Dose-evaluation Phase (24 weeks)
Subjects who met the above definition of deterioration were randomized in a 1:2:1 ratio to one of the three maintenance dose groups: 0.5 g/kg,1.0 g/kg or 2.0 g/kg.

6.1.3 Population

Inclusion Criteria
The study population consisted of male and female subjects with:

1. Definite or probable CIDP diagnosis according to the EFNS/PNS Guideline 2010; including Multifocal Acquired Demyelinating Sensory And Motor Neuropathy (MADSAM) or pure motor CIDP
2. Current dependence on treatment with IGIV or corticosteroids
3. Active disease (not in remission), with evidence of progression or relapse prior to trial start or during the Wash-out Phase
4. Weakness of at least 2 limbs
5. ≥ 18 years of age
6. Adjusted INCAT disability score between 2 and 9 (a score of 2 has to be exclusively from leg disability)
7. Ability and willingness to provide written informed consent.

Exclusion Criteria
Subjects with the following criteria were excluded from the study:

1. Unifocal forms of CIDP
2. Pure sensory CIDP
3. The separate condition of MMN with conduction block, defined as a lower motor neuron disorder with motor weakness in an upper limb, without sensory deficit and with proximal conduction block (50% decrease in amplitude/area on proximal compared with distal stimulation) in motor nerves and normal sensory nerve conduction studies (NCS)
4. Treatment with immunomodulatory/suppressive agents (cyclosporin, methotrexate, mitoxantrone, mycophenolate mofetil or azathioprine) during the six months prior to baseline visit
5. Current or prior treatment with rituximab, alemtuzumab, cyclophosphamide, or other intensive chemotherapeutic regimens, previous lymphoid irradiation or stem cell transplantation during the 12 months prior to baseline visit
6. Respiratory impairment requiring mechanical ventilation
7. Myelopathy or evidence of central nervous system demyelination or significant persisting neurological deficits from stroke, or central nervous system (CNS) trauma
8. Clinical evidence of peripheral neuropathy from another cause such as
    a. connective tissue disease or systemic lupus erythematosus (SLE)
    b. HIV infection, hepatitis, Lyme disease
    c. cancer (with the exception of basal cell skin cancer)
    d. IgM paraproteinemia with anti-myelin associated glycoprotein antibodies
9. Diabetic neuropathy
10. Cardiac insufficiency (New York Heart Association [NYHA] III/IV), cardiomyopathy, significant cardiac dysrhythmia requiring treatment, unstable or advanced ischemic heart disease
11. Severe liver disease (ALAT 3x > normal value)
12. Severe kidney disease (creatinine > 120 µM)
13. Hepatitis B, hepatitis C or HIV infection

14. Thromboembolic events: patients with a history of deep vein thrombosis (DVT) within the last year prior to baseline visit or pulmonary embolism ever; patients with susceptibility to embolism or DVT
15. Body mass index (BMI) ≥40 kg/m2
16. Uncompensated hypothyroidism (abnormally high Thyroid-Stimulating Hormone [TSH] and abnormally low Thyroxine [T4]) or known vitamin B12 deficiency if they don't receive adequate substitution therapy
17. Medical conditions whose symptoms and effects could alter protein catabolism and/or IgG utilization (e.g. protein-losing enteropathies, nephrotic syndrome)
18. Known IgA deficiency with antibodies to IgA
19. History of hypersensitivity, anaphylaxis or severe systemic response to immunoglobulin, blood or plasma derived products, or any component of NewGam
20. Known blood hyperviscosity, or other hypercoagulable states
21. Use of other blood or plasma-derived products within three months prior to Visit 2
22. Past or present history of drug abuse or alcohol abuse within the preceding five years prior to baseline visit
23. Inabillity on unwillingness to understand or comply with the study protocol
24. Participation in another interventional clinical study with IMP treatment currently or during the three months prior to Visit 2
25. Female subjects who were breast feeding, pregnant, or planning to become pregnant, or were unwilling to use an effective birth control method (such as implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence

6.1.4 Study Treatments or Agents Mandated by the Protocol

Each randomized subject received the following:

- An initial intravenous loading dose of 2.0 g/kg Panzyga divided into a daily dose of 1 g/kg given on two consecutive days,
- 7 infusions of the maintenance dose per their randomization allocation (i.e., 0.5, 1.0 or 2.0 g/kg Panzyga) administered over 2 consecutive days every 3 weeks (±4 days).
    - The same volumes and infusion rates were used for all three doses,
    - 0.9% w/v isotonic sodium chloride solution was used as appropriate to maintain the blinding.

Rescue medication: two doses of 2.0 g/kg Panyzyga given 3 weeks apart could be administered to subjects in the 0.5 and 1.0 g/kg arms in the following scenarios:

- If the subject deteriorated (defined as an increase in adjusted INCAT disability score of ≥1 point) after Week 3 and before Week 18,
- If there was no improvement in CIDP (defined as an unchanged adjusted INCAT disability score) at Week 6.

Following administration of rescue medication, the subject discontinued study treatment and attended an End of Study Visit 3 weeks after the second rescue dose. Subjects in the 2.0 g/kg arm with deterioration after Week 3 and before Week 18 or with no improvement at Week 6 also discontinued study treatment.

6.1.5 Directions for Use

Each subject received Panzyga via infusion pump. The initial infusion rate was 0.01 mL/kg/min (60 mg/kg/hr) for the first 30 minutes; if tolerated, it was slowly increased to 0.12 mL/kg/min (720 mg/kg/hr) for the rest of the infusion. From the third infusion on, the 30-minute interval for the 0.02 to 0.08 mL/kg/min infusion rates could be shortened to 15 minutes at the investigator's discretion. If AEs occurred during infusion, the rate was reduced to half the rate at which the event occurred, or the infusion was interrupted until symptoms subsided. The infusion could then be resumed at a rate tolerated by the subject. Subjects were monitored for any symptoms throughout the infusion period and at least 1 hour thereafter.

Pre-medication for AEs was only allowed in subjects who had adverse events during 2 consecutive infusions.

6.1.6 Sites and Centers

Subjects were enrolled at 25 study sites as follows:

- 1 site in Canada
- 5 sites in Russia
- 2 sites in Bulgaria
- 2 sites in Hungary
- 5 sites in Ukraine,
- 3 sites in Romania
- 3 sites in Czech Republic
- 3 sites in Poland and
- 1 site in Germany.

6.1.7 Surveillance/Monitoring

Study monitoring is outlined in Table 4 Schedule of Assessments.

Table 4 Schedule of Assessments

	Screening	Wash-out phase[1]	Dose-evaluation Phase[2]	Dose-evaluation Phase[2]	Dose-evaluation Phase[2]	Dose-evaluation Phase[2]	Dose-evaluation Phase[2]	Dose-evaluation Phase[2]	Dose-evaluation Phase[2]	Dose-evaluation Phase[2]	Dose-evaluation Phase[2]
	Visit 1 Week -15	**Week -12 to 0**	**Visit 2 Week 0**	**Visit 3 Week 3**	**Visit 4 Week 6**	**Visit 5 Week 9**	**Visit 6 Week 12**	**Visit 7 Week 15**	**Visit 8 Week 18**	**Visit 9 Week 21**	**Visit 10 Week 24**
Informed consent	X										
Medical history	X										
In-/Exclusion Criteria	X		X								
Randomization/Enrollment			X								
Concomitant medications		X[10]	X	X	X	X	X	X	X	X	X
Adverse Events		X[10]	X	X	X	X	X	X	X	X	X
Physical/neurological examination	X		X				X				X
ECG	X										
Clinical chemistry[3]; Hematology[4]	X		X	X	X	X	X	X	X	X	X
Serum IgG[5]			X	X	X	X	X	X	X	X	X
Urinalysis[6]	X										
Pregnancy test[11]	X										
Viral marker[7]	X		X								X
PGIC scale			X								
Adjusted INCAT score; I-RODS score, PI-NRS	X		X	X	X	X	X	X	X	X	X
Grip strength	X		X	X	X	X	X	X	X	X	X
MRC sum score	X		X				X				X
Modified FSS	X		X				X				X
Nerve Conduction studies	X		X				X				X
SF-36 Health survey	X		X				X				X
Vital signs[8]; Weight	X		X	X	X	X	X	X	X	X	X
Study drug infusion			X[9]	X	X, [X[12,13]]	X, [X[12,13]]	X, [X[12]]	X, [X[12]]	X, [X[12]]	X, [X[12]]	

1 Could have lasted up to 12 weeks (until deterioration): Selection of active patients requiring treatment after dosage reduction
2 Infusion visits take 2 days
3 Clinical chemistry: Na+, K+, glucose, ALT, AST, LDH, total bilirubin, BUN (blood urea nitrogen) or urea, creatinine, albumin, serum IgG
4 Hematology: Hematocrit, hemoglobin, complete blood count with differential
5 Serum IgG determined prior to infusion
6 Urinalysis: Protein, pH, glucose, ketones, leukocytes, hemoglobin and blood
7 Viral Markers: HIV, HBV and HCV
8 Vital signs: Pulse, blood pressure, respiratory rate and temperature
9 Loading dose of 2 0 g/kg *NewGam*
10 Only for patients on immunoglobulin treatment visiting the site for infusions
11 Pregnancy test was only be done in women of childbearing potential. Pregnancy test was mandatory at Visit 1. At Visit 2, 3, 4, 5, 6, 7, 8, 9 and End of Study Visit a pregnancy test was performed only if required by local regulations.
12 Two consecutive 3-weekly infusions of 2.0 g/kg *NewGam* only for patients on 0.5 or 1 0 g/kg *NewGam* who deteriorated after Week 3 and until Week 18
13 Two consecutive 3-weekly infusions of 2.0 g/kg *NewGam* only for patients on 0.5 or 1 0 g/kg *NewGam* who were stable by Week 6

Source: BLA 128=5587/70 Table 2, CSR, page 26.

An Independent Data Monitoring Committee (IDMC) was established by the Sponsor and was composed of experts in the field, not involved in the study. The IDMC reviewed relevant data periodically during the study and gave advice on the continuation, modification or termination of the study. A detailed, written study-specific procedure defined the composition, responsibilities and procedures of the IDMC.

A Steering Committee was also established to medically and scientifically advise and guide the Sponsor during the study progress. It consisted of four internationally known CIDP experts with experience in conducting clinical studies The Steering Committee was responsible for the overall study overview, could give recommendations for protocol amendments after discussion with the Sponsor and may be involved in publication writing together with the IDMC members and coordinating investigator.

6.1.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoint
The primary efficacy endpoint was the proportion of responders in the 1.0 g/kg Panzyga arm at Week 24 (End of Study Visit) relative to Baseline (Week 0). The responder rate under the standard dose (1.0 g/kg) was compared with the responder rates of the ICE and PRIMA studies as historical controls.

A responder was defined as a subject with a decrease of at least 1 point on the adjusted INCAT disability score (a scale from 0 to 10, from healthy to unable to make any purposeful movements with arms and/or legs).

The adjusted INCAT disability score is identical to the INCAT disability score with a range from 0 (no disability) to 10 (maximum disability), except for the exclusion of changes in upper limb function from 0 (normal) to 1 (minor symptoms) or from 1 to 0.

Secondary Efficacy Endpoints
- Proportion of responders in the 0.5 g/kg and 2.0 g/kg Panyzyga arms at Week 24 relative to baseline compared to the 1.0 g/kg arm, based on:
    - the adjusted INCAT disability score
    - the grip strength (Martin Vigorimeter) using the previously published minimum clinically important difference (MCID) cut-off of 8 kPa
    - the Inflammatory Rasch-built Overall Disability Scale (I-RODS) scores using the MCID concept related to the varying standard errors (MCID-SE).
- Time to first confirmed worsening on the adjusted INCAT disability scale by at least 1 point from the value at Baseline (Week 0)
- Time to first confirmed worsening on the I-RODS scale
- Time to 1-point decrease (improvement of disability) in adjusted INCAT disability score
- Time to decrease in I-RODS scores
- Mean change from Baseline (Week 0) to End of Study Visit in
    - grip strength of both hands (assessed by Martin Vigorimeter)
    - Inflammatory Rasch-built overall disability sum score (I-RODS using the concept of MCID-SE) and number of improvers (=responders)
    - sum of the distal evoked amplitude of 4 right-sided and 4 left-sided motor nerves (peroneal, tibial, ulnar and median)
    - Pain Intensity Numeric Rating Scale (PI-NRS)

Exploratory Efficacy Endpoints
- Mean change from Baseline (Week 0) to End of Study Visit in:
    - modified Fatigue Severity Scale (FSS; 7-item scale from 0-21 points)

  - number of improvers (=responders) by at least 4 points in the Medical Research Council (MRC) sum score (according to the universal rule of MCID)
  - SF-36 Health Survey physical composite score (PCS), mental composite score (MCS) and their 8 health domains
  - additional NCS analyses (e.g., individual nerve analysis)
- For MRC the following were done:
  - Time to decrease in MRC sum score to or below Baseline value after temporary improvement (increase)
  - Mean change from Baseline (Week 0) to Week 12 and to End of Study Visit
  - Number of improvers by at least 4 points from Baseline (Week 0) to Week 12 and to Week 24

Safety (throughout the entire Wash-out and Dose-evaluation Phases):

- Occurrence of all adverse events (AEs)
- Short term tolerance parameters including vital signs
- Physical/neurological examination
- Laboratory parameters (hematology and clinical chemistry) and tests for viral safety
- ECG (only at Screening visit)

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample Size

The sample size calculation was based on the proportion of responders in the 1.0 g/kg dose group.

Approximately 70 subjects would achieve a power of at least 80% to detect a difference of 0.18 from pre-defined threshold of 0.42 for the proportion of responders in the 1 g/kg dose group at a two-sided Type I error rate of 0.05. According to the randomization ratio of 1:2:1, 35 subjects (per dose arm) were planned to be enrolled into 0.5 g/kg and 2.0 g/kg dose groups. A total of 140 subjects were planned for this study.

Reviewer Comment:

The pre-defined threshold of 0.42 is based on the lower limit of the 95% Wilson-Score CI for the proportion of responders of the treated arm in the PRIMA study if rounded to the nearest integer. Of note, the upper limit of the two-sided 95% Wilson-Score CI was 34.7% in the placebo arm of Efficacy Period of the ICE study.

Analysis Populations

The following populations were considered for the statistical analysis:

- Safety set (SAF): including all randomized subjects who received at least part of one infusion of Panzyga.
- Full analysis set (FAS): including all subjects of the SAF for whom any data were collected post infusion of Panzyga. Every treated subject was considered in the analysis according to his/her randomized treatment/dose assignment.
- Per-protocol set (PPS): consisting of all subjects in the FAS excluding those with significant protocol deviations.

The evaluation of efficacy endpoints was performed primarily based on the FAS. The PPS was used for sensitivity analyses. The analysis of safety was based on the SAF.

Efficacy Analysis
The primary endpoint was analyzed by constructing the 95% Wilson-Score confidence interval (CI) for the percentage of responders on the adjusted INCAT disability score in the 1.0 g/kg dose arm. The study is considered successful if the lower limit of the 95% Wilson-Score CI for the observed proportion of responders in the 1.0 g/kg Panzyga arm is greater than the pre-defined threshold of 0.42. The threshold of 0.42 was chosen based on the results from previous studies with 1.0 g/kg IGIV dosing regimen in CIDP patients, including the ICE study.

Similar to the analyses for the primary efficacy endpoint, 95% Wilson-Score CIs were constructed for secondary efficacy endpoints (i.e. I-RODS, grip strength), and exploratory endpoint, MRC sum score.

Safety Analysis
The safety target variables throughout the entire 24-week Dose-evaluation Phase were as follows:
• Occurrence of all AEs
• Short term tolerance parameters including vital signs
• Physical/neurological examination
• Laboratory parameters: Serum IgG, hematology, clinical chemistry, urinalysis, pregnancy test, and tests for viral safety.

All medical history and reported AEs were coded according to Medical Dictionary for Regulatory Activities (MedDRA). Medications were coded using the WHO Drug Dictionary. An AE was defined as treatment-emergent if first onset or worsening was after the start of the first infusion of Panzyga. Only treatment-emergent AEs (TEAE) were accounted for in the analysis. A TEAE was considered to be temporally associated with the infusion if it started during or within 72 hours of the end of the infusion.

For each dose arm and for the study as a whole the following were given:
• Total number of TEAEs reported
• Number of temporally associated TEAEs
• Number and percentage of infusions temporally associated with one or more TEAE
• Number of temporally associated TEAEs divided by the total number of infusions.

Interim Analysis
There was no formal interim analysis planned or conducted for this study.

Missing Data Handling
If missing values occur in the analysis of the primary endpoint in the FAS, they were treated as non-responders. Subjects dropping out were not to be replaced, but were included in the sample size calculations.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The SAF included all 142 randomized subjects. Table 5 summarizes the analysis populations.

Table 5 Analysis Populations

	0.5 g/kg N=35 N (%)	1.0 g/kg N=69 N (%)	2.0 g/kg N=38 N (%)	Overall N=142 N (%)
Safety Set (SAF)	35 (100%)	69 (100%)	38 (100%)	142 (100%)
Full Analysis Set (FAS)	34 (97.1%)	69 (100%)	36 (94.7%)	139 (97.9%)
Per-Protocol Set (PPS)	29 (82.9%)	65 (94.2%)	35 (92.1%)	129 (90.8%)

Source: Modified from sBLA 125587/70; Module 5.3.5.1; CSR, Table 6, p59.

6.1.10.1.1 Demographics

Demographic characteristics is shown in Table 1. All enrolled subjects were White. The study enrolled more male subjects than female subjects.

Reviewer's Comment:
Demographics in NGAM-08 study were similar to ICE and PRIMA studies in regard to age, and sex and race distribution. ICE study was comprised of 90% White, and the PRIMA study consisted of 100% White. The overwhelming percentages of White in ICE, PRIMA, and NGAM-08 studies are consistent with the results of a 2010 United States CIDP patient survey which found that whites/Caucasians comprised 94% of CIDP patients therefore the study population is representative of the US population.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
The medical characterization of enrolled subjects is shown in Tables 6 and Table 7 below.

Table 6 Medical Characterization of Enrolled Subjects (SAF, N=142)

	0.5g/kg N=35 N (%)	1.0 g/kg N=69 N (%)	2.0 g/Kg N=38 N (%)	Total subjects N=142 N (%)
Type of CIDP				
Typical CIDP	34 (97.1)	62 (89.9%)	34 (89.5%)	130 (91.5%)
Atypical CIDP	1 (2.9%)	7 (10.1%)	4 (10.5%)	12 (8.5%)
Disease course				
Progressive	25 (71.4%)	50 (72.5%)	29 (76.3%)	104 (73.2%)
Relapsing	10 (28.6%)	18 (26.2%)	8 (21.1%)	36 (25.4%)
Other	0 (0.0%)	1 (1.4%)	1 (2.6%)	2 (1.4%)
Number of Limbs with weakness				
4	29 (82.9%)	54 (78.3)	31 (81.6%)	114 (80.3)
2	4 (11.4%)	13 (18.8%)	6 (15.8 %)	23 (16.2)
3	2 (5.7%)	2 (2.9%)	1 (2.6%)	5 (3.5)

Source: Adapted from sBLA 1255765/70 history by randomization stratum, Table 14.1.3.1.

Table 7 Adjusted INCAT Disability Scores at screening (FAS, N=139)

	0.5 g/kg (N=34)	1.0 g/kg (N=69)	2.0 g/kg (N=36)	Total All Subjects (N=139)
Mean (SD)	4.3 (1.0)	4.3 (1.2)	4.3 (1.1)	4.3 (1.1)
Min, Max	2.0, 7.0	2.0, 8.0	2.0, 6.0	2.0, 8.0

Source: Adapted from sBLA 1255765/70 Efficacy scores at screening Table 14.1.5.1.

Reviewer Comment:

The mean (SD) adjusted INCAT score 3.7 (1.4) points at baseline in the PRIMA study. Higher score represents more severe impairment. Disease severity seems comparable between the two study populations.

A total of 18 (13%) subjects had in the past 12 months regularly received IGIV (IGIV-pretreated). For the rest of subjects, it is unclear whether they were IG-naïve (i.e., never received any IG) or received IG but for a shorter time period (Table 8).

Table 8 IGIV-pretreated vs Corticosteroid pretreated

	0.5 g/kg (N=35)	1.0 g/kg (N=69)	2.0 g/kg (N=38)	Total All Patients (N=142)
IGIV-pretreated	5 (14.3%)	9 (13.0%)	4 (10.5%)	18 (12.7%)
Corticosteroid-pretreated*	30 (85.7%)	60 (87.0%)	34 (89.5%)	124 (87.3%)

*It is unclear what percentage of subjects in this category is IG-naïve.
Source: Generated by FDA statistical reviewer

6.1.10.1.3 Subject Disposition
A total of 171 patients were screened of whom 21 were screen failures. one hundred fifty (150) subjects entered the Wash-out Phase. Eight additional subjects failed screening during or at the end of the Wash-out Phase. Thus, 142 subjects were randomized to one of the three dose arms. All randomized subjects received at least part of one infusion of Pangyza, and 123 subjects (86.6%) completed the study. Of the 19 subjects (13.4%) who terminated early, the most common reasons were subject's decision in 7 subjects (4.9%) and AE in 6 subjects (4.2%). The highest incidence of early terminations was in the 0.5 g/kg dose arm (20.0%). There were no withdrawals due to protocol deviations, pregnancy or deterioration. Table 9 shows the detailed subject disposition.

Table 9 Subjects Disposition

	0.5g/kg N=35 N (%)	**1.0g/kg N=69 N (%)**	**2.0g/Kg N=38 N (%)**	**Total subjects N=142 N (%)**
Completed study	28 (80%)	61 (88.4%)	34 (89.4)	123 (86.6%)
Terminated early	7 (20.0%)	8 (11.6%)	4 (10.5%)	19 (13.4%)
Subject's decision	3 (8.6%)	3 (4.3%)	1 (2.6%)	7 (4.9%)
Adverse event	3 (8.6%)	2 (2.9%)	1 (2.6%)	6 (4.2%)
Withdrawal for safety reasons	0 (0.0%)	1 (1.4%)	1 (2.6%)	2 (1.4%)
Administrative Reasons	0 (0.0%)	0 (0.0%)	1 (2.6%)	1 (0.7%)
Other reason	1* (2.9%)	2** (2.9%)	0 (0.0%)	3 (2.1%)

*The subject was lost to follow-up.
**One subject was discontinued due to meeting the exclusion criteria relating to intermittent atrial fibrillation and susceptibility to embolism or DVT, and the other subject was lost to follow-up.
Source: Adapted from sBLA 125587/70, CSR Table 14.1.1.1.

6.1.11 Efficacy Analyses

Data Sets Analyzed
All 142 randomized subjects were included in the SAF. FAS and PPS sets were used for efficacy analysis (Table 10).

Table 10 Analysis populations

	0.5g/kg N=35 N (%)	**1.0g/kg N=69 N (%)**	**2.0g/Kg N=38 N (%)**	**Total subjects N=142 N (%)**
Safety set	35 (100.0%)	69 (100.0%)	38 (100.0%)	142 (100.0%)
Full analysis set	34 (97.1%)	69 (100.0%)	36 (94.7%)	139 (97.9%)
Per protocol set	29 (82.9%)	65 (94.2%)	35 (92.1%)	129 (90.8%)

Source: Adapted from BLA 125587/70 submission, table 16.2.3.1.

FAS set included 139 subjects. Three subjects were excluded as no data were collected post-infusion of Panzyga:

- 1 in the 0.5 g/kg arm, subject [redacted] withdrew consent,
- 2 in the 2.0 g/kg arm, subject [redacted] was discontinued for administrative reasons, and subject [redacted] withdrew consent.

PPS set included 129 subjects after excluding additional 10 subjects:

- 5 in the 0.5 g/kg arm
  - 2 subjects due to dosing error
  - 3 subjects due to study discontinuation
- 4 in the 1.0 g/kg arm
  - 2 subjects due to dosing error
  - 2 subjects due to study discontinuation
- 1 in the 2.0 g/kg arm due to dosing error.

6.1.11.1 Analyses of Primary Endpoint(s)

The proportion of responders in the 1.0 g/kg Panzyga arm at Week 24 (End of Study Visit) relative to Baseline (Week 0) assessed by the adjusted INCAT disability score

The proportion of responders in the 1.0 g/kg arm was 79.71% (95% CI: 68.8, 87.5), with 55 out of 69 subjects classified as responders. The lower CI exceeded the predefined threshold of 42%. The analysis with the PPS resulted in 83.08% of subjects in the 1.0 g/kg responding (95% CI: 72.2, 90.3), thus supporting the result of the primary analysis (Table 11).

Table 11 Adjusted INCAT Disability Score Responders

Analysis Population	0.5 g/kg	1.0 g/kg	2.0 g/kg	Total
FAS	N=34	N=69	N=36	N=139
Number (%) of responders	22 (64.7%)	55 (79.7%)	33 (91.7%)	110 (79.1%)
95% CI	47.9, 78.5	68.8, 87.5	78.2, 97.1	71.6, 85.1
PPS	N=29	N=65	N=35	N=129
Number (%) of responders	21 (72.4%)	54 (83.1%)	32 (91.4%)	107 (83.0%)
95% CI	54.3, 85.3	72.2, 90.3	77.6, 97.0	75.5, 88.5

Source: FDA statistical reviewer's analysis

Reviewer's Comment:
It is unclear what percentage of subjects in the NGAM-08 study are IG-naïve subjects who are known to have lower responder rate as assessed by adjusted INCAT (e.g., In the PRIMA study, the responder rate was 47% and 77% for IGIV-naïve and IGIV-pretreated, respectively. In the ICE study, the responder rate was 43.6% and 55% for IGIV-naïve and IGIV-pretreated, respectively.) The lower limit of the 95% Wilson-Score CI for the proportion of responders in the 1 g/kg and 2 g/kg dose arms exceeded the responder rate of IGIV-naïve subjects.

6.1.11.2 Analyses of Secondary Endpoints

Proportion of responders in the 0.5 g/kg and 2.0 g/kg Panyzyga arms at Week 24 relative to baseline compared to the 1.0 g/kg arm, based on:

- the adjusted INCAT disability score

  Table 10 shows the proportion of responders assessed by adjusted INCAT disability score in the 0.5 g/kg and 2.0 g/kg Panyzyga arms. The proportion of responders appeared to get higher with increasing dose in both FAS analysis population and PPS analysis population.

  Mean changes (SD) in adjusted INCAT disability score from baseline to Week 24 are shown in Table 12.

Table 12 Change from Baseline in INCAT Disability Score (FAS, N=139)

	0.5 g/kg N=34 N (%)	**1.0g/kg N=69 N (%)**	**2.0 g/Kg N=36 N (%)**	**Total subjects N=139 N (%)**
Baseline INCAT score				
Mean (SD)	5.50 (1.0)	5.39 (1.3)	5.4 (1.2)	5.4 (1.2)
Min, Max	4.0, 8.0	2.0, 9.0	4.0, 8.0	2.0, 9.0
Change from baseline to Week 24				
Mean	-2.2 (1.8)	-2.2 (1.5)	-2.8 (1.8)	-2.3 (1.7)
Min, Max	-6.0, 0.0	-6.0, 1.0	-7.0, 0.0	-7.0, 1.0

Source: Adapted from sBLA 125587/70 Table 14.2.1.1.1 and Table 14.2.1.2.

- the grip strength

  The proportion of responders assessed by grip strength appeared to get higher with increasing dose in both FAS population and PPS population (Table 13).

Table 13 Grip Strength Responders

Analysis Population	**0.5 g/kg**	**1.0 g/kg**	**2.0 g/kg**	**Total**
FAS	N=34	N=69	N=36	N=139
Number (%) of responders	19 (55.9%)	45 (65.2%)	30 (83.3%)	94 (67.6%)
95% CI	39.5, 71.1	53.4, 75.4	68.1, 92.1	59.5, 74.8
PPS	N=29	N=65	N=35	N=129
Number (%) of responders	18 (62.1%)	44 (67.7%)	29 (82.9%)	91 (70.5%)
95% CI	44.0, 77.3	55.6, 77.8	67.3, 91.9	62.2, 77.7

Source: FDA statistical review memo

- the Inflammatory Rasch-built Overall Disability Scale (I-RODS) scores

  Table 14 summarized the proportions of responders based on I-RODS across 3 dose arms in both FAS and PPS analysis populations. The proportion of I-RODS responders appeared to get higher with increasing dose in both FAS population and PPS population.

Table 14 I-RODS Responders

Analysis Population	**0.5 g/kg**	**1.0 g/kg**	**2.0 g/kg**	**Total**
FAS	N=34	N=69	N=36	N=139
Number (%) of	13 (38.2%)	38 (55.1%)	26 (72.2%)	77 (55.4%)
95% CI	23.9, 55.0	43.4, 66.2	56.0, 84.2	47.1, 63.4
PPS	N=29	N=65	N=35	N=129
Number (%) of	13 (44.8%)	38 (58.5%)	25 (71.4%)	76 (58.9%)
95% CI[d]	28.4, 62.5	46.3, 69.6	54.9, 83.7	50.3, 67.0

Source: FDA statistical review memo

Reviewer Comment:
The above results suggest a dose-response of Panzyga for treatment of CIDP.

Based on Clinical Pharmacology review, because there was the option of rescue treatment with two consecutive blinded infusions of 2.0 g/kg Panzyga at 3-week intervals (±4 days) for all subjects in the 0.5 and 1.0 g/kg Panzyga arms who were either stable at Week 6 or deteriorated after Week 3 and before Week 18, the actual administered dose for the three dose groups was: 0.91 ± 0.4 (n=35), 1.24 ± 0.2 (n=69) and 1.97 ± 0.2 (n=38) g/kg for 0.5, 1 and 2g/kg, respectively. The % change in mean IgG from baseline to the end of study (EOS) assessment was 46% in the 0.5 g/kg group, 57% in the 1.0 g/kg group and 88% in the 2.0 g/kg group. The IgG trough level and efficacy data for the 0.5 g/kg should be interpreted carefully since the actual administered dose was almost 1 g/kg.

Time to first confirmed worsening on the adjusted INCAT disability scale by at least 1 point from the value at Baseline (Week 0)

Only 1 subject worsened in the 1.0 g/kg arm. An analysis of the time to first worsening was not done due to the small number of subjects that worsened.

Time to first confirmed worsening on the I-RODS scale

In both FAS and PPS sets, 1 subject in the 0.5 g/kg arm and 2 subjects in the 1.0 g/kg group worsened on the I-RODS scale. An analysis of the time to first worsening was not done due to the small number of subjects that worsened.

Time to 1-point decrease (improvement of disability) in adjusted INCAT disability score

In the analysis of the time to first response in the FAS, 91.2% of subjects in the 0.5 g/kg arm, 88.4% in the 1.0 g/kg arm and 91.7% in the 2.9 g/kg arm had a response with a median time of 22, 26 and 23 days, respectively.

Time to decrease in I-RODS scores

In the analysis of the time to first response in the FAS, 61.76% of subjects in the 0.5 g/kg group, 63.77% of subjects in the 1.0 g/kg group and 77.78% of subjects in the 2.0 g/kg group had a response, with a median time to response of 63, 64 and 43.5 days, respectively. Similar results were observed in the PPS.

Mean change from Baseline (Week 0) to End of Study Visit in

- grip strength

  Mean changes (SD) in grip strength from baseline to Week 24 were 27.15 (25.14), 21.62 (20.23) and 29.61 (26.10) for 0.5 g/kg, 1.0 g/kg and 2.0 g/kg groups in FAS population, respectively. Results were similar in the PPS population.

- I-RODS

  Mean changes (SD) in I-RODS score from baseline to Week 24 were 11.4 (12.5), 10.3 (10.8) and 13.9 (12.0) for 0.5 g/kg, 1.0 g/kg and 2.0 g/kg arms in FAS population, respectively. Results were similar in PPS population.

6.1.11.3 Subpopulation Analyses

Subpopulation analysis performed for the primary efficacy endpoint by randomization stratum and types of CIDP (typical vs atypical) is presented in Table 15.

The proportion of responders appeared to get higher with increasing dose in subjects who had previously on corticosteroids and in subjects with typical CIDP.

There were no consistent trends regarding the proportion of responders among the three dose arms in subjects who had previously on immunoglobulins and in subjects with atypical CIDP. However, the number of subjects with atypical CIDP and the number of subjects who had previously on immunoglobulins were too small to make meaningful assessments.

Table 15 Adjusted INCAT Disability Score Responders by Randomization Stratum and CIDP Type (FAS, N=139)

		0.5g/kg N=34	1.0g/kg N=69	2.0g/Kg N=36	Total subjects N=139
Randomization stratum					
Corticosteroids	N	29	60	32	121
	Number (%) of responders	19 (65.5%)	50 (83.3%)	30 (93.8%)	99 (81.8%)
	95% CI	47.3, 80.1	72, 90.7	79.9, 98.3	74.0, 87.7
Immunoglobulins	N	5	9	4	18
	Number (%) of responders	3 (60.0%)	5 (55.6%)	3 (75.0%)	11 (61.1%)
	95% CI	23.1, 88.2	26.7, 81.1	30.1, 95.4	38.6, 79.7
CIDP Variant					
Typical CIDP	N	33	62	32	127
	Number (%) of responders	21 (63.6%)	49 (79.0%)	30 (93.8%)	100 (78.7%)
	95% CI	46.6, 77.8	67.4, 87.3	79.9, 98.3	70.8, 85.0
Atypical CIDP	N	1	7	4	12
	Number (%) of responders	1 (100.0%)	6 (85.7%)	3 (75.0%)	10 (83.3%)
	95% CI	20.7, 100	48.7, 97.4	30.1, 95.4	55.2, 95.3

Source: FDA statistical review memo.

Reviewer's Comment:

The proportion of responders in subjects who were previously on corticosteroids is higher than that in subjects who had previously on immunoglobulin in the 1g/kg group. It is not clear how many of those subjects in corticosteroids stratum were immunoglobulin naïve (i.e., they have never tried immunoglobulin). In addition, the number of subjects in the immunoglobulin stratum is too small to make any reliable conclusion.

Analysis of the primary endpoint by sex and age is shown in Table 16. Panzyga appeared to be effective in treating CIDP for 1.0 g/kg dose arm in all age groups; however, for subjects older than 60 years, a higher dose of 2.0 g/kg seems more beneficial. Proportion of responders seems comparable between male and female subjects in both 1.0 g/kg and 2.0 g/kg arms.

Table 16 Adjusted INCAT Disability Score Responders by Age and Sex (FAS, N=139)

		0.5 g/kg (N=34)	1.0 g/kg (N=69)	2.0 g/kg (N=36)	Total Subjects (N=139)
Age Group					
Age ≤50	N	13	17	11	41
	# (%) of Responder	7 (53.9%)	13 (76.5%)	10 (90.9%)	30 (73.2%)
	95% CI	29.1; 76.8	52.7; 90.4	62.3; 98.4	58.1; 84.3
50 < Age ≤ 60	N	7	25	7	39
	# (%) of Responder	5 (71.4%)	24 (96%)	7 (100%)	36 (92.3%)
	95% CI	35.9; 91.8	80.5; 99.3	64.6; 100	79.7; 97.4
Age > 60	N	14	27	18	59
	# (%) of Responder	10 (71.4%)	18 (66.7%)	16 (88.9%)	44 (74.6%)
	95% CI	45.4; 88.3	47.8; 81.4	67.2; 96.9	62.2; 83.9
Sex					
Female	N	13	31	13	57
	# (%) of Responder	10 (76.9%)	24 (77.4%)	12 (92.3%)	46 (80.7%)
	95% CI	49.7; 91.8	60.2; 88.6	66.7; 98.6	68.7; 88.9
Male	N	21	38	23	82
	# (%) of Responder	12 (57.1%)	31 (81.6%)	21 (91.3%)	64 (78.1%)
	95% CI	36.6; 75.5	66.6; 90.8	73.2; 97.6	68.0; 85.6

Source: FDA statistical review memo

6.1.11.4 Dropouts and/or Discontinuations

Nineteen subjects (13.4%) terminated early. The most common reasons were subject's decision in 7 subjects (4.9%) and AE in 6 subjects (4.2%). The highest incidence of early termination was seen in the 0.5 g/kg arm (20.0%); while the incidence in the other 2 dose arms was 10% (Table 9).

6.1.11.5 Exploratory and Post Hoc Analyses

Medical Research Council (MRC) Sum Score

Subjects were defined as responders if they had an increase from Week 0 of at least 4 points and did not receive rescue treatment. The proportion of MRC sum score responders appeared to get higher with increasing dose in FAS analysis population. The results showed similar pattern in PPS analysis population (Table 17).

Table 17 MRC Sum Score Responders

Analysis Population	0.5 g/kg	1.0 g/kg	2.0 g/kg	Total
FAS	N=34	N=69	N=36	N=139
Number (%) of responders	20 (58.8%)	50 (72.5%)	31 (86.1%)	101 (72.7%)
95% CI	42.2,73.6	61.0, 81.6	71.3, 93.9	64.7, 79.4
PPS	N=29	N=65	N=35	N=129
Number (%) of responders	19 (65.5%)	49 (75.4%)	30 (85.7%)	98 (76.0%)
95% CI	47.3, 80.1	63.7, 84.2	70.6, 93.7	67.9, 82.5

Source: FDA statistical reviewer's analysis

6.1.12 Safety Analyses

6.1.12.1 Methods

An independent data monitoring committee (IDMC) composed of experts in the field of peripheral neuropathy was established to periodically review safety data and provide advice on the continuation, modification or termination of the study.

The following safety information was collected:

- Adverse events (AEs) and serious adverse events (SAEs) temporally associated with administration of Panzyga or saline solution
- Pregnancies, drug overdose, interaction, medication error, lack of efficacy and poststudy SAEs

The analysis of safety was based on the SAF consisting of all 142 randomized subjects.

An AE was defined as treatment-emergent if first onset or worsening was after the start of the first infusion of Panzyga. Only treatment-emergent AEs (TEAE) were accounted for in the analysis.

A TEAE was considered to be temporally associated with the infusion (or 'infusional') if it started during or within 72 hours of the end of the infusion.

All TEAEs for each subject, including multiple occurrences of the same event, were listed in full detail, including reported term, MedDRA preferred term (PT) and system organ class (SOC), onset, duration, time to the AE occurrence from last dose, causality, dosage, severity, seriousness and actions taken.

6.1.12.2 Overview of Adverse Events

Overall, 142 subjects received a total of 982 infusions during the study. Eighty-nine of the 142 subjects (62.7%) experienced a total of 286 TEAEs. Sixty-nine of the 142 subjects (48.6%) experienced temporally-associated TEAEs, and 68 of the 142 subjects (47.9%) had TEAEs that were considered related to Panzyga.

Among the 286 TEAEs, 226 were mild in intensity, 52 were moderate and 8 were severe. The 8 severe adverse events were encountered in 4 subjects, 3 subjects were in the 1 g/kg arm and 1 in the 2 g/kg arm. Subject (b) (6) had severe osteomyelitis, subject (b) (6) had respiratory arrest, decubitus ulcer, pneumonia, cardiorespiratory arrest and aspiration, subject (b) (6) had severe unilateral deafness and subject

(b) (6) (2.0 g/kg group) had severe encephalitis. None of the severe AEs was considered related to Panzyga.

A summary of TEAEs is shown in Table 18 below.

Table 18 Summary of TEAEs (SAF, N=142)

	0.5g/kg N=35 N (%) n	**1.0g/kg N=69 N (%) n**	**2.0g/Kg N=38 N (%) n**	**Total subjects N=142 N (%) n**
TEAEs	20 (57.1%) 54	45 (65.2%) 153	24 (63.2%) 79	89 (62.7%) 286
TEAEs related to Panzyga	16 (45.7%) 37	32 (46.4%) 80	20 (52.6%) 56	68 (47.9%) 173
Temporally-associated TEAEs	16 (45.7%) 41	34 (49.3%) 89	19 (50.0%) 54	69 (48.6%) 184
Related temporally associated TEAEs	15 (42.9%) 33	30 (43.5%) 64	19 (50.0%) 50	64 (45.1%) 147
Severe TEAEs	0 (0.0%) 0	3 (4.3%) 7	1 (2.6%) 1	4 (2.8%) 8
Serious TEAEs	1 (2.9%) 1	4 (5.8%) 9	1 (2.6%) 1	6 (4.2%) 11
Related serious TEAEs	0 (0.0%) 0	1 (1.4%) 2	0 (0.0%) 0	1 (0.7%) 2
TEAEs leading to discontinuation of study drug	2 (5.7%) 2	1 (1.4%) 2	2 (5.3%) 2	5 (3.5%) 6
TEAEs leading to death	0 (0.0%) 0	1 (1.4%) 1	1 (2.6%) 1	2 (1.4%) 2

N=number of patients; n=number of events
Source: Adapted from sBLA125587/70: Table 14.3.1.1

Two hudrend nine adverse reactions (ARs), defined as AEs considered at least possibly causally related by the investigator/applicant and/or AEs that were temporally related to administration of Panzyga (within 72 hours) were reported for 73 out of the 142 subjects (51.4%). Table 19 summarizes the most frequent ARs that occurred in more than 5% of subjects. Generally, the incidence of ARs was similar across the dose groups; the only AR where a dose effect was evident was headache, with an incidence of 2.9% in the 0.5 g/kg group, 14.5% in the 1.0 g/kg group and 23.7% in the 2.0 g/kg group.

Table 19 ARs Occurred in >5% of Subjects

AR	**No. of Subjects with TEAE (percentage of subjects)**
Headache	21 (14.8 %)
Fever	40 (14.1%)
Dermatitis	14 (9.9%)
Blood Pressure Increased	11 (7.7%)

Source: Adapted from Product Insert, Table 3

6.1.12.3 Deaths

There were 2 deaths (1.4%) reported, one each in the1.0mg/kg and 2.0mg/kg group.

- Subject [redacted] only received a total of 1 infusion/dose of the study medication over the course of the study, administered over two consecutive days. The SAE

'aspiration leading to respiratory arrest' occurred 1 hour and 30 minutes after the end of the second infusion. Over the course of the next several days the subject experienced bilateral pneumonia due to nosocomial infection and several episodes of cardio-respiratory arrest leading to his death. The investigator reported the event 'aspiration leading to respiratory arrest' as unlikely related to the study drug, and the events 'bilateral pneumonia due to nosocomial infection' and 'repeated cardiorespiratory event' as not related.

- Subject [redacted] received a total of 1 infusion/dose of the study medication over the course of the study, administered over two consecutive days. The SAE of encephalitis occurred 17 days after the last infusion. The investigator considered the SAE as unrelated.

Reviewer Comment:
The reviewer agrees that neither case of death is likely related to product administration.

6.1.12.4 Nonfatal Serious Adverse Events

Six subjects (4.2%) experienced 11 serious TEAEs, including

- 5 TEAEs experienced by the 2 subjects who died (above).
- 6 TEAEs experienced by 4 subjects; two of these events were considered related to Panzyga (Table 20).

Table 20 Nonfatal Serious TEAEs

Subject No	Treatment Group	MedDRA Preferred Term	Intensity	Outcome	Causality
(b) (6)	1.0 g/kg	Osteomyelitis	Severe	Resolved	Not related
(b) (6)	1.0 g/kg	Deafness unilateral	Severe	Resolved	Not related
(b) (6)	0.5 g/kg	Osteonecrosis	Moderate	Resolved	Unlikely
(b) (6)	1.0 g/kg	Headache Vomiting Meningioma	Moderate Moderate Mild	Resolved Resolved Resolved	Probable Probable Not related

Source: Adapted from sBLA 125573/70, Table 14.3.2

6.1.12.5 Adverse Events of Special Interest (AESI)

There were no Adverse Events of Special Interest. No cases of thromboembolic events (TEs) or hemolysis were reported.

6.1.12.6 Clinical Test Results

The most commonly reported AEs relating to laboratory abnormalities were leukopenia in 6 subjects (4.2%) and blood lactate dehydrogenase (LDH) increased in 5 subjects (3.5%). All laboratory AEs were mild in intensity, except for 2 events of leukopenia and 1 event of neutropenia that were considered moderate. Three of the leukopenia events and all of increased LDH events were considered related to the study drug. All related events have resolved.

6.1.12.7 Dropouts and/or Discontinuations

Five subjects (3.5%) experienced 6 TEAEs that led to discontinuation of Panzyga. None of the events are considered related (Table 21).

Table 21 TEAEs Leading to Discontinuation of Panzyga (SAF, N=142)

Patient Number	Treatment Group	MedDRA Preferred Term	Intensity	Outcome	Causality	SAE
(b) (6)	0.5 g/kg	Autoimmune hepatitis	Moderate	Not Resolved	Not related	No
(b) (6)	2.0 g/kg	Fibrin D dimer increased	Mild	Unknown	Likely not related	No
(b) (6)	0.5 g/kg	Osteonecrosis	Moderate	Not Resolved	Likely not related	Yes
(b) (6)	2.0 g/kg	Encephalitis	Severe	Fatal	Not related	Yes
(b) (6)	1.0 g/kg	Dermatitis allergic Urinary tract infection	Moderate Moderate	Resolved Resolved	Probable Not related	No No

Source: Adapted from sBLA125573/70, Source Listing 16.2.7.5

6.1.13 Study Summary and Conclusions

Study NGAM-08 met its primary endpoint, the proportion of responders in the 1.0 g/kg PANZYGA arm at Week 24 relative to Baseline (Week 0). Efficacy was supported by the proportion of responders in the 2.0 g/kg dose arm in the adjusted INCAT disability score, and the proportion of responders in the 1.0 g/kg and 2.0 g/kg dose arms in the grip strength, I-RODS and MRC sum scores. Risks of Panzyga observed in the study include headache, fever, dermatitis and increase in blood pressure. Results from the randomized, double-blind, multi-dose study support a conclusion that Panzyga has a favorable benefit risk profile for treatment of adult patients with CIDP.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

Treatment of adults with CIDP.

7.1.1 Methods of Integration

Since the application contains only Study NGAM-08, there is no integration or pooling of results in this review. Please see Section 6 for detailed efficacy analysis.

8. INTEGRATED OVERVIEW OF SAFETY

There is no integration of safety since the BLA efficacy supplement included only Study NGAM-08 to support the new indication. Please see Section 6 for details.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

No human data are available to indicate the presence or absence of drug-associated risk. Animal reproduction studies have not been conducted with PANZYGA. It is also not

known whether PANZYGA can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Immune globulins cross the placenta from maternal circulation increasingly after 30 weeks of gestation. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

9.1.2 Use During Lactation

No human data are available to indicate the presence or absence of drug-associated risk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PANZYGA and any potential adverse effects on the breastfed infant from PANZYGA or from the underlying maternal condition.

9.1.3 Pediatric Use and PREA Considerations

The safety and effectiveness of Panzyga have not been established in pediatric patients with CIDP.

Pediatric patients with CIDP were not studied in study NGAM-08. Panzyga is subject to the Pediatric Research and Equity Act (PREA) because of the new indication. The FDA Pediatric Review Committee (PeRC) agreed with the partial pediatric waiver request for ages zero to < 2 years and a pediatric study deferral for ages 2 years to <17 years. See appendices for the details of the phase 4 pediatric study to be conducted as a PREA postmarketing requirement (PMR).

9.1.4 Immunocompromised Patients

There are no human data available for the use of PANZYGA in immunocompromised patients. IgA-deficient patients with antibodies against IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions to PANZYGA.

9.1.5 Geriatric Use

Thirty-six subjects older than 65 years were included in the study. The safety and effectiveness of Panzyga in subjects with CIDP older than 65 years was similar to those 65 years of age and younger.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

Not applicable.

10. CONCLUSIONS

The efficacy and safety data of Study NGAM08 support the use of Panzyga for the treatment of adults with chronic inflammatory demyelinating polyneuropathy (CIDP) to improve neuromuscular disability and impairment. Current studies do not support extension of the indication for [redacted].

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Given the serious nature of CIDP, the observed improvements in functional neurologic scales (such as adjusted INCAT disability scale, grip strength, I-RODS score and MRC sum score) in Study NGAM-08 predict clinically meaningful improvement in the target

population. The benefits compare favorably in a quantitative (frequency-based) sense to the known and observed risks of Panzyga.

Table 22 Benefit / Risk Assessment

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• CIDP is a serious disease that can be associated with considerable morbidity	• CIDP is a serious disease.
Unmet Medical Need	• Gamunex-C brand IGIV is licensed for treatment of CIDP in adults to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse. • Privigen brand IGIV is licensed for treatment of CIDP in adults to improve neuromuscular disability and impairment.	• There is no clear unmet medical need; however, it is desirable to have more brands of IGIV product approved for CIDP given the possibility of recalls and shortages of any available brand(s) of IGIV product.
Clinical Benefit	• Study NGAM-08 was a prospective, parallel group, double-blind, randomized, dose controlled multicenter phase 3 efficacy study that demonstrated a statistically significant and clinically relevant improvement in functional neurologic scales (such as adjusted INCAT disability scale, grip strength, I-RODS score and MRC sum score) • The benefits compare favorably in a quantitative (frequency-based) sense to the known and observed risks of Panzyga.	• The efficacy data of Study NGAM08 support the use of Panzyga for the treatment of adults with chronic inflammatory demyelinating polyneuropathy (CIDP) to improve neuromuscular disability and impairment. The efficacy data do not support extension of the indication for (b) (4)
Risk	• Class effects associated with Panzyga appear to result primarily from the immunoglobulin component. Serious risks include thrombosis and renal dysfunction (including acute renal failure) and are listed in a Box Warning in the PI. Other risks include hypersensitivity (anaphylaxis) in patients with a history of anaphylaxis or those with antibodies against IgA (contraindication), fluid overload, aseptic meningitis, hemolysis, and, theoretically, CJD agent	• Clinical benefit exceeds risk.
Risk Management	Risk management plan includes • Adequate information provided in package insert • Routine pharmacovigilance	The risks can be mitigated through routine medical management, adequate PI and routine pharmacovigilance without requiring other regulatory measures such as REMS, or safety PMR.

11.2 Risk-Benefit Summary and Assessment

Panzyga is effective in improving neuromuscular disability and impairment in adult subjects with CIPD. Risk of thrombosis and renal dysfunction appear to be low.

11.3 Discussion of Regulatory Options

Approval of Panzyga for the treatment of adults with chronic inflammatory demyelinating polyneuropathy (CIDP) to improve neuromuscular disability and impairment.

11.4 Recommendations on Regulatory Actions

Please see 11.3.

11.5 Labeling Review and Recommendations

See amended PI.

11.6 Recommendations on Postmarketing Actions

I recommend a PREA PMR in pediatric subjects with CIDP that enrolls a population reflecting U.S. demographics characteristics.

APPENDIX 1 – REVIEW OF APPLICANT'S OUTLINE OF PHASE 4 PREA PMR STUDY PROTOCOL

The applicant has submitted an iPSP requesting:

- a waiver in Children with CIDP between 0 and 2 years of age and
- deferral of studies in children with CIDP between 2 and 17 years of age

The sponsor has submitted a protocol outline for a PREA PMR study with the following associated milestone dates:

Protocol submission date: June 18, 2021
Study initiation date: September 30, 2021
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Review of Initial Pediatric PREA PMR Protocol Outline

Disease Background in Pediatric Patients
CIDP represents 3% of polyneuropathies in childhood. Most cases of CIDP in children present with symmetric, mainly motor polyneuropathy, gait disturbance and falling (more frequently reported than in adults). Two major clinical types of CIDP have been described in pediatric populations. A monophasic disorder getting maximal weakness over 3 months. These children are more likely to recover entirely. The second is a slowly progressive disorder predisposed to have a relapsing and remitting course. It appears that children with CIDP have a more favorable long-term course than adults but subacute onset and relapses are more common in childhood. The prevalence of CIDP in children is estimated at less than 0.48 per 100,000. Approximately 1550 children under the age of 17 years may have CIDP in the United States. The most commonly used therapies for CIDP in children are corticosteroids and IGIV. Children are considered to respond worse than adults to plasma exchange. No controlled clinical trials have been conducted in children with CIDP to determine an appropriate dose regimen of IGIV. The most frequently used IGIV dosage regimen for CIDP in children is 400 mg/kg IV daily x five days, given either as a single treatment course, or as repeated courses administered every three to four weeks. Alternate regimens include 2g/kg total administered over two or three days, 1 g/kg administered over two days per month, or 800 mg/kg weekly.

Title of study: NGAM-11: Multicentre, prospective, open-label, randomized study to evaluate efficacy and safety of different panzyga dose regimens in paediatric CIDP patients.

Protocol Design Summary
This will be a multicenter, prospective, randomized, open-label clinical trial that will be conducted in 2 stages: pediatric subjects will receive an initial PANZYGA loading dose followed by a randomized 24 weeks dose-evaluation phase.
At least 30 IVIg-naïve and IVIG-pre-treated pediatric subjects will be enrolled.
Each patient will receive an initial 2.0 g/kg PANZYGA loading dose at Week 0 (Baseline Visit). At Week 3, the patients will enter a 1:1 randomized dose-evaluation phase and will be treated with either 0.5 g/kg or 1.0 g/kg PANZYGA every three weeks over the period of 21 weeks. The randomization will be stratified by whether subjects are IVIG naïve or not. Subjects deteriorating during the dose-evaluation phase at or after

Week 6 will be switched to rescue medication.

Primary objective: To evaluate the efficacy of 2 PANZYGA dose regimens by determining the percentage of subjects with CIDP relapse in the dose-evaluation phase.

Secondary objectives:

- To evaluate the safety of PANZYGA (occurrence of treatment emergent adverse events (TEAEs)).
- To further evaluate the efficacy of PANZYGA (including time to relapse and subgroup analyses).
- To assess the effect of PANZYGA on the modified Rankin Scale (mRS)

Inclusion Criteria

1. Age of ≥2 years and ≤17 years.
2. subjects with a diagnosis of definite or probable CIDP.

Exclusion Criteria

1. Subjects with previously diagnosed CIDP who lack any CIDP symptoms
2. Subjects with a history of inherited neuropathy or a family history of inherited neuropathy
3. Thromboembolic events: subjects with a history of deep vein thrombosis (DVT) or pulmonary embolism
4. Subjects with known or suspected hypersensitivity, anaphylaxis or severe systemic response to immuno-globulins, blood or plasma derived products, or any component of PANZYGA
5. Female subjects who are breast feeding, pregnant, or planning to become pregnant, or, are unwilling to use an effective birth control method (such as implants, injectables, combined oral contraceptives, intrauterine devices (IUDs), sexual abstinence or vasectomized partner) while on study.

Endpoints
Primary Endpoints
The primary efficacy endpoint is the percentage (%) of patients with CIDP relapse in the dose-evaluation phase. CIDP relapse, defined as an increase in modified Rankin Scale by ≥ 1 point from baseline, is monitored for up to week 24.

Secondary Efficacy Endpoints
The secondary efficacy endpoints are:
• Time to CIDP relapse or withdrawal for any other reason.
• Changes in mRS from Baseline Visit to End of Study Visit (up to 24 weeks).

Secondary Safety Endpoints
• Occurrence of all TEAEs (Treatment Emergent Events)
• Short term tolerance parameters including vital signs
• Safety laboratory parameters

Reviewer Comment:
It is clinically important to assess subjects with an excellent outcome defined by the Modified Rankin Scale (mRS) of 0 to 1.