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Applicant	OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.
Established Name	Immune Globulin Intravenous (Human) - ifas 10%
(Proposed) Trade Name	Panzyga
Pharmacologic Class	Immunoglobulins
Formulation(s), including Adjuvants, etc	Immune Globulin Infusion (Human) 10%
Dosage Form(s) and Route(s) of Administration	Liquid solution containing 10% IgG (100 mg/mL), for intravenous use only
Dosing Regimen	Loading Dose: 2 g/kg (20 mL/kg), divided into two daily doses of 1 g/kg (10 mL/kg) given on two consecutive days Maintenance dose: 1 - 2 g/kg (10 - 20 mL/kg) every 3 weeks. Maintenance dose should be individualized.
Indication(s) and Intended Population(s)	Treatment for Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

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GLOSSARY

AE(s)	Adverse event(s)
BLA	Biologics license application
BMI	Body mass index
CIDP	Chronic Inflammatory Demyelinating Polyneuropathy
CNS	Central nervous system
DVT	Deep Vein Thrombosis
EFNS	European Federation of Neurological Societies
FSS	Fatigue Severity Scale
IDMC	Independent Data Monitoring Committee
IgG	Immunoglobulin G
IGIV	Immunoglobulin Intravenous
INCAT	Inflammatory Neuropathy Cause and Treatment
IND	Investigational New Drug
I-RODS	Inflammatory Rasch-built Overall Disability Scale
ITT	Intent-to-treat
IUDs	Intrauterine devices
MADSAM	Multifocal Acquired Demyelinating Sensory and Motor Neuropathy
MCID	Minimum clinically important difference
MCID-SE	MCID related to the varying standard errors
MMN	Multifocal Motor Neuropathy
MRC	Medical Research Council
NCS	Nerve conduction studies
PCS	Physical composite score
PEX	Plasma exchange
PI-NRS	Pain Intensity Numeric Rating Scale
PNS	Peripheral Nerve Society
PP	Per-protocol
SAE	Serious adverse event
SAF	Safety set
SAP	Statistical Analysis Plan
S.D.	Standard Deviation
TEAE	Treatment-emergent adverse event
TSH	Thyroid-stimulating hormone

1. EXECUTIVE SUMMARY

This is a biologics license application (BLA) supplement for indication expansion of the applicant's product, Panzyga (formerly Newgam). Panzyga is a 10% (100 mg/mL) human normal immunoglobulin G (IgG) for intravenous administration (IGIV) which was originally approved by the FDA in 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. In this BLA efficacy supplement (STN 125587/70), the applicant seeks to expand the clinical indication of Panzyga to treatment of patients with chronic inflammatory demyelinating polyneuropathy (CIDP).

This submission included the results from one pivotal study, Study NGAM-08, to provide the primary evidence of efficacy and safety in support of the proposed expanded indication of Panzyga. Study NGAM-08 was a prospective, parallel-group, double-blind, randomized, multicenter, Phase 3 study conducted under IND 14096 in Canada, Russia and Europe. The primary objective was to provide confirmatory data on the effect of 1.0 g/kg Panzyga in patients with active CIDP. The primary efficacy endpoint was the proportion of responders at Week 24, where a responder was defined as a patient with a decrease of at least one point on the adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) disability score relative to Baseline.

A total of 142 subjects with CIDP were randomized in this study, ranging in age from 18 to 83 years old. 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 analysis for the primary efficacy endpoint using the full analysis set (FAS) in the 1.0 g/kg dose group revealed that the lower limit of the 95% Wilson-Score confidence interval (CI) for the proportion of responders exceeded the predefined threshold of 42% (79.7%; 95% CI: 68.8, 87.5). The analysis with the per-protocol set (PPS) showed 83.1% of responders (95% CI: 72.2, 90.3) in the 1.0 g/kg dose group. Similar results were also observed in subgroup analyses using the FAS population in the 1.0 g/kg group. Proportions of responders based on the primary efficacy score (i.e. adjusted INCAT disability score) appeared to get higher with increasing dose across the 3 dose groups in the FAS analysis with 64.7% in the 0.5 g/kg group, 79.7%, in the 1.0 g/kg group and 91.7% in the 2.0 g/kg group.

Proportions of responders based on different efficacy scores also appeared to get higher with increasing dose across the 3 dose groups in FAS analysis. Specifically, 38.2% was observed in the 0.5 g/kg group, 55.1% in the 1.0 g/kg group and 72.2% in the 2.0 g/kg group based on Inflammatory Rasch-built Overall Disability Scale (I-RODS); and 55.9% was observed in the 0.5 g/kg group, 65.2% in the 1.0 g/kg group and 83.3% in the 2.0 g/kg group based on grip strength. The results showed similar pattern in PPS analysis.

One subject in 1.0 g/kg dose group and 1 subject in 2.0 g/kg dose group died during the study. None of the death events were treatment related. Five subjects experienced 9 non-fatal serious adverse events (SAEs) and 2 of which were considered probably related to Panzyga. Further analysis of safety data is deferred to the clinical team.

The efficacy results of Study NGAM-08 provided statistical evidence to support expanding the indication of Panzyga to treatment of patients with CIDP.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a distinct acquired chronic progressive or relapsing and spontaneously remitting neuropathy characterized by progressive weakness, reduced or absent tendon reflexes and impaired sensation over more than 2 months. CIDP is divided into typical and atypical forms, and into those un-associated or associated with systemic diseases. Approximately 4% to 17% of CIDP patients die from the disease, whereas 50% require persistent treatment, and 13% are permanently disabled.

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

As CIDP is generally considered to be an autoimmune disease, corticosteroids were the first treatment introduced for CIDP. However, the doses of corticosteroids needed are often large and treatment has to be prolonged for months or years. Plasma exchange (PEX) has been shown to be beneficial, but the usefulness of PEX as a treatment for CIDP is limited by its inconvenience, requirement for hospital attendance and specially trained staff.

Over the last 20 years, high-dose Immunoglobulin intravenous (IGIV) administration has become an effective and safe therapeutic option for CIDP in adults. However, the optimal dosage of IGIV for treatment of CIDP patients is not known and has never been systematically examined.

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

The original BLA was submitted to the FDA on April 15, 2015 and the approval letter from CBER was issued on August 2, 2018. Panzyga (formerly Newgam), Immune globulin intravenous (IGIV) - human-ifas 10%, is currently indicated 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 to treatment of patients with CIDP.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

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

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

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

5.1 Review Strategy

The applicant submitted one pivotal study (Study NGAM-08) in support of this BLA supplement application. This review memo focuses on efficacy and safety analyses of Study NGAM-08.

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

The documents reviewed in submission STN 125587/70.0 include:

- Draft Labeling (Module 1.14.1)
- Clinical Overview (Module 2.5)
- Summary of Clinical Efficacy (Module 2.7.3)
- Summary of Clinical Safety (Module 2.7.4)
- Listing of Clinical Studies (Module 5.2)
- Clinical Study Report (CSR) for Study NGAM-08 (Module 5.3.5.1)
- Study protocol (Version 4) (module 5.3.5.1)
- Statistical Analysis Plan for Study NGAM-08 (SAP, Version 4) (module 5.3.5.1)

Analyses performed within this review are based on the following analysis-ready datasets provided by the applicant.

- adsl.xpt, adae.xpt, adeff.xpt, adtte.xpt and adcidp.xpt (module 5.3.5.1)

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study NGAM-08

Study NGAM-08 was a Phase 3 trial and conducted under IND 14096. Results from Study NGAM-08 form the primary evidence for evaluating the efficacy and safety of Panzyga for this BLA supplement application.

6.1.1 Objectives (Primary, Secondary, etc.)

The primary objective was to provide confirmatory data on the effect of 1.0 g/kg Panzyga every 3 weeks in patients with active CIDP based on the percentage of responders at

Week 24, to corroborate the existing evidence on efficacy of IGIV in CIDP as known from published literature.

6.1.2 Design Overview

The study was a prospective, parallel-group, double-blind, randomized, multicenter, Phase 3 study in patients with definite or probable CIDP according to the European Federation of Neurological Societies / Peripheral Nerve Society (EFNS/PNS) Criteria. The study consisted of a Screening Phase, Wash-out Phase, and a Dose-evaluation Phase. After a Wash-out Phase, during which the current medication (immunoglobulins or corticosteroids) was reduced stepwise until the patient deteriorated, subjects were randomized 1:2:1 to receive first a loading dose of 2 g/kg and then either 0.5 g/kg, 1.0 g/kg or 2.0 g/kg Panzyga for 7 maintenance infusions at 3-week (± 4 days) intervals during the 24-week Dose-evaluation Phase. The randomization was stratified by prior treatment with immunoglobulins or corticosteroids. The end of the study was defined as the last visit of the last patient participating in the study. No interim analyses were planned.

6.1.3 Population

Male or female subjects with a documented diagnosis of CIDP by a neurologist specialized and experienced in neuromuscular diseases were enrolled in this study.

Main inclusion criteria were:

1. Patients with a diagnosis of definite or probable CIDP according to the EFNS/PNS Guideline 2010
2. Patients currently depending on treatment with immunoglobulins or corticosteroids
3. Patients with active disease, i.e., not in remission, who were progressive or relapsing prior to study start or during the Wash-out Phase
4. Weakness of at least 2 limbs
5. ≥18 to <80 years of age
6. Adjusted INCAT disability score between 2 and 9 (with a score of 2 coming exclusively from leg disability)

Main exclusion criteria were:

1. Unifocal forms of CIDP
2. Pure sensory CIDP
3. Multifocal Motor Neuropath (MMN) with conduction block
4. Patients who previously failed immunoglobulin treatment
5. Treatment with immunomodulatory/suppressive agents during the 6 months prior to Baseline visit
6. Patients on or treated with rituximab, alemtuzumab, cyclophosphamide, or other intensive chemotherapeutic regimens, previous lymphoid irradiation or stem cell transplantation during the 12 months prior to Baseline visit
7. Respiratory impairment requiring mechanical ventilation

6.1.4 Study Treatments or Agents Mandated by the Protocol

Panzyga is a 10% IGIV delivered in glass bottles as a ready-to-use solution for intravenous administration. In the Dose-evaluation Phase, all subjects received a loading dose of 2.0 g/kg Panzyga (administered over 2 consecutive days), followed by 7 infusions of the maintenance dose the patient has been randomized to (i.e., 0.5, 1.0 or 2.0 g/kg Panzyga), also administered over 2 consecutive days every 3 weeks (±4 days). The same volumes and infusion rates were used regardless of the randomized group, with supplementation with an authorized 0.9% w/v isotonic sodium chloride solution as appropriate to maintain the blinding.

6.1.6 Sites and Centers

This study was conducted in Canada, Russia and Europe. In total, 41 study sites were initiated, of which 25 study sites recruited subjects who were included in the analysis (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

An Independent Data Monitoring Committee (IDMC) was established by the applicant. The IDMC reviewed relevant data periodically during the study and gave advice on the continuation, modification or termination of the study.

6.1.8 Endpoints and Criteria for Study Success

<u>Primary Efficacy Endpoint</u>
The primary efficacy endpoint was the proportion of responders at Week 24. A responder is defined as a patient with a decrease of at least 1 point on the adjusted INCAT disability score relative to Baseline (Week 0).

The hypotheses for evaluation of the primary endpoint was written as follows:

$$H_0: R < 0.42 \text{ vs. } H_1: R \geq 0.42$$

where R is the proportion of responders. The study is considered successful if the lower limit of the 95% Wilson-Score confidence interval (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.

Proportion of responders based on the adjusted INCAT disability score in the 0.5 g/kg and 2.0 g/kg Panzyga arms are also presented with CIs.

<u>Secondary Efficacy Endpoints</u>

- Proportion of responders in the 0.5 g/kg, 1.0 g/kg arm and 2.0 g/kg Panzyga arms at Week 24 relative to Baseline at Week 0 based on the grip strength (Martin Vigorimeter) using the previously published minimum clinically important difference (MCID) cut-off of 8 kPa.

- Proportion of responders in the 0.5 g/kg, 1.0 g/kg arm and 2.0 g/kg Panzyga arms at Week 24 relative to Baseline at Week 0 based on the Inflammatory Rasch-built Overall Disability Sum Score (I-RODS) 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 or more from the value at Baseline
- Mean change from Baseline (Week 0) to End of Study Visit in
  - grip strength of both hands (assessed by Martin Vigorimeter)
  - I-RODS (using the concept of MCID-SE) and number of improvers
  - 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)
- 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 Termination Visit in:
  - modified Fatigue Severity Scale (FSS)
  - SF-36 Health Survey physical composite score (PCS), mental composite score (MCS) and their 8 health domains
  - Additional nerve conduction studies (NCS) analyses (e.g. individual nerve analysis)

Exploratory Efficacy Endpoints

- For Medical Research Council (MRC) sum score, the following will be 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 Termination Visit (Week 24)
  - number of improvers by at least 4 points from baseline (Week 0) to Week 12 and to Week 24

Safety Endpoints

- 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

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample Size

Approximately 70 subjects will 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 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.

Analysis Populations
The safety set (SAF) includes all randomized subjects who received at least part of one infusion of Panzyga.

The full analysis set (FAS) includes all subjects of the SAF for whom any data was collected post infusion of Panzyga. Every treated subject was considered in the analysis according to his/her randomized treatment/dose assignment.

The per-protocol set (PPS) consists of all subjects in the FAS excluding those with significant protocol deviations.

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

Analysis for Efficacy Endpoints
The primary endpoint was analyzed by constructing the 95% Wilson-Score confidence interval for the proportion of responders based on the adjusted INCAT disability score in the 1.0 g/kg dose arm.

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

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 analyzed as non-responders.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

All 142 randomized subjects were included in the SAF. Table 1 shows a summary of the study analysis sets.

Table 1. 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	35 (100%)	69 (100%)	38 (100%)	142 (100%)
Full Analysis Set	34 (97.1%)	69 (100%)	36 (94.7%)	139 (97.9%)
Per-Protocol Set	29 (82.9%)	65 (94.2%)	35 (92.1%)	129 (90.8%)

Source: Modified from sBLA 125587/70.0; Module 5.3.5.1; CSR, Table 6, p59.

6.1.10.1.1 Demographics

The demographic characteristics are summarized by dose groups for FAS population in Table 2. Subjects between 18 and 83 years of age were enrolled in the study. Overall, there were more male subjects (59.0%) than female subjects (41.0%). All patients were white. The height of the patients ranged from 153 cm to 200 cm, and the weight of the patients was between 48 kg and 122 kg. The subject demographics of the three study groups were approximately balanced.

Table 2. Demographics (FAS)

Category	0.5 g/kg (N=34)	1.0 g/kg (N=69)	2.0 g/kg (N=36)	Total (N=139)
Age (years)				
N	34	69	36	139
Mean (SD)	53.3 (13.9)	56.3 (14.6)	56.9 (13.2)	55.7 (14.1)
Median	57.0	59.0	61.0	59.0
Range (Min, Max)	26.0, 73.0	18.0, 83.0	30.0, 75.0	18.0, 83.0
Q1, Q3	40.0, 64.0	51.0, 67.0	49.0, 66.0	49.0, 66.0
Sex, n (%)				
Female	13 (38.2%)	31 (44.9%)	13 (36.1%)	57 (41.0%)
Male	21 (61.8%)	38 (55.1%)	23 (63.9%)	82 (59.0%)
Race, n (%)				
White	34 (100.0%)	69 (100.0%)	36 (100.0%)	139 (100.0%)
Weight (kg)				
N	34	69	36	139
Mean (SD)	84.0 (16.8)	81.74 (16.3)	78.36 (17.1)	81.42 (16.6)
Median	82.5	80.0	76.5	80.0
Range (Min, Max)	56.0, 120.0	49.0, 122.0	48.0, 122.0	48.0, 122.0
Q1, Q3	72.0, 97.0	71.0, 93.0	66.0, 89.0	70.0, 93.0
Height (cm)				
N	34	69	36	139
Mean (SD)	173.2 (9.5)	172.81 (8.3)	171.75 (9.2)	172.62 (8.8)
Median	172.0	172.0	171.5	172.0
Range (Min, Max)	153.0, 191.0	155.0, 191.0	154.0, 200.0	153.0, 200.0
Q1, Q3	165.0, 182.0	167.0, 178.0	165.0, 177.0	166.0, 178.0

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

6.1.10.1.3 Subject Disposition

In total, 171 subjects were screened of whom 21 were screen failures and 150 entered the Wash-out Phase. Eight subjects failed screening during or at the end of the Wash-out Phase (a total of 29 screen failures) and thus 142 were randomized to 1 of the 3 treatment groups. A total of 123 subjects (86.6%) completed the study. Of the 19 subjects (13.4%) who terminated early, the most common reasons were patient's decision in 7 subjects (4.9%) and AE in 6 subjects (4.2%). Table 3 shows the detailed subject disposition.

Table 3. Subject Disposition

	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 (%)**
Randomized	35 (100.0%)	69 (100.0%)	38 (100.0%)	142 (100.0%)
Completed	28 (80.0%)	61 (88.4%)	34 (89.5%)	123 (86.6%)
Terminated early	7 (20.0%)	8 (11.6%)	4 (10.5%)	19 (13.4%)
Adverse event	3 (8.6%)	2 (2.9%)	1 (2.6%)	6 (4.2%)
Administrative reasons	0 (0.0%)	0 (0.0%)	1 (2.6%)	1 (0.7%)
Withdrawal for safety	0 (0.0%)	1 (1.4%)	1 (2.6%)	2 (1.4%)
Patient's decision	3 (8.6%)	3 (4.3%)	1 (2.6%)	7 (4.9%)
Other reason	1 (2.9%)	2 (2.9%)	0 (0.0%)	3 (2.1%)

Source: Modified from sBLA 125587/70.0; Module 5.3.5.1; CSR, Table 4, p56.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint

Table 4 shows the analyses for the proportions of responders based on adjusted INCAT disability score across 3 dose groups in both FAS and PPS analysis sets.

For the primary analysis of the endpoint, the proportion of responders in the 1.0 g/kg group was 79.71% (95% CI: 68.8, 87.5), with 55 out of 69 subjects classed as responders in FAS set. As the lower limit of CI exceeded the predefined threshold of 42%, Panzyga was shown to be effective in treating CIDP. The analysis with the PPS in the 1.0 g/kg dose group resulted in the similar results with 83.08% of responders (95% CI: 72.2, 90.3).

The proportion of INCAT responders appeared to get higher with increasing dose (64.7% in the 0.5 g/kg group, 79.7% in the 1.0 g/kg group and 91.7% in the 2.0 g/kg group in FAS population). The results showed similar pattern in PPS analysis population.

Table 4. 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.

Mean changes (SD) in adjusted INCAT disability score from baseline to Week 24 were -2.24 (1.81), -2.16 (1.47) and -2.75 (1.83) for 0.5 g/kg, 1.0 g/kg and 2.0 g/kg groups in FAS population, respectively. Results were similar in PPS population.

The median times to one point decrease in adjusted INCAT disability score were 22, 26 and 23 days for 0.5 g/kg, 1.0 g/kg and 2.0 g/kg groups in FAS population, respectively. Similar results were shown in PPS population.

6.1.11.2 Analyses of Secondary and Exploratory Endpoints

Inflammatory Rasch-built Overall Disability Sum Score (I-RODS)

Table 5 summarized the analyses for the proportions of responders based on I-RODS across 3 dose groups in both FAS and PPS analysis sets. The proportion of I-RODS responders appeared to get higher with increasing dose (38.2% in the 0.5 g/kg group, 55.1% in the 1.0 g/kg group and 72.2% in the 2.0 g/kg group in FAS population). The results showed similar pattern in PPS analysis population (Table 5).

Table 5. 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 responders	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 responders	13 (44.8%)	38 (58.5%)	25 (71.4%)	76 (58.9%)
95% CI	28.4, 62.5	46.3, 69.6	54.9, 83.7	50.3, 67.0

Source: FDA statistical reviewer's analysis.

Mean changes (SD) in I-RODS score from baseline to Week 24 were 11.38 (12.49), 10.32 (10.84) and 13.86 (11.98) for 0.5 g/kg, 1.0 g/kg and 2.0 g/kg groups in FAS population, respectively. Results were similar in PPS population.

Grip Strength

Table 6 shows the analyses for the proportions of responders based on grip strength across 3 dose groups in both FAS and PPS analysis sets. The proportion of grip strength responders appeared to get higher with increasing dose (55.9% in the 0.5 g/kg group, 65.2% in the 1.0 g/kg group and 83.3% in the 2.0 g/kg group in FAS population). The results showed similar pattern in PPS analysis population (Table 6).

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.

Table 6. 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 reviewer's analysis.

Medical Research Council (MRC) Sum Score

Table 7 summarized the analyses for the proportions of responders based on MRC sum scores across 3 dose groups in both FAS and PPS analysis sets. The proportion of MRC sum score responders appeared to get higher with increasing dose (58.8% in the 0.5 g/kg group, 72.5% in the 1.0 g/kg group and 86.1% in the 2.0 g/kg group in FAS population). The results showed similar pattern in PPS analysis population (Table 7).

Table 7. 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.

Mean changes (SD) in grip strength from baseline to Week 24 were 6.26 (5.07), 6.80 (5.08) and 9.39 (6.53) 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.

6.1.11.3 Subpopulation Analyses

Table 8 summarizes the subgroup analyses by age, sex, randomization stratum and CIDP variant using the FAS population across 3 dose groups. Panzyga appeared to be effective in treating CIDP for 1.0 g/kg dose group in each subgroup.

Table 8. Adjusted INCAT Disability Score Responders by Subgroups (FAS)

Subgroup	0.5 g/kg	1.0 g/kg	2.0 g/kg	Total
Age Group				
Age <= 50	N=13	N=17	N=11	N=41
Number (%) of responders	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	N=25	N=7	N=39
Number (%) of responders	5 (71.4%)	24 (96.0%)	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	N=27	N=18	N=59
Number (%) of responders	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	N=31	N=13	N=57
Number (%) of responders	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	N=38	N=23	N=82
Number (%) of responders	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
Randomization Stratum				
Corticosteroids	N=29	N=60	N=32	N=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
Immunoglobulin	N=5	N=9	N=4	N=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	N=62	N=32	N=127
Number (%) of responders	21 (63.6%)	49 (79.0%)	30 (93.6%)	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	N=7	N=4	N=12
Number (%) of responders	1 (100%)	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 reviewer's analysis.

6.1.11.4 Dropouts and/or Discontinuations

Since there were no missing data for the primary efficacy endpoint, no sensitivity analyses were performed.

6.1.12 Safety Analyses

6.1.12.3 Deaths

One out of 69 (1.4%) subjects in 1.0 g/kg dose group and 1 out of 38 (2.6%) subjects in 2.0 g/kg dose group died during the study. None of the death events were treatment related for both groups.

6.1.12.4 Nonfatal Serious Adverse Events

Four subjects (4/69; 5.8%) in 1.0 g/kg dose group experienced a total of 8 nonfatal SAEs, in which 2 were probable treatment related and 6 were not treatment related. One subject (1/35; 2.9%) in 0.5 g/kg dose group had 1 nonfatal SAEs and it was unlikely to be treatment related.

6.1.12.5 Adverse Events of Special Interest (AESI)

No thrombotic events were observed for all 3 dose groups.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Study NGAM-08 was a prospective, double-blind, randomized, multicenter Phase III study conducted under IND 14096 in Canada, Russia and Europe. The primary objective was to provide confirmatory data on the effect of 1.0 g/kg Panzyga in patients with active CIDP. The primary efficacy endpoint was the proportion of responders at Week 24, where a responder was defined as a patient with a decrease of at least one point on the adjusted INCAT disability score relative to Baseline.

A total of 142 subjects with CIDP aged between 18 and 83 years were randomized to one of 3 Panzyga dose groups (i.e. 0.5 g/kg, 1.0 g/kg or 2.0 g/kg) in this study. The prmiary analysis for the primary efficacy endpoint in FAS showed that the lower limit of the 95% Wilson-Score CI for the proportion of responders exceeded the predefined threshold of 42% in the 1.0 g/kg group (79.71%; 95% CI: 68.8, 87.5). The analysis with the PPS population resulted in 83.08% of responders (95% CI: 72.2, 90.3) in the 1.0 g/kg group. Similar results were also observed in subgroup analyses for the primary efficacy endpoint using the FAS population in the 1.0 g/kg group. Proportions of responders based on the primary efficacy score (i.e. adjusted INCAT disability score) appeared to get higher with increasing dose across the 3 dose groups in the FAS analysis with 64.7% in the 0.5 g/kg group, 79.7%, in the 1.0 g/kg group and 91.7% in the 2.0 g/kg group.

The primary efficacy analysis results were supported by the analyses of the secondary efficacy endpoints. Proportions of responders based on different efficacy scores also appeared to get higher with increasing dose across the 3 dose groups in FAS analysis. Specifically, 38.2% was observed in the 0.5 g/kg group, 55.1% in the 1.0 g/kg group and 72.2% in the 2.0 g/kg group based on I-RODS and 55.9% was observed in the 0.5 g/kg

group, 65.2% in the 1.0 g/kg group and 83.3% in the 2.0 g/kg group based on grip strength. These results were supported by the PPS analysis.

Two subjects died from treatment-unrelated events during the study, 1 in 1.0 g/kg dose group and 1 in 2.0 g/kg dose group. Five subjects experienced 9 non-fatal SAEs and 2 of which were considered probably related to Panzyga. Further analysis of safety data is deferred to the clinical team.

10.2 Conclusions and Recommendations

The efficacy results of Study NGAM-08 provided statistical evidence to support expanding the indication of Panzyga to treatment of patients with CIDP.