Application Type	BLA efficacy Supplement
STN	125105/2023
CBER Received Date	March 31, 2023
PDUFA Goal Date	January 29, 2024
Division / Office	CBER/OTP/OCE/DCEGM/GMB2
Committee Chair	Andy (Wenyu) Sun
Clinical Reviewer(s)	Andy (Wenyu) Sun
Project Manager	Adriane Fisher
Priority Review	No
Reviewer Name(s)	Md Tanbin Rahman, Ph.D. TEB1/DB/OBPV
Review Completion Date / Stamped Date	
Supervisory Concurrence	Tingting Zhou, Ph.D., Team Leader TEB1/DB/OBPV
	Boguang Zhen, Ph.D., Branch Chief TEB1/DB/OBPV
Applicant	Baxalta US Inc. (Owned by Takeda)
Established Name	Immune Globulin Infusion (Human), 10% Solution
(Proposed) Trade Name	GAMMAGARD LIQUID
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	
Dosage Form(s) and Route(s) of Administration	Induction dose is 2 g/kg in divided doses over 2 to 5 consecutive days, followed by maintenance infusions.
Dosing Regimen	Maintenance dose is 1 g/kg, administered every 3 weeks
Indication(s) and Intended Population(s)	To improve neuromuscular disability and impairment in adult patients with Chronic inflammatory Demyelinating Polyneuropathy (CIDP)

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GLOSSARY

ADL	Activities of daily living
AESI	Adverse events of special interest
AKI	Acute kidney injury
BLA	Biologics License Application
BW	Body weight
CI	Confidence interval
CIDP	Chronic Inflammatory Demyelinating Polyneuropathy
EFNS/PNS	European Federation of Neurological Societies/Peripheral Nerve Society
EOT	End of treatment
EU	European Union
FDA	Food and Drug Administration
GGL	GAMMAGARD LIQUID
IGI	Immune globulin infusion
IGIV	Intravenous immunoglobulin
INCAT	Inflammatory Neuropathy Cause and Treatment
IR	Interquartile range
ITP	Immune thrombocytopenia
IV	Intravenous
kPA	Kilopascal
Max	Maximum
MCAR	Missing completely at random
MID	Minimal clinical important difference
Min	Minimum
MMN	Multifocal motor neuropathy
MNAR	Missing not at random
MRC	Medical Research Council
OAI	Official action indicated
PRO	Patient Reported Outcome
R-ODS	Rasch-built Overall Disability Scale
RWD	Real-World Data
RWE	Real-World Evidence
SAP	Statistical analysis plan
sBLA	Supplemental BLA
TESAE	Treatment-emergent serious adverse event
US	United States

1. EXECUTIVE SUMMARY

Immune Globulin Infusion (Human), 10% (IGI 10%), under the trade name GAMMAGARD LIQUID (GGL) in the United States (US) and KIOVIG in the European Union (EU), is currently approved as a replacement therapy for primary humoral immunodeficiency in adult and pediatric subjects ≥2 years of age and as a maintenance therapy to improve muscle strength and disability in adult subjects with multifocal motor neuropathy (MMN) in the US. Baxalta US Inc. (part of Takeda) submitted the completed results from the pivotal study 161403 in this supplemental Biologics Licensing Application (sBLA) to expand the current indication to a therapy to improve neuromuscular disability and impairment in adult subjects with Chronic Inflammatory Demyelinating Polyneuropathy (CIDP).

Study 161403 was a Phase 3, prospective, multicenter study with 2 treatment periods: Epoch 1 and Epoch 2. Epoch 1 was a double-blind, placebo-controlled, subcutaneous (SC) treatment period of up to 6 months, where eligible subjects were randomized in a 1:1 ratio to receive HYQVIA (IGI 10% with recombinant Human Hyaluronidase [rHuPH20]) or 0.25% albumin placebo solution with rHuPH20. The detailed statistical review of Epoch 1 can be found under BLA 125402/885. Epoch 2 was an open-label intravenous (IV) treatment period of 6 months for subjects who relapsed during Epoch 1 to restore functional ability following a relapse and deterioration in functional ability. Subjects in Epoch 2 received CGL/KIOVIG or GAMUNEX (US sites only). With new efficacy data from Epoch 2, the applicant is seeking licensure of GGL for the indication of CIDP in the US.

Epoch 2 included 18 subjects after excluding Site 530: 3 subjects received HYQVIA, and 15 subjects received placebo during Epoch 1. The primary efficacy endpoint was the responder rate to GGL/KIOVIG in Epoch 2 among subjects who relapsed while receiving placebo in Epoch 1. Responder was indicated as an improvement in functional ability defined as a decrease of ≥1 point in the adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) disability score at the completion of the IV treatment period [6 months] or at the last study visit of the IV treatment period, relative to the pre-IV treatment baseline score. Among the 15 subjects, the responder rate was 100% (95% confidence interval [CI]: 79.61, 100.00). The lower confidence limit exceeded the pre-specified benchmark of 24%. The responder rate for all the subjects who relapsed (n=18) during Epoch 1 was 94.4% (95% CI: 74.24, 99.01).

There were no treatment-emergent serious adverse events (TESAEs), protocol-specified treatment-emergent adverse events of special interest (AESIs) during Epoch 2. No death was reported during the study with GGL/KIOVIG.

I verified the efficacy results from Epoch 2 that appear in the proposed updated label. Based on the available data, the statistical evidence supports approval of the applicant's labeling update to expand the indication to a therapy to improve neuromuscular disability and impairment in adult subjects with CIDP.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

CIDP is an acquired progressive chronic sensory and motor neuropathy with a relapsing and remitting or progressive course of more than 2 months, characterized by proximal weakness, positive sensory symptoms, areflexia without wasting, and impaired sensation with a preferential loss of vibration or joint position sense. Worldwide estimates of the prevalence of CIDP range from 1.9 to 8.9/100000 and an annual incidence of 1.6/100000 new cases each year. While CIDP can occur in all ages, it occurs more often in the middle-aged and elderly population with a male predominance. The peak incidence of CIDP is between the ages of 30 to 60 years. Approximately 60% of subjects have a chronic progressive form and are typically older. Approximately 30% have a relapsing remitting course and these subjects tend to be younger.

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

There are several IGIV formulations currently approved for treatment of CIDP in the US. GAMUNEX-C/GAMMAKED received labeling expansion for CIDP in 2008 in the US. Subsequently, other IGIV products PRIVIGEN and PANZYGA received FDA approval for labeling expansions to include treatment of CIDP.

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

GGL is an immune globulin infusion (human) 10% (IGI) solution. In the US, it is indicated as replacement therapy for primary humoral immunodeficiency in adult and pediatric subjects ≥2 years of age and as maintenance therapy to improve muscle strength and disability in adult subjects with MMN. GGL was originally approved by the FDA in 2005 for the treatment of primary humoral immunodeficiency, and subsequently, the treatment of MMN in 2012 (GGL Prescribing Information, March 2021). In the US, while GGL is not FDA approved for CIDP, it is routinely used for CIDP treatment.

In the EU, it is marketed as KIOVIG and indicated for adults, children, and adolescents (1) as replacement therapy for primary immunodeficiency syndromes with impaired antibody production and for secondary immunodeficiencies in subjects who suffer from severe or recurrent infections, ineffective antimicrobial treatment, and either proven specific antibody failure or serum IgG level of <4 g/L and (2) for immunomodulation in primary immune thrombocytopenia (ITP), in subjects at high risk of bleeding or prior to surgery to correct the platelet count, Gullain-Barre syndrome, Kawasaki disease (in conjunction with acetylsalicylic acid), CIDP, and MMN (GGL Summary of Product

Characteristics, April 2022). KIOVIG has been approved for treating CIDP in the EU since 2019, and it is also indicated for CIDP in 16 other countries worldwide.

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

Regulatory history with statistical implications is summarized below:

Pre-submission

1. On October 16, 2014, a Type B Pre-IND meeting request was submitted to discuss the proposed clinical study to evaluate the safety and efficacy of GGL/KIOVIG and HYQVIA for treatment of CIDP. In the meeting package, Takeda proposed to conduct a single Phase 3 global clinical trial with two treatment periods Epoch 1 (HYQVIA) treatment period and Epoch 2 (GGL/KIOVIG) treatment period under IND 014381.
2. On December 16, 2014, a written response (WRO) to the Type B Pre-IND Meeting was provided to Takeda.
3. On March 31, 2015, a follow-up meeting was requested to seek clarification on the WRO.
4. On April 20, 2015, in response to the request, the FDA proposed changes to the Interim Safety Analysis Plan and requested that Takeda provided more convincing evidence that GGL/KIOVIG is effective in CIDP before using it as rescue therapy for Epoch 1 subjects who relapse while on HYQVIA and/or placebo.
5. On September 11, 2015, sponsor revised the study protocol 161403 to specify the use of an approved Immune Globulin product (GAMUNEX-C) as a rescue therapy for Epoch 1 subjects who relapse while on HYQVIA and/or placebo. The agency agreed to this change.
6. On May 29. 2020, a Type C meeting package was submitted by the sponsor to discuss a potential supplemental BLA to support CIDP indication for GGL/KIOVIG. In this package, the sponsor proposed approaches to generate a body of safety and efficacy evidence supportive of GGL/KIOVIG use in CIDP including use of real-world data or real-world evidence (RWD/RWE). FDA provided feedback on the proposed approach on August 4, 2020, via WRO. Based on FDA's feedback, Takeda submitted a revised Study 161403 protocol amendment and an SAP draft on June 3, 2021.

Post-submission

7. On October 17, 2023, a clinical information request was sent to Takeda regarding Site 530. The reliability of the data generated was found to be questionable after the inspection of the site. Hence, the FDA recommended re-conducting the efficacy analyses, excluding two subjects from Site 530.
8. On October 31, 2023, Takeda responded back with revised efficacy analyses excluding subjects from Site 530.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

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

3.2 Compliance With Good Clinical Practices And Data Integrity

Site 530 resulted in an official action indicated (OAI) classification. As a result, the review team decided to exclude these 2 subjects from Site 530 from the analyses.

This review is based on the updated efficacy results excluding two subjects from Site 530.

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

5.1 Review Strategy

This review memo reviews the efficacy and safety results of Study 161403 Epoch 2 for the indication of CIDP.

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

The review memo was based on the draft labeling (module 1.14.1); the protocol and its amendments (module 5.3.5.1), the SAP and its amendments (module 5.3.5.1), clinical trial report (module 2.7.3), the data files (module 5.3.5.1) for Study 161403 submitted on STN 125105/223. In addition, clinical information amendment (module1.11.3) and the data files (module 5.3.5.1) from STN 125105/223.06 were reviewed.

5.3 Table of Studies/Clinical Trials

Table 1: Tabular listing of all clinical studies on IGI, 10% included in the submission for CIDP

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Efficacy	161403	Epoch 2: To evaluate the efficacy of GGL for the treatment of CIDP to improve neuromuscular disability and impairment.	Epoch 2: Phase 3, open label, noncontrolled, multi-center study	Epoch 2: IGI 10% induction dose of 2 g/kg BW administered in divided doses over 2 to 5 consecutive days, followed by maintenance infusions at the same monthly dose as the subject's prerandomization IGIV doses administered every 3 weeks. Administration was by IV route.	Epoch 2: 20 subjects dosed with GGL	Epoch 2: Subjects who experienced CIDP relapse during Epoch 1 (worsening by ≥ 1 point relative to the pre-Epoch 1 baseline score in 2 consecutive adjusted INCAT disability scores)	Epoch 2: IV treatment period of 6 months
Safety	TAK-771-4002	To evaluate the safety of GGL for the treatment of patients with CIDP.	RWE safety study: non-interventional, nonrandomized, active-comparator, new-user, cohort study	IVIG 10% (GammaGard Liquid and Gammunex-C/Gammaked, Privigen) as prescribed and administered in real-world clinical practice.	6068, 2,085 GGL patients and 4001 patients receiving Gammunex-C, Gammaked, Privigen	New users of IGIV with ≥ 2 recorded diagnoses of CIDP before IGIV initiation	Followed from the date of IGIV initiation until occurrence of an outcome or censoring at 31 Dec. 2019, disenrollment from the data source, end of continuous use of the IGIV, or switching to/adding another Ig product.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study 161403 Epoch 2

Study 161403 was titled “A Phase III Study to Evaluate the Efficacy, Safety, and Tolerability of Immune Globulin infusion 10% (Human) with Recombinant Human Hyaluronidase (HYQVIA/HyQvia) and Immune Globulin Infusion (Human), 10% (GAMMAGARD LIQUID/KIOVIG) for the Treatment of Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)”.

Study 161403 had 2 treatment periods: Epoch 1 and Epoch 2. Epoch 1 was a double-blind, placebo-controlled, subcutaneous (SC) treatment period of up to 6 months, where eligible subjects were randomized in a 1:1 ratio to receive HYQVIA (IGI 10% with rHuPH20) or 0.25% albumin placebo solution with rHuPH20. The detailed statistical review of Epoch 1 can be found under BLA 125402/885. The statistical reviewer for that submission is Zhong Gao. My review memo is focused on Epoch 2.

6.1.1 Objectives (Primary, Secondary, etc)

Epoch 2:
Primary Objective:

- To evaluate the efficacy of GGL/KIOVIG for the treatment of CIDP to improve neuromuscular disability and impairment.

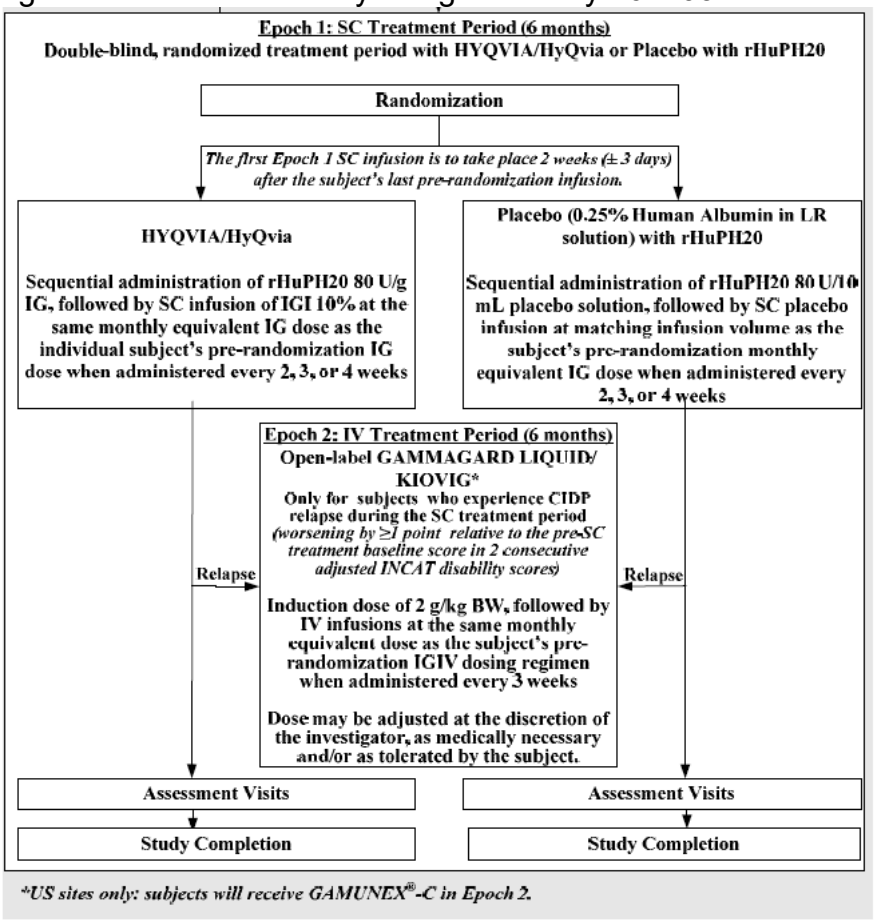
Secondary Objectives:

- To assess safety and tolerability of GGL/KIOVIG
- To assess the effect of GGL/KIOVIG on activities of daily living (ADL)

6.1.2 Design Overview

Study 161403 was a Phase 3, prospective, multicenter study with 2 treatment periods: Epoch 1 and Epoch 2. Figure 1 provides an overview of the study design for Study 161403.

Figure 1: The overall study design of Study 161403



Source: BLA 125105/2023 (Module 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication) 161403 – 16.1 Protocol and Amendment, Protocol version 6, Figure 21-1 Study Design for Clinical Study 161403, page 151.

6.1.3 Population

Key inclusion criteria:

- A documented diagnosis of definite or probable typical/atypical CIDP (with the exclusion of focal atypical CIDP or pure sensory atypical CIDP), in accordance with the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) 20210 guidelines
- Responded to IgG treatment in the past and must be currently on stable doses of IgG treatment within the dose range equivalent to a cumulative monthly dose of 0.5 to 2.4 g/kg body weight (BW) administered intravenous (IV) for at least 3 months prior to screening.
- An INCAT disability score between 0 and 7

Epoch 2 of the study included subjects who relapsed during Epoch 1, regardless of their treatment assignment.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Epoch 2
Investigational Product: GGL/KIOVIG (IGI 10%)
The induction dose was 2 g/kg BW administered in divided doses over 2 to 5 consecutive days, followed by maintenance infusions at the same monthly dose as the subject's pre-randomization IGIV doses administered every 3 weeks.
Route of administration: IV

GAMUNEX-C (US sites only)
The induction dose 2 g/kg BW was administered over 2 to 4 consecutive days. The maintenance infusions of 1 g/kg BW (10 mL/kg BW) were administered over 1 day or divided into 2 doses of 0.5 g/kg BW (5 mL/kg BW) given on 2 consecutive days, every 3 weeks. The initial infusion rate was 2 mg/kg/min (0.02 mL/kg/min). If the infusion was well-tolerated, the rate was allowed to be gradually increased to a maximum of 8 mg/kg/min (0.08 mL/kg/min).
Route of administration: IV

The dose level of IGIV treatment was adjusted at the discretion of the investigator, as medically necessary and/or as tolerated by the subject.

6.1.6 Sites and Centers

Subjects were enrolled from 14 sites in Argentina, Colombia, Germany, Israel, Italy, Poland, Serbia, and Spain.

6.1.8 Endpoints and Criteria for Study Success

Primary efficacy endpoint:

- Responder rate defined as the proportion of subjects with an improvement in functional ability defined as a decrease of ≥1 point in the adjusted INCAT disability score at the completion of the IV treatment period [6 months] or at the last study visit of the IV treatment period, relative to the pre-IV treatment baseline score.

Secondary efficacy endpoint:

- Proportion of subjects with an improvement in functional ability defined as a decrease of ≥1 point in the adjusted INCAT disability score at 2 consecutive time points OR who experience CIDP improvement (defined as ≥8 Kilopascal (kPa) increase in the hand grip strength in the more affected hand or ≥4 points increase in R-ODS) at the completion of the IV treatment period [6 months] or at the last study visit of the IV treatment period, relative to the pre-IV treatment baseline score.

Criteria for study success:
The lower limit of the two-sided 95% Wilson Score confidence interval (CI) of the responder rate as defined in the primary efficacy endpoint exceeds 24%.

The benchmark of 24% was based on a previous study, GAMUNEX-C pivotal (ICE) study, where none of the 12 IGIV-experienced subjects randomized to placebo were non-responders, representing a responder rate of 0% (0/12). The upper bound of the two-sided 95% CI using the Wilson score method was 24%.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Statistical Hypothesis:
Null: Responder rate among subjects who relapsed in Epoch 1 while on placebo with rHuPH20 treatment is not higher than 24%
Alternative: Responder rate is greater than 24%

Sample Size Estimation:
The sample size for Epoch 2 depends on the sample size for Epoch 1 and the responder rate.

For Epoch 1, the applicant initially planned a total of 174 subjects. Based on revised sample size calculation, the applicant revised the total sample size to at least 120 subjects randomized and dosed to achieve 90% power, assuming 15% of the subjects would prematurely discontinue from the study.

The applicant assumed that at least 19 subjects would enroll into Epoch 2. Assuming a responder rate of 65% to GGL/KIOVIG based on responder rates of 55% and 77% observed in the subset of treatment-experienced subjects in the ICE study and the PRIMA study, respectively, the sample size would achieve a power of more 90% at a two-sided 5% significance level.

Analysis Population:

The Epoch 2 Safety Set: all subjects who had a relapse in Epoch 1, entered Epoch 2, and received IGIV treatment with either GGL/KIOVIG or GAMUNEX®-C in Epoch 2.

The E1:Placebo Relapse / E2:GGL/KIOVIG Set: a subset of subjects who had a relapse while on placebo in Epoch 1, entered Epoch 2, and were treated with GGL/KIOVIG in Epoch 2. This is the primary analysis set for Epoch 2 (the IV treatment period) non-safety data.

The E1:HYQVIA Relapse / E2:GGL/KIOVIG Set: a subset of subjects who had a relapse while on HYQVIA in Epoch 1, entered Epoch 2, and were treated with GGL/KIOVIG in Epoch 2. This is a supplemental analysis set for Epoch 2.

The E1:Combined Relapse / E2: GGL/KIOVIG Set: all subjects who relapsed in Epoch 1, entered Epoch 2, and were treated with GGL/KIOVIG. This is a supplemental analysis set for Epoch 2.

Relapse in Epoch 1 was defined as worsening of functional disability, an increase of ≥ 1 point relative to the pre-SC treatment baseline score in adjusted INCAT disability score at 2 consecutive time points.

Statistical Methods:

Primary Efficacy Endpoint:

The responder rate and the two-sided 95% Wilson Score CI of the responder rate were computed on the E1:Placebo Relapse / E2:GGL/KIOVIG set. This analysis was based on a complete case analysis assuming missing completely at random (MCAR). Subjects with a missing response status at the completion of the IV treatment period (6 months) or the last study visit of the IV treatment period were not to be imputed.

Sensitivity analyses: a two-sided 95% CI for the responder rate using the Clopper-Pearson method was calculated. In addition, to assess the robustness of the inferences from Epoch 2 primary analysis to departures from the MCAR premise, an analysis assuming missing not at random (MNAR) premise was performed. For this analysis, subjects with missing response status at the completion of the IV treatment period (6 months) or the last study visit of the IV treatment period were imputed as non-responders.

Secondary Efficacy Endpoints

Descriptive statistics, including number and percentage of subjects within each category, were computed. Two-sided 95% Wilson Score CIs were calculated.

Subgroup analyses

Analysis of the primary efficacy endpoint by age (≤55 vs >55 years), sex (Female vs Male) and race (White, Black or African American, Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, Other and Not reported) were performed.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Out of 62 subjects on HYQVIA during Epoch 1, 6 subjects relapsed, and 6 subjects had missing relapse determination. Out of the 70 subjects on placebo during Epoch 1, 22 subjects relapsed, and 2 subjects had missing relapse determination.

Out of the 28 subjects who relapsed during Epoch 1, a total of 21 subjects were enrolled into Epoch 2. Twenty subjects received CGL/KIOVIG and only one

subject received GAMUNEX-C in Epoch 2. In the GGL/KIOVIG cohort, 4 subjects relapsed while on HYQVIA, and 16 subjects relapsed while on placebo.

Reviewer's comment: Two subjects in the GGL/KIOVIG cohort were from site 530 and were excluded from analyses presented in following sections.

6.1.10.1.1 Demographics

Table 2 provides a summary of demographic data. In the primary efficacy analysis set, E1:Placebo Relapse / E2:GGL/KIOVIG set, 9 (60%) subjects were female and 6 (40%) subjects were male. Most subjects were White (73.3%), in contrast to no Black or African American enrolled in the study. Two subjects (13.3%) were of American Indian or Alaska native origin, and two subjects (13.3%) with missing race information. The mean age was 53.4 years old, ranging from 28 to 67 years old. The mean height, weight, and BMI were 164.3 cm, 75.92 kg and 28.15 kg/m^2, respectively. The demographic data were similar for the E1:Combined Relapse / E2: GGL/KIOVIG set as there were only 3 subjects in E1:HYQVIA Relapse / E2: GGL/KIOVIG set.

Table 2: Baseline demographics

	E1:Placebo Relapse / E2: GGL/KIOVIG	E1: HYQVIA Relapse / E2: GGL/KIOVIG	E1: Combined Relapse / E2: GGL/KIOVIG
Number of subjects	15	3	18
Age (years)			
Mean (SD)	53.4 (12.88)	36.3 (15.57)	50.6 (14.42)
Median	57.0	38	52.0
Min, Max	28, 67	20, 51	20, 67
Age group, N(%)			
≤55 years	7 (46.7)	3 (100.0)	10 (55.6)
>55 years	8 (53.3)	0 (0.0)	8 (44.4)
Sex, N(%)			
Male	6 (40.0)	1 (33.3)	7 (38.9)
Female	9 (60.0)	2 (67.7)	11(61.1)
Race, N(%)			
White	11 (73.3)	3 (100.0)	14 (77.8)
American Indian or Alaska Native	2 (13.3)	0	2 (11.1)
Not Reported	2 (13.3)	0	2 (11.1)
Height (cm)			
Mean (SD)	164.3 (8.00)	172.3 (13.31)	165.6 (9.12)
Median	164	169	164.5
Min, Max	150, 184	161, 187	150, 187
Weight (kg)			
Mean (SD)	75.92 (11.62)	89.33 (35.65)	78.16 (16.94)
Median	73	74.5	73.05
Min, Max	59.0, 94.0	63.5, 130.0	59.0, 130
BMI (kg/m^2)			
Mean (SD)	28.15 (4.07)	29.27 (6.92)	28.3 (4.41)
Median	27.80	26.1	27.75
Min, Max	21.6, 35.7	24.5, 37.2	21.6, 37.2

cm=centimeters; kg=kilogram; m^2=meters; N=number of subjects; %=percentage; SD=standard deviation

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
The CIDP history of the subjects enrolled into Epoch 2 of the study is given in Table 3. The average time to CIDP symptom was 5.75 years with a range of 0.5 to 15.7 for the E1:Combined Relapse/E2:GGL/KIOVIG cohort. As for E1:Placebo/E2 GGL/KIOVIG, it was 6.08 years compared to 4.23 years in the E1:HYQVIA Relapse/E2:GGL/KIOVIG. The mean time to CIDP diagnosis was 4.30, 2.67 and 4.03 years in the E1:Placebo Relapse/E2:GGL/KIOVIG, E1:HYQVIA Relapse/ E2:GGL/KIOVIG and E1:Combined Relapse/E2:GGL/KIOVIG, respectively. Lastly, the mean age at diagnosis is

49.0, 33.67 and 46.4 years for E1:Placebo Relapse/E2:GGL/KIOVIG, E1:HYQVIA Relapse/ E2:GGL/KIOVIG and E1:Combined Relapse/E2:GGL/KIOVIG, respectively. None of the subjects received plasma exchange within 6 months prior to screening in Epoch 1.

Table 3: CIDP History at Screening by Treatment Cohort

	E1:Placebo Relapse / E2: GGL/KIOVIG	E1: HYQVIA Relapse / E2: GGL/KIOVIG	E1: Combined Relapse / E2: GGL/KIOVIG
Time since first CIDP symptoms (years) at Epoch 1 enrollment (n)	14	3	17
Mean (SD)	6.08 (4.32)	4.23 (3.44)	5.75 (4.15)
Median	5.35	2.30	5.30
Min, Max	0.5, 15.7	2.20, 8.20	0.5, 15.7
Time since CIDP Diagnosis (years) at Epoch 1 enrollment (n)	15	3	18
Mean (SD)	4.30 (3.40)	2.67 (2.47)	4.03 (3.26)
Median	3.60	2.00	3.20
Min, Max	0.30, 11.5	0.60, 5.40	0.30, 11.5
Subject Age at First Diagnosis of CIDP (years) (n)	15	3	18
Mean (SD)	49.0 (13.28)	33.67 (14.29)	46.4 (14.28)
Median	50.0	37.0	47.5
Min, Max	25.0, 66.0	18.0, 46.0	18.0, 66.0

min=minimum; max=maximum; n=number of subjects; SD=standard deviation

6.1.10.1.3 Subject Disposition
All subjects who entered Epoch 2 completed the study.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The responder rate to GGL/KIOVIG in Epoch 2 among subjects who developed relapse while on placebo in Epoch 1 and received GGL/KIOVIG Epoch 2 was 100% (15 subjects). The lower limit of the 95% Wilson CI was 79.61, which exceeded the pre-specified 24% defined in the hypothesis testing. The study met its prespecified success criteria. Table 4 summarizes the results.

As part of the sensitivity analysis, the Clopper-Pearson 95% CI was also calculated (95% CI: 78.20%, 100%), which also exceeded the pre-specified

benchmark 24%. The conclusion from the sensitivity analysis was consistent with that from the primary efficacy analysis.

Additional supplementary analysis was carried out on all subjects who were treated with GGL/KIOVIG (subjects who were treated with either placebo or HYQVIA during Epoch 1). The responder rate was 94.4% (95% CI: 74.24, 99.01).

Table 4: Responder rate, the proportion of subjects with an improvement in functional ability defined as a decrease of ≥1 point in the adjusted INCAT disability score at the completion of the IV treatment period [6 months] or at the last study visit of the IV treatment period, relative to the pre-IV treatment baseline score

	E1: Placebo Relapse/E2: GGL/KIOVIG	E1: HYQVIA Relapse/GGL/KIOVIG	E1: Combined Relapse/E2: GGL/KIOVIG
Subjects, N	15	3	18
Subjects who responded, N (%)	15 (100.0)	2 (66.7)	17 (94.4)
Wilson 95% CI	79.61, 100.00	NA*	74.24, 99.01

Source: BLA 125105/2023.6 (Module 1.11.3 Clinical Information Amendment) efficacy-information-amendment-st01416-q1-updates.pdf, Table 14.2.3.5.4.b, page 4 of 308.
*Two-sided 95% Wilson Score CIs are not provided for any cohort with less than or equal to 5 subjects.
CI=confidence interval; N=number of subjects; NA=not applicable; %=percentage

6.1.11.2 Analyses of Secondary Endpoints

The proportion of subjects with an improvement in functional ability defined as a decrease of ≥1 point in the adjusted INCAT disability score at 2 consecutive time points or ≥8 Kilopascal (kPa) increase in the hand grip strength in the more affected hand or ≥4 points increase in R-ODS) and the 95% Wilson CIs, based on observed cases, are presented in Table 5. In the primary analysis set, all 15 subjects were responders, so the proportion of responders was 100% (95% CI: 79.61, 100.00).

The proportion among all subjects who were treated with GGL/KIOVIG, i.e., subjects who were treated with either placebo or HYQVIA during Epoch 1, was also 100% (95% CI: 82.41, 100.00).

Table 5: Subjects with an improvement in functional ability defined as a decrease of ≥1 point in the adjusted INCAT disability score at 2 consecutive time points or ≥8 Kilopascal (kPa) increase in the hand grip strength in the more affected hand or ≥4 points increase in R-ODS

	E1: Placebo Relapse – E2: GGL/KIOVIG	E1: HYQVIA Relapse – GGL/KIOVIG	E1: Combined Relapse – E2: GGL/KIOVIG
Subjects, N	15	3	18
Subjects who responded, N(%)	15 (100.0)	3 (100.0)	18 (100.00)
Wilson 95% CI	79.61, 100.00	NA*	82.41, 100.00

Source: BLA 125105/2023.6 (Module 1.11.3 Clinical Information Amendment) efficacy-information-amendment-st01416-q1-updates.pdf, Table 14.2.3.6.1.b, page 8 of 308.
*Two-sided 95% Wilson Score CIs are not provided for any cohort with less than or equal to 5 subjects.
CI=confidence interval; N=number of subjects; NA=not applicable; %=percentage

6.1.11.3 Subpopulation Analyses

Subgroup analyses by age categories, sex, and race of the primary efficacy endpoint were performed. Since most subjects were white, subgroup analyses by race were not informative. The responder rates for all the subgroups were 100%. The 95% Wilson CIs could not be calculated for two subgroups by race due to very small sample sizes. The lower limit of all calculated 95% Wilson CIs exceeded the pre-specified benchmark of 24%.

6.1.11.4 Dropouts and/or Discontinuations

There were no missing data due to dropouts or discontinuations.

6.1.11.5 Exploratory and Post Hoc Analyses

The following exploratory analyses are presented in the label and will potentially be included in the label per clinical review team.

Time to improvement in functional ability (defined as a decrease of ≥1 point in the adjusted INCAT score)
The median time to improvement in functional ability was 25 days for all subjects, 23 days for subjects who had relapsed while on placebo in Epoch 1, and 85 days for subjects who had relapsed while on HYQVIA.

Change from pre-intravenous treatment baseline in adjusted INCAT disability score
At pre-IV baseline, the median INCAT score was 5.0 (interquantile range (IQR)): 4.0-7.0), and at the end of Epoch 2, the median INCAT score was 4.0 (IQR: 3.0-

4.0). The mean change from pre-IV treatment baseline in adjusted INCAT disability score was -2.1 points (Interquartile range (IQR (: -3.0 - -1.0 points).

Change from pre-intravenous treatment baseline in medical research council (MRC) sum score
In the GGL/KIOVIG cohort, the mean change from baseline to end of treatment (EOT) in MRC sum score was 5.4 points.

Change from pre-intravenous treatment baseline in R-ODS
In the GGL/KIOVIG cohort, the mean change from baseline to Week 24 in centile R-ODS score was 15.0 points and exceeds the minimal clinical important difference (MID; 4 points based on centile) proposed for R-ODS.

Change from pre-intravenous treatment baseline in hand grip strength score
In the GGL/KIOVIG cohort, the mean change from baseline to EOT in hand grip strength was 13.8 kPa in the more affected hand and 9.8 kPa in the less-affected hand. Both changes exceed MID (8 kPa) threshold for grip strength in CIDP.

6.1.12 Safety Analyses

6.1.12.3 Deaths

No deaths were reported during the study.

6.1.12.4 Nonfatal Serious Adverse Events

No TESAEs occurred in the study.

6.1.12.5 Adverse Events of Special Interest (AESI)

AESIs included thrombotic events, acute kidney infection (AKI), hemolytic events. No subjects experienced protocol-specified treatment-emergent AESIs during Epoch 2.

6.1.12.7 Dropouts and/or Discontinuations

No dropouts or early study discontinuations occurred in the study.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

I verified the primary and key secondary efficacy results from Epoch 2 of Study 161403 that appear in the proposed updated label.

Study 161403 was a Phase 3, prospective, multicenter study with 2 treatment periods: Epoch 1 and Epoch 2. Epoch 1 was a double-blind, placebo-controlled, subcutaneous (SC) treatment period of up to 6 months, where eligible subjects

were randomized in a 1:1 ratio to receive HYQVIA (IGI 10% with rHuPH20) or 0.25% albumin placebo solution with rHuPH20. Epoch 2 was an open-label intravenous (IV) treatment period of 6 months for subjects who relapsed during Epoch 1. Subjects in Epoch 2 received CGL/KIOVIG or GAMUNEX (US sites only). After excluding Site 530, Epoch 2 efficacy analyses included 18 subjects: 3 subjects received HYQVIA and 15 subjects received placebo during Epoch 1.

The primary efficacy endpoint was the responder rate to GGL/KIOVIG in Epoch 2 among subjects who relapsed while receiving placebo in Epoch 1. Responder was indicated as an improvement in functional ability defined as a decrease of ≥1 point in the adjusted INCAT disability score at the completion of the IV treatment period [6 months] or at the last study visit of the IV treatment period, relative to the pre-IV treatment baseline score. Among the 15 subjects who relapsed while on placebo in Epoch 1, the responder rate was 100% (95% confidence interval [CI]: 79.61, 100.00). The lower confidence limit exceeded the pre-specified benchmark 24%. The responder rate for all the subjects who relapsed (n=18) was 94.4% (95% CI: 74.24, 99.01).

The median time to clinical improvement, defined by at least a 1-point decrease in INCAT, was 25 days after initiating GGL therapy. The mean INCAT score improved by 2.1 points. Medical Research Council (MRC) sum score in Epoch 2 improved by a mean of 5.4 points. The mean change in centile Rasch-built Overall Disability Scale (R-ODS) score was 15.0 points. Grip strength improved by a mean of 13.8 kPa in the more affected hand and 9.8 in the less affected hand.

No TESAEs and no protocol specified AESIs occurred during Epoch 2. No death was reported during the clinical trial.

10.2 Conclusions and Recommendations

The submission includes data from a single-arm open label study (Study 16143 Epoch 2) for evaluating the efficacy of GGL for treatment of CIDP. There were no statistical issues identified during the review of sBLA. The interpretations of efficacy and safety results are limited by the single-arm design. However, the lower CI (79.61) for the primary efficacy endpoint was substantially greater than the pre-specified benchmark of 24% which potentially mitigates biases introduced by the single-arm, externally controlled nature of the trial.

Based on the available data, the statistical evidence supports approval of the applicant’s labeling update to expand the indication to a therapy to improve neuromuscular disability and impairment in adult subjects with CIDP.