BLA Clinical Review Memorandum

Application Type	Efficacy Supplement
STN	125105/2023
CBER Received Date	March 31, 2023
PDUFA Goal Date	January 29, 2024
Division / Office	DCEGM / OCE / OTP
Priority Review (Yes/No)	No
Reviewer Name(s)	Wenyu Sun, MD, MPH
Review Completion Date / Stamped Date	January 26, 2024
Supervisory Concurrence	Rosa Sherafat-Kazemzadeh, MD Lei Xu, MD, PhD Tejashri Purohit-Sheth, MD
Applicant	Baxalta US Inc. (a subsidiary of Takeda)
Established Name	Immune Globulin Infusion (Human), 10% Solution
Trade Name	GAMMAGARD LIQUID
Pharmacologic Class	Immune Globulin
Formulation(s), including Adjuvants, etc.	Aqueous solution containing 10% IgG (100 mg/mL)
Dosage Form(s) and Route(s) of Administration	Solution, for intravenous (IV) administration
Dosing Regimen	Induction dose is 2 g/kg in divided doses over 2 to 5 consecutive days, followed by maintenance infusions. 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)
Orphan Designated (Yes/No)	No

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GLOSSARY

AE	adverse event
ADL	activities of daily living
AESI	adverse events of special interest
AKI	acute kidney injury
AR	adverse reaction
BIMO	Bioresearch Monitoring
BLA	biologics license application
CI	confidence interval
CIDP	Chronic Inflammatory Demyelinating Polyneuropathy
EOE2T	End of Epoch 2 treatment
FDA	Food and Drug Administration
GGL	GAMMAGARD LIQUID
INCAT	Inflammatory Neuropathy Cause and Treatment
IG	immune globulin
IGIV	immune globulin intravenous
IQR	interquartile range
IV	intravenous
MRC	Medical Research Council
NCT	National Clinical Trial
OUS	outside United States
PREA	Pediatric Research Equity Act
R-ODS	Rasch-built Overall Disability Scale
SAE	serious adverse event
SAP	statistical analysis plan
sBLA	supplemental biologics license application
TACO	transfusion-associated circulatory overload
TEAE	treatment-emergent adverse event
TRALI	transfusion-related acute lung injury

1. EXECUTIVE SUMMARY

In this BLA efficacy supplement, the Applicant, Baxalta US Inc. (a subsidiary of Takeda), proposes to add a new indication of GAMMAGARD LIQUID administered intravenously "as a therapy to improve neuromuscular disability and impairment in adult patients with Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)."

GAMMAGARD LIQUID is an immune globulin infusion (human) (IGI). It is a purified, functionally intact IgG solution formulated with 0.25M glycine (for a stabilizing effect) at 10% w/v (weight by volume) protein concentration and a pH of 4.6-5.1. In the United States, GAMMAGARD LIQUID is indicated, (i) as replacement therapy for primary humoral immunodeficiency in adult and pediatric patients ≥2 years of age and, (ii) as a maintenance therapy to improve muscle strength and disability in adult patients with multifocal motor neuropathy. GAMMAGARD LIQUID has been approved for CIDP (marketed as KIOVIG) in the European Union since 2019, and in 16 other countries worldwide.

CIDP is a neurological disorder causing progressive weakness and impaired sensory function in the legs and arms due to the immune-mediated damage to the myelin sheath of peripheral nerves. It can occur at any age and in both genders; however, most patient's with CIDP are male, and the prevalence of CIDP increases with age. The prevalence rate is estimated at approximately 2.81 per 100,000 persons (95% confidence interval [CI] 1.58 to 4.39; prediction interval 0.12 to 8.78) (Broers et al. 2019).

The efficacy and safety of intravenous (IV) administration of GAMMAGARD LIQUID in adults with CIDP was evaluated in Study 161403 Epoch 2, a prospective, open-label, single-arm, multicenter study. Subjects were enrolled from 14 sites in Argentina, Colombia, Germany, Greece, Israel, Italy, Poland, Serbia, and Spain. To further support the safety of GAMMAGARD LIQUID in patients with CIDP, the Applicant performed a retrospective study, Study TAK-771-4002, using data from two real-world healthcare delivery databases.

Study 161403 consisted of two study epochs. The study enrolled subjects ≥18 years of age (male or female) at the time of screening who had a documented diagnosis of definite or probable CIDP per the European Federation of Neurological Societies/Peripheral Nerve Society 2010 criteria. All eligible subjects had responded to immune globulin (IG) treatment in the past (partial or complete resolution of neurological symptoms and deficits) and were on a stable dose of immune globulin intravenous (IGIV) treatment. In Epoch 1, subjects were randomized in a 1:1 ratio to receive either Hyqvia [immune globulin (IG) infusion 10% (human) with recombinant human hyaluronidase (rHuPH20)] or 0.25% albumin placebo solution with rHuPH20 administered subcutaneously in a double-blind fashion for a period of 6 months or until relapse. Subjects who experienced a relapse during Epoch 1 were offered to receive GAMMAGARD LIQUID IV in the open-label, single-arm Epoch 2 to restore functional ability. The treatment consisted of an induction dose of 2 g/kg divided over 2 to 5 consecutive days, followed by 1 g/kg maintenance doses divided over 1 to 4 days consecutive days, every 3 weeks. The focus of this sBLA is on Study 161403 Epoch 2

and does not include Epoch 1 as the safety and efficacy of GAMMAGARD LIQUID was not evaluated in Epoch 1.

The primary objective of Study 161403 Epoch 2 was to evaluate the efficacy of IV administration of GAMMAGARD LIQUID for the treatment of adults with CIDP to improve neuromuscular disability and impairment. The secondary objectives included evaluation of safety and tolerability of GAMMAGARD LIQUID and assessment of the effect of GAMMAGARD LIQUID on activities of daily living (ADL). The primary efficacy endpoint was responder rate, where a responder was defined as a subject who demonstrated an improvement of functional disability, indicated by at least a 1 point decrease in the adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) disability score at the completion of the IV treatment period (6 months) or the last study visit of the IV treatment period, relative to pre-IV treatment baseline.

Overall, a total of 21 subjects in Study 161403 Epoch 1, who relapsed while on Hyqvia (n=4) or placebo (n=17), were enrolled in the open-label, single-arm, part of the study, Epoch 2. Among the 21 subjects, 20 subjects received GAMMAGARD LIQUID and only 1 subject who relapsed while on placebo in Epoch 1 received Gamunex-C. All subjects completed the study. All 20 treated subjects who received GAMMAGARD LIQUID were analyzed for safety. For the analysis of efficacy, 2 subjects from Study Site 530 were excluded due to serious study conduct concerns identified during Bioresearch Monitoring (BIMO) inspection. The 15 subjects (intent-to treat [ITT] population) who had a relapse while on placebo in Epoch 1 and were treated with GAMMAGARD LIQUID in Epoch 2 comprised the primary analysis set for Epoch 2 efficacy data analysis as prespecified in the statistical analysis plan (SAP). Due to the limited number of study subjects in Epoch 2, a supplementary analysis was conducted on the overall responder rates comprised of all 18 subjects who had a relapse in Epoch 1, including the15 subjects who received placebo and 3 subjects who received Hyqvia in Epoch 1, and was considered as the modified intent-to-treat population (mITT).

In the primary analysis set, the responder rate was 100% for subjects who experienced relapse while on placebo in Epoch 1 and received GAMMAGARD LIQUID in Epoch 2 (N=15, 95% CI: 79.6% to 100.0%). The responder rate in the mITT population was 94.4% (N=18, 95% CI: 74.2% to 99.0%). The study met its prespecified success criterion, where the lower limits of the 95% Wilson CI were 74.2% and 79.6%, in the mITT and ITT population, respectively, which exceeded the pre-specified 24% lower limit as defined in the hypothesis testing.

For the analyses of the secondary efficacy endpoint, improvement in functional ability, all subjects (N=15) in the primary analysis set had improvement, i.e., 100% (95% CI: 79.6, 100.0). All subjects who were treated with GAMMAGARD LIQUID also had improvement, i.e., 100% (N=18, 95% CI: 82.4, 100.0). Functional ability was a composite measure based on meeting any of the following criteria: decrease of ≥1 point in the adjusted INCAT disability score, increase of ≥8 kPa in hand grip strength in the more affected hand, or increase of ≥4 points in raw summed Rasch-built Overall Disability Scale (R-ODS) score.

This study demonstrated that GAMMAGARD LIQUID was effective in the treatment of adults with CIDP to improve neuromuscular disability and impairment. In 17 out of 18 subjects (94.4%), the INCAT score at Month 6, returned to baseline values. The mean adjusted INCAT score showed an improvement by 2.1 points. The Medical Research Council (MRC) sum score in Epoch 2 improved by a mean of 5.4 points. The mean change in centile 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 kPa in the less affected hand.

A total of 389 infusions of GAMMAGARD LIQUID were administered during the Study 161403 Epoch 2. Overall, 14 out of the 20 subjects treated with GAMMAGARD LIQUID reported 60 treatment-emergent adverse events (TEAEs) and two subjects experienced severe events (marked impairment of function or can lead to a temporary inability to resume normal life pattern; requires prolonged intervention or results in sequelae). There were 39 adverse reactions (ARs) defined as adverse events occurring during or within 72 hours of infusion or any causally related event occurring within the study period, reported in 13 subjects (65%), and 31 ARs were related to GAMMAGARD LIQUID in 11 subjects (55%). One subject (5%) experienced one severe adverse reaction (AR) (headache) related to GAMMAGARD LIQUID. No AR resulted in early discontinuation or death, and no serious AR was reported.

ARs occurring with a frequency ≥5% in Study 161403 Epoch 2 were: headache (40%), pyrexia (10%), abdominal pain upper, anemia, blood creatinine increased, chills, dizziness, illness, leukopenia, migraine, nasal dryness, nasopharyngitis, neutropenia, pain in extremity, somnolence, tremor, and vomiting (5%).

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In conclusion, the submitted data from a single adequate and well-controlled study (Study 161403 Epoch 2) plus the confirmatory evidence from the approved pharmacologically-related, IGIV products for the CIDP indication (Gamunex-C, Privigen) provided substantial evidence of effectiveness of GAMMAGARD LIQUID as a therapy to improve neuromuscular disability and impairment in adult patients with CIDP. Data from Study 161403 Epoch 2 and the real-world data from Study TAK-771-4002 provided sufficient evidence of safety. Therefore, the clinical reviewer recommends approval of GAMMAGARD LIQUID, administered intravenously, at induction dose 2 g/kg in divided doses over 2 to 5 consecutive days, maintenance dose 1 g/kg in divided doses over 1 to 4 consecutive days, every 3 weeks, as a therapy to improve neuromuscular disability and impairment in adult patients with CIDP.

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1.1 Demographic Information: Subgroup Demographics and Analysis Summary

A total of 20 subjects who had a relapse while receiving Hyqvia (n=4) or placebo (n=16) in Epoch 1 were enrolled in Epoch 2 and received open-label GAMMAGARD LIQUID in Epoch 2. The baseline demographic characteristics for Study 161403 Epoch 2 are summarized in Table 1.

Table 1. Demographic and Other Screening Characteristics, Safety Analysis Set, Study 161403 Epoch 2

Demographic Characteristic	E1: Placebo Relapse – E2: GAMMAGARD LIQUID (N=16)	E1: HYQVIA Relapse – E2: GAMMAGARD LIQUID (N=4)	E1: Combined Relapse – E2: GAMMAGARD LIQUID (N=20)
Age (years)	-	-	-
N	16	4	20
Mean (SD)	52.0 (13.7)	46.3 (23.6)	50.9 (15.5)
Median	55.0	44.5	52.0
Min, max	28, 67	20, 76	20, 76
Age group [n (%)]	-	-	-
≤55 years	8 (50.0)	3 (75.0)	11 (55.0)
>55 years	8 (50.0)	1 (25.0)	9 (45.0)
Sex [n (%)]	-	-	-
Male	7 (43.8)	2 (50.0)	9 (45.0)
Female	9 (56.3)	2 (50.0)	11 (55.0)
Race [n (%)]	-	-	-
White	12 (75.0)	4 (100.0)	16 (80.0)
Black or African American	0	0	0
Asian	0	0	0
Japanese	0	0	0
Non-Japanese	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
American Indian or Alaska Native	2 (12.5)	0	2 (10.0)
Other	0	0	0
Not reported	2 (12.5)	0	2 (10.0)
Ethnicity [n (%)]	-	-	-
Hispanic or Latino	6 (37.5)	0	6 (30.0)
Not Hispanic or Latino	6 (37.5)	4 (100.0)	10 (50.0)
Not reported	4 (25.0)	0	4 (20.0)

Source: Modified, summary-clin-safety-cipd.pdf, Table 5, page 22-23
Abbreviations: SD, standard deviation

1.2 Patient Experience Data

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☒	Patient-reported outcome	6.1.11.5
☐	Observer-reported outcome	
☒	Clinician-reported outcome	6.1.11.1
☒	Performance outcome	6.1.11.2
☐	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:	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

Reviewer Comment: *The Applicant evaluated the PRO, Treatment Satisfaction Questionnaire for Medication (TSQM-9), as a tertiary outcome. Because the clinical meaningfulness of improvement in TSQM-9 is not clear, it was considered as an exploratory endpoint and the analysis was not included in the SAP. However, the Applicant conducted a post-hoc analysis of TSQM-9. The results are discussed in section 6.1.11.5 , but were not included in the USPI.*

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

CIDP is a 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. It can occur at any age and in both genders. According to a review article, most patients with CIDP are male, and the incidence and prevalence of CIDP increases with age (Broers et al. 2019). The presenting symptoms often 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.

The underlying pathophysiology of CIDP has not been fully elucidated. Peripheral nerve injury appears to result from “a synergistic interaction of cell-mediated and humoral immune responses directed against [self] peripheral nerve antigens that have not been completely characterized” (Ripellino et al. 2014).

A meta-analysis by Broers et al., 2019, provided a pooled crude incidence rate for CIDP of 0.33 per 100,000 person-years (95% CI 0.21 to 0.53; prediction interval 0.11 to 0.98) and a pooled crude prevalence rate of 2.81 per 100,000 persons (95% CI 1.58 to 4.39; prediction interval 0.12 to 8.78). Reported incidence and prevalence of CIDP showed

substantial heterogeneity across studies. This heterogeneity may be partly explained by the use of different CIDP diagnostic criteria (Broers et al. 2019).

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 et al. 2014).

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

Treatment of CIDP includes IG, plasma exchange, and corticosteroids. Based on the most recent Cochrane Review of Treatments for CIDP, Oaklander and colleagues (Oaklander and Gimigliano 2019) discussed the evidence in support of these treatments, and their drawbacks:

- IG: Please see below (Section 2.3 Safety and Efficacy of Pharmacologically Related Products).
- Plasma exchange: According to two randomized controlled trials (RCTs) with a total of 59 subjects, twice-weekly plasma exchange produced more short-term improvement in disability than did sham exchange. In the largest observational study, 3.9% of plasma exchange procedures had complications.
- Corticosteroids: Corticosteroids are commonly used based on widespread availability, low cost, and clinical experience; however, there is very low-quality evidence from observational studies in support of their effectiveness. One review concluded that the effectiveness of daily oral prednisone compared to no treatment in decreasing neurological impairment is uncertain because of the limitations of the study [a single RCT involving 28 subjects (Hughes et al. 2008)]. Observational studies have shown that prolonged use of corticosteroids frequently causes serious adverse events (SAEs). Numerous ARs associated with corticosteroid use for a variety of indications are well-described in the medical literature. Expected ARs to corticosteroids may be divided into ARs that may occur after brief duration of therapy (diabetes mellitus and hyperglycemia; hypertension; hypokalemia; psychiatric disturbances; and peripheral edema), and those occurring after longer-term therapy of several months' duration (suppression of the hypothalamic-pituitary-adrenal axis, Cushingoid features, cataracts, glaucoma, weight gain, osteoporosis, osteonecrosis, gastrointestinal ulcer, myopathy, and increased risk of infections).

Other immunosuppressive drugs, including azathioprine, methotrexate, cyclosporine A, mycophenolate mofetil, cyclophosphamide, and rituximab, have also been used to treat CIDP. These drugs have been utilized primarily in patients whose symptoms are refractory to other treatments; in severely affected patients as part of combined therapy with other classes of medications; or together with corticosteroids during a maintenance phase to prevent relapse during steroid taper, and/or for steroid-sparing effect.

Physiotherapy may also be of benefit for CIDP. The National Institute of Neurological Disorders and Stroke website notes that "physiotherapy may improve muscle strength, function and mobility, and minimize the shrinkage of muscles and tendons and

distortions of the joints (National Institute of Neurological Disorders and Stroke)," in patients with CIDP.

2.3 Safety and Efficacy of Pharmacologically Related Products

The first IG product approved by the FDA for treatment of CIDP was Gamunex-C, based on results of the study titled "Intravenous Immune Globulin for the Treatment of Chronic Inflammatory Demyelinating Polyradiculoneuropathy (ICE)," described below. Results of 5 RCTs (involving a total of 269 subjects) conducted prior to the ICE study demonstrated that treatment with IGIV resulted in more short-term improvement in patients with CIDP than placebo. Although adverse events (AEs) were more commonly observed in subjects randomized to the IGIV group than those to the placebo group, SAEs were not more common in the IGIV group (data from 3 RCTs, with 315 total subjects) (Oaklander et al. 2017).

One RCT in 19 subjects showed little or no difference in short-term improvement of neurological impairment with plasma exchange compared with IGIV. In addition, little or no difference in short-term improvement of disability was observed with IGIV versus oral prednisolone (1 RCT with 29 subjects) or IV methylprednisolone (1 RCT with 45 subjects).

IG Products

- Gamunex-C (immune globulin intravenous [human], 10% solution) was approved by the U.S. FDA for CIDP in 2008. The current CIDP indication for Gamunex-C includes 1) treatment to improve neuromuscular disability and impairment; and 2) maintenance therapy to prevent relapse (Grifols Therapeutics Inc. 2015). Approval was based on the ICE study, a multicenter, randomized, double-blind, placebo-controlled clinical trial (Hughes et al. 2008). The ICE study included two separately randomized periods to demonstrate superiority of Gamunex-C over placebo for treatment of CIDP, both for improvement of 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).
- Privigen was the second IGIV product to receive a CIDP indication in the United States (2017). The Privigen Impact on Mobility and Autonomy Study (PRIMA Study), a 25-week prospective, multicenter, open-label, external-controlled, single-arm clinical trial, provided the primary evidence of safety and efficacy for the regulatory approval of Privigen for treatment of adult patients with CIDP to improve neuromuscular disability and impairment.
- Hizentra was approved for the treatment of adults with CIDP as maintenance therapy to prevent relapse (2018). The approval was based on results of the Polyneuropathy and Treatment with Hizentra study (PATH Study), a multicenter, double-blind, randomized, placebo-controlled, parallel-group study that evaluated the efficacy, safety, and tolerability of two different weekly doses of Hizentra (0.4 g/kg body weight [BW] and 0.2 g/kg BW), administered subcutaneously, versus placebo in 172 adult subjects with CIDP who were previously treated with IGIV.
- Panzyga [10% IGIV (human)] was approved for the treatment of adults with CIDP to improve neuromuscular disability and impairment (2021).

- Hyqvia [immune globulin (IG) infusion 10% (human) with recombinant human hyaluronidase (rHuPH20)], for subcutaneous administration was approved for the treatment of CIDP as maintenance therapy to prevent relapse of neuromuscular disability and impairment in adults (2024). The approval was based on the results of Study 161405 Epoch 1, demonstrating a statistically significant difference between the relapse rate in the Hyqvia group (N=57, 14.0%) and that in the placebo group (N=65, 32.3%) (p=0.031).

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

GAMMAGARD LIQUID was first licensed in the United States in 2005 for IV treatment of primary immunodeficiency associated with defects in humoral immunity. In the European Union , KIOVIG was first licensed in 2006 for replacement therapy in primary and secondary immunodeficiency syndromes, idiopathic thrombocytopenic purpura , Guillain-Barré syndrome, and Kawasaki syndrome. According to the Applicant's post-marketing data, since launch (April 27, 2005 through May 31, 2022), (b) (4) grams of GAMMAGARD LIQUID were sold cumulatively. The estimated cumulative mean number of patients exposed to GAMMAGARD LIQUID is 44,110.

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

On December 7, 2018, FDA sent preliminary meeting responses to questions contained in the meeting package (CRMTS 11482). FDA argued that Study 161403 as designed, including the proposed use of an historical control for the evaluation of efficacy of GAMMAGARD LIQUID when used as rescue therapy, will not be adequate to support an indication of initial/induction therapy of GAMMAGARD LIQUID for treatment of CIDP. FDA stated that "To support a new indication for treatment of CIDP with GAMMAGARD LIQUID, we recommend that you conduct a randomized, placebo-controlled study similar to the ICE trial."

On August 4, 2020, FDA provided the Applicant written response to Type C meeting to discuss a potential supplemental biologics license application (sBLA) in support of an additional indication of GAMMAGARD LIQUID for the treatment of CIDP. In the written responses, FDA agreed that the open-label clinical study in which GAMMAGARD LIQUID is used as a rescue treatment for approximately 20 subjects with CIDP who experience a worsening of functional disability while receiving Hyqvia or placebo will likely provide supportive evidence of effectiveness of GAMMAGARD LIQUID for CIDP indication to improve neuromuscular disability and impairment. However, FDA recommended a concurrent-controlled trial with provision for early rescue as a preferable study design.

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There was no pre-sBLA meeting for this submission. The Applicant submitted this efficacy supplement (STN 125105/2023) on March 31, 2023, to expand the clinical indication of GAMMAGARD as therapy to improve neuromuscular disability and impairment in adult patients with CIDP.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

Submission quality and completeness were considered acceptable.

3.2 Compliance With Good Clinical Practices and Submission Integrity

During the sBLA review, routine BIMO inspections were conducted at 4 clinical study sites (Site 181, 363, 530, and 121) that participated in Study 161403. Significant clinical study conduct issues were identified at Site 530. Specifically, the investigators at Site 530 failed to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation. The BIMO reviewer recommended excluding all study subjects from Site 530 for efficacy analysis. Exclusion of the data for 2 subjects from this site did not significantly impact the efficacy analysis.

3.3 Financial Disclosures

There were no significant financial disclosures.

Covered clinical study (name and/or number): Study 161403 Epoch 2
Was a list of clinical investigators provided? ☒ Yes ☐ No (Request list from Applicant)
Total number of investigators identified: 125
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): 581 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 data were included in the efficacy supplement.

4.2 Assay Validation

No functional assay specific to CIDP or other immunomodulatory actions of GAMMAGARD LIQUID has been developed by the Applicant.

4.3 Nonclinical Pharmacology/Toxicology

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

4.4 Clinical Pharmacology

The Clinical Pharmacology review confirmed that the proposed dosing regimen resulted in trough IgG levels throughout the study. Please see FDA Clinical Pharmacology review memo.

4.4.1 Mechanism of Action

The mechanisms of the immunomodulating properties of IGIV in the treatment of CIDP are not well understood.

4.4.2 Human Pharmacodynamics (PD)

Not applicable

4.4.3 Human Pharmacokinetics (PK)

The full pharmacokinetic profile of GAMMAGARD LIQUID was not evaluated but serum trough IgG levels were measured in subjects with CIDP following administrations of GAMMAGARD LIQUID in the clinical study 161403. In 16 subjects who had previously received placebo in the preceding study (Epoch 1) and started administration of GAMMAGARD LIQUID after relapse (Epoch 2), the median (range, number of subjects) serum trough IgG levels at baseline, Week 13, and Week 25 were 1220 (449 to 2220, N=16) milligram/dL, 1810 (590 to 3200, N=13) milligram/dL, and 1615 (712 to 3480, N=14) milligram/dL, respectively.

4.5 Statistical

Please see FDA statistics review memo. The statistical reviewer verified that the primary study endpoint analyses cited by the Applicant were supported by the submitted data.

4.6 Pharmacovigilance

No significant issues were identified that would warrant any postmarketing safety studies, and routine pharmacovigilance surveillance will be sufficient. Please see FDA pharmacovigilance review memo.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

The clinical review focuses on the protocols, statistical analysis plan (SAP), and final study report for Study 161403 (Epoch 2) (National Clinical Trial [NCT] number: NCT02549170) and the safety study report of TAK-771-4002 (NCT05363358).

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

The clinical review focuses on the final study report for Study 161403 Epoch 2, its protocol and amendments, SAP, data listings, and data sets. The safety review also includes the Applicant's real-world evidence (RWE) study report of TAK-771-4002.

5.3 Table of Studies/Clinical Trials

Table 2. Tabular List of Clinical Studies Reviewed for This sBLA

Type of Study	Study Identifier	Location of Study Report	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	Study Status; Type of Report
Efficacy	161403	5.3.5.1	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	Complete, CSR
Safety	TAK-771-4002	5.3.5.4	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.	Complete, CSR

Source: Original tabular-listing-cipd.pdf
Abbreviations: CIDP, Chronic Inflammatory Demyelinating Polyradiculoneuropathy; CSR, clinical study report; GGL, GAMMAGARD LIQUID; IG, immunoglobulin; IGIV, Intravenous immunoglobulin; INCAT, Inflammatory Neuropathy Cause and Treatment; IV, intravenous; RWE, real-world evidence

5.4 Consultations

No consultations were obtained for this application.

5.4.1 Advisory Committee Meeting (if applicable)

There were no significant issues that were identified that warranted an Advisory Committee meeting.

5.4.2 External Consults/Collaborations

None

5.5 Literature Reviewed (if applicable)

Broers, MC, C Bunschoten, D Nieboer, HF Lingsma, and BC Jacobs, 2019, Incidence and prevalence of chronic inflammatory demyelinating polyradiculoneuropathy: a systematic review and meta-analysis, Neuroepidemiology, 52(3-4):161-172.

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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: Study 161403

Study Title: A Phase 3 Study to Evaluate the Efficacy, Safety, and Tolerability of Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase (Hyqvia) and Immune Globulin Infusion (Human), 10% (GAMMAGARD LIQUID) for the Treatment of Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) (NCT02549170)

The study comprised two treatment periods:

- Epoch 1: A double-blind, placebo-controlled, SC treatment period of up to 6 months. Eligible subjects were randomized in a 1:1 ratio to receive either Hyqvia or the 0.25% albumin placebo solution with rHuPH20.
- Epoch 2: An open-label IGIV treatment period of 6 months for subjects who relapsed during Epoch 1 to restore functional ability following a relapse and deterioration in functional ability.

Reviewer Comment: *For this sBLA review, we focused on Epoch 2.*

6.1.1 Objectives (Primary, Secondary, Tertiary)

Epoch 2: IV Treatment Period with GAMMAGARD LIQUID (GAMMAGARD LIQUID)

Primary Objective:

1. To evaluate the efficacy of GAMMAGARD LIQUID for the treatment of CIDP to improve neuromuscular disability and impairment.

Secondary Objectives:

1. To assess the safety and tolerability of GAMMAGARD LIQUID.
2. To assess the effect of GAMMAGARD LIQUID on ADL.

Tertiary Objectives:

3. To assess the time to improvement during GAMMAGARD LIQUID treatment.
4. To evaluate the effects of GAMMAGARD LIQUID on additional clinical outcome measures, including change in functional ability, ADL, hand grip strength, and muscle strength in subjects with CIDP.
5. To assess the effects of GAMMAGARD LIQUID on quality of life, health utility, health resource utilization, treatment satisfaction, treatment preference, and patient global impression of change .
6. To assess the effect of GAMMAGARD LIQUID on the total number and appearance of new demyelinating abnormalities (DAs) on electrodiagnostic (EDX) studies.

6.1.2 Design Overview

Epoch 2: An open-label 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.

6.1.3 Population

Subjects had to be ≥18 years of age (male or female) at the time of screening; had a documented diagnosis of definite or probable CIDP as confirmed by a neurologist specializing in neuromuscular diseases to be consistent with the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) 2010 criteria; had responded to immunoglobulin G (IgG) treatment in the past (partial or complete resolution of neurological symptoms and deficits) and was on a stable dose of IGIV treatment within the dose range equivalent to a cumulative monthly dose of 0.4 to 2.4 g/kg body weight (BW, inclusive) administered intravenously for at least 12 weeks prior to screening; and had an INCAT disability score between 0 and 7 (inclusive).

Subjects with focal atypical CIDP, pure sensory atypical CIDP, multifocal motor neuropathy or secondary neuropathies, or had received immunomodulatory /immunosuppressive agents within 6 months prior to screening or had received corticosteroids 8 weeks prior to screening were excluded from the study.

Reviewer Comment: *The study did not enroll any IGIV-naïve subjects.*

6.1.4 Study Treatments or Agents Mandated by the Protocol

Epoch 2 (IV Treatment Period With GAMMAGARD LIQUID)

GAMMAGARD LIQUID (IGI 10%)

The induction dose was 2 g/kg of BW as divided doses over 2 to 5 consecutive days, followed by maintenance infusions at the same monthly dose as the individual subject's prerandomization IGIV doses, administered over 1 to 4 days every 3 weeks.

Gamunex-C (U.S. 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 infusion rate was allowed to be gradually increased to a maximum of 8 mg/kg/min (0.08 mL/kg/min).

Reviewer Comment: *Only one placebo relapse subject was treated with Gamunex-C in Epoch 2. This subject was excluded from any efficacy or safety analysis sets for GAMMARGARD LIQUID.*

6.1.5 Directions for Use as provided to investigators

- Initial infusion rate s 0.5 mL/kg/hr (0.8 mg/kg/min). Infusion rate may be increased if tolerated up to 5.4 mL/kg/hr (9 mg/kg/min).
- Monitor subject vital signs throughout the infusion. Certain ARs such as headaches, flushing, and changes in pulse rate and blood pressure may be related to the rate of infusion. Slow or stop infusion if ARs occur. If symptoms subside promptly, the infusion may be resumed at a lower rate that does not result in recurrence of the symptoms.

- *Adverse reactions may occur more frequently in subjects receiving immune globulin for the first time, upon switching brands or if there has been a long interval since the previous infusion. In such cases, start at lower infusion rates and gradually increase as tolerated.*

Reviewer Comment: *There is a caveat on the infusion rate. For patients over 65 years of age or judged to be at risk for renal dysfunction or thrombotic events, administer GAMMAGARD LIQUID at the minimum infusion rate practicable. This has been highlighted on the label.*

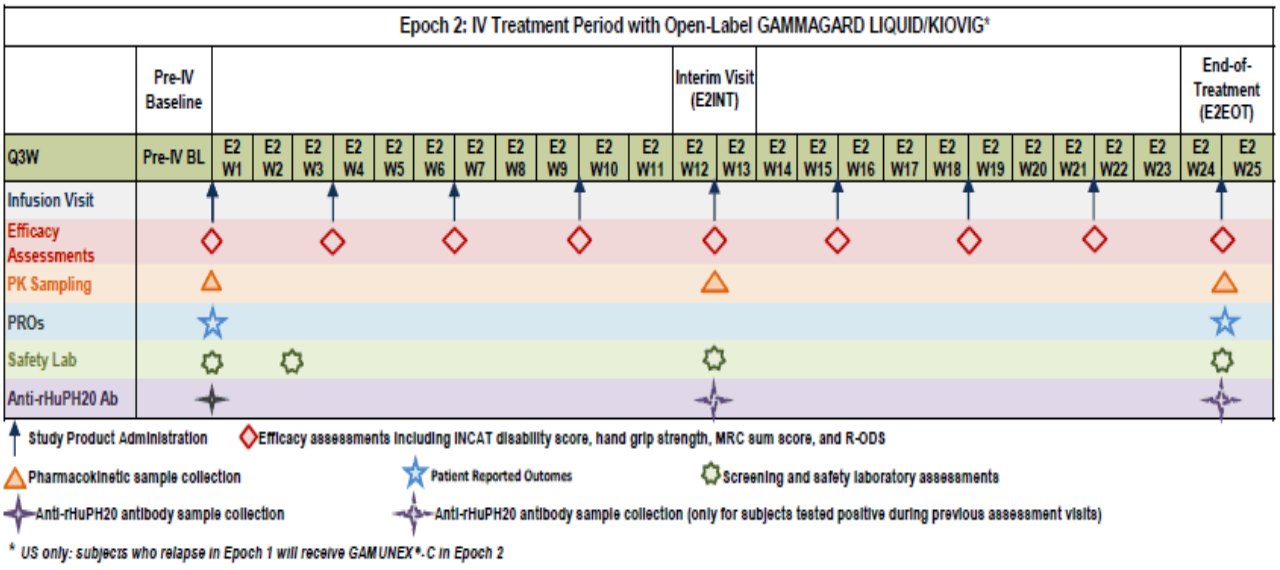
6.1.6 Sites and Centers

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

Reviewer Comment: *Only one subject from a US site, enrolled in the placebo group in Study 161403 Epoch 1, experienced relapse and was enrolled in Epoch 2. This subject was treated with Gamunex-C in Epoch 2 and was excluded from any efficacy or safety analysis sets for GAMMARGARD LIQUID. Given the condition and the product, the data from OUS patients can be extrapolated to the US population.*

6.1.7 Surveillance/Monitoring

Figure 1. Planned Infusion and Assessment Visits During the IV Treatment Period (Epoch 2)



Source: Original Study 161403 protocol amendment August 25, 2015, Figure 21-3, Page 121
Abbreviations: IV, Intravenous

6.1.8 Endpoints and Criteria for Study Success

Epoch 2

Primary Endpoint

Responder rate defined as the proportion of subjects with clinically meaningful 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.

Reviewer Comment: *The adjusted INCAT score was used to assess dysfunction in the upper and lower limbs. The standard INCAT score separately evaluates the upper and the lower limbs, on a scale of 0 to 5; the two numbers are then added to yield a total score ranging from 0 to 10. Lower scores indicate no or minimal disability (e.g., no arm dysfunction, or no walking abnormalities). Higher scores correspond to greater disability (e.g., limited or no purposeful arm movement, or restricted to wheelchair). The adjusted INCAT score is otherwise identical to the standard INCAT score, except that change in upper limb function from 0 (normal) to 1 (minor symptoms) or from 1 to 0 is excluded. Such changes involving minor symptoms in the fingers that do not impair functional activities are excluded because they are not considered by regulatory agencies to be clinically significant in all subjects.*

Secondary Endpoints

Efficacy

Proportion of subjects with clinically meaningful improvement in functional ability, a composite measure based on meeting any of the following criteria: decrease of ≥1 point in the adjusted INCAT disability score, increase of ≥8 kPa in hand grip strength in the more affected hand, or increase of ≥4 points in raw summed R-ODs score.

Reviewer Comment: *The R-ODS is a patient self-reported, linearly-weighted, overall disability scale that was designed to capture activity and social participation limitations in patients with immune-mediated peripheral neuropathies, including CIDP. Functional deterioration or improvement was based on the raw summed R-ODS score of a 4-point minimal, clinically important difference (decrease or increase, respectively).*

In this study, hand grip strength was assessed using a (b) (4) *Hand Dynamometer. The* (b) (4) *Hand Dynamometer is a widely used instrument with established test-retest, inter-rater and intra-rater reliability. Grip strength, reflecting distal strength and upper limb function, is a prognostic indicator of clinical and functional recovery and is useful in monitoring the effect of treatment. ≥8 kPa increase in hand grip strength have been used in clinical trials to define clinically meaningful improvement in functional ability.*

Safety

7. Number (percentage) of subjects experiencing any treatment-emergent SAEs and/or AEs, regardless of causality.
8. Number (percentage) of subjects experiencing causally related SAEs and/or AEs.

9. Number (percentage) of subjects with serious and/or nonserious Ars plus suspected ARs.
10. Number (percentage) of treatment-emergent SAEs and/or AEs associated with infusions, regardless of causality.
11. Number (percentage) causally related SAEs and/or AEs associated with infusions.
12. Number (percentage) of AEs temporally associated with infusions (defined as AEs occurring during or within 72 hours after completion of an infusion).
13. Number (percentage) serious and/or nonserious ARs plus suspected ARs associated with infusions.
14. Number (percentage) of treatment-emergent systemic AEs associated with infusions.
15. Number (percentage) of treatment-emergent local infusion site reactions associated with infusions.
16. Number and proportion of infusions for which the infusion rate was reduced and/or the infusion was interrupted or stopped due to intolerability and/or AEs.
17. Rates of systemic and local AEs, regardless of causality, expressed as number of events per infusion, per subject, and per subject-year.
18. Rates of causally related systemic and local AEs, expressed as number of events per infusion, per subject, and per subject-year.
19. Rates of systemic and local ARs plus suspected ARs, expressed as number of events per infusion, per subject, and per subject-year.

Tertiary Endpoints

Efficacy

20. Proportion of subjects whose adjusted INCAT disability score had returned to pre-SC baseline (or better) during or at the completion of the IV treatment period [6 months] or at the last study visit of the IV treatment period, after previously worsening by ≥1 point during Epoch 1.
21. Proportion of subjects whose hand grip strength in the more affected hand had returned to pre-SC baseline (or better) during or at the completion of the IV treatment period [6 months] or at the last study visit of the IV treatment period, after previously worsening by ≥8 kPa during Epoch 1.
22. Proportion of subjects whose R-ODS score had returned to the pre-SC baseline (or better) during or at the completion of the IV treatment period [6 months] or at the last study visit of the IV treatment period, after previously worsening by ≥4 points during Epoch 1.
23. Time to improvement in functional ability (defined as a decrease of ≥1 point in the adjusted INCAT score).
24. Change from pre-IV treatment baseline in adjusted INCAT disability score.
25. Change from pre-IV treatment baseline in R-ODS.
26. Change from pre-IV treatment baseline in hand grip strength score.
27. Change from pre-IV treatment baseline in MRC sum score.
28. Proportion of subjects who require an increase in IGIV 10% dose due to worsening of CIDP.
29. Proportion of subjects who returned to prerandomization adjusted INCAT disability score.

30. Change from pre-IV treatment baseline in the total number or appearance of new Das on EDX studies.

Subject-Reported Outcomes

1. Change from pre-IV treatment baseline in short form-36 (SF-36) scores.
2. Change from pre-IV treatment baseline in European quality of life 5 dimensions (EQ-5D) scores.
3. Health resource utilization (such as days off school/work, unscheduled doctor visits, hospitalization, and ER visits).
4. Treatment satisfaction.
5. Treatment preference.
6. Patient global impression of change .

Other

1. Serum trough IgG levels.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample Size Calculation:

Assuming 19% of enrolled IGIV-pretreated subjects were in remission (and thus would not relapse upon withdrawal of treatment) and based on the probability of relapse of 48% for the placebo group, a relapse rate of 39% ([1 – 0.19] × 48%) in the Epoch 1 SC placebo treatment group was assumed. These remission and placebo relapse rate estimates were based on random effect meta-analyses of the relevant literature.

With at least 60 subjects randomized to the SC placebo treatment group in Epoch 1 and allowing for a 15% dropout rate in Epoch 1, it was expected that 19 or more subjects (60 × [1–0.15] × 0.39) would relapse and subsequently receive GAMMAGARD LIQUID treatment in Epoch 2.

Assuming a responder rate of 65% to GAMMAGARD LIQUID based on responder rates of 55% and 77% observed in the subset of treatment-experienced subjects in the ICE study (Hughes et al. 2008) and the PRIMA study (Léger et al. 2013), respectively, the estimated sample size of at least 19 subjects would provide more than 90% power to reject the null hypothesis that the responder rate was at most 24% at the two-sided 5% significance level and allowing for a 15% dropout rate in Epoch 2.

Planned Statistical Analysis:

The primary outcome measure in Epoch 2 was the response rate; the endpoint analysis was performed on the E1: Placebo Relapse – E2: GAMMAGARD LIQUID analysis set. This analysis was a complete case analysis implicitly based on the missing completely at random (MCAR) premise where 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 imputed. The two-sided 95% Wilson score CI was used for the estimated response rate and compared to a historical control rate of the responder rate being at most 24%.

Sensitivity analyses were planned to assess the robustness of the inferences from the Epoch 2 primary analysis relating to the normal approximation to the binomial distribution inherent in the Wilson score interval, and to the departures from the MCAR premise.

Supplementary analyses were conducted with overall responder rates presented for the following analysis cohorts: E1:Placebo Relapse/E2: IGIV, E1: Hyqvia Relapse/E2:GAMMAGARD LIQUID, and E1: Hyqvia Relapse/E2: IGIV. In addition, overall results were presented for the following combined cohorts: E1: Placebo Relapse – E2: GAMMAGARD LIQUID and E1: Hyqvia Relapse/E2: GAMMAGARD LIQUID combined, and E1: Placebo Relapse/E2: IGIV and E1: Hyqvia Relapse/E2: IGIV combined.

Reviewer Comment: *Considering the limited number of study subjects in Epoch 2, the review team agreed with the Applicant's proposal to include in the U.S. prescribing information (USPI), the supplementary analysis on the overall responder rate. The overall analysis consists of all the subjects who had a relapse in Epoch 1 (N =18), 15 had received placebo and 3 had received Hyqvia in Epoch 1.*

The analysis cohorts were the same for all secondary and tertiary endpoints.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

A total of 21 subjects who relapsed while on Hyqvia (n=4) or placebo (n=17) in Epoch 1 were enrolled in Epoch 2 and received open-label IGIV in Epoch 2. Only 1 placebo relapse subject in this group was treated with Gamunex-C in Epoch 2; the remaining 20 received GAMMAGARD LIQUID. All subjects completed the study. All 20 treated subjects who received GAMMAGARD LIQUID were analyzed for safety. For the analysis of efficacy, 2 subjects from Study Site 530 were excluded due to the site's failure to prepare for and maintain adequate case histories; therefore, 18 subjects (3 receiving Hyqvia and 15 receiving placebo in Epoch 1) were considered as the modified intent-to-treat population and analyzed for efficacy.

6.1.10.1.1 Demographics

Table 1 summarizes baseline demographic characteristics for Study 161403 Epoch 2. In the combined GAMMAGARD LIQUID cohort (N=20), 55.0% of subjects were female, 80.0% were white. The mean age was 50.9 years. The proportion of subjects aged ≤55 years was 55.0%. There were no Black or African American or Asian subjects and 2 subjects (10%) were American Indian or Alaska native.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Overall, for the GAMMAGARD LIQUID cohort (N=20), nearly all subjects (95%, 19/20) had used IgG products within 6 months prior to screening in Epoch 1. Of the 20 subjects, the use of IgG products was not recorded in the database for 1 subject and was considered as missing for this subject.

Overall, in the GAMMAGARD LIQUID cohort, ≥75% of subjects took concomitant medications during the study in Epoch 2. The most commonly used concomitant medication (≥5 subjects) in the GAMMAGARD LIQUID cohort was paracetamol (9 out of 20 subjects [45%]). The rest of the concomitant medications and nondrug therapies were reported in <5 subjects.

6.1.10.1.3 Subject Disposition

Table 3. Subject Disposition in Epoch 2 (Subjects who Entered Epoch 2)

Disposition	E1: Placebo Relapse - E2: GGL/KIOVIG n (%)	E1: HYQVIA Relapse - E2: GGL/KIOVIG n (%)	E1: Combined Relapse - E2: GGL/KIOVIG n (%)
Subjects who entered Epoch 2 (Epoch 2 Enrolled Set)	16	4	20
Subjects who received IP (Epoch 2 Safety Set) [a]	16 (100.0)	4 (100.0)	20 (100.0)
Subjects who completed study [a]	16 (100.0)	4 (100.0)	20 (100.0)
Subjects who discontinued study early [a]	0	0	0

Source: Original, Clinical Study Report, P136
Abbreviations: GGL, GAMMAGARD LIQUID; IP, investigational product

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The primary endpoint in Epoch 2 was the responder rate, indicated by ≥1 point decrease in the adjusted INCAT disability score at the completion of IV treatment period (6 months) or the last study visit of the IV treatment period, relative to pre-IV treatment baseline.

Table 4. Responder Rate

Variable	E1: Placebo Relapse/E2: GAMMAGARD LIQUID	E1: HYQVIA Relapse/GAMMAGARD LIQUID	E1: Combined Relapse/E2: GAMMAGARD LIQUID
Subjects, N	15	3	18
Subjects who responded, N (%)	15 (100.0)	2 (66.7)	17 (94.4)
Wilson 95% CI	79.6, 100.0	NA*	74.2, 99.0

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.
Abbreviations: CI, confidence interval; N, number of subjects; NA, not applicable

Reviewer Comment: *The lower limit of the 95% Wilson CI was 79.61, which exceeded the pre-specified 24% defined in the hypothesis testing. Therefore, the primary efficacy analysis of the study met its prespecified success criteria.*

6.1.11.2 Analyses of Secondary Endpoints

The proportion of Epoch 2 subjects with a clinically meaningful 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, based on observed cases, is summarized in Table 5.

Table 5. Subjects With an Improvement in Functional Ability

Variable	E1: Placebo Relapse – E2: GAMMAGARD LIQUID	E1: HYQVIA Relapse – GAMMAGARD LIQUID	E1: Combined Relapse – E2: GAMMAGARD LIQUID
Subjects, N	15	3	18
Subjects who responded, N(%)	15 (100.0)	3 (100.0)	18 (100.00)
Wilson 95% CI	79.6, 100.0	NA*	82.4, 100.0

Source: Modified, 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.
Abbreviations: CI, confidence interval; N, number of subjects; NA, not applicable

6.1.11.3 Subpopulation Analyses

Because eighty percent of the study population were white and the study sample size (N=18) was small, subgroup analyses by race were not informative. The 95% Wilson Cis could not be calculated for two subgroups by race due to very small sample sizes. Subgroup analyses by sex and age categories were performed. 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

Proportion of Subjects Whose Adjusted INCAT Disability Score had Returned to Pre-Subcutaneous Baseline

The proportion of subjects whose adjusted INCAT disability scores had returned to pre-SC baseline or better after worsening by ≥1 point in Epoch 1 was 94.4% (17 out of 18 subjects). Only 1 subject (Subject (b) (6) , a placebo relapse in Epoch 1, exhibited INCAT improvement by ≥1 point, but did not return to the subject's pre-SC baseline INCAT or better by the end of Epoch 2.

Change From Pre-intravenous Treatment Baseline in Adjusted INCAT Disability Score

At pre-IV baseline, the median INCAT score was 5.0 (interquartile range (IQR): 4.0 to 7.0), and at the end of Epoch 2, the median INCAT score was 4.0 (IQR: 3.0 to 4.0). The

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

Change From Pre-intravenous Treatment Baseline in R-ODS Score

The mean change from baseline to Week 24 in centile R-ODS score was 15.0 points and exceeded the proposed minimal clinical important difference (MCID; 4 points based on centile) for R-ODS.

Change From Pre-Intravenous Treatment Baseline in MRC Sum Score

The mean change from baseline to end of treatment in MRC sum score was 5.4 points.

Change From Pre-Intravenous Treatment Baseline in Hand Grip Strength

The mean change from baseline to end of treatment in hand grip strength was 13.8 kPa in the more affected hand and 9.8 kPa in the less-affected hand. Both changes exceeded MCID (8 kPa) threshold for grip strength in CIDP.

Subject-Reported Outcomes

Treatment Satisfaction

Responses to the Treatment Satisfaction Questionnaire for Medication (TSQM-9) were obtained for 17 of 18 subjects in the GGL cohort at End of Epoch 2 treatment (EOE2T). At the pre-IGIV (Epoch 1 SC) baseline, overall mean scores for 17 of 18 subjects were 38.9 for effectiveness, 55.2 for convenience, and 45.4 for global satisfaction. At EOE2T, the overall mean scores for 17 of 18 subjects were 70.9 for effectiveness, 65.4 for convenience, and 73.1 for global satisfaction. This increase in mean scores indicates greater satisfaction with Epoch 2 study treatment than prestudy treatment.

Reviewer Comment: *Because the clinical meaningfulness of improvement in TSQM-9 is not clear and the analysis was not included in the SAP, this exploratory, post-hoc analysis of TSQM-9 data was not included in the USPI.*

6.1.12 Safety Analyses

6.1.12.1 Methods

The Epoch 2 safety analysis set included all 20 subjects who had a relapse in Epoch 1, entered Epoch 2, and received treatment with GAMMAGARD LIQUID.

With regards to exposure to GAMMAGARD LIQUID in Study 161403 Epoch 2, the median duration of exposure was 5.6 months, and majority of the subjects (19 subjects [95.0%]) had a duration of exposure ranging from 3 to <6 months, and one had a duration of exposure ≥6 months.

6.1.12.2 Overview of Adverse Events

Overall, 14 of 20 GAMMAGARD LIQUID subjects (70.0%) reported 60 TEAEs. The Applicant reported that among these 60 TEAEs, 31 TEAEs were related to the investigational product and 2 TEAEs were severe. One severe TEAE was related to the investigational product (headache that resolved on the same day of being reported). There were no treatment-emergent serious adverse events (TESAEs), TEAEs with an outcome of death, or TEAEs that led to early discontinuation from treatment.

Adverse reactions with a frequency ≥5% (defined as adverse events occurring during or within 72 hours of infusion or any causally related event occurring within the study period) are shown in Table 6.

Table 6. Adverse Reactions Occurring in ≥5% of CIDP Subjects (Epoch 2 Safety Analysis Set)

Events	**By Infusion N (%) (N=389 Infusions)**	**By Subject N (%) (N=20 Subjects)**
Headache	20 (5.1%)	8 (40.0%)
Pyrexia	3 (0.8%)	2 (10.0%)
Abdominal pain upper	1 (0.3%)	1 (5.0%)
Anemia	1 (0.3%)	1 (5.0%)
Blood creatinine increased	1 (0.3%)	1 (5.0%)
Chills	2 (0.5%)	1 (5.0%)
Dizziness	1 (0.3%)	1 (5.0%)
Illness	1 (0.3%)	1 (5.0%)
Leukopenia	1 (0.3%)	1 (5.0%)
Migraine	1 (0.3%)	1 (5.0%)
Nasal Dryness	1 (0.3%)	1 (5.0%)
Nasopharyngitis	1 (0.3%)	1 (5.0%)
Neutropenia	1 (0.3%)	1 (5.0%)

Events	**By Infusion N (%) (N=389 Infusions)**	**By Subject N (%) (N=20 Subjects)**
Pain in extremity	1 (0.3%)	1 (5.0%)
Somnolence	1 (0.3%)	1 (5.0%)
Tremor	1 (0.3%)	1 (5.0%)
Vomiting	1 (0.3%)	1 (5.0%)

Source: Original, Package Insert, Table 11

6.1.12.3 Deaths

There was no death reported in Study 161403.

6.1.12.4 Nonfatal Serious Adverse Events

No SAEs were reported during Epoch 2.

6.1.12.5 Adverse Events of Special Interest

No subjects experienced a protocol-specified treatment-emergent adverse event of special interest (thrombotic events, AKI, hemolytic events), during Epoch 2.

6.1.12.6 Clinical Test Results

There were no new safety concerns identified with GAMMAGARD LIQUID administration.

6.1.12.7 Dropouts and/or Discontinuations

No subjects experienced a TEAE that led to early discontinuation of treatment.

6.1.13 Study Summary and Conclusions

Study 161403 Epoch 2 was a prospective, open-label, single-arm, multicenter clinical study that provided the primary evidence of effectiveness of GAMMAGARD LIQUID as a therapy to improve neuromuscular disability and impairment in adult patients with CIDP. Study 161403 Epoch 2 met its primary efficacy endpoint, demonstrating a 100% response rate to GAMMAGARD LIQUID among subjects who relapsed while on placebo in Epoch 1 and received GAMMAGARD LIQUID in Epoch 2, indicating an improvement of functional disability in the adjusted INCAT disability score. Result of the secondary efficacy endpoint supported the primary efficacy findings indicating that GAMMAGARD LIQUID was effective in improving functional disability in adults with CIDP.

Analysis of the safety data in Study 161403 Epoch 2 indicated a favorable safety profile of IV administered GAMMAGARD LIQUID. Most ARs/SARs (see Table 6) were mild in

severity and were consistent with the known safety profile of GAMMAGARD LIQUID and other immunoglobulin products.

6.2 Trial #2: Study TAK-771-4002

Study title: Evaluating the Safety of GAMMAGARD LIQUID for the Treatment of Patients With Chronic Inflammatory Demyelinating Polyradiculoneuropathy (NCT05363358)

6.2.1 Objectives

The study evaluated the comparative safety of off-label use of GAMMAGARD LIQUID and other brands of IGIV products indicated for the treatment of patients with CIDP in real-world healthcare delivery databases (Optum and MarketScan) in the United States. Analyses were performed separately in cohorts of Ig-naive and Ig-experienced patients with CIDP, as IGIV treatment response may vary by Ig-experience status.

Primary Objectives

- In participants with CIDP who have not previously been treated with any Ig product(Ig-naive, new-to-class cohort), to determine whether rates of AESIs (thrombotic events, AKI, and hemolytic events) among participants initiating GAMMAGARD LIQUID differ from rates among participants initiating comparator IGIV products
- In participants with CIDP who have previously used another Ig product (Ig-experienced, new-to-drug cohort), to determine whether rates of AESIs (thrombotic events, AKI, and hemolytic events) among participants initiating GAMMAGARD LIQUID differ from rates among participants initiating a comparator IGIV product

Secondary Objective(s)

- To determine whether rates of AESIs (thrombotic events, AKI, and hemolytic events) among participants initiating GAMMAGARD LIQUID differ from rates among participants initiating a comparator IGIV product in clinically meaningful subgroups (age group, sex, pre-existing renal disease, form of previous Ig use)
- In participants with CIDP regardless of prior use of other Ig products (combined Ig-naive and Ig-experienced cohorts), to determine whether rates of AESIs (thrombotic events, AKI, and hemolytic events) among participants initiating GAMMAGARD LIQUID differ from rates of AESIs among participants initiating a comparator IGIV product, if appropriate
- To determine whether rates of other AEs (anaphylaxis, transfusion-related acute lung injury [TRALI], transfusion-associated circulatory overload [TACO]/fluid overload) among participants initiating GAMMAGARD LIQUID differ from rates of other AEs among participants initiating comparator IGIV products in the Ig-naive and Ig-experienced cohorts
- To describe the characteristics of participants initiating GAMMAGARD LIQUID and comparator IGIV products in the Ig-naive and Ig-experienced cohorts

6.2.2 Design Overview

This is a nonrandomized, active-comparator, observational, retrospective cohort study. The treatment group consisted of subjects initiating GAMMAGARD LIQUID, and the comparator group was a combined group of subjects initiating an IGIV specifically indicated for the treatment of CIDP (Gamunex-C, or Privigen). Analyses were performed separately in cohorts of Ig-naive and Ig-experienced participants and in a combined cohort where applicable.

6.2.3 Population

The source population for this study was adult patients (≥18 years of age) in the United States with CIDP who initiated one of the study IGIV products. Patients were identified at the first observed use of one of the study IGIV products during the cohort entry period. All patients who met the inclusion/exclusion criteria were included in the study and no prespecified sample size was calculated.

Participants initiating an IGIV product were categorized as either naive to Ig products (Ig-naive) or having prior experience with Ig products (Ig-experienced) based on Ig use before the index date. Patients were excluded if they had a diagnosis of another condition typically treated with IGIV. Participants were followed from the date of IGIV initiation until occurrence of an outcome or censoring on December 31, 2019, disenrollment from the data source, end of continuous use of the IGIV, or switching to or adding another Ig product.

In Optum, this study identified 1,021 participants in the Ig-naive cohort and 916 in the Ig-experienced cohort. In MarketScan, this study identified 2,452 participants in the Ig-naïve cohort and 1,697 in the Ig-experienced cohort.

Reviewer Comment: *Although Studies TAK-771-4002 and 161403, both evaluated the use of GAMMAGARD and other IGIV products in patients with CIDP, the patient populations differed. Study TAK-771-4002 included data from Ig-naïve and Ig-experienced patients, but in Study 16103 Epoch 2, only Ig-experienced subjects were enrolled.*

6.2.4 Endpoints and Criteria for Study Success

Primary outcomes were thrombotic events: specifically, acute ischemic stroke (AIS), acute myocardial infarction (AMI), venous thromboembolism (VTE); acute kidney insufficiency, and hemolytic events.

Secondary outcomes were anaphylaxis, TRALI and TACO.

6.2.5 Statistical Considerations & Statistical Analysis Plan

Analysis of AESI rates and comparison between GAMMAGARD LIQUID and comparator (non-GAMMAGARD LIQUID) products were performed within each database and within each cohort (Ig-naïve versus Ig-experienced). The study also analyzed changes in risk over time.

6.2.6 Safety Analyses

The number of subjects included in each cohort by treatment group and data source is shown in Table 7.

Table 7. Number of Participants Included in Each Outcome-Specific Analysis Set by Study Cohort by Treatment Group and Data Source

	Ig-naïve Cohort		Ig-experienced Cohort		Combined Cohort	
Analytic Data Set	GGL N	Comparator N	GGL N	Comparator N	GGL N	Comparator N
Optum						
Overall (descriptive)	320	701	324	592	644	1,293
Thrombotic events (composite)	239	527	250	442	489	969
AKI	276	601	287	508	563	1,109
Hemolytic events	313	677	321	579	634	1,256
Anaphylaxis	320	698	324	590	644	1,288
TRALI/TACO/fluid overload	309	682	324	577	633	1,259
MarketScan						
Overall (descriptive)	850	1,602	591	1,106	1,441	2,708
Thrombotic events (composite)	684	1,323	481	902	1,165	2,225
AKI	759	1,429	543	997	1,302	2,426
Hemolytic events	836	1,570	577	1,088	1,413	2,658
Anaphylaxis	850	1,599	590	1,100	1,440	2,699
TRALI/TACO/fluid overload	835	1,576	587	1,089	1,422	2,665

Source: Original, CSR TAK-771-4402, Table 5, Page 66
Note: A patient may appear in the combined cohort more than once if they were included in both the Ig naïve and Ig experienced cohorts. Therefore, the unit of analysis for the combined cohort was the combination of patient and index date.
Abbreviations: AKI, acute kidney injury; GGL, GAMMAGARD LIQUID; Ig, immunoglobulin; TACO, transfusion associated circulatory overload; TRALI, transfusion associated lung injury

Identified cases of the primary and secondary study outcomes were rare for almost all outcomes among all cohorts.

Results for the composite thrombotic events outcome were inconsistent across data sources and over time; in Optum, more cases of thrombotic events occurred early after treatment initiation among the GAMMAGARD LIQUID group than among the comparator group but GAMMAGARD LIQUID group had a lower overall risk than the comparator group after one year; in MarketScan, the two groups were similar throughout follow-up. The hazard ration (HR), 1-year risk ratio (RR), and 1-year risk difference (RD) estimates in the combined cohort pooled across data sources for composite thrombotic events were consistent with no overall difference between groups (HR =1.35, 95% CI 0.84-2.15; RR =0.86, 95% CI 0.47-1.57; RD = −0.0008, 95% CI −0.0138 to 0.0122).

Pooled combined cohort results across data sources for AKI were consistent with no difference across groups (HR not estimated due to violation of proportional hazards assumption; RR =1.03, 95% CI, 0.58-1.85; RD = −0.0001, 95% CI −0.0142 to 0.0139).

Analyses of hemolytic events were limited by small case counts, but the Ig-naive and Ig-experienced cohort 1-year RD estimates pooled across the data sources were also consistent with no difference in risk between groups (Ig-naive cohort RD = −0.0032, 95% CI −0.0098 to 0.0035; Ig-experienced cohort RD =0.0085, 95% CI −0.0019 to 0.0189; pooled analyses of the combined cohort not performed).

Analyses of secondary outcomes (i.e., anaphylaxis and TACO were limited by very small case counts. No cases of TRALI were identified during follow-up in either data source.

Reviewer Comment: *The Applicant performed analyses of changes in risk over time and generated time-specific relative risk (RR) and risk difference (RD) estimates. Results for thrombosis, AKI, hemolytic events and secondary outcomes did not show overall statistically significant differences between GAMMAGARD LIQUID and IGIV comparator groups.*

After consulting with pharmacovigilance review team, we decided not to include the results of this study on the label due to the following limitations that may affect the interpretability of the study results.

2. *There is a potential that the two datasets contain the same subjects.*
3. *There is a possibility that subjects who did not meet the full CIDP diagnostic criteria were included in the analyses.*
4. *AESIs are rare and the limited sample size (study was not powered for any specific safety outcome) led to outcome analyses that were less precise than originally planned.*
5. *Results may be biased because of unmeasured confounders that is not included in the propensity score approach.*
6. *The study analyzed administrative claims databases. Multiple subjects variables such as weight, height, lifestyle factors and other prescription drug use that may have had an impact on dosing and safety are unknown. Accurate dosing information cannot be obtained because of the limitations of administrative claims databases.*

7. Integrated Overview of Efficacy

There is no integration or pooling of efficacy results in this review since the application's efficacy data contains only Study 161403 Epoch 2. Please see Section 6 for detailed efficacy analysis.

8. Integrated Overview of Safety

There is no integration or pooling of safety results in this review as the second study TAK-771-4002 was a nonrandomized, observational, retrospective cohort study in both Ig-naïve and Ig-experienced patients with CIDP. Study 161403 only enrolled Ig-experienced subjects. Therefore, the patient populations in Studies 16103 and TAK-771-4002 differed.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

There were no reports of pregnancies in Study 161403 Epoch 2.

9.1.2 Use During Lactation

No data from Studies 161403 Epoch 2 are available regarding use during lactation.

9.1.3 Pediatric Use and PREA Considerations

The safety and effectiveness of GAMMAGARD LIQUID for the treatment of CIDP have not been established in pediatric patients under 18 years of age.

The Applicant requested a partial waiver for GAMMAGARD LIQUID 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.

9.1.4 Immunocompromised Patients

GAMMAGARD LIQUID is indicated for treatment of primary humoral immunodeficiency in adults and pediatric patients 2 years of age and older. No information regarding potential, concomitant immune deficiency and CIDP was included in this efficacy supplement.

9.1.5 Geriatric Use

GAMMAGARD LIQUID was administered intravenously for the treatment of CIDP in 5 subjects aged 65 years and above and 15 subjects aged below 65 years. Although, the safety and efficacy results were similar in both age groups, there was an insufficient number of subjects aged 65 years and above to determine whether they responded differently from younger subjects.

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

10. CONCLUSIONS

The submitted data from Study 161403 Epoch 2 and TAK-771-4002 provide substantial evidence of effectiveness and sufficient evidence of safety of GAMMAGARD LIQUID as a therapy to improve neuromuscular disability and impairment in adult patients with CIDP.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 8. Risk-Benefit Considerations and Recommendations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• CIDP is a serious disease that can be associated with considerable morbidity. • Data are limited regarding the long-term prognosis of CIDP. Approximately 40 percent of patients achieve cure or remission, while approximately 18 percent have unstable active disease with a progressive or relapsing course.	• CIDP is a serious disease.
Unmet Medical Need	• To date, three IG products have been licensed for treatment of adult patients with CIDP to improve neuromuscular disability and impairment: - Gamunex-C brand IGIV - Privigen brand IGIV - Panzyga brand IGIV	• 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 161403 Epoch 2 was a prospective, open-label, single-arm, multicenter clinical study that demonstrated a statistically significant and clinically relevant improvement in responder rates by adjusted INCAT scale: the responder rate was 100% for subjects who experienced relapse while on placebo in Epoch 1 and treated with GAMMAGARD LIQUID in Epoch 2 (N=15, 95% CI: 79.6% to 100.0%); and the responder rate was 94.4% for all subjects who were treated with GAMMAGARD LIQUID (N=18, 95% CI: 74.2% to 99.0%). The study met its prespecified success criteria with the lower limits of the 95% Wilson CI 74.2% and 79.6%, which exceeded the pre-specified 24% defined in the hypothesis testing. • This primary efficacy endpoint was supported by positive findings favoring GAMMAGARD LIQUID treatment in the secondary efficacy endpoint: All subjects (N=18) who developed a relapse in Epoch 1 and who received GAMMAGARD LIQUID in Epoch 2 had improvement in functional ability.	• The efficacy data of Study 161403 Epoch 2 support the use of GAMMAGARD LIQUID as a therapy to improve neuromuscular disability and impairment in adult patients with CIDP. • The open-label single-arm design of the study should not be recommended for future CIDP studies of other IGIV products given its design limitations. Rather, a placebo-controlled trial with provision for early rescue is considered a preferable study design.
Risk	• No new safety concerns were identified.	• The benefit-risk profile remains favorable.
Risk Management	• No major changes are proposed to the Warnings and Precautions listed on the existing PI for HYQVIA. • Adequate information is provided in package insert.	• Routine pharmacovigilance is considered adequate.

11.2 Risk-Benefit Summary and Assessment

Data submitted to the BLA supplement provide substantial evidence of benefit of GAMMAGARD LIQUID, administered intravenously with an induction dose 2 g/kg divided over 2 to 5 consecutive days, followed by 1 g/kg maintenance doses divided over 1 to 4 days consecutive days, every 3 weeks to improve neuromuscular disability and impairment in adult patients with CIDP. No additional risks of GAMMAGARD LIQUID over the standard IGIV therapies have been identified. Therefore, the overall benefit-risk remains favorable.

11.3 Discussion of Regulatory Options

This BLA supplement is recommended for traditional approval based on a single adequate and well-controlled trial with confirmatory evidence.

11.4 Recommendations on Regulatory Actions

The clinical reviewer recommends approval of GAMMAGARD LIQUID, administered intravenously with an induction dose 2 g/kg divided over 2 to 5 consecutive days, followed by 1 g/kg maintenance doses divided over 1 to 4 days consecutive days, every 3 weeks to improve neuromuscular disability and impairment in adult patients with CIDP, with a PREA, post-marketing requirement to conduct a pediatric study in subjects with CIDP aged 2 years to <17 years. A partial waiver is recommended for pediatric studies in subjects with CIDP under age 2 years.

11.5 Labeling Review and Recommendations

The final labeling was agreed upon and was submitted, consistent with requirements as noted by the Advertising, Promotions and Labeling Branch.

11.6 Recommendations on Postmarketing Actions

Routine pharmacovigilance is considered adequate for postmarketing safety surveillance.