**NON-INTERVENTIONAL SAFETY STUDY**

**PROTOCOL**

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

**Study number:** TAK-771-4002

**Version number and date:** 1.0, 25 January 2022

**Ethics statement:** This study will be conducted in compliance with the protocol, the Declaration of Helsinki, International Society for Pharmacoepidemiology Guidelines for Good Epidemiology Practices, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance Guidelines for Methodological Standards in Pharmacoepidemiology, Good Pharmacovigilance Practices, and all applicable regulatory requirements.

## Signature page

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**Sponsor** **Signature and date** (DD/Month/YYYY)

[redacted]
Outcomes Research and Epidemiology

____/____/____

**Investigator**

[redacted]
USA

____/____/____

**Study information**

| | |
|---|---|
| **Title** | Evaluating the Safety of GAMMAGARD LIQUID for the Treatment of Patients With Chronic Inflammatory Demyelinating Polyradiculoneuropathy: A Cohort Study |
| **Protocol version identifier** | 1.0 |
| **Date of last version of protocol** | 25 January 2022 |
| **EU PAS register number** | Not yet registered |
| **Active substance** | ATC code J06BA02, Immune Globulin (Human) 10% |
| **Medicinal product** | GAMMAGARD LIQUID |
| **Product reference** | Not applicable |
| **Procedure number** | Not applicable |
| **Marketing authorization holder(s)** | Baxalta US Inc.*,<br>300 Shire Way, Lexington, MA 02421<br>AND<br>Baxalta Innovations GmbH*,<br>Industriestrasse 67, A-1221 Vienna<br>* Baxalta is now part of Shire/Takeda |
| **Joint PASS** | No |
| **Research question and objectives** | The study evaluates the safety of GAMMAGARD LIQUID (GGL) in patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in real-world healthcare delivery databases in the United States. The primary objectives are to evaluate rates of adverse events of special interest (thrombosis, acute kidney injury, hemolysis) among patients with CIDP initiating GGL compared with rates among patients with CIDP initiating comparator intravenous immunoglobulin (IVIG) products. |
| **Country(-ies) of study** | United States |
| **Author** | [redacted] USA<br>Telephone: [redacted]<br>Fax: [redacted]<br>Email: [redacted] |

**Marketing authorization holder(s)**

| | |
|---|---|
| Marketing authorization holder(s) | Baxalta US Inc.*<br>300 Shire Way, Lexington, MA 02421<br>AND<br>Baxalta Innovations GmbH*,<br>Industriestrasse 67, A-1221 Vienna<br>* Baxalta is now part of Shire/Takeda |
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## 1.0 TABLE OF CONTENTS

**TABLE OF FIGURES**



**TABLE OF TABLES**

## 2.0 LIST OF ABBREVIATIONS

| | |
|---|---|
| ADR | adverse drug reaction |
| AE | adverse event |
| AESI | adverse event of special interest |
| AKI | acute kidney injury |
| AMI | acute myocardial infarction |
| BEST Initiative | Biologics Effectiveness and Safety Initiative |
| CBER | Center for Biologics Evaluation and Research |
| CI | confidence interval |
| CIDP | chronic inflammatory demyelinating polyradiculoneuropathy |
| COVID-19 | coronavirus disease 2019 |
| CPT | Current Procedural Terminology |
| CVT | cerebral venous thrombosis |
| DVT | deep vein thrombosis |
| EMA | European Medicines Agency |
| EU | European Union |
| FDA | Food and Drug Administration |
| GGL | GAMMAGARD LIQUID |
| GPP | Good Pharmacoepidemiology Practices |
| HCPCS | Healthcare Common Procedure Coding System |
| HR | hazard ratio |
| ICD-10-CM | *International Classification of Diseases, Tenth Revision, Clinical Modification* |
| ICD-10-PCS | *International Classification of Diseases, Tenth Revision, Procedure Coding System* |
| ICD-9-CM | *International Classification of Diseases, Ninth Revision, Clinical Modification* |
| ICE | Intravenous Immunoglobin for Chronic Demyelinating Polyradiculoneuropathy |
| IG | immunoglobulin |
| IgA | immunoglobulin A |
| IRB | institutional review board |
| IRR | incidence rate ratio |
| ISPE | International Society for Pharmacoepidemiology |
| ISPOR | ISPOR: The Professional Society for Health Economics and Outcomes Research |
| ITP | idiopathic thrombocytopenic purpura |

| | |
|---|---|
| IVIG | intravenous immunoglobulin |
| MMN | multifocal motor neuropathy |
| MRI | magnetic resonance imaging |
| NDC | National Drug Code |
| OQA | Office of Quality Assurance |
| OR | odds ratio |
| PAS | post-authorization study |
| PASS | post-authorization safety study |
| PATH | Polyneuropathy And Treatment with Hizentra |
| PE | pulmonary embolism |
| PID | primary immunodeficiency disease |
| PPV | positive predictive value |
| PQI | product quality issue |
| PRIMA study | Privigen® Impact on Mobility and Autonomy study |
| ProCID study | Prospective, Double-blind, Randomized, Multicenter Phase III Study Evaluating Efficacy and Safety of Three Different Dosages of NewGam in Patients With Chronic Inflammatory Demyelinating Poly(radiculo)neuropathy |
| QC | quality control |
| RD | risk difference |
| RR | risk ratio |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| RWE | real-world evidence |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SCIG | subcutaneous immunoglobulin |
| SID | secondary immunodeficiency |
| SOP | standard operating procedure |
| SSR | Special Situation Report |
| STaRT-RWE | Structured Template and Reporting Tool for Real World Evidence |
| STROBE | Strengthening the Reporting of Observational Studies in Epidemiology |
| TACO | transfusion-associated circulatory overload |

| | |
|---|---|
| TRALI | transfusion-related acute lung injury |
| US | United States |
| VTE | venous thromboembolism |

## 3.0 RESPONSIBLE PARTIES

| |
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| [redacted], [redacted], Biostatistics |
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| [redacted], [redacted], Epidemiology |

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| [redacted], [redacted], Statistics |
| [redacted], [redacted], Safety Pharmacoepidemiology |
| [redacted], [redacted], Safety Pharmacoepidemiology |

## 4.0 ABSTRACT

### Title

Evaluating the Safety of GAMMAGARD LIQUID for the Treatment of Patients With Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Version 1.0, 25 January 2022

[redacted], PhD, [redacted]


### Rationale and background

GAMMAGARD LIQUID (GGL) is an intravenous immunoglobulin (IVIG) authorized in the United States (US) for use in primary immunodeficiency diseases and multifocal motor neuropathy. Based on GGL's existing approval for use in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in the European Union (EU), the labeling of similar IVIG products for CIDP in the US, and the observed off-label use in CIDP in the US, Takeda is seeking a labeling expansion for GGL in the US for use in patients with CIDP. To supplement clinical trial efficacy and safety data, the real-world safety of GGL and comparator IVIG products in patients with CIDP will be evaluated in existing healthcare data.

### Research question and objectives

To evaluate rates of adverse events of special interest (thrombotic events, acute kidney injury [AKI], and hemolytic events) among patients with CIDP initiating GGL compared with rates among patients with CIDP initiating comparator IVIG products, with or without previous immunoglobulin (Ig) use.

### Study design

Nonrandomized, active-comparator, new-user, retrospective cohort study of patients with CIDP. Two distinct study cohorts, the Ig-naive and Ig-experienced cohorts, will include patients with CIDP initiating GGL or a comparator IVIG product (Gamunex-C, Gammaked, Privigen) either as their first Ig product (Ig naive), or after use of another Ig product (Ig experienced).

### Population

Adult patients aged ≥ 18 years with CIDP initiating IVIG treatment in the US in the years 2008 through 2019.

### Variables

IVIG initiation and use will be evaluated with medical procedure and pharmacy claims data. CIDP status and other patient demographic and clinical characteristics will be evaluated with medical diagnosis, procedure, and pharmacy dispensing coding and enrollment information on or before IVIG initiation. Claims-based algorithms for CIDP disease status and IVIG initiation will be validated with a medical record review. Validation efforts will be described separately in the Validation Plan. Primary outcomes (thrombosis, AKI, hemolysis) and other secondary outcomes will be evaluated in medical diagnosis claims data using claims-based algorithms validated in IVIG users, when available.

**Data sources**

Two healthcare insurance claims databases in the US will be used: IBM MarketScan Research Databases, and Optum Clinformatics Data Mart. These contain information from individuals with employer-based commercial insurance, Medicare Advantage plans, employer-based supplementary Medicare insurance, or state Medicaid data. Analyses will be performed separately in each data source and pooled, if appropriate. A central statistical analysis plan (SAP) will detail operational definitions for all derived study variables, construction of analytic cohorts, and statistical methods for estimating effect measures. The Programming Specifications will detail the applications of common methods to both data sources.

**Study size**

For the analyses of the primary outcomes of thrombosis, AKI, and hemolysis, the probability of the upper limit of the 95% confidence limit of the risk ratio (RR) being < 2.0 if the true RR is 1.0 is generally above 80% at sample sizes of approximately 7,000 or greater. Given the multiple large data sources, the precision of our resulting RR estimates is anticipated to be very good at expected sample sizes.

**Data analyses**

Data analysis in the data sources will be guided by the SAP. The cumulative incidence of outcomes will be estimated in propensity score–weighted treatment groups accounting for baseline confounding. Time period–specific RR and absolute risk differences will be estimated using the daily cumulative incidence estimates, and 95% confidence intervals will be estimated with nonparametric bootstrapping. Secondary analyses, sensitivity analyses, and a quantitative bias analysis will be performed.

**Milestones**

The study implementation will occur during 2022. The study protocol will be registered in the EU PAS register before the start of data collection. The final report will be available by the end of 2022.

## 5.0 AMENDMENTS AND UPDATES

None to date.

## 6.0 MILESTONES

| Milestone | Planned date | Comments |
|---|---|---|
| Start of data collection | Q1 2022 | |
| End of data collection | Q4 2022 | |
| Registration in EU PAS register[a] | Q1 2022 | Before beginning of data extraction |
| Final report of study results | Q4 2022 | |

EU = European Union; PAS = post-authorization safety study.

[a] Additional registration in other public registries for observational research protocols will also be considered.

## 7.0 RATIONALE AND BACKGROUND

GAMMAGARD LIQUID [immune globulin (human)] 10% (GGL) is 1 of 4 human immunoglobulin (Ig) infusions produced by Takeda (formerly Shire and Baxalta) and is indicated in the United States (US) for patients with primary humoral immunodeficiency (PID) and multifocal motor neuropathy (MMN). GGL is an intravenous immunoglobulin (IVIG) product, and it was originally approved by the US Food & Drug Administration (FDA) in 2005.

Other IVIG formulations are currently approved in the US for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), a rare inflammatory disorder that can gradually destroy the myelin sheath of the nerves, resulting in sensory and motor deficits and substantial functional disability. Gamunex-C/Gammaked—the first IVIG product to receive FDA approval for CIDP—received a US labeling expansion for the CIDP indication in 2008. Supporting evidence for Gamunex-C/Gammaked's approval came from the Intravenous Immunoglobin for Chronic Demyelinating Polyradiculoneuropathy (ICE) study, a randomized, placebo-controlled trial [1]. However, IVIG's effectiveness for CIDP treatment was acknowledged long before Gamunex-C/Gammaked's approval [2-4]. Subsequent IVIG products have been FDA approved for the treatment of adults with CIDP to improve neuromuscular disability and impairment supported by small, single-arm studies with observed response rates compared with historical controls. Privigen, a similar IVIG 10% product, was approved in 2017 with primary support of safety and efficacy coming from the PRIMA (Privigen® Impact on Mobility and Autonomy) study, a 25-week, single-arm, open-label, historically controlled, prospective study of 28 patients (15 Ig naive, 13 Ig experienced), with secondary evidence from an ad hoc evaluation of a pre-randomized phase of the PATH (Polyneuropathy And Treatment with Hizentra) study [5]. Panzyga, another IVIG 10% product, was FDA approved for CIDP in 2021, with both primary and secondary evidence of efficacy and safety coming from different dosage arms of the ProCID study (Prospective, Double-blind, Randomized, Multicenter Phase III Study Evaluating Efficacy and Safety of Three Different Dosages of NewGam in Patients With Chronic Inflammatory Demyelinating Poly(radiculo)neuropathy), a 24-week, historically controlled, prospective study arm with 69 treatment-experienced patients in the 1.0 g arm and 36 patients in the 2.0 g arm [6-8]. Gamunex-C/Gammaked, Privigen, and Panzyga all received FDA approval for CIDP treatment without large studies powered to evaluate rare adverse events (AEs).

Most US payers have approved reimbursement for all IVIG products as a class as first-line treatment for CIDP, and medical society treatment guidelines for CIDP do not differentiate between IVIG brands [9]. Thus, GGL is used off-label for the treatment of CIDP in the US; approximately one-third of new IVIG initiators with CIDP initiated treatment with GGL [10]. In the European Union (EU), GGL is marketed as Kiovig and has been approved for the treatment of CIDP since 2019, alongside all other IVIG 10% products. Based on the existing approval for use in CIDP in the EU, the labeling of similar IVIG products for CIDP in the US, and the observed off-label use for CIDP in the US, Takeda is seeking a labeling expansion for GGL in the US for use in patients with CIDP so that the approved indications match the actual, real-world use of GGL and are consistent with the labels of other IVIG products.

IVIG products may be associated with rare, serious outcomes, and they carry boxed warnings in the US for thrombosis, renal dysfunction, and acute renal failure [11-14]. The safety of GGL during clinical use was evaluated in a European post-authorization safety study (PASS) of 88 patients [15]; drug-related adverse reactions (ARs) occurred in 27 patients (30.7%), but no

severe adverse drug reactions (ADRs) were observed. All but 2 reactions were transient, and no thromboembolic ADRs occurred; 1 serious drug-related AE (moderate urticaria) was observed, but it resolved within the study period. However, patients with CIDP were not included in the PASS, as CIDP was not an approved indication in the EU at the time of the PASS.

The safety of IVIG products as a class has also been evaluated in US real-world administrative claims data sources. An FDA-led evaluation of IVIG use in the FDA's Sentinel Initiative data system (which included patients with CIDP as well as other indicated conditions for IVIG use) used a self-controlled risk interval design to estimate the association of IVIG receipt with arterial thromboembolic events within 2 days of IVIG administration (n = 19,008) and with venous thromboembolic events within 13 days of IVIG administration (n = 13,888) compared with control periods within the same individuals 14 to 27 days after IVIG administration. The reported incidence rate ratio (IRR) and 95% confidence interval (CI) estimates were as follows: arterial thromboembolic events, IRR = 3.72 (95% CI, 1.75-7.84); venous thromboembolic events, IRR = 1.04 (95% CI, 0.47-2.34); composite thromboembolism events, IRR = 2.05 (95% CI, 1.16-3.62). No meaningful difference was seen by brand of IVIG [16].

Three other real-world studies (led by researchers including those from the US FDA) evaluated IVIG safety, but the study populations were not restricted only to patients with CIDP and also included patients with a variety of other approved and off-label indications with varying dosage recommendations. These studies reported overall rates of AEs occurring on the same day as IVIG administration, including thrombotic events (n = 14,944; 15.6 events per 1,000 persons; 95% CI, 13.6-17.6) [17], hemolytic reactions (n = 20,440; 10.32 events per 1,000 persons; 95% CI, 1.41-17.68) [18], and acute renal failure (n = 20,440; 7.97 events per 1,000 persons; 95% CI, 1.60-17.30) [19]. Some of these studies have suggested that risk of some safety outcomes may vary by IVIG brand, with GGL having lower same-day risks of some events than some other IVIG products [17-19]. In the study of thrombotic events after IVIG administration, GGL was used as the reference group, and both Vivaglobin (odds ratio [OR], 2.74; 95% CI, 1.19-6.32) and Gammaplex (OR, 20.96; 95% CI, 2.45-179.33) demonstrated higher risks than GGL, with most other IVIGs being similar to GGL [17]. GGL was also used as the reference in the study of hemolytic reactions after IVIG administration, and the risk associated with Octagam was elevated compared with GGL (OR, 2.36; 95% CI, 1.04-5.35) [18].

Although other studies have evaluated the risks associated with IVIG products in patient groups with multiple indications (including but not restricted to CIDP) and potentially suggest a comparable or slightly reduced risk of rare and severe adverse events (SAEs) associated with GGL compared with other IVIGs, data on GGL's comparative safety specifically in patients with CIDP are limited. The safety profile in CIDP may differ between CIDP and non-CIDP populations owing to differences in patient demographics, comorbidities, and recommended IVIG dose. Given the real-world use of GGL for the treatment of CIDP, more specific data on the comparative safety of GGL and other IVIGs when used in patients with CIDP are needed.

To supplement efficacy and safety data from Epoch 2 of the ADVANCE-1 clinical trial of Ig use in patients with CIDP [20], the real-world safety of GGL and comparator IVIG products will be evaluated in existing healthcare data. This US-based study seeks to evaluate the safety of GGL by comparing the incidence of safety events of special interest in users of GGL with users of comparator IVIG products with approved indications for use in patients with CIDP in existing real-world data sources.

## 8.0 RESEARCH QUESTION AND OBJECTIVES

The study is planned to evaluate the comparative safety of GGL and other comparator IVIG products that are indicated for treatment of patients with CIDP in real-world healthcare delivery databases in the US. Analysis will be performed separately in cohorts of Ig-naive and Ig-experienced patients, as IVIG treatment response may vary by Ig experience status.

The primary objectives of the study are to accomplish the following:

- In patients with CIDP who have not previously been treated with any Ig product (Ig-naive, new-to-class cohort), to determine whether rates of adverse events of special interest (AESIs) (thrombotic events, acute kidney injury [AKI], and hemolytic events) among patients initiating GGL differ from rates among patients initiating comparator IVIG products
- In patients 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 patients initiating GGL differ from rates among patients initiating a comparator IVIG product

The secondary objectives of the study are as follows:

- To determine whether rates of AESIs (thrombotic events, AKI, and hemolytic events) among patients initiating GGL differ from rates among patients initiating a comparator IVIG product in clinically meaningful subgroups (age group, sex, preexisting renal disease, form of previous Ig use)
- In patients 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 patients initiating GGL differ from rates among patients initiating a comparator IVIG product, if appropriate
- To determine whether rates of other AEs (anaphylaxis, transfusion-related acute lung injury [TRALI], transfusion-associated circulatory overload [TACO]) among patients initiating GGL differ from rates among patients initiating comparator IVIG products in the Ig-naive and Ig-experienced cohorts
- To describe the characteristics of patients initiating GGL and comparator IVIG products in the Ig-naive and Ig-experienced cohorts

## 9.0 RESEARCH METHODS

### 9.1 Study design

This study is a nonrandomized, active-comparator, new-user, retrospective cohort study of patients with CIDP initiating treatment with an IVIG product that will be based in existing real-world healthcare databases in the US. The primary exposure group will consist of patients initiating GGL.

The comparator group will be identified in the same data sources and during the same study period as the GGL exposure group. The comparator IVIG group will consist of a combined group of patients initiating an IVIG product that was indicated for the treatment of CIDP during the study period, including the following:

- Gammaked [Immune Globulin Injection (Human) 10% Caprylate/Chromatography Purified]
- Gamunex-C [Immune Globulin Injection (Human), 10% Caprylate/Chromatography Purified]
- Privigen [Immune Globulin Intravenous (Human), 10% Liquid]

Of note, Panzyga is another IVIG product approved for use in CIDP in the US, but it will not be included within the comparator IVIG group as Panzyga was not approved for CIDP within the study period.

Patients will all be identified at the initiation of 1 of the study IVIG products. To achieve the primary objectives, the following 2 distinct study cohorts of adult IVIG initiators (aged ≥ 18 years) diagnosed with CIDP will be identified:

- The Ig-naive (new-to-class) cohort will consist of patients who initiate GGL or 1 of the comparator IVIG products who have no record of previous use of any Ig product (i.e., study IVIG products, nonstudy IVIG products, subcutaneous Ig products, or brand-unspecified Ig products) in all available baseline study data before the date of the index IVIG initiation (a minimum of 6 months of baseline data required).
- The Ig-experienced (new-to-drug) cohort will consist of patients who initiate either GGL or a comparator IVIG product with no record of previous use of that specific IVIG product but with previous use of any other Ig product in all available study data before the date of the index IVIG initiation. Although patients may use multiple IVIG products during the study period, only the first eligible IVIG initiation in an Ig-experienced patient will be included.

The separate Ig-naive and Ig-experienced cohorts will minimize selection bias and confounding, as the eligibility criteria will be equivalent across treatment groups, and patients will be aligned as comparable points in their disease trajectory and treatment experience.

Observing patients in both groups beginning at initiation of 1 of the study IVIG products will minimize many key biases by aligning treatment groups at equivalent points in their treatment history and ensuring correct timing of measurement of baseline confounding variables relative to the start of follow-up [21]. Previous research has suggested that a large proportion of post-IVIG events occurs after the first received dose of an IVIG product [18,19], thus observing all time on treatment with a specific IVIG product starting from initiation is important to accurately characterize potential differences in risk and how they may change over time.

Patient data will be evaluated from the time of IVIG product initiation (index date) until censoring, which will occur at IVIG product discontinuation, switching to or adding a different Ig product, loss to follow-up, or end of study period. Safety outcomes will be evaluated individually, and within each outcome-specific analysis, the first event occurring for each person during follow-up will be identified (patients may have different follow-up times for different outcomes). Cumulative incidence curves of outcomes will be generated to evaluate occurrence of outcomes over time. Rates of outcomes occurring in patients receiving GGL will be compared with rates in patients receiving comparator IVIG products within propensity score–matched samples on relative and absolute scales. Sensitivity analysis and quantitative bias analysis will be performed to evaluate the robustness of the study design (Section 9.7.5, Section 9.7.7).

## 9.2 Setting

### 9.2.1 Study population

The source population for this study will consist of adult patients (aged ≥ 18 years) in the US with CIDP who initiate 1 of the study IVIG products (GGL, Gammaked, Gamunex-C, or Privigen) during the study period.

The study period will begin on 1 January 2008 as Gamunex-C/Gammaked—the first IVIG to receive FDA approval for use in CIDP—was approved for the CIDP indication in 2008, and there was a change in Healthcare Common Procedure Coding System (HCPCS) procedure coding for IVIG products effective on 1 January 2008. The study period will end on 31 December 2019 to avoid the onset of substantial disruptions in healthcare delivery in the US due to the COVID-19 (coronavirus 2019) pandemic in 2020.

Patients will be identified at the first observed use of one of the study IVIG products during the study period. However, available patient data from before the beginning of the study period will be used to define patient characteristics. All patients meeting the study's eligibility criteria will be included in the study.

Figure 1 and Figure 2 illustrate the study design for both the Ig-naive cohort and the Ig-experienced cohort. Most eligibility criteria will remain the same between the 2 cohorts, except for history of Ig use. Patients initiating an IVIG product without Ig use before the index date will be eligible for the Ig-naive cohort; patients initiating an IVIG product with previous use of a different Ig product before the index date will be eligible for the Ig-experienced cohort. Patients may be eligible for both cohorts at different time points (e.g., if individuals who were included in the Ig-naive cohort at their first use of any IVIG product later initiate a different study IVIG product, they may be eligible for the Ig-experienced cohort at the initiation of the new product).

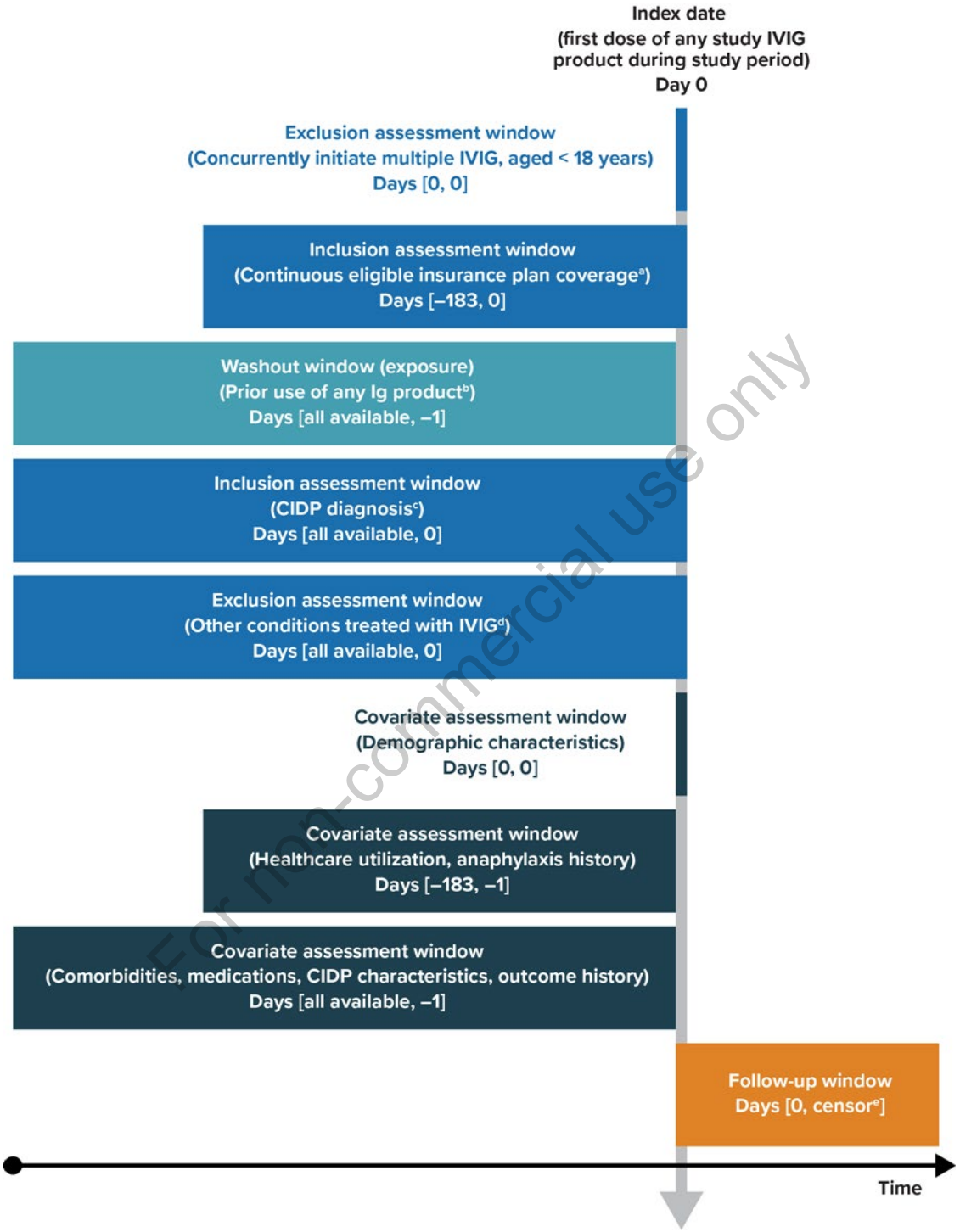
These study cohorts should be broadly representative of patients with CIDP initiating a new IVIG product in the data sources. Some patients with CIDP may use other, nonstudy IVIG products not specifically indicated for CIDP, but for the purposes of this study, the primary comparison of GGL with IVIG products specifically indicated for CIDP is of interest. Other nonstudy IVIG products will be used to define Ig experience and switching, but they will not be considered as part of the exposure or comparator groups.

#### *9.2.1.1 Ig-naive (new-to-class) cohort*

In the Ig-naive cohort, patients will be identified at the first observed use of any of the study IVIG products during the study period; the calendar date of the first observed use will serve as the index date upon which the inclusion and exclusion criteria, covariate assessment windows, and follow-up periods will be anchored. To ensure initiation (new use) of any IVIG product, the patient must be free of use of any Ig product in all available data before the index date (a

minimum of 6 months of continuous enrollment before the index date will be required, but all available baseline data will be used to identify previous Ig use).

**Figure 1 Cohort eligibility and inclusion criteria for the Ig-naive IVIG cohort**






CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; Ig = immunoglobulin; IVIG = intravenous immunoglobulin.
[a] Continuous eligible enrollment includes medical and pharmacy coverage. Gaps in enrollment ≤ 31 days are permitted.
[b] Study IVIG products, nonstudy IVIG products, subcutaneous Ig products, or brand-unspecified Ig products.
[c] ≥ 2 claims with recorded diagnoses of CIDP (in any coding position) separated by at least 14 days.

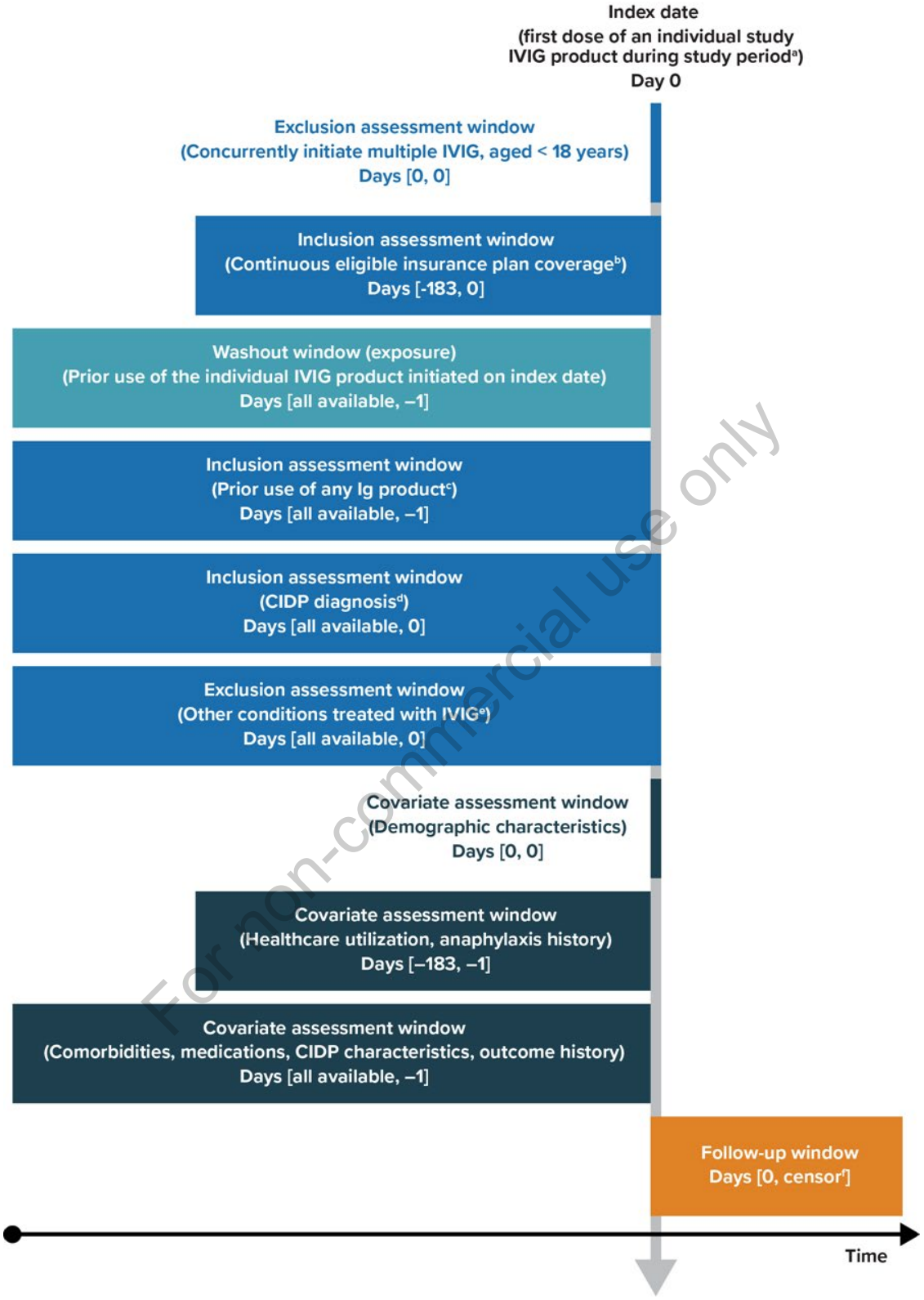
[d] Primary immunodeficiency disease, secondary immunodeficiency, idiopathic thrombocytopenic purpura, dermatomyositis or polymyositis, systemic sclerosis/scleroderma, myasthenia gravis.
[e] Study outcome, 31 December 2019 (end of the study period), disenrollment from eligible coverage, end of continuous use of index IVIG product, or switching to or adding a different IVIG product.
Note: Figure template available [22].

#### *9.2.1.2 Ig-experienced (new-to-drug) cohort*

In the Ig-experienced cohort, the first use of 1 of the individual study IVIG products during the study period will be identified and evaluated for eligibility. Patients may potentially initiate multiple IVIG products during the study period, but only the first instance of IVIG product initiation meeting all inclusion and exclusion criteria per person will be included in the Ig-experienced cohort.

For each individual study IVIG product, the calendar date of the first observed use of that product will serve as the index date. To ensure initiation (new use) of the individual study IVIG product, the patient must be free of use of that individual product in all available data before the index date. However, to be included in the Ig-experienced cohort, patients must have previously used any other Ig product before the index date.

**Figure 2 Cohort eligibility and inclusion criteria for the IG-experienced IVIG cohort**






CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; IG = immunoglobulin; IVIG = intravenous immunoglobulin.

[a] The first use of each study IVIG product (GAMMAGARD LIQUID, Gamunex-C/Gammaked, Privigen) within an individual will be identified and evaluated separately; only the first IVIG initiation meeting all eligibility criteria per person will be included.
[b] Continuous eligible enrollment includes medical and pharmacy coverage. Gaps in enrollment ≤ 31 days are permitted.
[c] Study IVIG products, nonstudy IVIG products, subcutaneous Ig products, or brand-unspecified Ig product other than the product initiated on the index date.
[d] ≥ 2 claims with recorded diagnoses of CIDP (in any coding position) separated by at least 14 days.
[e] Primary immunodeficiency disease, secondary immunodeficiency, idiopathic thrombocytopenic purpura, dermatomyositis or polymyositis, systemic sclerosis/scleroderma; myasthenia gravis.
[f] Study outcome, 31 December 2019 (end of the study period), disenrollment from eligible coverage, end of continuous use of index IVIG product, or switching to or adding a different IVIG product.
Note: Figure template available [22].

### 9.2.2 Inclusion criteria

To be eligible for inclusion in either study cohort, identified patients will be required to meet the following inclusion criteria:

- Have a minimum of 6 months of continuous enrollment in the study database with medical and pharmacy coverage before the index date (to accurately define patient characteristics). Gaps in continuous enrollment ≤ 31 days are permitted.
- Fulfill the CIDP diagnosis algorithm on or before the index date using all available baseline data for each patient (Section 9.3.2)

Additionally, to be eligible for the Ig-naive (new-to-class) cohort, patients will be required to meet the following inclusion criterion:

- Be free of any previous recorded use of any Ig product (i.e., study IVIG products, nonstudy IVIG products, or subcutaneous Ig products) at any point before IVIG initiation

To be eligible for the Ig-experienced (new-to-drug) cohort, patients will be required to meet the following inclusion criterion:

- Have any previous recorded use of an Ig product (i.e., study IVIG products, nonstudy IVIG products, or subcutaneous Ig products) at any point before the index date

### 9.2.3 Exclusion criteria

Patients in both study cohorts will be excluded if they fulfill any of the following exclusion criteria:

- Having claims for ≥ 2 different IVIG products on the index date, as accurate categorization of the index IVIG product would not be possible
- Recorded diagnosis of any of the following conditions on or before the index date, to reduce the potential for misclassification of CIDP status among patients using IVIG
    - PID, as PID is an approved indication for treatment with GGL
    - Evidence of secondary immunodeficiency (SID), including patients with recorded diagnoses of hematological malignancy (e.g., diagnosis of multiple myeloma or chronic lymphocytic leukemia) or treatment with rituximab, as short courses of IVIG may be used for SID treatment
    - Idiopathic thrombocytopenic purpura (ITP) as ITP is an approved indication for other IVIG products

- Dermatomyositis or polymyositis, which may be treated with IVIG
- Systemic sclerosis/scleroderma, which may be treated with IVIG
- Myasthenia gravis, which may be treated with IVIG

CIDP misdiagnosis is frequent [23], and patients with CIDP may be misdiagnosed with other, similar chronic neuropathic conditions before receiving a confirmed diagnosis of CIDP [24,25]. Therefore, patients with prior diagnoses of other chronic neuropathies (including MMN, another indication for GGL) will not be excluded. The study will not impose additional exclusion criteria based on comorbidities (e.g., diabetic neuropathy, other neuropathies, multiple sclerosis) or prior treatments (e.g., high-dose systemic corticosteroids, plasma exchange/plasmapheresis, immunosuppressant or immunomodulatory medication use), such as those implemented in randomized clinical trials of Ig products in this population, in order to include a large number of patients who accurately reflect the real-world use of IVIG in CIDP [26]. Instead, these factors will be identified and included in propensity score models in the analyses.

### 9.2.4 Follow-up

Patient follow-up will begin on the index date (inclusive) and end at the first occurrence of any of the following events:

- First occurrence of the outcome, in outcome-specific analyses (i.e., patients may have different lengths of follow-up for analyses of different outcomes)
- Censoring for any of the following events:
  - 31 December 2019 (end of the study period)
  - Disenrollment from continuous eligible medical and pharmacy coverage in the database
  - End of continuous use of index IVIG product (Section 9.3.1.1)
  - Switching to or adding a different Ig product or a brand-unspecified Ig product (Section 9.3.1.3)

## 9.3 Variables

Operational definitions—including the number and/or combination of codes, setting, coding position, and other necessary factors to define each variable—for all study variables will be documented in the statistical analysis plan (SAP) with sufficient detail to ensure consistency across data sources and replicability of the study approach [27]. Code lists for each variable will outline the necessary diagnostic, procedure, or medication codes necessary to define each variable. Code lists for diagnosis-based variables will be developed using both ICD-9-CM[1] and ICD-10-CM[2] diagnosis coding systems, as the study period overlaps the US transition from ICD-9-CM to ICD-10-CM coding systems. Due to differences in ICD-9-CM and ICD-10-CM coding systems (e.g., granularity of codes, conceptual organization of codes), some variable definitions may not translate directly between coding systems. Where required, diagnosis-based

[1] *International Classification of Diseases, 9th Revision, Clinical Modification*

[2] *International Classification of Diseases, 10th Revision, Clinical Modification*

code lists may be translated between ICD-9-CM and ICD-10-CM coding systems using the Centers for Medicare and Medicaid Services General Equivalence Mappings forward-mapping and backward-mapping crosswalks. The 2018 crosswalks were the final mappings provided, and as this study will include ICD-10-CM codes from 2019, all mapped code lists will be manually reviewed to ensure conceptual consistency and completeness after mapping [28].

### 9.3.1 Exposure assessment

Use of individual study IVIG products (Table 1) will be identified in the study data sources during the study period. To minimize exposure misclassification, IVIG claims will be evaluated with either procedure coding for IVIG administration or pharmacy dispensing records for IVIG products. A feasibility evaluation based in administrative claims reported that 11.2% of IVIG administrations were identified through pharmacy dispensing data, and the rest were identified through procedure coding; other claims-based evaluations of IVIG have also utilized both procedure and pharmacy claims [29].

**Table 1 Intravenous immunoglobulin products and procedure codes active during the study period**

| Role | IVIG product | Code type | Code | Description |
|---|---|---|---|---|
| Exposure | GAMMAGARD LIQUID | HCPCS | J1569 | Injection, immune globulin, (GAMMAGARD LIQUID), non-lyophilized, (e.g., liquid), 500 mg |
| Comparator | Gamunex-C/Gammaked | HCPCS | J1561 | Injection, immune globulin, (Gamunex-C/Gammaked), non-lyophilized (e.g., liquid), 500 mg |
| Comparator | Privigen | HCPCS | J1459 | Injection, immune globulin (Privigen), intravenous, non-lyophilized (e.g., liquid), 500 mg |

HCPCS = Healthcare Common Procedure Coding System; IVIG = intravenous immunoglobulin; SAP = statistical analysis plan.

Note: Product-specific National Drug Codes (NDC) will also be used to identify IVIG products; complete lists of current NDC codes will be given in the code lists accompanying the SAP.

Note: HCPCS coding for IVIG changed on 1 January 2008; older, nonactive product-specific codes will be used to identify history of Ig use.

Sources: Medicare Coverage Database [30].

Panzyga is another IVIG product that was indicated for the treatment of CIDP in the US in 2021 [7]; however, Panzyga will not be considered as a comparator for this study, as it was not approved for CIDP during the study period, and it lacks a product-specific HCPCS code.

The procedure and pharmacy claims used to define the exposure and comparator groups in this study differentiate between IVIG brands, except for Gamunex-C and Gammaked, which share the same procedure code. The procedure or pharmacy claims for IVIG products will provide the date of administration or dispensing, and the specific IVIG product administered or dispensed. There are HCPCS, Current Procedural Terminology (CPT) codes, ICD-9-CM procedure codes,

and ICD-10-PCS[3] codes for IVIG administration without specifying the brand of the product; these codes will not be used to define the index date of individuals or define treatment or comparator groups, but they will be used to define history of Ig use before the index date and censoring for switching Ig products.

As claims data represent records of administrations of IVIG rather than clinical records of IVIG prescribing, information on the prescribed dosing interval/duration will not be available within the claims data. Administered dose information may be available for procedure codes indicating the number of units of IVIG administered. As shown in Table 1, HCPCS codes indicate administration of up to 500 mg of IVIG; some procedure claims include a "units" variable indicating the number of 500 mg units of IVIG dispensed, allowing for an approximation of the total dose administered. Preliminary feasibility evaluations have indicated that this variable is not included in all years of the study data, and in many cases, contains infeasible values. The completeness and quality of the available dose information will be evaluated for potential use in sensitivity analyses.

#### *9.3.1.1 Study IVIG initiation and continuous use*

The date of a patient's first observed procedure or pharmacy claim for an individual study IVIG product during the study period meeting the study eligibility criteria for either cohort will be identified as the index date. The IVIG product initiated on the index date will be the index IVIG product. Patients initiating GGL will be the primary exposure group. Patients initiating Gamunex-C, Gammaked, or Privigen will be the comparator group. This electronic algorithm for identifying IVIG initiation status will be validated in a sample of patients with medical record review (Section 9.7.8) and will be fully described in a separate Validation Plan.

Patients will be considered exposed starting on the index date, inclusive, as AESIs may occur on the same date of administration [17-19], and most proposed potential mechanisms for safety events (e.g., changes in serum viscosity, platelet activation, anti-A/B reactivity, inflammation [29,31]) support a relatively acute risk period after IVIG administration.

Periods of continuous exposure to IVIG after initiation will be defined by identifying subsequent administration or dispensing records of the IVIG product; the duration of each dose will be assumed to be 9 weeks. The US labels of IVIG products approved for CIDP recommend dosing every 3 weeks with mean or median half-lives of IVIG products in adults from 30 to 45 days [12-14]; however, this study will allow for 9 weeks between doses to account for skipped or delayed doses, as variation in dose spacing greater than 3 weeks has been noted [32]. Patients will be considered continuously exposed to the index study IVIG product until the patient fails to receive a subsequent dose of the index study IVIG product within 9 weeks of the previous dose, at which point patients will be considered to have discontinued the IVIG. The discontinuation date will be the last day of the 9-week exposure period.

#### *9.3.1.2 Previous immunoglobulin use*

Patients initiating a study IVIG product will be categorized as either Ig naive (i.e., patients without previous use of Ig products for CIDP) or Ig experienced (i.e., patients who are new users of the individual study IVIG product but who have previously used other Ig products). Procedure

[3] *International Classification of Diseases, 10th Revision, Procedure Coding System*

coding and pharmacy dispensing records at any point before (and not including) the index date will be evaluated to identify use of Ig products. In addition to the primary exposure and comparator IVIG products shown in Table 1, use of the following Ig products will be identified before the index date:

- Nonstudy IVIG products
  - Asceniv
  - Bivigam
  - Carimune NF
  - Flebogamma
  - GAMMAGARD S/D
  - Gammaplex
  - Octagam
- Subcutaneous Ig (SCIG) products
  - Cutaquig
  - Cuvitru
  - Hizentra
  - HyQvia
  - Vivaglobin
  - Xembify
- Brand-unspecified IVIG administration (prior to 2006, there were HCPCS codes indicating administration of IVIG without specifying the product; additionally, there are brand-unspecified ICD-9-CM procedure codes and ICD-10-PCS codes.)

Patients without any use of the study IVIG products or these Ig products in all available baseline data before the index date (a minimum of 6 months) will be eligible for inclusion in the Ig-naive (new-to-class) cohort. Patients with Ig use before the index date will be eligible for inclusion in the Ig-experienced (new-to-drug) cohort.



#### *9.3.1.3 Immunoglobulin use during follow-up*

Use of all Ig products (study IVIG products, nonstudy IVIG products, SCIG products, brand-unspecified Ig products) other than the index IVIG product will be identified during follow-up to identify switching between Ig products, resulting in censoring of follow-up (Section 9.2.4).

### 9.3.2 CIDP disease status

The CIDP status of the identified patients initiating an IVIG product will be evaluated using diagnosis codes for CIDP in submitted claims. Patients will be required to have 2 claims with recorded diagnoses of CIDP (in any coding position) separated by at least 14 days at any point on or before the index date, with the later of the 2 diagnosis dates occurring on or before the index date.

Previous research based on US administrative claims data has relied on recorded CIDP diagnoses codes combined with IVIG treatment to identify true CIDP status [33]. However, the definition in this study requires 2 recorded claims in order to exclude patients with only a single recorded diagnosis, potentially recorded as a rule-out diagnosis during diagnostic workup. This electronic algorithm for CIDP status among patients initiating IVIG will be validated in a sample of identified patients with medical record review (Section 9.7.8); details will be given in the Validation Plan.

### 9.3.3 Outcomes

Adverse events of special interest and other safety outcomes will be identified during follow-up using diagnosis information from submitted claims from inpatient, emergency department, or outpatient providers, depending on the outcome. The date of the outcome will be defined as the date of the first claim during follow-up meeting the criteria for each outcome. For hospitalization claims, the date of admission will be considered the outcome date. Only the first occurrence of each outcome during follow-up will be considered.

The safety outcomes considered in this study include those shown in Table 2. These outcomes include severe events potentially too rare to be evaluated in clinical studies. These severe outcomes require medical intervention for management and treatment, and thus medically-diagnosed occurrences of these events would generally result in a healthcare encounter with a recorded diagnosis in administrative healthcare. Claims data frequently lack granular information on disease severity for many conditions, so the diagnosis setting and coding position will be used to infer severe cases, as appropriate, for each outcome (Table 2). Outcomes will be identified from claims-based diagnosis information using operational definitions and code lists to be detailed in the SAP. Wherever possible, outcome algorithms validated in IVIG users will be used.

To differentiate new-onset outcomes occurring during follow-up from continuing care for events occurring before IVIG initiation, each outcome will be evaluated in separate outcome-specific subcohorts after exclusion of patients with diagnoses of the outcome or other outcome-specific exclusion criteria before the index date. Patients with these outcome-specific exclusion criteria will be excluded from outcome-specific analyses, but not from the overall study cohorts. The occurrence of these outcome-specific exclusion criteria will be identified and used as covariates in descriptive analyses and propensity score models for other outcomes (Section 9.7.2).



**Table 2 Safety outcomes considered in this study and outcome-specific exclusion criteria**

| Safety outcome | Outcome algorithm | Outcome-specific exclusion criteria |
|---|---|---|
| **Primary adverse events of special interest** | | |
| Thrombotic events, composite | Diagnosis of acute ischemic stroke, AMI, or VTE in an inpatient facility claim | Composite thrombotic event diagnosis in any coding position or setting at any time before index date |

| Safety outcome | Outcome algorithm | Outcome-specific exclusion criteria |
|---|---|---|
| Acute ischemic stroke | Acute ischemic stroke diagnosis in the primary coding position on an inpatient facility claim | Composite thrombotic event diagnosis in any coding position or setting at any time before index date |
| Acute myocardial infarction (AMI) | AMI diagnosis in any coding position on an inpatient facility claim | Composite thrombotic event diagnosis in any coding position or setting at any time before index date |
| Acute venous thromboembolism (VTE), including DVT, PE, or CVT | VTE diagnosis in any coding position in an inpatient facility claim | Composite thrombotic event diagnosis in any coding position or setting at any time before index date |
| Acute kidney injury (AKI) | AKI diagnosis in any coding position or setting | AKI diagnosis in any coding position or setting at any time before index date |
| | | End-stage renal disease diagnosis in any coding position or setting at any time before index date |
| | | Procedure code for dialysis at any time before index date |
| Hemolytic events | Hemolysis diagnosis in any coding position or setting | Hemolytic event in any coding position or setting at any time before index date |
| | | Hereditary hemolytic anemia diagnosis of known etiology in any coding position or setting at any time before index date |
| **Secondary adverse events** | | |
| Anaphylaxis | Anaphylaxis diagnosis in any coding position in an inpatient or emergency department setting, or an anaphylaxis diagnosis in any coding position in an outpatient setting with an additional code indicating an acute event | Anaphylaxis diagnosis in any coding position or setting in the 183 days before index date |
| Transfusion-related acute lung injury (TRALI) | TRALI diagnosis in any coding position in an inpatient or emergency department setting | TRALI or TACO diagnosis in any coding position or setting, at any time before index date |
| Transfusion-associated circulatory overload (TACO) | TACO diagnosis in any coding position in an inpatient or emergency department setting | TACO or TRALI diagnosis in any coding position or setting at any time before index date |

AKI = acute kidney injury; AMI = acute myocardial infarction; CVT = cerebral venous thrombosis; DVT = deep vein thrombosis; PE = pulmonary thromboembolism; SAP = statistical analysis plan; TACO = transfusion-associated circulatory overload; TRALI = transfusion-related acute lung injury; VTE = venous thromboembolism.

Note: Full operational details of all outcome algorithms to be given in the SAP.

*9.3.3.1 Primary adverse events of special interest*

*Thrombotic events*

The labels of the study IVIG products all contain boxed warnings regarding thrombosis [11-14], and the FDA indicated that thrombotic events were a specific event of interest to evaluate in a potential safety evaluation. The association between use of IVIG products and thrombotic events within claims data has previously been evaluated by the FDA, though not specifically in patients with CIDP [16,17].

Thrombotic events will be evaluated together as 1 composite event and separately as acute ischemic stroke, acute myocardial infarction (AMI), and acute venous thromboembolism (VTE) events, consistent with previous FDA-led research within secondary data sources of thrombosis after IVIG in other disease areas [29,34]. For both the composite and the individual events, patients with a diagnosis of any of the thrombotic events in any diagnosis position and any setting before the index date will be excluded from outcome-specific analyses to ensure identification of new-onset thrombotic events. Thrombotic events will be evaluated in the following forms:

- Composite thrombotic events will be evaluated as a diagnosis of acute ischemic stroke, AMI, or VTE, as defined below.
- Acute ischemic stroke will be identified as an inpatient diagnosis code for cerebral infarction on a hospital facility claim in the primary diagnosis position. Numerous validation studies of acute ischemic stroke in administrative claims data have been performed [35], including studies led by FDA investigators among IVIG users in the FDA's Sentinel Initiative data system (though not necessarily in patients with CIDP) [36]. Across numerous studies and settings, positive predictive values of diagnosis codes have been shown to be generally high, particularly when evaluating explicit codes for cerebral infarction, rather than codes without mentioning infarction or codes regarding stroke sequelae. In IVIG users, diagnosis codes in the principal diagnosis position reported positive predictive value (PPV) of 60% (95% CI, 32-84), though it was based on just 15 cases; the PPV was slightly higher (64%) when restricted only to claims-based data systems or when excluding patients with previous acute ischemic stroke [36].
- AMI will be identified as an inpatient diagnosis code for AMI on a hospital facility claim in the primary or secondary coding positions. Inpatient diagnosis codes for AMI were validated in IVIG users in the FDA's Sentinel Initiative data system, including both facility and provider claims, and an overall PPV of 75% (95% CI, 65-84) was reported. When evaluating coding position and claim source (hospital facility or physician claim), a PPV of 93% (95% CI, 78-99) was reported for the primary diagnosis position on facility claims, and 88% (95% CI, 72-97) for secondary diagnosis positions on facility claims; the PPV of the secondary diagnosis position was even higher (96%) after excluding patients with previous AMI, as this study will do [37]. Thus, only hospital facility claims will be used to define AMI in this study.
- VTE will be identified as an inpatient facility code in any diagnosis position for pulmonary embolism (PE), lower-extremity or site-unspecified deep vein thrombosis (DVT), or cerebral venous embolism (CVT). In the Sentinel Initiative, codes for VTE (PE or DVT; no CVT cases were identified) were validated among IVIG users; the PPV was 90% (95% CI, 73-98)

for the primary diagnosis position and 80% (95% CI, 28-99) for the secondary diagnosis positions [38].

*Acute kidney injury (AKI)*

The US labels for all the study IVIG products contain boxed warnings for renal dysfunction and acute renal failure [11-14], although IVIG products that do not contain sucrose may be less likely to cause renal dysfunction (none of the included study IVIG products contains sucrose).

AKI will be identified as an inpatient, emergency department, or outpatient diagnosis code for acute renal failure in any diagnosis position. To identify new-onset AKI after IVIG initiation, patients with diagnoses of AKI or end-stage renal disease or procedure codes for dialysis at any point before the index date will be excluded from outcome-specific analyses. Patients with diagnoses of chronic kidney disease other than end-stage renal disease will not be excluded.

Prior research conducted by the FDA Center for Biologics Evaluation and Research (CBER) examined AKI on the same day as IVIG [19]. This work used diagnosis codes that were previously validated for identifying cases of inpatient AKI in the Sentinel Initiative data network [39]; when the gold standard included both definite and probable cases, PPV was 85% (95% CI, 78-91) and ranged from 79% and 90% across the data sources.

*Hemolytic events*

Hemolytic events were identified by the FDA as an outcome of interest in previous communications with Takeda, and these events have been studied previously in patients using IVIG [18,40]. Hemolytic anemia and hemolysis are mentioned in the warnings and precautions of GGL's US label [11] and the US labels of the comparator IVIG products [12-14]. CBER has evaluated algorithms for identifying hemolytic reactions, including acute hemolytic transfusion reactions, hemolytic anemia, and ABO/Rh (A, B, or O blood type/rhesus factor) incompatibility reactions [41]. Data-driven evaluations of diagnosis codes after receipt of any IVIG product in a feasibility analysis suggested anemia as a potential outcome of interest [42]; thus, hemolytic anemia will be evaluated in this definition.

Hemolytic events will be identified as an inpatient, outpatient, physician, or emergency department code for nonautoimmune hemolytic anemia, acquired hemolytic anemia, ABO incompatibility reaction, or hemolytic transfusion reaction.

Although this exact approach has not been formally validated, this algorithm aligns with previous work in the Sentinel System by the FDA among patients using IVIG [41,43]. Similar approaches have been used by CBER to evaluate hemolytic reactions after administration of other plasma therapies [41,44]. A Danish study validated codes for acquired hemolytic anemias and estimated the PPV at 83.4% (95% CI, 76.8%-88.8%) [45].

To identify new-onset disease after IVIG initiation, patients with diagnoses of any hemolytic event before the index date will be excluded from outcome-specific analyses. Additionally, patients with diagnoses of hereditary hemolytic anemias before the index date will also be excluded to differentiate acquired hemolytic anemia from continuing hemolytic anemias of other causes.

*9.3.3.2 Secondary adverse events*

*Anaphylaxis*

Anaphylaxis is listed in the warnings and precautions section of GGL's US label [11] and those of comparator IVIG products [12-14], though the warnings are generally related to patients who are Immunoglobulin A (IgA) deficient with anti-IgA antibodies.

Anaphylaxis will be identified as the first occurrence of either of the following conditions during a patient's follow-up:

- An inpatient or emergency department diagnosis code for anaphylactic reaction or anaphylactic shock in any position
- An outpatient diagnosis of code for anaphylactic reaction or anaphylactic shock in any position with an additional code on the same day indicating an acute event (e.g., additional acute complications, resuscitation, administration of anti-anaphylactic agents)

The performance of this algorithm was evaluated in the FDA's US Sentinel Initiative data system [46], and the PPV was 64% (95% CI, 58%-70%) and sensitivity was 95% (95% CI, 74%-99%) when outpatient codes were also included.

Anaphylaxis is an acute event, and individuals may have multiple, distinct anaphylaxis events within a year [47]. To differentiate new-onset anaphylaxis events from continuing care for events occurring before IVIG administration, patients with diagnoses of anaphylaxis in any setting and coding position in the 183 days before the index date will be excluded from anaphylaxis-specific analyses.

*Transfusion-related acute lung injury (TRALI)*

TRALI is listed in the warnings and precautions section of GGL's US label [11] and on comparator IVIG products [12-14], and data-driven evaluations of diagnosis codes after receipt of any IVIG product suggested dyspnea and respiratory abnormalities as potential outcomes of interest [42]. Dyspnea is a symptom of TRALI.

TRALI will be identified as an inpatient or emergency department diagnosis code for TRALI in any diagnosis position.

A validation conducted in the Sentinel Initiative data system examined 4 potential diagnosis code algorithms to identify inpatient TRALI following inpatient blood transfusions [48]; this definition had the highest PPV at 44%. As most IVIG administration is expected to occur outside hospital settings, diagnoses from emergency department settings will also be included.

To identify new-onset disease after IVIG initiation, patients with diagnoses of TRALI or TACO (as clinical manifestations of TRALI and TACO may be similar) in any setting at any time before the index date will be excluded from outcome-specific analyses.

*Transfusion-associated circulatory overload (TACO)*

The FDA identified volume overload as an outcome of interest in communications with Takeda, and volume overload is listed in the warnings and precautions sections of some IVIG products [12,13]. TACO will be identified as an inpatient or emergency department diagnosis code for TACO in any diagnosis position.

This definition has previously been used by researchers from CBER in evaluating complications after blood transfusion [49], although the algorithm was not validated. This approach also matches the definition employed by CBER in its planned evaluation of COVID-19 convalescent plasma [44]. These studies considered events only among inpatient blood transfusion recipients or patients hospitalized with COVID-19. As most IVIG is expected to occur outside hospitalized settings, diagnoses from emergency department settings will also be included.

To identify new-onset disease after IVIG initiation, patients with diagnoses of TRALI or TACO (as clinical manifestations of TRALI and TACO may be similar) in any setting at any time before the index date will be excluded from outcome-specific analyses.

### 9.3.4 Patient characteristics

Numerous patient characteristics will be identified for descriptive analyses and for use as covariates in comparative analyses. Characteristics will be identified in patient enrollment data and defined from diagnosis, procedure, and medication codes. Some characteristics will be measured in fixed time periods before the index date to best represent the patients' status at the time of IVIG initiation, while others will use all available baseline data to increase the probability of accurately classifying patients as having or not having the characteristic [50]. Where available, covariates will be defined using validated algorithms. Considered characteristics will include the following:

- Demographic characteristics, measured on the index date:
    - Patient age
    - Sex
    - Calendar year of IVIG initiation
    - Geographic region
    - Insurance type (commercial, Medicaid, Medicare)
    - Race/ethnicity (as available in each data source)
    - Markers of socioeconomic status, as available in each data source
- Healthcare utilization, measured in the 183 days before and not including the index date:
    - Routine screening tests
    - Clinic visits
    - Hospitalizations
    - Emergency department visits
    - Systemic anti-infective agent use
- Comorbidities and outcome risk factors, measured in all available baseline data before but not including the index date. Also included in this list is history of outcome events occurring before the IVIG initiation or other outcome-specific exclusion criteria; while individuals with these characteristics may be excluded from outcome-specific analysis, they will be used as covariates for analysis of other outcomes.
    - Hypertension

  - Lipid abnormality
  - Heart failure
  - Cardiac arrhythmia
  - AMI
  - Other cardiovascular disease
  - Acute ischemic stroke
  - Transient ischemic attacks
  - Venous thromboembolism
  - Peripheral vascular disease
  - Hemolysis
  - Cancer
  - Diabetes mellitus (type 1 or 2)
  - Other autoimmune disorders
  - Chronic kidney disease or renal disorders
  - End-stage renal disease
  - Receipt of dialysis
  - AKI
  - Liver disease
  - Pancreatitis
  - Hereditary hemolytic anemia
  - Other anemia
  - Adrenal insufficiency
  - Hypoparathyroidism
  - Aspiration pneumonia
  - Chronic pulmonary disease
  - Serious infection
  - Other components of the Charlson Comorbidity Index (dementia, peptic ulcer disease, liver disease, hemiplegia, AIDS)
  - Anaphylaxis
  - TRALI
  - TACO
- Co-medications, measured in all available baseline data before but not including the index date:

  - Cardiovascular medications
  - Opioids
  - Oral contraceptives
- Previous CIDP treatments, measured in all available baseline data before but not including the index date:
  - High-dose systemic corticosteroid use
  - Plasma exchange and/or plasmapheresis
  - Immunomodulatory agent use
- Related conditions or diagnoses, measured in all available baseline data before but not including the index date:
  - Hereditary and idiopathic neuropathy
  - Systemic lupus erythematosus
  - MMN
  - Drug-induced polyneuropathy
  - Diabetic neuropathy
  - Parkinson's disease
  - Multiple sclerosis/transverse myelitis
- Indicators of CIDP severity or functional status, measured in all available baseline data before but not including the index date:
  - Neuropathic or chronic pain
  - Difficulty walking
  - Abnormal nerve function
  - Weakness
  - Use of a wheelchair or walking aid
  - Falls and/or fractures
  - Stay in a skilled nursing facility
- Markers of CIDP diagnostic workup, measured in all available baseline data before but not including the index date:
  - Electrodiagnostic nerve studies
  - Nerve biopsy
  - Magnetic resonance imaging (MRI)
  - Spinal fluid testing
  - Serum Ig testing

- Markers of dependency in activities of daily living [51] or baseline disability [52], measured in all available baseline data before but not including the index date

In the Ig-experienced cohort, the following characteristics about previous Ig use will also be measured in all available baseline data before but not including the index date:

- Number of unique Ig products used
- Use of other Ig products in the following time windows before the index date
  - 30 days before index date
  - 31-90 days before the index date
  - > 90 days before the index date
- Form of Ig product (IVIG, SCIG, unspecified) used most recently before the index date

### 9.4 Data sources

This study will be conducted in US-based administrative claims databases, including the IBM MarketScan Research Databases, and the Optum Clinformatics Data Mart. Details of each data source are shown in Table 3, details of the application of this study within both data sources will be documented in the SAP, and data source–specific details will be given in the Programming Specifications.



**Table 3 Description of data sources utilized in this study**

| Data source | Data source type | Ages covered | Earliest years available |
|---|---|---|---|
| MarketScan Research Data | | | |
| Commercial Claims and Encounters | Employer-based commercial insurance for employees, spouses, and dependents (defined by the participating employers) | < 65 years | 2001 |
| Medicare Supplementary and Coordination of Benefit | Medicare supplementary insurance for retirees | ≥ 65 years | 2001 |
| Multistate Medicaid Data | Medicaid coverage for eligible person with qualifying incomes from 11 US states | < 65 years | 2001 |
| Optum Clinformatics Data Mart | | | |
| Commercial | Employer-based commercial insurance from United Health for employees, spouses, and dependents from UnitedHealthcare (organized at the level of the insurer) | < 65 years | 2000 |
| Medicare Advantage | Medicare supplementary insurance plans | ≥ 65 years | 2000 |

The selected data sources represent large populations from throughout the US receiving care in an array of geographic locations and settings and with a variety of different insurance types. Both the MarketScan and Optum research databases have been extensively used for epidemiologic analyses of medication use, safety, and effectiveness. Administrative claims databases such as those proposed for this study have been used by researchers, including those from the FDA, for

safety surveillance of many of these outcomes of interest in IVIG users, [16-19,29,33,40,43] including analyses within the Sentinel System (Optum is a data partner in the Sentinel System). Both data sources are also partners within CBER's Biologics Effectiveness and Safety (BEST) Initiative data system.

These data sources contain health insurance billing data for enrolled individuals, spouses, and dependents, and they were selected due to the large size and national coverage to identify a sufficient sample of individuals with this rare disease. These data sources both cover insured individuals from across the US with a variety of different insurance types (i.e., commercial, Medicaid, Medicare). Administrative claims data only capture information about medically attended events, but as IVIG use is typically a healthcare provider–administered infusion and the primary study outcomes are severe events requiring medical intervention, these data sources are appropriate to address the research question of how the safety profile of GGL compares with other IVIG products in the treatment of CIDP with regards to the primary outcomes of interest.

The use of payer-level insurance data ensures that care received from different providers and settings will be accessible for longitudinal research on patients over time and across healthcare settings or providers, as CIDP tends to be diagnosed in specialty care and IVIG treatment received in a variety of settings, including in the treating physician's office, in dedicated infusion centers, or at home (Table 4). Serious outcomes such as those evaluated in this study are likely to be treated in hospitals or emergency departments. Thus, data sources that receive information across providers and practice settings, such as this payer-level data, are critical for observing patients' complete treatment experience.



**Table 4 Use of IVIG for CIDP in the United States**

| Topic | Response |
|---|---|
| What are common physician specialties that diagnose CIDP? | Neurologists |
| What are common IVIG prescriber types for CIDP? | Neurologists |
| List common other treatments for CIDP | High-dose systemic corticosteroids, plasma exchange/plasmapheresis, immunosuppressant or immunomodulatory drugs [9] |
| Where does IVIG fit among all treatments for CIDP? | First line among patients with moderate or severe disability and purely motor CIDP [9] |
| Approved indications and dosages for IVIG | |
| GAMMAGARD LIQUID | Indicated for PID, MMN [11]. |
| | CIDP dosage in EU: loading dose, 2 g/kg: maintenance dose, 1 g/kg. Maintenance infusion, 1 or 2 infusions (consecutive days) every 3 weeks [53]. |
| Gamunex-C/Gammaked | Indicated for PID, ITP, CIDP [12,13]. |
| | CIDP dosage: loading dose, 2 g/kg: maintenance dose, 1 g/kg. Maintenance infusion every 3 weeks [12,13]. |
| Privigen | Indicated for PID, ITP, CIDP [14]. |
| | CIDP dosage: loading dose, 2 g/kg: maintenance dose, 1 g/kg. Maintenance infusion, 1 or 2 infusions (consecutive days) every 3 weeks [14]. |

CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; EU = European Union; ITP = idiopathic thrombocytopenic purpura; IVIG = intravenous immunoglobulin; MMN = multifocal motor neuropathy; PID = primary humoral immunodeficiency.

Multiple different insurance plans and types are included in these data sources, each with unique implications for continuity of continuous enrollment, including the following:

- For employer-based commercial insurance plans, covered individuals, spouses, and dependents participate in employer-sponsored insurance coverage. Individuals may enter or exit insurance plans at qualifying life events, such as changes in employment, changes in marital status, death or disability of self or spouse, age limits for dependents, or birth or adoption of a child. Additionally, employers may change the health plans offered.
- For state-administered Medicaid plans for individuals with low income, eligibility for coverage and the extent of services offered may vary by state and over time. Eligibility is typically based on income and family status. Eligibility may be assessed as frequently as monthly, and individuals may enter and exit eligible plans frequently, coinciding with changes in age, income, marital status, employment, or state eligibility requirements.
- Supplementary Medicare and Medicare Advantage plans contain information about individuals aged ≥ 65 years with Medicare coverage administered through commercial health insurers. Enrolled individuals may have more stable enrollment in these plans compared with employer-sponsored or Medicaid plans, as the Medicare population may be less likely to have changes in eligibility due to age- or employment-based criteria, but enrollment may vary based on individuals' personal enrollment decisions or plan's offerings.

Individual-level enrollment in each data source is documented, so periods of continuous enrollment (and thus presumed observed claims) can be defined for all enrollees. These data sources will include large numbers of patients of different age groups, socioeconomic status, and employment statuses being treated in a variety of different healthcare settings throughout the US. Even data sources with limited follow-up per person will be useful for this evaluation, as many of the outcomes of interest are short-term, acute events (previous research of post-IVIG events have considered follow-up periods as short as events on the same day as IVIG administration [17-19]) and periods of IVIG treatment tend to be relatively short [54].

These data sources all consist of billing claims for reimbursement from healthcare providers to payers. Claims from providers for services contain coded information about diagnoses and procedures. Diagnoses will be recorded with either ICD-9-CM or ICD-10-CM codes (the US transitioned from the use of ICD-9-CM to ICD-10-CM during October 2015). Information about procedures will be identified with procedure codes, including CPT codes, HCPCS codes, ICD-9-CM procedure codes, and ICD-10-PCS. Pharmacy-dispensed medications will be identified with National Drug Codes (NDC).

Within each data source, information about a unique patient can be identified across all relevant enrollment, medical claims, and pharmacy claims data files using an anonymized, individual-level patient identifier.

Preliminary feasibility evaluations identifying IVIG use in patients with CIDP have been undertaken in the MarketScan and Optum data [42]. No comparative analyses of outcomes or evaluations of outcomes by individual IVIG product have yet been undertaken. These feasibility evaluations demonstrated that important markers of CIDP symptoms and severity are evaluated by clinicians, as evidenced by recorded diagnoses for these conditions (e.g., other immunological or autoimmune disorders and symptoms such weakness, neuropathic or chronic pain, difficulty walking). Additionally, we observed claims for laboratory tests consistent with diagnosis and

evaluation of CIDP (e.g., electrodiagnostic nerve testing, MRIs) before and after IVIG initiation. Although administrative claims data contain insurance billing information across healthcare providers and settings, they lack detailed clinical data such as complete information about laboratory test results and recorded measurements of functional status scales (as opposed to recorded diagnoses of impaired functional status).

### 9.4.1 Optum Clinformatics Data Mart

The Optum Clinformatics Data Mart commercial administrative claims databases contain insurance claims for employees, their spouses, and their dependents with employer-based UnitedHealthcare commercial insurance coverage from throughout the US. Also included are individuals aged 65 years or older with managed Medicare Advantage insurance plans. The databases contain deidentified information on individuals' enrollment information, medical and pharmacy claims, and limited laboratory results data. The Optum databases can also provide for medical record requests and deidentified review.

### 9.4.2 MarketScan Research Databases

The IBM MarketScan Commercial Claims and Encounters and the Medicare Supplemental and Coordination of Benefits databases contain insurance claims for employees, retirees, and their spouses and dependents with employer-based commercial insurance from approximately 100 large employers from across the US. The Commercial Claims and Encounters database contains information on individuals aged less than 65 years. The Medicare Supplemental and Coordination of Benefits database contains information on individuals aged 65 years or older with employer-sponsored Medicare supplementary insurance plans. The Multistate Medicaid Database contains information about individuals enrolled in state-administered Medicaid plans from multiple, diverse US states. All databases contain deidentified information on insurance enrollment, inpatient and outpatient medical procedures and diagnoses, and pharmacy dispensings.



## 9.5 Study size

CIDP is a rare disease, with a worldwide prevalence estimated to be 2.81 cases per 100,000 persons and study-specific estimates ranging from 0.81 to 10.3 cases per 100,000 persons [55]. Thus, many previous clinical studies of IVIG products in CIDP supporting labeling expansions have utilized relatively small sample sizes to support claims of efficacy and safety, including a comparison of IVIG with placebo among 117 patients (59 treated with IVIG, and 58 treated with placebo) [1], a 28-patient historically controlled single-arm study [5,56], 142 patients across 3 doses (35, 69, and 38 patients in each dosage arm) with the 69-patient arm used to gain regulatory approval compared with a historical control [6]. However, to ensure a robust safety assessment, the study size for the proposed real-world comparative study is anticipated to be much larger, as this study will have an active-comparator design.

The administrative claims databases proposed for this study will ensure identification large numbers of patients in both the Ig-naive cohort and the Ig-experienced cohorts. All eligible patients identified in the data sets will be included in the study. The precision of the effect measure estimates in the study will be described with 95% CIs. To avoid misinterpretation of effect measure estimates resulting from this epidemiologic analysis, formal hypothesis testing using measures of statistical significance will not be performed [57-59].

This analysis will evaluate the risk of generally rare safety events in 2 treatment groups over time since initiation. The precision of the resulting estimates will be influenced by the size of the 2 treatment groups, the matching ratio, and the risk of the outcome in the comparator treatment group. Precision estimates of risk ratios (RRs) measuring the association between GGL and outcomes compared with comparator IVIG were informed by the following assumptions based primarily on preliminary feasibility analyses in US claims data and published literature can be made to inform the study size calculations:

- Of patients with CIDP initiating IVIG, 38% were users of GGL, for a comparator-to-GGL ratio of approximately 1.6 to 1.
- Identified rates of the primary events in all IVIG users (not evaluated separately by product or indication) have been reported, as shown in Table 5. Assuming 1 year of follow-up in the planned analysis, risks of the outcome in the comparator group of 0.003 to 0.01 events per 1 year were used in precision estimates.
- From commercial insurance, supplemental Medicare, and Medicaid claims data from 2008 through 2018, 3,975 patients with CIDP who were Ig-naive (new-to-class) initiators of study IVIG products were identified [10]; that analysis first identified individuals at CIDP diagnosis and then evaluated IVIG initiation later. The proposed approach of the current study of first identifying IVIG initiation and then evaluating CIDP status would be anticipated to yield a slightly different sample size due to the eligibility criteria being evaluated at the IVIG initiation date rather than at the first observed CIDP diagnosis, and a slightly more stringent CIDP diagnosis algorithm will be used. Additionally, larger sample sizes can be expected with the inclusion of more recent years of MarketScan data since the completion of the feasibility analysis, the additional inclusion of the Optum databases, and the new-to-drug Ig-experienced cohort. Given that a larger number of potential patients are expected in the proposed study, sample sizes of up to 12,000 patients were included in precision estimate calculations.

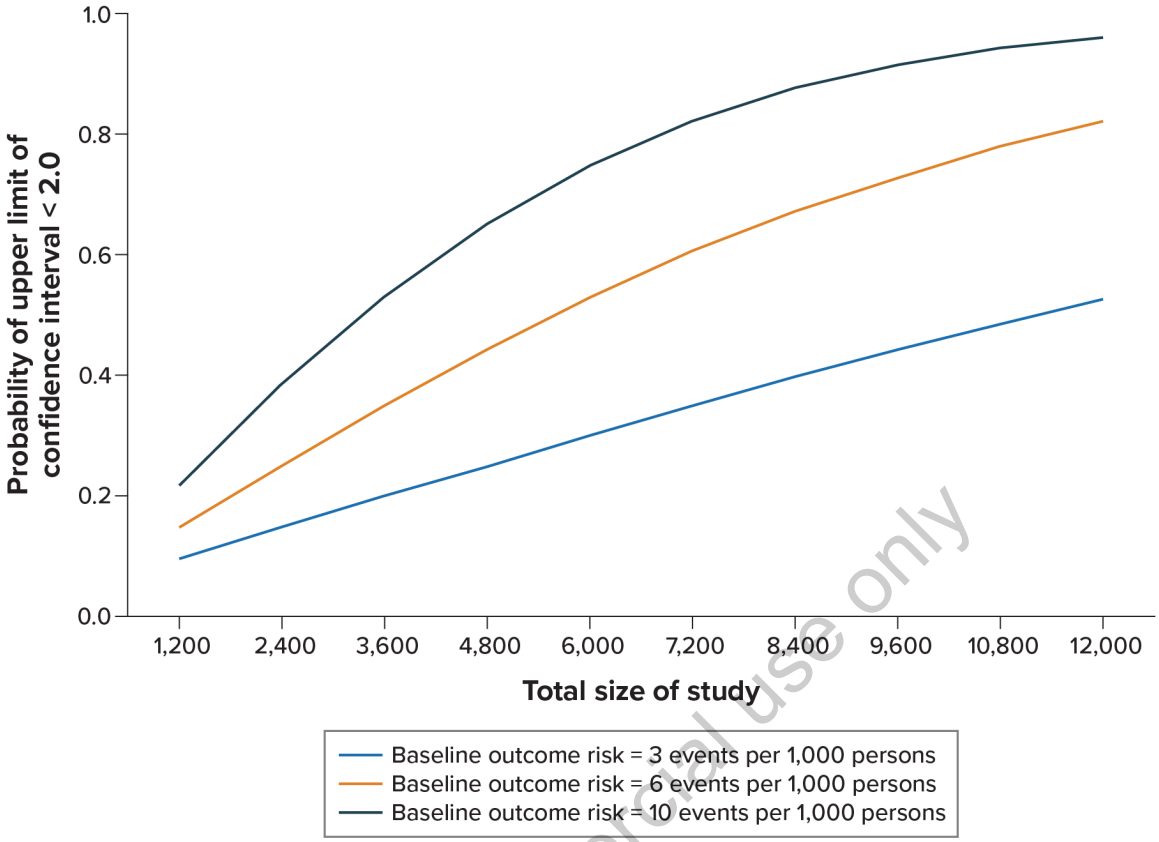
**Table 5 Reported rates of primary study outcomes in intravenous immunoglobulin users**

| Outcome | Time period | Expected rate in IVIG users |
|---|---|---|
| Thrombosis, composite | Same day as IVIG administration | 15.6 events per 1,000 persons [17] |
| Thrombosis, composite | 1 day after IVIG administration | 5.8 events per 1,000 persons [17] |
| Arterial thromboembolism (stroke or AMI) | 1-2 days after IVIG administration | 7.3 events per 1,000 person-years [16] |
| Venous thromboembolism (DVT, PE, and CVT) | 1-2 days after IVIG administration | 19.6 events per 1,000 person-years [16] |
| Acute kidney injury | Same day as IVIG administration | 7.97 events per 1,000 persons [19] |
| Hemolysis | Same day as IVIG administration | 10.3 events per 1,000 persons [18] |

AMI = acute myocardial infarction; CVT = cerebral venous thrombosis; DVT = deep vein thrombosis; IVIG = intravenous immunoglobulin; PE = pulmonary embolism.

Precision estimates based on these assumptions evaluated the probability that the upper CI of the RR estimate would be less than 2.0 if the true RR was 1.0 (i.e., null, no increased risk). Calculations were performed with Episheet [60]. Figure 3 displays the precision of RR estimates across a range of sample sizes and underlying risks of outcomes.

**Figure 3 Precision of study effect measure estimates**






For the primary events, the precision of our resulting RR estimates is anticipated to be very good at expected sample sizes. The estimated sample sizes were based on published outcome rate estimates generally measured in short, 1- or 2-day assessment windows after a single dose; our proposed study will longitudinally follow patients over time across multiple doses, so the cumulative incidence of events over follow-up may be larger than the short, single-dose estimates used for these calculations. Thus, these precision estimates may be conservative underestimates of the anticipated precision.

## 9.6 Data management

The standard operating procedures (SOPs) of the analytic site will be followed for data management, analysis, and quality control (QC) processes. The data management and analysis will be guided by centrally developed SAP and Programming Specifications, which will detail the identification and construction of all study analytic cohorts, operational definitions and for the derivation of all study variables, statistical models and analytic techniques, structuring of final analytic files, and adaptations for each included data source.

Analyses of the 2 data sources will be performed separately, and any necessary customization of the procedures described in the central SAP for each data source will be documented in the Programming Specifications. The SAP and final report will follow the documentation practices suggested by the Structured Template and Reporting Tool for Real World Evidence (STaRT-RWE) guidance [27]. The final analytic data files will be formatted in a standardized data format

suitable for regulatory submission. Details of the data transformation and curation will be given in the Programming Specifications.

All data management and analysis activities will be performed using SAS (SAS Institute; Cary, NC) Version 9.4 or higher. Transformations of raw data files will be documented in the Programming Specifications. Individual-level data files will be licensed from the respective data holders and will be stored on secure servers. Security processes will be in place to ensure the safety of all systems and data. Data classified as restricted confidential will be kept on secure servers with limited access rights so that they can only be accessed by selected study staff. Remote access to data classified as company confidential or restricted confidential will only be granted to appropriately authorized study staff outside Takeda. All applicable privacy and security requirements will be adhered to by the study team.

Routine procedures will include checking electronic files, maintaining security and data confidentiality, following analysis plans, and performing QC checks of all programs. Any patient-identifying information will be maintained securely on site according to internal SOPs or guidance documents.

Appropriate data storage and archiving procedures will be followed (i.e., storage on dedicated servers), with automatic backup of files. Standard procedures will be in place at each research center to restore files in the event of a hardware or software failure.



## 9.7 Data analysis

All analyses will be performed separately in the 2 data sources, and the data source–specific results will be reported separately. Pooling of the final results across data sources will be performed, if appropriate.

Within each data source, the 2 cohorts (Ig naive and Ig experienced) will be analyzed and reported separately, except in secondary analyses combining the 2 cohorts.

### 9.7.1 Descriptive analysis

The attrition of the study population due to application of the eligibility criteria will be described, including reporting of all patients excluded at each step by treatment group. The final cohorts for descriptive analyses will consist of all eligible patients before the application of the outcome-specific exclusion criteria.

Descriptive analyses will report the distributions of patient characteristics (Section 9.3.4) by treatment group. The relative balance of patient characteristics between treatment groups will be described with absolute standardized differences [61] to determine the comparability of patients in the treatment groups. Characteristics of IVIG use will be described, including the initial product used, the duration of use, and reasons for end of follow-up (e.g., switching Ig product, discontinuation, end of follow-up).

### 9.7.2 Propensity score estimation

Propensity score methods will be used to account for differences between treatment groups. As the outcomes (or groups of outcomes) each have unique, outcome-specific exclusion criteria (Table 2), the propensity scores and matching weights will be re-estimated within each outcome-specific subcohort after the application of the exclusion criteria. Within each outcome-specific

subcohort in each cohort in each data source, a propensity score, or the predicted probability of receiving GGL versus comparator IVIG products based on observed patient characteristics, will be estimated for each patient with a multivariable logistic regression model (i.e., the propensity score model), with GGL initiation versus comparator IVIG product initiation as the dependent variable and the a priori identified patient characteristics (Section 9.3.4) as independent variables. Patient characteristics were a priori selected as covariates due to their potential as confounders of the relationship between IVIG brand and outcomes, or risk factors for any of the study outcomes [62].

After estimation of the propensity score model, the distributions of the estimated propensity scores will be plotted by treatment group to visually inspect the extent of overlap, with greater overlap indicating better comparability of the treatment groups. Preliminary feasibility assessments demonstrated that initiators of GGL are highly similar to initiators of comparator IVIG products, with some differences between the groups in calendar year of initiation or geographic region, but with good balance between most clinical characteristics.

The propensity scores will be used to estimate matching weights—a propensity score–based weight that approximates 1:1 pairwise matching [63,64]. The matching weights will be applied to the individuals in both treatment groups to compare outcomes among patients using GGL with those among patients using comparator IVIG products in the weighted cohorts.

The distribution of characteristics of the matched treatment groups will be evaluated to ensure covariate balance between the treatment groups by plotting the absolute standardized differences between treatment groups for each covariate before and after matching [61]. If imbalances in the covariates after matching are observed, various methods to address the imbalance will be investigated, including the following:

- Re-estimation of the propensity score, including use of higher-order terms for continuous variables or interaction terms between binary variables
- Re-categorization or redefining covariate variables with more granularity
- Evaluation of the exclusion criteria to ensure equipoise between treatment groups for each outcome
- Asymmetrical trimming of the propensity score distribution, where extreme values in the tails of the propensity score distribution are excluded to remove unmeasured confounding typically caused by patients treated contrary to prediction



### 9.7.3 Outcome analyses

Each outcome will be evaluated separately in the outcome-specific subcohorts after the application of outcome-specific exclusion criteria. The characteristics of individuals excluded from outcome-specific analyses will be described. Both crude and adjusted effect measures will be estimated.

Crude analyses will describe the incidence of outcomes by treatment group in the crude, unweighted cohort. Only the first occurrence of each outcome during follow-up per individual will be considered. The overall incidence rate of outcomes will be estimated as the total number of outcome events occurring during follow-up divided by the total amount of person-time contributed by the patients in the treatment group. The exact method will be used to estimate 95% CIs [65]. As a summary of the crude comparative risk of safety events over all of follow-up,

the time to occurrence of safety outcomes after initiation of a study IVIG product will be compared between treatment groups using crude hazard ratios (HRs) and 95% CIs, which will be estimated with Cox proportional hazards models fit in the unweighted cohorts.

To evaluate the risks more granularly over time, the crude daily cumulative incidence of each outcome over follow-up time will be calculated as 1 minus the Kaplan-Meier estimator for each treatment group in the unweighted cohorts. The cumulative incidence curves for each outcome by treatment group will be plotted over all of follow-up.

Propensity score–weighted analyses will be performed to account for potential confounding variables. In the outcome-specific–weighted subcohorts, the incidence rates by treatment group, HRs and 95% CIs, and cumulative incidence curves by treatment group will be estimated.

For the primary analyses of AESIs, the change in risk over time since IVIG initiation will be assessed in the weighted cohort. Time-specific RRs and 95% CIs will be estimated from the weighted cumulative incidence curves at various time points during follow-up. The RR will be estimated as the cumulative incidence of the outcome in the GGL group divided by the cumulative incidence of the outcome in the comparator IVIG group at fixed time points. The 95% CIs will be calculated using nonparametric bootstrapping. The following time-period–specific RR will be estimated (other time periods may be added, as appropriate for each outcome):

- Day 0
- Day 3
- Day 14
- Day 30
- Day 90
- End of follow-up

To give an estimate of the absolute change in risk, risk differences (RD) and 95% CI will be estimated at the same time points as the risk in the GGL group minus the risk in the comparator group.

In accordance with the recommendations of the American Statistical Association [57], the International Committee for Medical Journal Editors [66], and expert opinion on the misuse of significance testing [67-69], reliance on statistical significance to interpret study results will be avoided. Instead of a dichotomous interpretation based on *P* values and significance testing, quantitative interpretations will consider the magnitude, precision, and possible bias in the derived and reported estimates. For epidemiologic studies, this approach is more appropriate than 1 that ascribes to chance any result that does not meet conventional criteria for statistical significance.

### 9.7.4 Secondary analyses

#### *9.7.4.1 Subgroup analyses*

Analyses of each study cohort will be repeated in subgroups to evaluate whether the risk of AEs varies between clinically meaningful subgroups. For example, previous research has suggested an increased risk of thrombotic events in older patients using IVIG compared with younger patients [17]; whether that risk varies by IVIG product is unknown.

Outcomes will be evaluated in the following subgroups:

- Sex (male/female)
- Age group (18-44 years, 45-64 years, ≥ 65 years)
- Patients with preexisting renal disease
- Most recent Ig form before index date (IVIG, SCIG) (Ig-experienced cohort only)

If the secondary analysis in the combined cohorts is conducted (Section 9.7.4.2), these subgroups will be evaluated only in the combined overall cohort (except for the history of IVIG or SCIG subgroups). The combined cohort will be the largest cohort, maximizing the sample size available for subgroup analysis, and it will have been determined that the treatment effects are equivalent in the Ig-naive and Ig-experienced patients. If the combined cohort analysis is not performed due to heterogeneity of the treatment effect measure estimates, the subgroup analyses will be performed in the separate Ig-naive and Ig-experienced cohorts.

#### *9.7.4.2 Combined cohorts*

All the primary analyses will be performed separately in the Ig-naive and Ig-experienced cohorts. Cohort-specific effect measure estimates will be reported for all analyses and evaluated for evidence of statistical heterogeneity using the $I^2$ statistic [70]. If the primary study results from the separate cohorts demonstrate a lack of heterogeneity between cohorts in the same data source (details to be given in the SAP), then the analyses will be repeated in that data source with the Ig-naive and Ig-experienced cohorts combined into 1 overall cohort. Some individuals may be included in both cohorts and would thus be included twice in the combined cohort: the estimation of the variance in the combined cohort will account for the repeated measures within individuals. A new overall propensity score model will be estimated for the combined cohort, and weighting will be repeated for individual outcome-specific subcohorts. If conducted, both the overall and subgroup analyses will be performed in the combined cohort.

If heterogeneity of the treatment effect estimates between the 2 cohorts is observed, potentially suggesting effect measure modification by history of Ig use, then combined analyses will not be performed.

### 9.7.5 Sensitivity analyses

Sensitivity analyses will be performed to test the robustness of study results across variations in study design and analytic approach. If the secondary analysis in the combined cohorts is conducted (Section 9.7.4.2), these sensitivity analyses will be performed only in the combined overall cohort. If the combined cohort analysis is not performed due to heterogeneity of the

treatment effect measure estimates, the sensitivity analyses will be performed separately in the Ig-naive and Ig-experienced cohorts.

- To evaluate the potential impact of informative censoring by discontinuation or switching/adding treatment (i.e., patients discontinuing IVIG treatment or switching due to early symptoms of an AE that would not be diagnosed until after discontinuation), an analysis will be conducted extending the length of the assumed duration of IVIG exposure (Section 9.3.1.1) from 9 weeks to 12 weeks. In some patients, this may bridge longer gaps between IVIG administrations, resulting in longer continuous exposure periods; in other patients, this may extend the discontinuation date by 3 additional weeks to observe late-occurring AEs.
- To evaluate the potential for misclassification of IVIG exposure, the availability and completeness of IVIG dosage information will be evaluated and described. If feasible, a sensitivity analysis restricted to those with complete, reasonable dosage information will be performed (details to be given in the SAP).
- To evaluate potential unmeasured residual confounding after propensity score weighting, a negative control outcome analysis will be performed where the association of GGL with unrelated outcomes unexpected to be affected by GGL will be evaluated. Negative control outcomes will be selected by generating a candidate list of hospitalized outcomes (as the primary outcomes of this study are generally hospitalized) that are not anticipated to be associated with GGL or comparator IVIG exposure; reviews of published literature and safety information will be performed to identify any potential association with IVIG, and outcomes will be excluded from consideration if a suggested association is identified. Further details will be given in the SAP. If non-null association is observed between GGL and the negative control outcomes in the weighted analysis, residual confounding may be assumed. Additional adjustment variables and approaches will be considered if residual confounding is observed.



### 9.7.6 Pooling across data sources

The analyses will be performed separately in the MarketScan and Optum data sources. The data sources use the same coding systems, but there may be differences in data structure, patient characteristics, practice patterns, or coverage benefits between data sources (although all data sources contain national-level data). Data source–specific effect measure estimates will be reported for all analyses and evaluated for evidence of statistical heterogeneity using the $I^2$ statistic [70]. If there is no evidence of statistical heterogeneity, the estimates for the primary cohort-specific analyses and secondary combined cohort analyses will be meta-analyzed using fixed effects meta-analytic methods. The meta-analyzed estimates will be presented with the data source–specific estimates.

### 9.7.7 Missing data and quantitative bias analysis

All study variables will be defined using existing healthcare data. Some personal characteristics will be identified in patient enrollment data, but most characteristics (including the primary exposure, outcomes, covariates, and eligibility criteria) will be identified using submitted and recorded diagnoses and procedures on insurance billing claims. The lack of a code for a particular condition will be interpreted as the patient not having that characteristic. No variables

will have explicitly missing values (i.e., for all characteristics, each patient will be marked as either having or not having the condition—no one will have a value of missing). No methods for correcting missing data will be used.

Patients' true CIDP disease statuses may be incorrectly categorized if claims or conditions they truly have are not submitted or are miscoded or if patients do not seek care for conditions. These missing data may result in misclassification. The potential misclassification of CIDP status will be addressed via validation by medical chart review with potential qualitative bias analysis, if feasible. Additionally, claims databases do not include records of some characteristics that may be risk factors for the outcomes evaluated in this study, such as the following: smoking, obesity, alcohol use, substance abuse, physical activity, or family history. Race/ethnicity information is not available in all of the included data sources. Lifestyle factors and behavioral characteristics such as healthcare seeking behavior, healthy lifestyle, and access to healthcare will be measured with proxies such as healthcare utilization and screening and preventive healthcare services. A negative control analysis will be performed as a sensitivity analysis to evaluate the adequacy of control for confounding, even if some variables may not be completely captured in the data.

The Optum data has some available information on socioeconomic status, including race, income, home ownership, and education level. The completeness of this information will be investigated for the study cohort (completeness is reported to be between 5% and over 90% for each variable); if some variables are found to have high completion for the study cohort, they may be considered for inclusion as covariates in analyses of the Optum data.

Misclassification of outcome events may result in bias of the estimated effect measure estimates, particularly if the misclassification is differential between treatment groups. Validated outcome algorithms will be used wherever possible, and many of the primary outcomes have been validated in administrative claims–based populations of IVIG users with promising measures of validity [36-38]. Feasibility evaluations have demonstrated minimal differences in demographic characteristics and almost no differences in clinical characteristics between users of different GGL and other IVIG products [10], and given the interchangeability of many IVIG products for CIDP treatment, differential outcome misclassification between IVIG brands seems unlikely. However, quantitative bias analyses will also be conducted to evaluate the potential impact of differential outcome misclassification on the estimated effect estimates for outcome algorithms with questionable validity; a quantitative bias analysis will use reported PPVs of the safety outcome algorithms to estimate an array of potential misclassification scenarios to estimate the extent of potential differential outcome misclassification necessary to substantively alter the observed study conclusion [71].



### 9.7.8 Validation

Validation of CIDP disease and IVIG initiation status performed among the IVIG-initiating patients identified for the primary study cohorts in the Optum Clinformatics Data Mart data source. The validation process will be guided by a separately developed Validation Plan. Validation will be performed in the Ig-naive and Ig-experienced cohorts combined. A sample of patients meeting all eligibility criteria to be included in the study cohorts and with medical records that can be identified will be selected for the validation sample.

Each patient's index date represents the electronic algorithm-identified date of initiation of a new IVIG product on or after a CIDP diagnosis. Available medical records from on or before the index date will be evaluated to adjudicate the electronic-defined algorithms.

#### *9.7.8.1 CIDP status*

Among the IVIG initiators in the validation sample with available medical record data, CIDP status will be adjudicated by an adjudication committee using available patient information from the medical record and claims data, including recorded symptoms and electrodiagnostic test results and clinician notes. Electronic algorithm-identified cases status will be adjudicated against accepted diagnostic and clinical criteria [9] as the gold standard, and the adjudication committee will categorize the CIDP status of each patient as a confirmed case or non-case or as being unable to be determined. Additional status designations of definitive, probable, or possible cases aligning with the European Federation of Neurological Societies/Peripheral Nerve Society diagnostic guidelines [9] may be considered, as feasible. Full details will be given in the Validation Plan.

As all identified patients in the validation sample will be those with algorithm-identified CIDP status, the PPV, or proportion of algorithm-identified cases that are true cases, will be the only validity parameter that can be estimated (e.g., the cohort will not include anyone without algorithm-identified CIDP, so sensitivity, specificity, and negative predictive value calculations cannot be estimated). It is anticipated that not all patients will have adequate information in the medical record to confirm case or non-case status (e.g., lacking laboratory results), so variations of the PPV will also be estimated including the unable-to-be-determined cases in the numerator and denominator and just the denominator to represent the extremes of possible PPV values if all unable-to-be-determined cases were either confirmed cases or confirmed non-cases.

#### *9.7.8.2 IVIG initiation status*

The index date will be the date of the first-identified administration of a specific study IVIG product after a 6-month minimum washout period free of any recorded use of the same study IVIG product. IVIG use is expected to be accurately identified in the data sources, especially for the procedure-based coding. However, there are codes for brand-unspecified IVIG products, and the possibility of missing data may result in algorithm-identified IVIG initiators actually being continuing users of the IVIG products. For the patients in the validation sample, medical records will be evaluated for any evidence of previous use of the index IVIG product before the index date. The adjudication committee will classify patients as having no evidence of previous use of the index IVIG (true initiators) or having previous use of the index IVIG (false positive initiators).

Similar to the CIDP status, all identified patients in the validation sample will be those with algorithm-identified IVIG initiation, and thus the PPV will be the only validity parameter that can be estimated. The PPV will be estimated as the proportion of algorithm-identified IVIG product initiators without evidence of previous use of the index IVIG.

### 9.8 Quality control

SOPs or internal process guidance at each research center will be used to guide the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, QC procedures for programming, standards for writing analysis plans, and requirements for senior scientific review. All key study documents, such as the SAP and study reports, will undergo QC review, senior scientific review, and editorial review.

For [redacted], an independent Office of Quality Assurance (OQA) will perform audits and assessments that involve various aspects of the project, including but not limited to education and training documentation, data entry and data transfer procedures and documentation, and institutional review board (IRB) documentation. Such audits will be conducted by the OQA according to established criteria in SOPs and other applicable procedures. A quality assurance audit of this study may be conducted by the sponsor or the sponsor's designees.

The study analysis will be performed at Takeda and will be guided by the protocol, SAP, and Programming Specifications, which will include detailed documentation for data transformation, variable definitions and operational algorithms, code lists, and statistical methods. The SOPs and guidance documents for the study analysts will include performing internal quality checks of data transformation and variable definitions to ensure alignment of the programming with the protocol and SAP and to evaluate potential errors in programming.

After data from the raw data files are extracted, they will be kept on Takeda SAS grid servers to develop analytical programs that generate results tables and figures. The primary programmer will be responsible for creating and documenting all project-specific SAS code, including comments as to why changes are made over the course of the project. In addition to evaluating diagnostic output independently, the programmer will also evaluate this output with the entire project team before results tables are generated.

Internal QC audits of all analysis and written materials will be performed. Internal audits will consist of a review of all final work product materials and the underlying analysis, including all programs, and supporting source documentation by a team member or another conflict-cleared employee who was not involved in the creation of the original work product. The code review programmer will work with the primary programmer in order to confirm that SAS code was written with correct syntax and generates results as specified in the analysis plan. Issues identified by the code reviewer will be documented and resolved.

QC review of study results will be conducted to ensure data presented in tables and graphs correctly match the analytic data in the database. Study teams will confirm that results are consistent across analysis tables and that the results are plausible contextually. If applicable, results will be compared with previous trend reports to ensure consistency. The coordinating center will review and compare aggregate results from both data sources to identify and rectify potential discrepancies.

Final results presented in reports and other study deliverables will undergo QC review to ensure concordance among all final documents as well as to evaluate content for accuracy and consistency.

Appropriate data storage and archiving procedures will be followed (i.e., storage on server), with periodic backup of files. Standard procedures will be in place to restore files in the event of a hardware or software failure at the analytic site.



### 9.9 Limitations of the research methods

The study will use administrative data to capture real-world use and safety of IVIG products. Although the intent of the study is to evaluate real-world use of GGL for the treatment of CIDP, which is currently off-label in the US, real-world practice patterns may result in confounding between users of GGL and comparator IVIG products if patients with certain patterns of characteristics are differentially prescribed 1 product or the other. Prior feasibility analyses have

demonstrated that most measured clinical characteristics of patients are well balanced between treatment groups, even prior to any statistical adjustment, suggesting limited measured confounding; some differences by calendar year and US geographic region were noted, likely resulting from fluctuations in product availability over time. Confounding by indication is not expected, as all study IVIG products are widely used for CIDP treatment. Although propensity score methods will be used to create exchangeable comparison groups, a quantitative bias analysis will be conducted to evaluate the effect of potential residual unmeasured confounding.

Selection bias may be possible if the way patients in the GGL and comparator groups are selected for the study differs in a way that results in a different relationship between IVIG products and the outcomes in the 2 groups. For example, if 1 product is systematically used as a second-line, later-stage treatment and thus all initiators of that product have longer event-free IVIG treatment time before the index date, a comparison of that product with other IVIG products may be subject to bias. However, we do not anticipate the presence of selection bias in this new-user, active-comparator study. The study IVIG products are generally used interchangeably for CIDP treatment, and the study design separately considering Ig-naive and Ig-experienced patients aligns patients more closely in treatment trajectories, further reducing the possibility of selection bias.

The study will use existing administrative claims databases and will not directly contact patients to collect data. Individual patients may move between insurance plans and thus be included in different data sources at different times: patients will not be identifiable across data sources. Claims data are generated for billing purposes, so they are not primarily intended for research purposes. Claims databases are organized at the level of the payer, and thus billable claims information from all healthcare providers and settings (including inpatient, outpatient, pharmacy dispensing, etc.) would be captured in them; however, claims data contain only billable information, and certain characteristics such as height, weight, laboratory test results, lifestyle factors, and over-the-counter medication use are not recorded in claims data. Patient weight will not be available, and IVIG dose information will not be available to estimate appropriate individual dosages. Due to differences in recording of IVIG information between procedure claims and pharmacy claims, and changes in the data availability over time, accurate dose information may not be available to evaluate dose effects. While the risk of some outcomes may be dose dependent, previous safety surveillance of IVIG conducted in claims data by FDA researchers did not include dose information, and these studies include patients using IVIG for a variety of indications with wide variation in recommended doses [16-19]; the cohort of patients with CIDP described in this protocol may be expected to have a more narrow range of potential dosages than cohorts with mixed indications. The availability and feasibility of using dose information will be evaluated in a sensitivity analysis (Section 9.7.5).

The use of administrative claims data rather than clinical records may result in misclassification of key study components, such as CIDP status, or some safety outcomes. CIDP may be confused with other, similar neuropathies, and initially recorded diagnoses may be incorrect until confirmed after a prolonged diagnosis period. Prior feasibility analyses have demonstrated that 47.6% of identified patients with a recorded CIDP diagnosis did not receive a subsequent CIDP diagnosis more than 30 days later, suggesting the recording of potentially unconfirmed diagnoses. However, many payers require documentation of CIDP as a condition for continued IVIG treatment; therefore, repeated CIDP diagnoses recorded in claims data may accurately reflect true CIDP status. CIDP status validation and bias analyses will be performed to evaluate

the potential impact of misclassification of CIDP status or outcomes on study results. Many claims databases do not contain information about cause of death, so fatal outcome events occurring outside the hospital may not be identified in the data sources; however, any potential missing outcome cases are not expected to occur differentially between treatment groups.

This study will use propensity score methods. Inclusion of instrumental variables (characteristics that predict the exposure but are independent of the outcome) in the propensity score model has been shown to result in inflation of bias from unmeasured confounders [62]. A priori identification of variables for inclusion in the propensity score model will be carefully considered to avoid inclusion of an instrumental variable.

## 10.0 PROTECTION OF HUMAN SUBJECTS

This study only involves the use of anonymized electronic healthcare records. The researchers will not have any access to named or identifiable patient information. Each database research partner will apply for an independent ethics committee review according to local regulations; in addition, [redacted] as the coordinating center will obtain approval or exemption from the [redacted] IRB.

[redacted] holds a Federal-Wide Assurance from the Department of Health and Human Services Office for Human Research Protections that allows the organization to review and approve human subjects protocols through its IRB committees. These IRBs committees have been audited by the US Food and Drug Administration and are fully compliant with applicable regulatory requirements. [redacted] will obtain approval for the study from the [redacted] IRB.

Data protection and privacy regulations will be observed in collecting, forwarding, processing, and storing data from study participants.

## 11.0 MANAGEMENT AND REPORTING OF ADVERSE EVENTS

### 11.1 Definitions

#### 11.1.1 Adverse events

An adverse event is any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, a new disease or worsening in severity or frequency of a concomitant disease, temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for a SAE
- A laboratory test result that requires the subject/patient to receive specific corrective therapy
- A laboratory abnormality that leads to discontinuation of therapy
- A laboratory abnormality that the healthcare provider considers to be clinically significant

#### 11.1.2 Serious adverse events

An SAE is any untoward medical occurrence that at any dose:

- Results in death. Note that death is an outcome of an event. The event(s) causing death should be recorded
- In the view of the healthcare provider, places the subject/patient at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- An SAE may also be any other medically important event that, in the opinion of the healthcare provider, may jeopardize the subject/patient or may require intervention to prevent 1 of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

#### 11.1.3 Adverse drug reactions

An adverse drug reaction is an AE for which there is at least a reasonable suspicion of a causal relationship between an AE and a suspected medicinal product.

### 11.1.4 Product quality issues

A product quality issue (PQI) refers to defects related to the safety, identity, strength, quality, or purity of the product or with the physical characteristics, packaging, labeling, or design of the product.

### 11.1.5 Special Situation Reports

A Special Situation Report (SSR) includes any of the following events:

- Pregnancy: Any case in which a pregnant patient is exposed to a Takeda Product or in which a female patient or female partner of a male patient becomes pregnant following treatment with Takeda Product. Exposure is considered either through maternal exposure or via semen following paternal exposure
- Breastfeeding: Infant exposure from breast milk
- Overdose: All information of any accidental or intentional overdose
- Drug abuse, misuse, or medication error: All information on medicinal product abuse, misuse or medication error (potential or actual)
- Suspected transmission of an infectious agent: Suspected (in the sense of confirmed or potential) transmission of an infectious agent by a medicinal product
- Lack of efficacy of Takeda Product
- Accidental/Occupational exposure
- Use outside the terms of the marketing authorization, also known as “off-label”
- Use of falsified medicinal product
- Use of counterfeit medicinal product
- Drug-drug interactions and drug-food interactions
- Inadvertent or accidental exposure with or without an AE
- Unintended benefit

A SSR should be reported even if there is no associated AE.



## 11.2 Collection and notifying of adverse events, special situation reports, and product quality issues to Takeda Pharmacovigilance

### 11.2.1 SAEs, AEs, ADRs, SSRs, and PQIs in the healthcare record or other applicable source data that are part of the study objectives or endpoints

Events/issues which are part of the study objectives or endpoints will be systematically identified and collected from healthcare records or other applicable source records and summarized as part of any interim analysis and in the final study report. Such events do not need to be notified as individual reports to Takeda Pharmacovigilance.

### 11.2.2 SAEs, AEs, SSRs, and PQIs in the healthcare records or other applicable source data that are not part of the study objectives and endpoints

Events/Issues which are not part of the study objectives and endpoints will not be abstracted or collected from healthcare records or other applicable source records.

### 11.2.3 SAEs, AEs, ADRs, SSRs, and PQIs spontaneously reported to the investigator(s) or research team

If during the conduct of the study the investigator(s) or a member of the research team is spontaneously informed by a healthcare professional or patient of an SAE, AE, ADR, SSR, or PQI where the event/issue pertains to a Takeda Product (or unbranded generic), such information should be forwarded to the relevant Takeda Pharmacovigilance department within 1 working day for fatal or life-threatening SAEs, within 4 calendar days for other SAEs, and within 7 calendar days for all other events. This includes events spontaneously notified to the investigator(s) or research team which are study endpoints and also events spontaneously notified which are not study endpoints. As such reports are spontaneously notified, causality of any AEs should be assumed unless there is evidence to the contrary.

## 11.3 Reporting of adverse drug reactions and special situation reports to regulatory agencies.

Based on current guidelines from the International Society for Pharmacoepidemiology (ISPE) [59] and the European Medicines Agency (EMA) Guideline on Good Pharmacovigilance Practices [72], for non-interventional study designs that are based on secondary use of data, such as studies based on medical chart reviews or electronic healthcare records, systematic reviews or meta-analyses, reporting of AEs/ADRs is not required. Reports of AEs/ADRs should only be summarized in the study report, where applicable.

## 12.0 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The final study report will contain a description of the background and motivation of the study, as well as a detailed description of the data management and analysis approach with enough granularity to replicate the derivation of all study elements and analytic models in the data sources. Any deviations from the preplanned approach specified in the protocol or SAP will be documented in the report with the date and rationale for the deviation. The results of all prespecified analyses will be reported with the conclusions and contextualization with existing research.

The study protocol, SAP, and final study report will be included in regulatory communications in line with regulatory reporting requirements. The STaRT-RWE principles for data documentation and reporting will be followed to allow for transparency and replicability [27].

Joint ISPE-International Society for Pharmacoeconomics Research (ISPOR) recommendations for good practice for real-world evidence studies of treatment effectiveness emphasize the need to publish study results [73]. Study results will be published following the International Committee of Medical Journal Editors [74] guidelines. When reporting results of this study, the appropriate STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist [75] will be followed.

Communication in appropriate scientific venues (e.g., Peripheral Nerve Society, American Academy of Neurology, ISPE) will be considered.

The marketing authorization holder and the investigator will agree upon a publication policy allowing the principal investigator to independently prepare publications based on the study results, irrespective of data ownership. The marketing authorization holder will be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication.

## 13.0 OTHER GOOD RESEARCH PRACTICE

This study adheres to the Guidelines for Good Pharmacoepidemiology Practices (GPP) [59] and the FDA draft guidance Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets [76] and Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decisions-Making for Drug and Biological Products [77].

The study will be registered in a public repository suitable for observational study protocol before the study implementation commences.

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## Appendices

### Annex 1 List of stand-alone documents

None.

## Annex 2 ENCePP checklist

Doc.Ref. EMA/540136/2009

# ENCePP Checklist for Study Protocols (Revision 3)

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

**Study reference number:** not yet registered

| **Section 1: Milestones** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 1.1 Does the protocol specify timelines for | | | | |
| 1.1.1 Start of data collection[4] | ☒ | ☐ | ☐ | 6.0 |
| 1.1.2 End of data collection[5] | ☒ | ☐ | ☐ | 6.0 |
| 1.1.3 Study progress report(s) | ☐ | ☐ | ☒ | 6.0 |
| 1.1.4 Interim progress report(s) | ☐ | ☐ | ☒ | 6.0 |
| 1.1.5 Registration in the EU PAS register | ☒ | ☐ | ☐ | 6.0 |
| 1.1.6 Final report of study results | ☒ | ☐ | ☐ | 6.0 |

Comments:

1.1.3, 1.1.4: There are no interim analyses or reports planned.

| **Section 2: Research question** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 2.1 Does the formulation of the research question and objectives clearly explain: | | | | |
| 2.1.1 Why the study is conducted? (e.g., to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue) | ☒ | ☐ | ☐ | 8.0 |
| 2.1.2 The objective(s) of the study? | ☒ | ☐ | ☐ | 8.0 |
| 2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalized) | ☒ | ☐ | ☐ | 9.2.1 |
| 2.1.4 Which hypothesis(-es) is (are) to be tested? | ☐ | ☐ | ☒ | |
| 2.1.5 If applicable, that there is no a priori hypothesis? | ☒ | ☐ | ☐ | 8.0 |



[4] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[5] Date from which the analytical dataset is completely available.

Comments:

| |
|---|
| 2.1.4: This study will not formally be statistically testing any specific hypotheses. |

| **Section 3: Study design** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 3.1 | Is the study design described? (e.g., cohort, case-control, cross-sectional, new or alternative design) | ☒ | ☐ | ☐ | 9.1 |
| 3.2 | Does the protocol specify whether the study is based on primary, secondary or combined data collection? | ☒ | ☐ | ☐ | 9.1, 9.4 |
| 3.3 | Does the protocol specify measures of occurrence? (e.g., incidence rate, absolute risk) | ☒ | ☐ | ☐ | 9.7.3 |
| 3.4 | Does the protocol specify measure(s) of association? (e.g., relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year) | ☒ | ☐ | ☐ | 9.7.3 |
| 3.5 | Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g., adverse events that will not be collected in case of primary data collection) | ☒ | ☐ | ☐ | 11.0 |

Comments:

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|---|
| |

| **Section 4: Source and study populations** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 4.1 | Is the source population described? | ☒ | ☐ | ☐ | 9.4 |
| 4.2 | Is the planned study population defined in terms of: | | | | |
| | 4.2.1 Study time period? | ☒ | ☐ | ☐ | 9.2.1 |
| | 4.2.2 Age and sex? | ☒ | ☐ | ☐ | 9.2.1 |
| | 4.2.3 Country of origin? | ☒ | ☐ | ☐ | 9.2.1 |
| | 4.2.4 Disease/indication? | ☒ | ☐ | ☐ | 9.2.1 |
| | 4.2.5 Duration of follow-up? | ☒ | ☐ | ☐ | 9.2.4 |
| 4.3 | Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria) | ☒ | ☐ | ☐ | 9.2.2, 9.2.3 |

Comments:

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| **Section 5: Exposure definition and measurement** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 5.1 Does the protocol describe how the study exposure is defined and measured? (e.g., operational details for defining and categorizing exposure, measurement of dose and duration of drug exposure) | ☒ | ☐ | ☐ | 9.3.1.1 |
| 5.2 Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation sub-study) | ☒ | ☐ | ☐ | 9.3.1, 9.7.4.2 |
| 5.3 Is exposure classified according to time windows? (e.g., current user, former user, non-use) | ☐ | ☒ | ☐ | |
| 5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug? | ☒ | ☐ | ☐ | 9.3.1.1 |

Comments:

5.3: This study does not classify exposure time as current user, former user, or non-use, as all included patients are new users of the study drug, and only time on drug is considered for the primary analysis.

| **Section 6: Outcome definition and measurement** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated? | ☒ | ☐ | ☐ | 8.0 |
| 6.2 Does the protocol describe how the outcomes are defined and measured? | ☒ | ☐ | ☐ | 9.3.3 |
| 6.3 Does the protocol address the validity of outcome measurement? (e.g., precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study) | ☒ | ☐ | ☐ | 9.3.3, 9.7.4.2 |
| 6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g., HRQoL, QALYs, DALYS, healthcare services utilization, burden of disease, disease management) | ☐ | ☐ | ☒ | |

Comments:

6.4: The objectives of this study are to evaluate specific safety outcomes.

| **Section 7: Bias** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 7.1 Does the protocol describe how confounding will be addressed in the study? | ☒ | ☐ | ☐ | 9.7.2, 9.7.3 |
| 7.1.1. Does the protocol address confounding by indication if applicable? | ☒ | ☐ | ☐ | 9.9 |
| 7.2 Does the protocol address: | | | | |

| **Section 7: Bias** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 7.2.1. Selection biases (e.g., healthy user bias) | ☒ | ☐ | ☐ | 9.1, 9.9 |
| 7.2.2. Information biases (e.g., misclassification of exposure and endpoints, time-related bias) | ☒ | ☐ | ☐ | 9.3.1, 9.4, 9.3.3 |
| 7.3 Does the protocol address the validity of the study covariates? | ☒ | ☐ | ☐ | 9.3.4, 9.7.7 |

Comments:

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| **Section 8: Effect modification** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 8.1 Does the protocol address effect modifiers? (e.g., collection of data on known effect modifiers, subgroup analyses, anticipated direction of effect) | ☒ | ☐ | ☐ | 9.7.4.1 |

Comments:

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| **Section 9: Data sources** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of: | | | | |
| 9.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview) | ☒ | ☐ | ☐ | 9.3.1 |
| 9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics) | ☒ | ☐ | ☐ | 9.3.3 |
| 9.1.3 Covariates? | ☒ | ☐ | ☐ | 9.3.4 |
| 9.2 Does the protocol describe the information available from the data source(s) on: | | | | |
| 9.2.1 Exposure? (e.g., date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber) | ☒ | ☐ | ☐ | 9.3.1 |
| 9.2.2 Outcomes? (e.g., date of occurrence, multiple event, severity measures related to event) | ☒ | ☐ | ☐ | 9.3.3 |
| 9.2.3 Covariates? (e.g., age, sex, clinical and drug use history, comorbidity, co-medications, lifestyle) | ☒ | ☐ | ☐ | 9.3.4, 9.7.7 |
| 9.3 Is a coding system described for: | | | | |
| 9.3.1 Exposure? (e.g., WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System) | ☒ | ☐ | ☐ | 9.3.1, 9.4 |
| 9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA)) | ☒ | ☐ | ☐ | 9.3.3, 9.4 |

| **Section 9: Data sources** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 9.3.3 Covariates? | ☒ | ☐ | ☐ | 9.3.4, 9.4 |
| 9.4 Is a linkage method between data sources described? (e.g., based on a unique identifier or other) | ☐ | ☐ | ☒ | |

Comments:

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|---|
| 9.4: There will be no linkage of the claims data with external data sources. |

| **Section 10: Analysis plan** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 10.1 Is the choice of statistical techniques described? | ☒ | ☐ | ☐ | 9.7 |
| 10.2 Are descriptive analyses included? | ☒ | ☐ | ☐ | 9.7.1 |
| 10.3 Are stratified analyses included? | ☒ | ☐ | ☐ | 9.7.4.1 |
| 10.4 Does the plan describe methods for adjusting for confounding? | ☒ | ☐ | ☐ | 9.7.2 |
| 10.5 Does the plan describe methods for handling missing data? | ☒ | ☐ | ☐ | 9.7.7 |
| 10.6 Is sample size and/or statistical power estimated? | ☒ | ☐ | ☐ | 9.5 |

Comments:

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|---|
| 10.6: Rather than estimate power to formally test a specific hypothesis, the precision of potential study results is estimated. |

| **Section 11: Data management and quality control** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 11.1 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving) | ☒ | ☐ | ☐ | 9.6 |
| 11.2 Are methods of quality assurance described? | ☒ | ☐ | ☐ | 9.7.8 |
| 11.3 Is there a system in place for independent review of study results? | ☒ | ☐ | ☐ | 9.7.8, 12.0 |

Comments:

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| **Section 12: Limitations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 12.1 Does the protocol discuss the impact on the study results of: | | | | |
| 12.1.1 Selection bias? | ☒ | ☐ | ☐ | 9.1, 9.9 |
| 12.1.2 Information bias? | ☒ | ☐ | ☐ | 9.9 |

| **Section 12: Limitations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 12.1.3 Residual/unmeasured confounding? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods) | ☒ | ☐ | ☐ | 9.9 |
| 12.2 Does the protocol discuss study feasibility? (e.g., study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment) | ☒ | ☐ | ☐ | 9.5 |

Comments:

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| **Section 13: Ethical issues** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 13.1 Have requirements of Ethics Committee/ Institutional Review Board been described? | ☒ | ☐ | ☐ | 10.0 |
| 13.2 Has any outcome of an ethical review procedure been addressed? | ☐ | ☐ | ☒ | |
| 13.3 Have data protection requirements been described? | ☒ | ☐ | ☐ | 9.6, 10.0 |

Comments:

| |
|---|
| 13.2: The study has not yet been submitted for ethical review |

| **Section 14: Amendments and deviations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 14.1 Does the protocol include a section to document amendments and deviations? | ☒ | ☐ | ☐ | 5.0 |

Comments:

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| **Section 15: Plans for communication of study results** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 15.1 Are plans described for communicating study results (e.g., to regulatory authorities)? | ☒ | ☐ | ☐ | 12.0 |
| 15.2 Are plans described for disseminating study results externally, including publication? | ☒ | ☐ | ☐ | 12.0 |

Comments:

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