

Privigen® Post-Authorization Safety Study (PASS) information

Title	Privigen® use and haemolytic anaemia in adults and children and the Privigen® safety profile in children with CIDP – an observational hospital-based cohort study in the US
Protocol version identifier	Version 1.0 (17 December 2013)
Date of last version of protocol	Not applicable
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Medicinal product	Privigen®
Product reference	EU numbers: EU/1/08/446/001 - 007
Procedure number	EMEA/H/C/000831
Marketing authorisation holder(s)	CSL Behring GmbH
Joint PASS?	No
Research question and objectives	The research questions are: <ol style="list-style-type: none"> 1. Is the incidence of haemolytic anaemia lower following implementation of the two risk minimization measures “Screening of Plasma Donors” and “Introduction of an Immunoaffinity Chromatography Step” in the Manufacturing Process of Privigen®? 2. What is the safety profile of Privigen® in children (0-18 years) with CIDP? The study objectives are to: <ol style="list-style-type: none"> 1. Measure and compare the incidence of

	<p>haemolytic anaemia in adults and children before and after implementation of each of the two risk minimization measures “Screening of Plasma Donors” and “Introduction of an Immunoaffinity Chromatography Step in the Manufacturing Process of Privigen”</p> <p>2. Evaluate the safety profile of Privigen® in children (0-18 years) with CIDP</p>
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2. List of abbreviations

Abbreviation	Definition
ABO	A system used to designate human blood type (A, B, O and AB)
AE	Adverse event
ATC	Anatomical Therapeutic Chemical Classification System
CHMP	Committee for Medicinal Products for Human Use
CIDP	Chronic inflammatory demyelinating polyneuropathy
FDA	Food and Drug Administration
FAERS	FDA Adverse Event Reporting System
HA	Haemolytic anaemia
HES	Hospital Episodes Statistics
HPA	Hospital Pharmacy Audit
HTI	Hospital Treatment Insights
ICD-9 CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10	International Classification of Diseases, Tenth Revision
CCI	Charlson Comorbidity Index
CPT	Current Procedural Terminology
CPT-4	Current Procedural Terminology, Fourth Edition
Hb	Haemoglobin
HCPS	Healthcare Common Procedure Coding System
HIPAA	Health Insurance Portability and Accountability Act
ITP	Immune thrombocytopenic purpura
IRB	Institutional Review Board
IV-IG	Intravenous immunoglobulins
MIMS	Monthly Index of Medical Specialities
NHS	National Health Service
OPCS-4	Office of Population Censuses and Surveys: Classification of Interventions and Procedures, version 4
PHI	Personal Healthcare Information
PI	Principal investigator
PID	Primary immune deficiency
RBC	Red blood cell
SID	Secondary immune deficiency
UK	United Kingdom

3. Responsible parties

CSL Behring GmbH is the sponsor of this study. Contact details for responsible parties and the list of all investigators is kept in a stand-alone document available upon request (see Annex 1).

4. Abstract

Title: Privigen® use and haemolytic anaemia in adults and children and the Privigen® safety profile in children with CIDP – an observational hospital-based cohort study in the US.

Version 1.0 (17 Dec 2013).

PI: Carlos Martinez, MD MSc. Consultant epidemiologist. Im Dinkelfeld 32, 60388 Frankfurt, Germany.

Rationale and background: Treatment with intravenous immunoglobulin (IV-IG) is associated with acute haemolysis and subsequent haemolytic anaemia (HA) due to enhanced red blood cell (RBC) sequestration, and so risk minimization measures are being implemented in the manufacturing process of Privigen®. Furthermore, in March 2013, the additional Privigen® indication chronic inflammatory demyelinating polyneuropathy (CIDP) was approved for Privigen® in the European Union. However, only limited experience is available on the safety profile use of IV-IGs in children with CIDP as CIDP is a rare condition in children. Some data are available for off-label use of Privigen® for CIDP in the US. *Study design:* This is a retrospective and prospective hospital-based observational cohort study with objectives (1) to measure the incidence of HA before and after implementation of each of the two risk minimization measures “Screening of Plasma Donors” and “Introduction of an Immunoaffinity Chromatography Step in the Manufacturing Process of Privigen®” in adults and children who have been administered Privigen®, and (2) to evaluate the safety profile of Privigen® in children (0-18 years) with CIDP. Whereas Part 1 of the study will be conducted comparing results from three separate calendar-time periods to assess the effects of risk minimization measures, Part 2 will be on data accumulated over the whole study period to assess the adverse event (AE) profile in children with CIDP.

Population: Adult and paediatric patients with at least one dispensing for Privigen® in US hospitals.

Variables: The exposure variable of interest is Privigen®. The outcome variable to be assessed in both adults and children in Part 1 of the study is HA. The outcome variables to be assessed in children with CIDP in Part 2 of the study include diagnosis codes for aseptic meningitis, acute renal failure, thromboembolic events and anaphylactic reactions.

Data sources: The data source is the Premier Perspective™ database in the United States.

Study size: As of 30 July 2013, Premier contained data on 9149 patients with inpatient Privigen® treatment and 15854 patients with outpatient Privigen® treatment. Overall, about 25,000 patients were treated with Privigen® at least once in either setting; 2417 of them were aged <18. Seven patients aged <18 were treated with Privigen® for CIDP, and these 7 patients had 46 treatment episodes (21 as inpatients and 25 as outpatients).

Data analysis: For Part 1 results will include descriptive statistics of the standardized incidence of first-time occurrence of HA during the different calendar-time periods. Cox Proportional hazards modelling will be used to compare the hazard rate of the first-time occurrence of HA following the implementation of each of the two risk minimisation measures to the baseline hazard of HA (before the measures were introduced). For Part 2 results will include the incidence rates of AEs for the paediatric population with CIDP during the cumulative study period.

Milestones: For the analyses to address Part 1 of the study, the first interim report, using data collected up to the implementation of the risk minimisation measure “Screening of Plasma Donors”, will be available 15 Oct 2014. The second interim report, using data collected after implementation of the risk minimisation measure “Screening of Plasma Donors” and before the implementation of the “Immunoaffinity Chromatography Step in the Manufacturing Process of Privigen®”, will be available 1 November 2016. The final report, using data collected after the second risk minimisation measure has been implemented, will be available 1 November 2019. The analyses to address Part 2 of the study will also be done on the above schedule looking at cumulative results over the whole study period.

5. Amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
None				

6. Milestones

Separate study reports will be prepared as data become available during the three separate calendar-time periods of the study, and will be provided to the regulators.

Milestone	Planned date
Start of data collection	15 Nov 2013
End of data collection	15 April 2019
Interim report 1	15 Oct 2014
Interim report 2	1 Nov 2016
Registration in the EU PAS register	To be determined
Final report of study results	1 Nov 2019

7. Rationale and background

Privigen®, Immune Globulin Intravenous (Human), is indicated in Europe and the US for the treatment of patients of all ages with primary immune deficiency (PID) and for immunomodulation for the treatment of immune thrombocytopenic purpura (ITP). In Europe, Privigen® is also licensed for secondary immune deficiency (SID), Guillain-Barré syndrome and Kawasaki disease.

Treatment with intravenous immunoglobulin (IV-IG) is associated with acute haemolysis and subsequent haemolytic anaemia (HA) due to enhanced red blood cell (RBC) sequestration, and so risk minimization measures are being implemented in the manufacturing process of Privigen®.

After the appearance of an increased number of haemolytic reactions after the administration of Human Normal Immunoglobulin, a comparison of various IV-IGs and the rate of haemolysis reactions were evaluated by the FDA and European Competent Authorities. The analysis of this data showed a signal of disproportionate reporting of haemolysis for IV-IGs including Privigen.

In that context and in connection with CSL Behring's focus on patient's safety, health and well-being, CSL Behring proactively proposed two risk minimization measures in the context of the Privigen RMP Version 2.4, dated 08-Feb-2013 and started with a "Screening of Plasma Donors Step" and is planning the implementation of an "Immunoaffinity Chromatography Step" in the manufacturing process of Privigen; aiming at reduction of the isoagglutinin titres in the final product.

Furthermore, in March 2013, the additional Privigen® indication chronic inflammatory demyelinating polyneuropathy (CIDP) was approved for Privigen® in the European Union. However, only limited experience is available on the safety profile use of IV-IGs in children with CIDP as CIDP is a rare

condition in children. As part of the CHMP positive opinion for the Privigen Type II variation [EMEA/H/C/000831/II/0063: addition of indication Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)] CSL Behring was requested to allow the evaluation of the overall Privigen safety profile in children treated for CIDP in the context of this Post Authorisation Safety Study (PASS) based on the EU European Commission (EC) Decision on 14-Mar-2013 with regard to the granted EU Marketing Authorisation Renewal of Privigen.

The largest database in Europe or the United States with detailed data on treatment with Privigen® is the Premier Perspective™ (hereafter referred to as Premier) database which covers 620 hospitals across the US and includes approximately one-sixth of all hospital discharges in the US.

The study has two objectives, covered in Parts 1 and 2.

Part 1: Haemolytic anaemia (HA)

Treatment with intravenous IV-IG can lead to acute haemolysis and then subsequent haemolytic anaemia (HA) due to enhanced red blood cell (RBC) sequestration from 12 hours to 10 days later. HA is defined as anaemia due to a shortened survival of circulating RBCs. Haemolysis is a known class effect of IV-IGs, and Privigen® is subject to these class effects.

The incidence of HA and of haemolysis in the general population is unknown. Over a 2.5-year observational period, 16 cases of haemolysis were identified in approximately 1000 patients receiving IV-IG (1.6%). Of the 16 cases, 15 had had a high cumulative dose of IV-IG with a total of 100g of IG administered in 2 to 4 days. Therefore, the incidence of HA and of haemolysis will also depend on the proportion of patients who are given high doses of immunoglobulin. [Daw 2008]

[REDACTED]

Haemolysis has been more commonly observed in patients receiving IV-IG for a neurologic illness than in those receiving IV-IG for immune deficiencies. [Wilson 1997] The most likely explanations

for this are (1) the dose-dependent passive transfer of pathogenic blood group antibodies as the cumulative immune modulating dose in neurologic indications, which is five times higher than that for immune replacement [Yin 2008], (2) the passive transfer of ABO isoagglutinins to non-O blood group patients, and (3) the enhanced activity of the immune system in patients with an underlying inflammatory state, with accelerated removal of sensitized RBCs from the circulation. The latter mechanism has been supported by the observation of IV-IG-associated haemolytic reactions in patients with serologic evidence of inflammatory conditions including pneumonia, Kawasaki disease and juvenile dermatomyositis. [Clemenz 2013]

Characteristics predisposing patients to IV-IG-related HA are (i) a high cumulative dose of IV-IG therapy, (ii) non-O blood group, (iii) female gender, and (iv) positive inflammatory serologic markers. [Daw 2008]

The safety of IV-IG is hypothesized to be linked to the levels of antibody titers in IV-IG. [Daw 2008] Given that blood products are pooled from approximately 14,000 recovered or 5,000 source plasma donations, improved safety could be achieved by exclusion of donors with high anti-A and anti-B titers and by introducing manufacturing to further reduce antibody titers.

Since January 2013, CSL Behring screens plasma donors for anti-A titres and excludes high titer donations from manufacturing pools. The wash-out period for the current lots to be completely replaced with the donor-screened lots is about 9 months. Furthermore, CSL Behring will implement an immunoaffinity chromatography step in the manufacturing process of Privigen® to further reduce isoagglutinins (anti-A and anti-B titers) in the final product without affecting product quality.

The aim of Part 1 of this study is to evaluate the effectiveness of the above manufacturing changes.

Part 2: Safety in children with CIDP

An application for the registration of chronic inflammatory demyelinating polyneuropathy (CIDP) as an additional indication for Privigen® was filed in Europe in May 2012. Currently, CSL Behring does not intend to seek approval for the indication CIDP in the US. Chronic inflammatory demyelinating polyneuropathy (CIDP) as an additional indication for Privigen® was approved in the European Union in March 2013. There is only limited experience available on the safety profile of IV-IGs in children with CIDP as CIDP is a rare condition with a prevalence of 5.7 per million under 19 years. [Chio 2007] Based on the US census of 2010 and the Census of 2011 in the England, there are 83.27 million persons of 19 years or younger in the US and 12.7 million in England resulting in an estimated 475 children with current CIDP in the US and 72 in England. Some data are available for off-label use of Privigen® for CIDP in the US. Therefore the safety profile of all children aged 0-18 with CIDP treated with Privigen® will be evaluated in Part 2 of this study. Although any patients in the US treated with Privigen® for CIDP are being treated off-label at present, and the number of cases will be small, this information is considered a valuable addition to the existed safety information.

8. Research question and objectives

The research questions are:

Part 1: Is the risk of haemolytic anaemia lower following implementation of the two risk minimization measures “Screening of Plasma Donors” and implementation of the “Immunoaffinity Chromatography Step in the Manufacturing Process of Privigen®” in the manufacturing process of Privigen®?

Part 2: What is the safety profile of Privigen® in children (0-18 years) with CIDP?

The research objectives are to:

Part 1: Estimate the risk of HA in adults and children before and after implementation of each of the two risk minimization measures

Part 2: Evaluate the safety profile of Privigen® in children (0-18 years) with CIDP, including aseptic meningitis, acute renal failure, anaphylaxis, thromboembolic complications and other AEs.

9. Research methods

Part 1

The first-time occurrence of HA (hereafter referred to simply as incidence of HA) will be estimated in the adult and paediatric population in three different calendar-time periods:

Period 1: The period before implementation of the risk minimisation measure “Screening of Plasma Donors” (Jan 2008 to Dec 2012),

Period 2: The period after implementation of donor screening until implementation of an immunoaffinity chromatography step in the manufacturing process of Privigen® to reduce isoagglutinin titres in the final product, i.e. when almost no old lots manufactured before donor screening are being administered in the US (ca. October 2013 to ca. December 2015),

Period 3: The period after implementation of the immunoaffinity chromatography step in the manufacturing process to reduce isoagglutinin titres in the final products, i.e. when almost no old lots manufactured before using immunoaffinity chromatography are being administered in the US (ca. October 2016 to April 2019).

Part 2

The safety profile in children with CIDP will be assessed over the whole study period, with interim and final analyses performed on the same schedule as the analyses for Part 1.

9.1. Study design

This will be an observational, non-interventional, hospital-based retrospective and prospective cohort study of adult and paediatric patients administered Privigen®. Part 1 of the study, in adults and children, will be conducted in three distinct phases during different calendar-time periods between 2008 and 2019 such that the effects of the risk minimization measures for Privigen® on the study outcomes can be evaluated in a scientifically robust manner. Part 2 of the study in children (aged 0 to 18 years) with CIDP will be conducted over the whole study period.

9.2. Setting

In the US, Privigen® is almost always administered in hospitals either in the inpatient or outpatient setting so this will be a hospital-based study. The study patients' data will be extracted from the Premier database which has data from 620 hospitals across the US and includes approximately one-sixth of all hospital discharges in the US. Some patients are administered Privigen® as inpatients (with overnight stay) and although some patients receive Privigen® as outpatients (ambulatory day-care in hospital).

9.3. Variables

Exposure

The exposure variable of interest is Privigen®. Each treatment episode of Privigen® during the study period will be evaluated. The time period during which the risk of HA related to IV-IG is thought to occur ranges from 12 hours to up 10 days after administration. [Daw 2008] Therefore in both Parts 1 and 2 of the study, the at-risk period begins on the date the first Privigen® infusion is administered, and ends 10 days after the last infusion assuming no subsequent infusion was given. If subsequent infusions are given within 10 days, the treatment episode continues until no infusion is given for 10 consecutive days. If Privigen® is again administered more than 10 days after the last infusion from the prior treatment episode, such treatment will constitute a new treatment episode. As part of the chart review of patients with HA, Privigen lot numbers will be obtained when available; the isoagglutinin titers of the identified Privigen lots (using data on file with the Sponsor) will be reported.

It is expected that most cases of HA will be within the same hospitalization as the administration of Privigen®. However, patients may still be regarded as potential cases after hospital discharge if there is subsequent evidence of HA within 10 days of the last administration of Privigen®, i.e. patients admitted to hospital in a second hospital admission and with HA as a diagnosis on admission.

Patients who switch from treatment with Privigen® after January 2008 to another IV-IG will be censored; subsequent Privigen® treatment episodes after the switch will be excluded from the analysis. Depending on the indication for Privigen® use, the recommended Privigen® dose per treatment episode ranges from 100mg/kg bodyweight every 3-4 weeks for primary immune deficiency

(PID) to 2g/kg bodyweight for chronic immune thrombocytopenic purpura (ITP). Table 1 in Annex 3 contains the recommended doses per indication. The cumulative dose of Privigen® administered can be calculated from the doses recorded in Premier. Therefore, it should be possible to calculate the total Privigen® dose administered during one treatment episode. During the analysis of the first calendar period, the accuracy and plausibility of the data on total Privigen® dose will be explored. If administered dose data are not available, alternative methods to estimate dose of Privigen® (e.g., amount dispensed) will be explored as a proxy for dose administered.

Outcomes

The outcome variable for assessing the effect of the two risk minimization measures in the manufacturing of Privigen® is a diagnosis of HA. HA occurring in patients of any age will be identified from ICD-9 CM codes with or without a code for blood transfusion. Patients with an ICD code for HA listed in Tables 3-4 of Annex 3. A recording of HA diagnosed during the at-risk exposure period of Privigen® will be attributed to Privigen® use. The outcome variables to assess the safety profile of Privigen® administered to children with CIDP, in addition to HA, are diagnoses for aseptic meningitis, acute renal failure, thromboembolic events, anaphylactic reactions, and other adverse events (AEs) possibly associated with Privigen® use. An ICD-9 CM recording of any of the AEs of interest newly diagnosed during the at-risk exposure period of Privigen® will be attributed to Privigen®. With respect to HA diagnoses recorded during a second hospital admission, only those diagnoses present on admission may be considered study outcomes. In the absence of access to haemoglobin concentration results, severity of HA will be defined as non-serious if no blood transfusions are administered and as serious if one or more blood transfusions are administered during the same hospitalisation.

Validation of study outcomes in Part 1

Patients with evidence of HA during the observational period will be identified in the database with the respective ICD-9 CM codes (Tables 3-4, Annex 3). A chart review is planned for a large proportion of the potential HA cases to confirm the diagnosis and severity of HA graded into non-serious and serious HA. The information to be extracted will include blood group, body weight, Privigen® dose, last serum haemoglobin count before the administration of Privigen® and all other serum haemoglobin counts with dates, absolute reticulocyte count, direct Coombs' test, positive direct antiglobulin, haptoglobin, lactate dehydrogenase, unconjugated bilirubin, presence of significant spherocytosis, free haemoglobin in the serum and urine. See Annex 3 for the proposed operational algorithm for validation and grading of severity of potential HA with access to medical charts. All information available in the Premier database on potential HA cases, the information extracted by chart review, and anonymized copies of hospital discharge diagnoses will be provided to medical

experts. The medical experts will review the information available and assess the likelihood of HA, CIDP and the other study outcomes.

Validation of CIDP diagnosis and study outcomes in Part 2

It is intended to conduct a medical chart review of all patients comprising the CIDP cohort to confirm the diagnosis of CIDP and all study outcomes in this cohort recorded with an ICD-9 CM code of aseptic meningitis, arterial or venous thromboembolic events, anaphylactic reactions and acute renal failure. All processes that Premier uses to conduct chart reviews are HIPAA compliant as well as compliant with individual hospital requirements in performing medical record reviews (see section **10. Protection of Human Subjects**).

Chart review process for the manual validation

First, all hospitals will be ranked according to Privigen® use for Part 1 and Part 2 separately. Then, in hospitals with a higher volume of Privigen® use, IRB approval will be sought to get approval for the hospital or a third party to review the patients' charts and to extract disease-specific medical information, laboratory test results and treatment information. This may then be expanded to include all hospitals providing consent depending on the quality of the data and the results of the validation in the first interim analysis piloting this approach.

All information available in the Premier database, the information extracted by chart review, and anonymized copies of hospital discharge diagnoses will be provided to medical experts. The medical experts will review the information available and assess the likelihood of HA, CIDP and the other study outcomes.

In principle it is possible for Premier to contact all the hospitals and to request hospital discharge letters or other clinically relevant information. However, it is not possible to estimate the proportion of hospitals responding to such requests. Therefore, one objective of the analysis of the first calendar period (i.e., during the feasibility/methods development phase) is to set up the logistics including ethics committee approval for requesting additional data. Where chart review is possible, all cases of HA identified from ICD-9 CM codes will be validated using hospital discharge letters and other medical charts in compliance with all applicable privacy laws and regulations. Similarly, the data on all the children with CIDP will be validated as far as possible using hospital discharge letters and other medical charts. Adverse events in Part 2 will be identified by the recording of a discharge diagnosis for aseptic meningitis, acute renal failure, thromboembolic events, and anaphylactic reactions (see Annex 3 for ICD-9 CM codes), and by the manual review of hospital discharge letters for all children with assumed CIDP. All potential cases will be validated using all concomitant medications given during the hospital stay to define the date of the AE occurrence and the likelihood of the specific event.

Further validation will be performed by review of hospital discharge letters and other medical charts in compliance with all applicable privacy laws and regulations. It is to be ensured that the information to be extracted from manual review of discharge letters and other hospital charts is obtained in a standard manner using the same criteria for different types of information. Such criteria will be defined and a checklist prepared after the first interim analysis of this study. These stand-alone documents will be available upon request (see Annex 1).

Risk factors for Part 1 and Part 2

Age, gender, total dose of Privigen®, indication for IV-IG use.

Co-morbidities for Part 1 and Part 2

1. The Charlson Comorbidity Index (CCI) is a single summary score calculated from a set of specific diagnoses that have been shown, in aggregate, to be useful to adjust for confounding by comorbidity in a variety of settings. The CCI is based on: history of anaemia, myocardial infarction, congestive heart failure, cardiac arrhythmias, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, mild liver disease, diabetes, hemiplegia or paraplegia, renal disease, any malignancy including lymphoma and leukaemia except malignant neoplasm of skin, moderate or severe liver disease, metastatic solid tumour, AIDS and HIV. Other comorbidities include renal transplant rejection, hereditary spherocytosis, history of incompatible blood transfusions, or history of autoimmune disorders.

Co-medications and other blood products for Part 1 and Part 2

Use and total dose of other IV-IG products in previous hospitalizations (within the same hospital), previous blood transfusions, history and current use of systemic corticosteroids, cephalosporins, levofloxacin, penicillin and its derivatives, NSAIDs, mycophenolate mofetil and methotrexate.

Potential confounding variables and effect modifiers for Part 1 and Part 2

For Part 1, two potential confounding variables are noted: patient blood group and total Privigen® dose. Blood group will only be obtained for cases of potential HA with medical chart review (see Section 9.9 Limitations of the Research Methods). Potential confounding factors for Part 2 are not identified.

9.4. Data sources

9.4.1 Databases

The database with the largest number of patients treated with Privigen® in Europe or the US is the Premier database from Premier Research Services™, Premier Inc., 13034 Ballantyne Corporate Place, Charlotte, NC 28277.

Initially, to obtain data on European patients, the Hospital Treatment Insights (HTI) database in England was considered. HTI is owned by IMS Health and links data from the IMS Hospital Pharmacy Audit (HPA) and the Hospital Episodes Statistics (HES). However, as of 8 April 2013, the HTI contained only 847 patients with at least one Privigen® administration, including 102 patients below 18 years. Furthermore, medical discharge diagnoses in HES are provided with 4-character ICD-10 codes only, thereby not capturing the 5-character-specific CIDP code.

The Premier database was chosen as a large data source with the potential for validating recorded information. It is a privately-owned dataset that contains data from 620 hospitals across the US, and includes approximately one-sixth of all hospital discharges in the US. Data exist from calendar year 2000 onward. Currently (30 July 2013), the most recent data available is up to December 2012. Patients can be tracked across the inpatient and hospital outpatient settings at the same facility using a unique person identifier. This unique identifier allows the patient to be followed over time for all visits to that provider. All procedures and diagnoses are captured for each patient, as well as all drugs and devices received. Drug utilization information is available and includes date, quantity, dosing, strength used, and cost. Premier is fully compliant with and meets or exceeds all HIPAA privacy and security requirements (see section **10. Protection of Human Subjects**).

To date, the Premier database includes data on over 38 million unique hospital discharges. The Premier database was developed for measuring quality and use of health care. Premier is currently partnered with the FDA to study drug utilization in hospitalized patients. The database is a repository of hospital administrative data. Participating hospitals represent all regions of the US. The hospitals are predominantly middle-sized teaching facilities and serve a largely urban patient population. The patients' ages, gender, lengths of stay, mortality, primary discharge diagnoses, and primary procedure groups seem to be representative of hospitalized patients in the US.

Premier has developed a Standard Product List, with over 44,000 items, of common service charges. Premier has created a "map" that connects each hospital's charge master item with a Standard Product List item. The resulting map is reviewed in detail with hospital finance and clinical department managers to ensure the quality of the resulting data set. All billing and administrative information in the Premier database can be cross-linked to hospital pharmacy billing records. Patient demographic characteristics (age, gender, ethnicity and region), discharge diagnoses, and discharge status (including death, but not its cause) are available for all Premier hospitals. Data from hospital-owned clinics and emergency rooms are included. Service-level data include charges for medications, procedures and laboratory tests, but no laboratory results are available; the characteristics of the hospitals and the study patients' surgeons are also available. In addition to the information available in the standard hospital-discharge file, date-stamped logs of all billed items for each patient, including medications and laboratory, diagnostic, and therapeutic services, are available as well. Premier can access hospital charts for additional clinical data not coded but found in patient medical records, including laboratory

data. All hospitalizations are entered into the database for all payors, not just Medicare. Hospital discharge diagnoses are coded with ICD-9 CM codes while medications are identified using a text description of the product and dose that is contained in the hospitals chargemaster. In 2009 a flag was introduced to indicate which diagnoses were present at hospital admission.

A patient with repeated hospital episodes can only be linked if the patient visited the same hospital. Outpatient medications are not available in the Premier database. Prescription medications dispensed in the community can be made available for a subset of 3 to 8% of patients in the Premier database by a link with the United Healthcare health plan (UHC).

Medical Records for patients in the Premier database may be accessed for review and additional data abstraction as described in section **9.3 Variables, Validation of CIDP diagnosis and study outcomes in Part 2.**

Coding of diseases and hospital medical procedures is with ICD-9 CM. In addition, medical, surgical, and diagnostic services and procedures are described with the Current Procedural Terminology, Fourth Edition (CPT-4). The back-log to include data in Premier is 6 to 7 months.

9.4.2 Study cohort

Part 1

Patients with at least one administration of Privigen®, regardless of whether as an inpatient or outpatient, during the study period will form the study cohort for Part 1 of the study. The date of first administration (index day) defines the patient's cohort entry date (and the start date of the first treatment episode, whether as inpatient or outpatient).

Patients with a history of HA any time before the first administration of Privigen® will be excluded for the outcome HA to avoid potential bias introduced by “channelling” of patients with prior HA to certain treatments. This exclusion will be applied to patients in each successive calendar-time period; a patient with an HA outcome in one period will be excluded from analysis in subsequent calendar-time periods.

The second and third calendar periods will have some patients who are newly entered into the study cohort and some patients who entered earlier and were included in the analysis of previous calendar-time periods. For each new calendar period in the analysis of the adults, patients will have a new index day assigned. The index day in the second and third calendar-time period will be date of the first administration of Privigen® in the respective calendar-time period.

Part 2

CIDP is a chronic and very rare disease with a prevalence of 5.7 per million children of 19 years or younger. [Chio 2007] Based on the US census of 2010 and the Census of 2011 in the UK there are

83.27 million persons of 19 years or younger in the US [Age and Sex Composition: 2010 - US] and 12.7 million in England resulting in an estimated 475 children with current CIDP in the US and 72 in England. Some data are available for off-label use of Privigen® for CIDP in the US. The majority of CIDP patients are managed on an outpatient basis. Patients with CIDP are only admitted as inpatients (with overnight stay) if they are new cases referred for evaluation and treatment, require inpatient rehabilitation, require plasma exchange via central catheter, or for practical reasons as a convenience to the patient and family.

Thus, most children with CIDP will receive their first dose of Privigen® as inpatients and most if not all subsequent doses in outpatient settings. Therefore, in Part 2, any patient aged <18 receiving Privigen® for CIDP will be included, regardless of whether they were treated as an inpatient or as an outpatient. The date of first administration (index day) defines the patient's cohort entry date (and the start date of the first treatment episode).

All children with CIDP aged 0-18 treated with Privigen®, regardless of whether as an inpatient or outpatient, and all their treatment episodes with Privigen® will be included in the analysis, but results will be presented separately for inpatient and outpatient treatment. Patients with CIDP will be identified from all Privigen® users aged 0-18 years with an ICD-9 CM diagnosis Code 357.81 'Chronic inflammatory demyelinating polyneuritis' (see Annex 3, Table 2). It is intended to obtain hospital discharge letters and to review the patient charts (in compliance with all applicable privacy laws and regulations) of all children with a diagnosis of CIDP who are treated with Privigen® in order to validate the indication for Privigen® use and to assess study outcomes. A search will be made for any AEs in the patient charts. However, some hospitals may not agree for the patient charts and discharge letters to be reviewed. In such cases, the ICD-9 CM codes for an AE will be the only way to identify an AE.

9.4.3 Observational period

The total study period for Part 1 will be from Jan 2008 until ca. Dec 2018, separated into the three defined calendar-time periods. The total study period for Part 2 will be over the whole study period until ca. Dec 2018. The observational period covers the time in which the patient is considered to be at risk of the study outcomes or up to censoring.

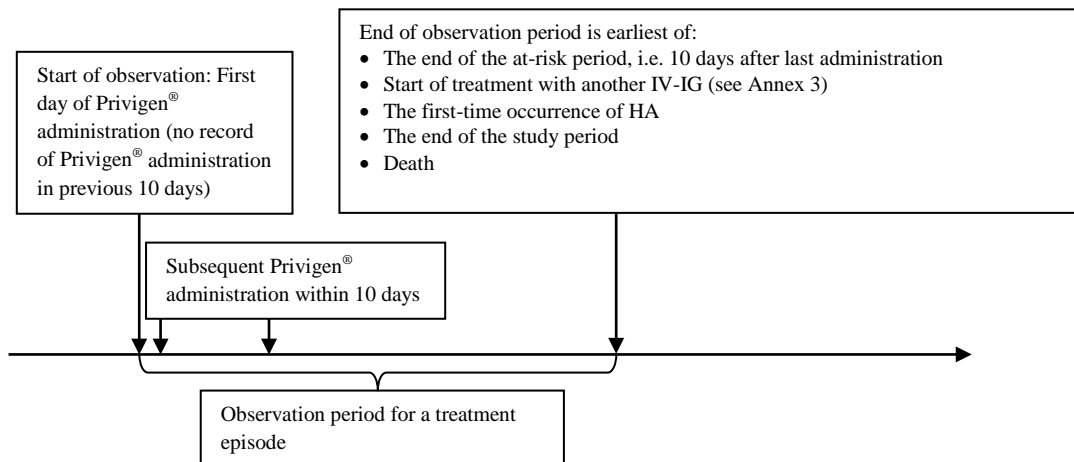
For Parts 1 and 2, patients included in the study will be identified using their date of first inpatient or outpatient administration of Privigen® as their cohort entry date. The observation period for each treatment episode starts with the administration of Privigen® and ends with the earliest of:

- The end of the at-risk period, defined as 10 days after last administration of Privigen®
- Start of treatment with another IV-IG (see Annex 3)
- The occurrence of the outcome of interest

- The end of the study period
- Death

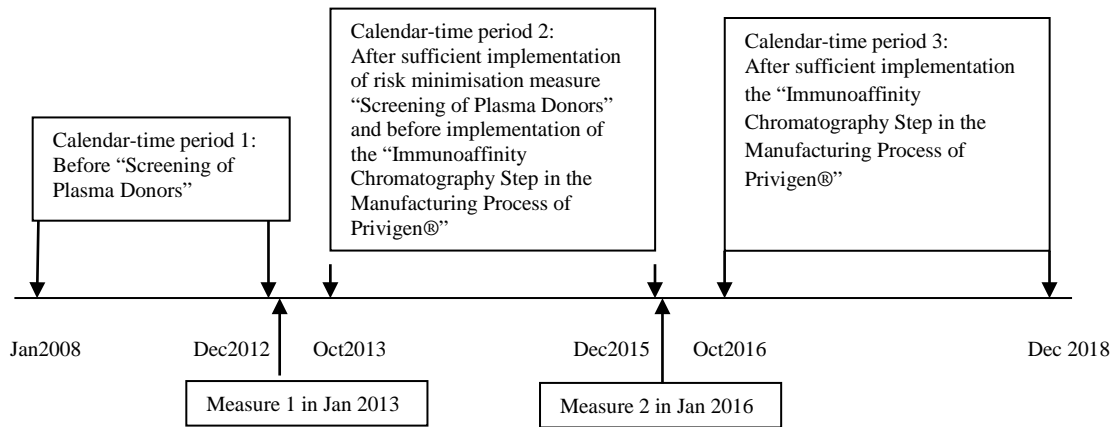
New admissions to hospital with a diagnosis at admission of HA (Part 1) or another study outcome (Part 2) will be identified by an ICD-9 CM code.

Figure 1: Observation period for a treatment episode



Most children with CIDP will receive their first dose of Privigen® as inpatients and all subsequent doses in outpatient settings. Therefore, in Part 2, any patient aged <18 receiving Privigen® for CIDP will be included, regardless of whether they are treated as an inpatient or as an outpatient. The date of first administration (index day) defines the patient's cohort entry date (and the start date of the first treatment episode). The at-risk period of 10 days will be the same as for patients in Part 1, but keeping in mind that there is limited surveillance for adverse events in outpatients treated with Privigen® (see Section 9.9 on Study Limitations).

Figure 2: The three expected calendar-time periods for evaluating HA



Note, the dates of sufficient implementation of the risk minimisation measures need to be confirmed, and if the date of measure 2 changes, this will change the corresponding calendar-time periods 2 and 3.

9.5. Study size

All available patients meeting criteria for entry in to the study will be included in each phase of the study.

As of 30 July 2013, the Premier database contained approximately 25,000 in- and outpatients (9100 inpatients and 15,800 outpatients) with at least one inpatient Privigen® administration during the period 1 Jan 2008 through 31 Dec 2012. Of those, 2417 were below the age of 18 years (Table 1). These approximately 25,000 patients have received approximately 39,000 patient-days of Privigen® treatment (19746 days for 9149 inpatients and 19266 days for 15854 outpatients). Information concerning the dose of Privigen® received will be provided in the Interim Report 1 which is scheduled for 15 Oct 2014.

In the Premier database there are 7 CIDP patients aged <18 who have received Privigen® over 46 treatment episodes (21 as inpatients and 25 as outpatients).

Table 1: Number of unique patients receiving Privigen® in Premier during the period 1 Jan 2008 through 31 Dec 2012 (as of 30 July 2013)

Inpatients and outpatients			Inpatients			Outpatients		
All ages	Ages <18	Ages ≥18	All ages	Ages <18	Ages ≥18	All ages	Ages <18	Ages ≥18
25,003	2417	22,586	9149	1634	7515	15,854	783	15,071

Among the patients with at least one inpatient Privigen® administration, [REDACTED] patients had a diagnosis of HA in his/her record ([REDACTED] among inpatients and [REDACTED] among outpatients). Therefore, the estimated crude incidence rate of HA per 100 person-days of treatment for inpatients was [REDACTED]. A more precise estimate of the incidence rates of HA among patients at risk during and following Privigen® administration, and the severity of those events, will be provided in the Interim Report 1.

The expected risk reduction in the incidence of HA following the introduction of the risk minimization measures is not known. The statistical power of the study to detect different reductions in the incidence of HA between period 2 and period 1 (baseline), and periods 3 and period 1, is estimated using the asymptotic power of the Wald's test for Poisson regression [Lyles 2007]. Power calculation for the specified comparisons is based on the above estimated crude rates of HA

[REDACTED]

[REDACTED] Under these assumptions, the study is estimated to have the statistical power (with one-sided alpha = 0.025) as shown in Table 2 for different reductions of incidence rates of HA in period 2 compared to period 1 (baseline), and of different reductions in period 3 compared to period 1.

Table 2: Estimated statistical power to detect varying levels of HA incidence rate reduction during periods 2 vs. period 1, and period 3 vs. period 1 (with one-sided alpha = 0.025)

Assumed reduction in HA incidence rates in period 2 vs. period 1	Estimated statistical power*		Assumed reduction in HA incidence rates in period 3 vs. period 1	Estimated statistical power*
5%	0.069		5%	0.072
10%	0.157		10%	0.169
15%	0.303		15%	0.328
20%	0.491		20%	0.531
25%	0.684		25%	0.728
30%	0.838		30%	0.874
35%	0.933		35%	0.954
40%	0.978		40%	0.987
* Lyles RH, Lin HM, Williamson JM. A practical approach to computing power for generalized linear models with nominal, count, or ordinal responses. Stat Med. 2007 Mar 30;26(7):1632-48. PubMed PMID: 16817148.				

9.6. Data management

The study data will be collected by Premier Research Services™.

Data retrieval and preparation of data for delivery to the principal investigator (PI) will be done by Premier Research Services™. The validity of the data and the quality of the data management is the responsibility of Premier Research Services™. Programs used to retrieve the data and to prepare the data sets for delivery to the PI will be archived by Premier Research Services™ for the period required.

9.7. Data analysis

For the Part 1 objective to estimate the incidence of HA in adults and children before and after implementation of each of the two risk minimization measures, the interpretation of the results will focus on the observed incidence rates of HA (and their precision) during the study periods, the clinical meaningfulness of the differences in incidence rates over time, and the apparent validity of any inferences concerning the effect of the risk minimization measures on those differences. Irrespective of the statistical significance of the results all findings will be interpreted taking into account the absolute changes in incidence rates observed, the observational nature of the study design and the potential for bias or confounding that may potentially affect the results, as discussed in **9.9. Limitations of the Research Methods.**

Analyses will be conducted by the PI or a delegated specialist. The grouping of characteristics and building of analytic models will be determined using an iterative process that includes inspection of the data to determine the most reasonable and appropriate methods. All treatment episodes (whether inpatient or outpatient) occurring after an outcome event of interest (HA or an AE in children) within the same calendar period will be excluded from the respective analyses for that outcome event.

9.7.1 Part 1 – incidence of HA before and after implementation of the risk minimisation measures

Descriptive summary statistics of demographic and medical history data, including age, gender, ethnicity, indication for Privigen® use, underlying diseases, previous use of other IV-IG, Charlson comorbidity index, concomitant diseases and medications will be presented as of the index day (first administration of Privigen® in the calendar-time period) for each of the 3 separate calendar-time periods. The number of administrations and the number of treatment episodes with administration of Privigen® in each patient during each study period and overall, as well as the total dose and the average dose over different treatment episodes, will be summarized.

The number of treatment episodes that were fully inpatient, fully outpatient or mixed inpatient and outpatient administrations will be summarized for each study period and overall; summary statistics on

the total dose and the average dose over different types of treatment episodes (inpatient, outpatient or mixed) will also be provided.

The characteristics of patients with HA will be described. Lot numbers for the Privigen received by these patients will be obtained when available, and the isoagglutinin titers of the identified Privigen lots (using data on file with the Sponsor) will be reported.

The crude incidence of HA for the total of all administrations of Privigen® will be provided with a confidence interval over all age groups for each of the 3 separate calendar-time periods whereby each treatment episode will be a unit in the analysis. Cox regression models will be used to derive hazard ratios for period 2 vs. period 1 (baseline) and period 3 vs. period 1 (baseline). Adjustment will be performed for all potential confounders available in the Premier database.

Depending on the number of HA cases, the overall incidence of HA will be adjusted to the ratio of inpatient to outpatient administrations, Charlson comorbidity index, concomitant diseases and medications, and to the distribution of indications for Privigen® use in the first period. Incidence estimates of HA will also be presented separately for inpatient and outpatient treatment episodes, and for first and subsequent treatment episodes in the inpatient and outpatient setting. Furthermore, incidence estimates will be adjusted for indication for Privigen® use as the overall incidence will be influenced by indication for Privigen® use since different indications require different dose regimens. Patients with multiple Privigen® exposure episodes during a calendar-time period will have multiple entries in the analysis for that period.

Results will also be presented separately for inpatient and outpatient treatment episodes that are for first recorded Privigen® use only (i.e. also no previous record of outpatient use). Repeat use will also be evaluated separately to assess whether the crude incidence of HA among new and repeat users of Privigen® is uniform.

As Privigen® was launched in February 2008 in the US it is likely that Privigen®-treatment-naïve patients can be identified in Premier.

For the crude incidence rate calculations, the numerator will be the number of treatment episodes with an outcome event during the corresponding exposure period, and the denominator will be the number of treatment episodes, with the result expressed as a percentage.

For the analysis using just first exposures, the numerator will be the number of patients with an outcome event during their first exposure period, and the denominator will be the number of patients with a first exposure, again expressed as a percentage.

The feasibility of performing these analyses will depend on the number of Privigen® users in the Premier. The number of first and repeat Privigen® users by calendar year seen in the first period before implementation of the risk minimisation measure “Screening of Plasma Donors” will help

determine the ultimate duration needed to conduct the study and the expected power to detect differences in the incidence of HA before and after the implementation of the two risk minimization measures. The comparison in the study of the incidence rate of HA in the three calendar-time periods of interest will require the standardization of the Privigen® population at risk and stratification by Privigen® total dose. Therefore, the characteristics of the Privigen® population in the first calendar-time period will be used to standardize the overall incidence rate of HA and of serious HA in subsequent calendar-time periods. Standardization will include age band, gender, cumulative Privigen® dose (or proxy), proportion of inpatient treatment episodes and indication for Privigen® use.

Using this same dataset of treatment episodes, the association between cumulative Privigen® dose and HA will be estimated by stratification of incidence rates of HA by cumulative dose.

For the analysis of cumulative exposure, each treatment episode will be identified as with either a high or a low cumulative dose of Privigen®, and rates will be calculated for the high and the low cumulative dose episodes. Daw [2008] used a definition of a high cumulative dose for adults of ≥ 100 grams of IV-IG. However, it is proposed for this study to define high and low doses depending on the observed distribution of cumulative doses over all the treatment episodes. For example, the median or the upper quartile cumulative dose in treatment episodes from calendar-time Period 1 could be used to define low and high doses, and this definition could be used for the subsequent periods, or cut-points for low, medium and high could be obtained from the tertiles. Different cut-points will be necessary for children and possibly also for men and women.

Treatment episodes occurring after an outcome event of HA will not be included in these analyses of cumulative dose. For the analysis of high cumulative dose, the numerator will be number of high cumulative dose treatment episodes with an outcome event during the corresponding exposure period, and the denominator will be the number of high cumulative dose treatment episodes, again expressed as a percentage. The corresponding proportion will be calculated for the treatment episodes with a low cumulative dose of Privigen®.

All HA cases will be summarized in a table which will include the age, gender, indication, concomitant diseases and medications, cumulative IV-IG dose in mg, cumulative Privigen® dose in mg, Privigen® dose in the episode with HA in mg, estimated cumulative Privigen® dose in mg/kg body weight, estimated Privigen® dose in the episode with HA in mg/kg body weight, assumed body weight, body weight as extracted from medical charts, blood group, severity grade of HA, number of blood transfusions in the episode with HA, and HA laboratory signs during the episode with HA as listed in Annex 3. The assumed body weight for men and women in different age groups can be obtained from summary statistics of US median weights, although it is noted that patients requiring

Privigen® will tend to have lower body weight than others of the same age and gender in the general population.

Analyses will be presented overall and for adults and children separately.

9.7.2 Part 2 – safety profile in children with CIDP

Descriptive summary statistics of demographic and medical history data, including age, gender, socioeconomic status, ethnicity, underlying diseases, previous use of other IV-IG, concomitant medications and Charlson comorbidity index will be presented as of the index day (first administration of Privigen® in the study). The number of administrations and the number of treatment episodes with administration of Privigen® in each patient, as well as the total dose and the average dose over different treatment episodes, will be summarized. Results will be presented on cumulative data over the whole study period. Since most children with CIDP will receive their first dose of Privigen® as inpatients and all subsequent doses in outpatient settings, a treatment episode may include both inpatient and outpatient administrations. The number of treatment episodes that were entirely as an inpatient, the number that were mixed as inpatient and outpatient, and the number that were entirely as an outpatient will be summarized. The number of inpatient and the number of outpatient administrations and the total number of administrations for each child in the study cohort will also be summarized. Summary statistics on the total dose and the average dose over different treatment episodes will be provided.

For the treatment episodes including some inpatient observation, the incidence will be provided for aseptic meningitis, acute renal failure, thromboembolic events, anaphylactic reactions, and other AEs possibly associated with administration of Privigen®. Only descriptive results will be provided, and no statistical tests will be performed. The overall crude incidence for each AE of interest will be provided in each report, and updated when additional data become available; in other words each successive report will present cumulative results to date. Thus, in the final report, results will be provided for the whole study period to ca. Dec 2018. For these rates, the numerator will be the number of episodes with the outcome event and the denominator will be the number of treatment episodes, expressed as a percentage.

Some children may have had their first Privigen® dose as an inpatient in one hospital and then continue with their long-term Privigen® treatment at a local hospital day clinic as an outpatient. The data from the different hospitals cannot be linked so such a patient would be counted as two different patients in the database (if both hospitals are participating hospitals in Premier). Therefore, only rates by treatment episode will be presented, whereby subsequent treatment episodes from patients with an outcome event will be excluded from the analysis of the respective outcome. Results will also be presented by categories of cumulative Privigen® dose. The incidence of the AEs of interest will also be

reported for treatment episodes of Privigen® only covering outpatient visits, but keeping in mind that detection of AEs during the short hospital visit (day-care) is limited.

9.8. Quality control

9.8.1. Database updates and data management procedures

The 620 participating hospitals send Premier data files monthly via a secure FTP site (80% of data are submitted monthly and available approximately 45-60 days post-discharge; the other 20% of data are submitted quarterly and are available approximately 60 days post quarter-close).

Master files include: department codes, charge codes, physicians and physician specialties, payors, patient types, and pharmacy file.

Mapping files: Premier has developed a standard set of “mappings” to compare patient data and hospital information including: physician specialties, payors, patient type, CDM Codes, UB92 Codes (admission source, admission type, discharge status).

Patient Detail files include: discharge summary (patient ID, physicians, demographic information), patient billing (patient ID, charge code, quantity, total charge, total cost), CPT (patient ID, CPT-4/HCPS codes), ICD (patient ID, ICD-9 admitting, diagnosis and procedure codes)

9.8.2. Data cleaning and Editing Procedures

Once Premier receives the data, it is imported into their “engine” where the mapping, error correcting, and quality assurance analysis takes place. Data are validated by verification of file formats and record counts. Total discharges, charges, and costs calculated from the records are compared to the totals submitted by the hospital. Should there be any discrepancy the entire file is returned to the hospital for correction and resubmission. The data undergo an initial reconciliation when the totals on the discharge data tape are compared to financial data submitted separately by the hospital. This comparison allows for a limited variance between the totals, e.g., discharges from both sources cannot vary more than 0.5%. If the variance threshold is exceeded the entire tape is returned to the hospital for correction and resubmission.

Data in each record are compared to acceptable values and ranges. Codes are compared to code master tables. Records in error are returned to the facility for correction within seven days. Once data are corrected, a final reconciliation process is repeated to ensure that the corrected data have not resulted in a discrepancy between the discharge records and the financial data. Data then undergo review to determine if the values are consistent with what would be expected from a clinical quality assurance perspective, e.g., anaesthesia time and operating theatre time must be within a certain range of each other.

A final review of the data is performed manually to check for errors that cannot be found through automated processes, e.g., is the outlier percentage consistent with other values. Once all validations are complete, the data are moved to the Perspective Data Warehouse. Once data are in the warehouse one more check is made. The current data file is compared to historical patterns to see if the number of cases with specific characteristics varies from the hospital's historical experience. These data in the Perspective Data Warehouse are those on which subsequent analyses are performed.

9.9. Limitations of the research methods

Definition of study cohort as without prior outcome event

The study populations for both Parts 1 and 2 of this study include patients with at least one dispensing for Privigen® in a US hospital. In Part 1 and in Part 2, patients with a prior outcome event will be excluded from the analysis of that event. This is done to avoid the potential for channelling bias in the assessment of the outcome with the exposure introduced by treatment decisions (e.g., changes in dose, switching to another treatment, enhanced surveillance for signs of the outcome event) made by clinicians with knowledge that a given patient previously suffered from the outcome event. Thus, the interpretation of the results must take into account the fact that the outcomes are new incident events.

Inclusion of inpatient and outpatient Privigen® treatment episodes in Part 1

Patients receiving Privigen® in the outpatient setting, such as a day clinic, and then discharged home are less likely to get an HA diagnosis as Premier does not include diagnoses and therapies in primary care. HA could be recorded in patients administered Privigen® in the outpatient setting if (1) HA occurred during the outpatient visit, (2) another complication during the outpatient visit required hospitalization thereby increasing the chance of detection of HA, or (3) HA developed after the outpatient hospital visit and required hospitalization. As outpatients are less likely to be diagnosed with HA and any such diagnosis may not be recorded in Premier, the inclusion of outpatients may result in an underestimation of the risk of HA. For this reason it was opted to provide an overall incidence of HA in the inpatient and outpatient setting and also to provide stratified incidence estimates. To be able to compare the overall incidence of HA for the three periods of the study, it will be necessary also to adjust or to standardise the incidence estimates according to the ratio of inpatient and outpatient treatment episodes with Privigen®.

Evaluation of outpatient Privigen® treatment episodes in Part 2

Since most children with CIDP will receive their first dose of Privigen® as inpatients and all subsequent doses in outpatient settings, the data from their outpatients episodes will also be evaluated. However, as mentioned for Part 1, AEs are less likely to be recorded in connection with outpatient visits so data will be limited.

Lack of patient identifier across different hospitals

Patients can only be tracked across the inpatient and hospital outpatient settings at the same facility using a unique person identifier. However, admissions to a different hospital for a study outcome that occurs within 10 days of the last Privigen® treatment will not be detected. This will lead to an underestimate of the incidence, which may be higher in the outpatient setting.

Evaluation of severity of HA in Part 1

The identification of cases of HA will be from specific ICD-9 CM codes for HA with or without an ICD-9 CM code for blood transfusion (see Annex 3, Tables 3-5). As the date and hour of in-hospital administered medications, blood products and interventions are available in the database, it will be evaluated whether HA-specific treatment could be used to validate the HA diagnosis and indicate the severity of the HA. Another approach to assess the severity of HA is the review of hospital discharge letters and other hospital charts for changes in the haemoglobin levels, but it is possible that some hospitals will not provide the medical charts and discharge records of the patient with HA. The presence of codes for blood transfusions in a patient's record and laboratory test results may indicate the severity of HA. Only blood transfusions in association with HA will be used to define serious HA. Some mild, sub-clinical cases of HA may be unrecorded.

Potential for variability among patients in risk of outcomes

There may be relevant differences between patients with only one episode of IV-IG use and those with many episodes, but each episode will be treated equally in the analysis of all treatment episodes. Results will also be presented separately for all treatment episodes that are for first recorded IV-IG use with an IV-IG treatment-free period of at least 182 days and for all treatment episodes that are for a repeat use.

Non-O blood group is a known important risk factor for HA. [Privigen® Summary of Product Characteristics] In this study, data on blood group will only be obtained for patients with potential HA and in whom medical chart review is possible. Thus, it will not be possible to standardize incidence rates of HA among different time periods by blood type. Differences in blood group will only confound the comparison of HA incidence rates for the different calendar periods if the decision to treat with Privigen® changes over time depending on knowledge about risks for patients with non-O-blood group.

Exposure details

The actual dose of Privigen® expressed as mg per kilogram bodyweight administered to the patient will not be available for all patients; it will be available only for those patients with potential HA and in whom medical chart review is possible. Therefore, for dose-related analyses the total amount of Privigen® dispensed to the patients will be used.

First-time treatment with Privigen® and cumulative dose

It will not be known if patients were previously treated with Privigen® in another hospital as only links to previous hospitalizations within the same hospital can be made. Therefore, some patients noted as having first-time treatment with Privigen® may in fact have had previous administrations of Privigen® in other hospitals. This also means that the estimated cumulative dose of Privigen® would be too low for such patients.

Potential for information bias due to changes in the ascertainment, classification and recording of HA over time in Part 1

Because of the publicity and awareness of HA in association with IV-IG use, it is possible that true cases of HA that were previously coded with the unspecific ICD-9 CM term “Anaemia unspecified” are now coded as HA. Furthermore, milder cases of HA may become more likely to be recorded in the future. Thus, the diagnostic bias with milder cases of HA now being recorded as HA and the shift from unspecified anaemia to HA may contribute to masking the effectiveness of manufacturing changes. Thus information bias (case misclassification) will result if there are changes in the surveillance or in the coding over time (as mentioned due to changes in the validity of the ICD-9 coding for HA or for example due to a new health reimbursement formula), and the bias would lead to an apparently increased or decreased incidence of HA.

Another information bias (exposure misclassification) will result if cases of HA linked with Privigen® use are not detected in the Premier database because they were diagnosed and handled outside the hospital setting, or if they required hospitalization in a different hospital from where the Privigen® was administered. This underestimation of HA will only be a problem if the degree of underestimation changes across the 3 calendar-time periods.

Information bias will be addressed by two approaches. The first will be to estimate the quarterly incidence of HA in order to detect any trends within the calendar-time periods. If there are changes within a calendar-time period, then we would need to adjust for this in the comparisons across the three calendar-time periods. Thus, to meet the study objectives, it is not necessary to estimate the extent of underestimation but to determine whether there was any change, and then if necessary to standardize or adjust for (relative) changes in the HA incidence over time within a study period.

The second approach will be by medical chart review to detect any changes over time in whether cases are recorded as HA. Haemoglobin levels before and after Privigen® administrations are not available in Premier, but the medical charts and discharge records of all HA cases will be reviewed.

Haemoglobin levels before and after Privigen® administration will be extracted to assess the proportion of HA cases with haemoglobin changes of more than 20 g/L, and the proportion requiring blood transfusions will also be evaluated, again looking at quarterly results within the calendar-time periods to detect trends.

Change in the proportion with high dose Privigen® in the three time periods.

IV-IG is increasingly used for immunomodulation in adults and children, and immunomodulation requires high doses of IV-IG. If the risk of HA is associated with the dose of IV-IG, then an increase of the proportion of IV-IG users with high doses could result in an apparent increase of the incidence of HA even if the dose-specific incidence of HA and other AEs is reduced. Therefore, the comparison of incidence estimates for the three time periods will be stratified by total IV-IG dose.

Small numbers of children with CIDP treated with Privigen®

Since CSL Behring is currently not intending to seek approval for Privigen® for the indication CIDP in the US, all Privigen® use for CIDP in the Premier database is off-label. This will limit the number of patients available for analysis.

Collection of Privigen lot numbers in patients with HA

The Premier database does not contain information about Privigen lot numbers. The data may be available in the patient charts. All attempts will be made to collect Privigen lot numbers as part of the chart review of patients with HA. The isoagglutinin titers of the identified Privigen lots (using data on file with the Sponsor) will be reported. It will not be possible to estimate incidence rates of HA according to Privigen lot number nor to the titer of specific lots because the lot numbers will not be collected for patients who do not experience HA. The study is designed such that the different study periods serve as a proxy measure of the changes in manufacturing processes (and isoagglutinin titers) for Privigen (see Figure 2 in section 9.4.3 Observational period).

9.10. Other aspects

Not applicable

10. Protection of human subjects

This will be a retrospective and prospective analysis of data in the Premier database. Identification of individual patients will not be possible, and so there will be no risk to patients as a result of the study. Premier is fully compliant with and meets or exceeds all HIPAA privacy and security requirements. De-identification policies and practices ensure that Premier meets all HIPAA requirements. Premier will not use or disclose Personal Healthcare Information (PHI) received from Premier customers except as authorized by Premier customer contracts or otherwise permitted under the law. Premier has adopted administrative, technical, and physical safeguards as part of the Premier Corporate Information Security Program to protect the privacy of PHI.

All processes that Premier uses to conduct chart reviews are HIPAA compliant as well as compliant with individual hospital requirements in performing medical record reviews. Reviewers are generally

clinicians (nurses, pharmacists, doctors, etc.) with experience in chart reviews. In some cases licensed Medical Records Technicians may be used. Some protected patient information is required in order to identify the records of interest. Handling of that data as well as the handling of the abstracted data is detailed in the Study Protocol that is submitted by Premier to its regional IRB as well as each hospital's IRB, if required. Patient level data or abstracted data that could be used to identify an individual patient is not shared directly with Study Sponsors.

All data is compliant with current US Department HHS HIPAA guidelines. Accordingly, no raw de-identified data is allowed to be delivered outside of US borders. Additional restrictions of data may be applied due to Data Use Agreements between Premier and the submitting hospitals.

11. Management and reporting of adverse events/adverse reactions

This is a non-interventional study based on secondary use of data; therefore AE reporting is not required and will not be done. The AEs specified as study outcomes for analysis in this protocol will be summarised in aggregate in the study reports.

12. Plans for disseminating and communicating study results

The results of the study will be published in a peer-reviewed journal. The final study report will be posted on the EU PAS Register.

13. References

- Age and Sex Composition: 2010 - U.S. Department of Commerce Economics and Statistics Administration U.S Census Bureau. Available from <http://www.census.gov/prod/cen2010/briefs/c2010br-03.pdf>, accessed 10 April 2013
- Chiò A, Cocito D, Bottacchi E, Buffa C, Leone M, Plano F, Mutani R, Calvo A; PARCIDP. Idiopathic chronic inflammatory demyelinating polyneuropathy: an epidemiological study in Italy. *J Neurol Neurosurg Psychiatry*. 2007 Dec;78(12):1349-53. Epub 2007 May 10. PubMed PMID: 17494979; PubMed Central PMCID: PMC2095630.
- Clemenz MR, McGowan Iv JW, Shuler MJ, Lynn AW. Intravenous immunoglobulin-induced hemolytic anemia in a patient with juvenile dermatomyositis. *J Drugs Dermatol*. 2013 Jan 1;12(1):111-3.
- Daw Z, Padmore R, Neurath D, Cober N, Tokessy M, Desjardins D, Olberg B, Tinmouth A, Giulivi A. Hemolytic transfusion reactions after administration of intravenous immune (gamma) globulin: a case series analysis. *Transfusion*. 2008;48:1598-601.

European database of suspected adverse drug reaction reports. Available from:

<http://www.adrreports.eu/dashboards/20130202/product/PRIVIGEN.pdf>, accessed 6 March 2013.

FAERS, FDA Adverse Event Reporting System until Q2 2012. Available from:

<http://www.drugcite.com/indi/?q=PRIVIGEN&s=&a=&i=HAEMOLYTIC+ANAEMIA>, accessed 6 March 2013.

Gamunex®-C Dosing and administration. Available from: <http://www.gamunex-c.com/html/hcp-about-gamunex-c-dosing-and-administration.htm>, accessed 4 April 2013.

Lyles RH, Lin HM, Williamson JM. A practical approach to computing power for generalized linear models with nominal, count, or ordinal responses. *Stat Med.* 2007 Mar 30;26(7):1632-48. PubMed PMID: 16817148.

Immune Globulin Intravenous (IGIV) Indications in the US. Available from

<http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm133691.htm>.

Privigen® Summary of Product Characteristics]. Available from:

<http://www.medicines.org.uk/emc/medicine/21359/SPC/Privigen+100mg+ml+solution+for+infusion/>, accessed 5 April 2013.

Wilson JR, Bhoopalam H, Fisher M. Hemolytic anemia associated with intravenous immunoglobulin. *Muscle Nerve.* 1997 Sep;20(9):1142-5.

Yin F, Nesbitt JA, Tobian AA, Holt PA, Mikdashi J. Hemolytic anemia following intravenous immunoglobulin administration. *Am J Hematol.* 2008 Oct;83(10):825.

Annex 1. List of stand-alone documents*

Number	Document reference number	Date	Title
1	To be determined	To be determined	Procedures for validation of CIDP, HA, other defined study outcomes and adverse events by review of hospital charts and discharge letters will be determined during the feasibility/methods development phase (Part 1) of the project
* Available upon request			

Annex 2. ENCePP Checklist for Study Protocols (Revision 2, amended)

Study title:

Privigen® use and haemolytic anaemia in adults and children and the Privigen® safety profile in children with CIDP – an observational hospital-based cohort study in the US

Study reference number:

<u>Section 1: Milestones</u>	Yes	No	N/A	Page Number(s)
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection ¹	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7
1.1.2 End of data collection ²	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7
1.1.3 Study progress report(s)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7
1.1.4 Interim progress report(s)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7
1.1.5 Registration in the EU PAS register	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
1.1.6 Final report of study results.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7

Comments:

Registration in the EU PAS register to be determined

<u>Section 2: Research question</u>	Yes	No	N/A	Page Number(s)
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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7-8
2.1.2 The objective(s) of the study?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	10
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	11

¹ 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.

² Date from which the analytical dataset is completely available.

<u>Section 2: Research question</u>	Yes	No	N/A	Page Number(s)
generalised)				
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
2.1.5 If applicable, that there is no <i>a priori</i> hypothesis?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

This is a descriptive study and no formal hypothesis will be tested

<u>Section 3: Study design</u>	Yes	No	N/A	Page Number(s)
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	11
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	12
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	21-22

Comments:

<u>Section 4: Source and study populations</u>	Yes	No	N/A	Page Number(s)
4.1 Is the source population described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	11
4.2 Is the planned study population defined in terms of:	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	10
4.2.1 Study time period?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	17
4.2.2 Age and sex?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	11
4.2.3 Country of origin?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	11,15

<u>Section 4: Source and study populations</u>	Yes	No	N/A	Page Number(s)
4.2.4 Disease/indication?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
4.2.5 Co-morbidity?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
4.2.6 Seasonality?				
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	16-17

Comments:

Age applicable to Part 2 of the study

<u>Section 5: Exposure definition and measurement</u>	Yes	No	N/A	Page Number(s)
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	11-12,16
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	27
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	17-18
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	11
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	21-22

Comments:

5.4 At-risk period for exposure time is derived from the literature

<u>Section 6: Endpoint definition and measurement</u>	Yes	No	N/A	Page Number(s)

<u>Section 6: Endpoint definition and measurement</u>	Yes	No	N/A	Page Number(s)
6.1 Does the protocol describe how the endpoints are defined and measured?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	12-14
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	12-13

Comments:

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<u>Section 7: Confounders and effect modifiers</u>	Yes	No	N/A	Page Number(s)
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	14
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	27

Comments:

Effects modifiers addressed for Part 1

<u>Section 8: Data sources</u>	Yes	No	N/A	Page Number(s)
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	14-17
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	12-14
8.1.3 Covariates?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	14
8.2 Does the protocol describe the information				

<u>Section 8: Data sources</u>	Yes	No	N/A	Page Number(s)
available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	17
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	12
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	14
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	16
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	16
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	15

Comments:

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<u>Section 9: Study size and power</u>	Yes	No	N/A	Page Number(s)
9.1 Is sample size and/or statistical power calculated?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	19-20

Comments:

<u>Section 10: Analysis plan</u>	Yes	No	N/A	Page Number(s)
10.1 Does the plan include measurement of excess risks?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
10.2 Is the choice of statistical techniques described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	21-24

<u>Section 10: Analysis plan</u>	Yes	No	N/A	Page Number(s)
10.3 Are descriptive analyses included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	21-22
10.4 Are stratified analyses included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	19,20,23
10.5 Does the plan describe methods for adjusting for confounding?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	22
10.6 Does the plan describe methods addressing effect modification?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	23

Comments:

10.5 and 10.6 addressed for Part 1

<u>Section 11: Data management and quality control</u>	Yes	No	N/A	Page Number(s)
11.1 Is information provided on the management of missing data?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	25-26
11.3 Are methods of quality assurance described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	25-26
11.4 Does the protocol describe possible quality issues related to the data source(s)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	25-26
11.5 Is there a system in place for independent review of study results?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

Comments:

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<u>Section 12: Limitations</u>	Yes	No	N/A	Page Number(s)
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	26-29

<u>Section 12: Limitations</u>	Yes	No	N/A	Page Number(s)
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)				
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	19-20
12.3 Does the protocol address other limitations?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	26-29

Comments:

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<u>Section 13: Ethical issues</u>	Yes	No	N/A	Page Number(s)
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
13.2 Has any outcome of an ethical review procedure been addressed?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
13.3 Have data protection requirements been described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	29

Comments:

Ethical review will only applicable to chart review of selected cases and will follow procedures already established by Premier.

<u>Section 14: Amendments and deviations</u>	Yes	No	N/A	Page Number(s)
14.1 Does the protocol include a section to document future amendments and deviations?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6

Comments:

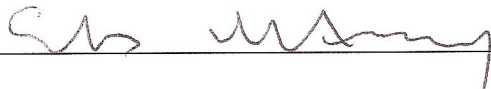
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Section 15: Plans for communication of study results	Yes	No	N/A	Page Number(s)
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6
15.2 Are plans described for disseminating study results externally, including publication?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	30

Comments:

Name of the main author of the protocol: Carlos Martinez

Date: 17 Dec 2013

Signature:  _____

Annex 3. Additional information

Procedures for validation and grading of HA and HA severity

For the purpose of a standardised case definition of HA in the presence of additional data to be abstracted from medical charts and review, the following operational definition of HA is proposed. The proposed list may be adapted by the clinical experts and may also serve a form for the data to be abstracted from medical charts.

1. Definition of HA for potential HA cases with access to medical charts:

The following laboratory signs must be present:

1. a fall of at least 10 g/L in haemoglobin (Hb)

AND

2. a positive direct antiglobulin test (DAT)

AND

3. at least two of the following:

- a. increased reticulocyte count
- b. increased lactate dehydrogenase
- c. low haptoglobin
- d. unconjugated hyperbilirubinaemia
- e. haemoglobulinaemia
- f. haemoglobinuria
- g. presence of significant spherocytosis

2. Severity Grade for HA in the presence of haemoglobin concentration results:

Non-serious HA:	Hb fall \leq 20 g/L, if starting Hb \leq 100 g/L OR Hb fall of \leq 30 g/L, if starting Hb $>$ 100 g/L
Serious HA	Hb fall $>$ 20 g/L, if starting Hb \leq 100 g/L OR Hb fall $>$ 30 g/L, if starting Hb $>$ 100 g/L

**Table 1a: Priviligen® dosage recommendations by indication for adults and children
[Priviligen® Summary of Product Characteristics]**

	Dose	Frequency of injections
<u>Replacement therapy</u>		
Primary immunodeficiency (PID)	Starting dose: 0.4-0.8 g/kg bw Thereafter: 0.2-0.8 g/kg bw	Every 3-4 weeks to obtain IgG trough levels of at least 5-6 g/l
Secondary immunodeficiency	0.2-0.4 g/kg bw	Every 3-4 weeks to obtain IgG trough levels of at least 5-6 g/l
Congenital AIDS	0.2-0.4 g/kg bw	Every 3-4 weeks
Hypogammaglobulinaemia (< 4 g/l) in patients after allogeneic haematopoietic stem cell transplantation	0.2-0.4 g/kg bw	Every 3-4 weeks to obtain IgG trough level above 5 g/l
<u>Immunomodulation:</u>		
Primary immune thrombocytopenia (ITP)	0.8-1 g/kg bw or 0.4 g/kg bw/d	On day 1, possibly repeated once within 3 days for 2-5 days
Guillain-Barré syndrome	0.4 g/kg bw/d	for 5 days
Kawasaki disease	1.6-2 g/kg bw or 2 g/kg bw	In divided doses over 2-5 days in association with acetylsalicylic acid In one dose in association with acetylsalicylic acid
Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)	Starting dose: 2 g/kg bw Thereafter: 1 g/kg bw	In divided doses over 2-5 days Every 3-4 weeks

Abbreviations: bw: body weight; d: day; g: gram; IgG: immunoglobulin G; l: liter; kg: kilogram

**Table 1b: Gamunex®-C: recommended dose by treatment of CIDP in the USA
[Gamunex®-C Dosing and administration]**

	Dose	Frequency of injections
Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)	Starting dose: 2 g/kg bw	In divided doses over 2-5 days
	Thereafter: 1 g/kg bw	Every 3-4 weeks

Abbreviations: bw: body weight; g: gram; kg: kilogram

Table 2: ICD-9 CM codes for chronic inflammatory demyelinating polyneuropathy (CIDP)

ICD CODE	ICD TERM
357.81	Chronic inflammatory demyelinating polyneuritis (CIDP)

Table 3: ICD-9 CM codes for haemolytic anaemia

ICD CODE	ICD TERM
283	Acquired hemolytic anemias
283.0	Autoimmune hemolytic anemias
283.1	Non-autoimmune hemolytic anemias
283.2	Hemoglobinuria due to hemolysis from external causes
283.9	Acquired hemolytic anemia, unspecified

Table 4: CPT-4 codes supporting haemolytic anaemia

CPT-4 codes	CPT-4 Procedure
868880	Coombs test, direct
850188	Hemoglobin
85044	Manual Reticulocyte Count
85045	Automated Reticulocyte Count
86000	Agglutinins, febrile
86156	Cold agglutinin, screen
86157	Cold agglutinin, titer
86900	Blood typing, ABO
86903	Blood typing, antigen screen
86904	Blood typing, patient serum
86905	Blood typing, RBC antigens
36430	Blood transfusion service

Table 5: ICD-9 CM codes for blood transfusion (to evaluate the severity of haemolytic anaemia)

ICD code	ICD-TERM
V58.2	Blood transfusion, without reported diagnosis
E873.0	Excessive amount of blood or other fluid during transfusion or infusion
E876.0	Mismatched blood in transfusion
E879.8	Other specified procedures (Blood transfusion)
E934.7	Natural blood and blood products (Blood plasma, Human fibrinogen, Packed red cells, Whole blood)

Table 6: ICD-9 CM codes for aseptic meningitis

ICD CODE	ICD TERM
047	Meningitis due to enterovirus
047.9	Unspecified viral meningitis (aseptic NOS)
100.81	Leptospiral meningitis (aseptic)
322	Meningitis of unspecified cause

Table 7: ICD-9 CM codes for thromboembolic events

ICD CODE	ICD TERM
Venous thromboembolism	
415.1x	Pulmonary embolism and infarction
444	Arterial embolism and thrombosis
451.1x	Phlebitis and thrombophlebitis
451.11	Femoral vein (deep) (superficial)
451.19	Other (Femoropopliteal vein, Popliteal vein, Tibial vein)
451.8	Of other sites
451.81	Iliac vein
451.83	Of deep veins of upper extremities (Brachial vein, Radial vein, Ulnar vein)
451.9	Of unspecified site
452	Portal vein thrombosis
453	Other venous embolism and thrombosis
453.2	Of vena cava
453.3	Of renal vein
453.4x	Venous embolism and thrombosis of deep vessels of lower extremity
453.40	Venous embolism and thrombosis of unspecified deep vessels of lower extremity (Deep vein thrombosis NOS, DVT NOS)
453.41	Venous embolism and thrombosis of deep vessels of proximal lower extremity (Femoral, Iliac, Popliteal, Thigh, Upper leg NOS)
453.42	Venous embolism and thrombosis of deep vessels of distal lower extremity (Calf, Lower leg NOS, Peroneal, Tibial)
453.8	Of other specified veins
453.9	Of unspecified site (Embolism of vein, Thrombosis (vein))
557.0	Acute vascular insufficiency of intestine
TIA/ischaemic stroke	
435	Transient cerebral ischemia
435.0	Basilar artery syndrome
435.1	Vertebral artery syndrome
435.2	Subclavian steal syndrome
435.3	Vertebrobasilar artery syndrome
435.8	Other specified transient cerebral ischemias
435.9	Unspecified transient cerebral ischemia Impending cerebrovascular accident Intermittent cerebral ischemia Transient ischemic attack [TIA]
434	Occlusion of cerebral arteries
434.0	Cerebral thrombosis Thrombosis of cerebral arteries
434.1	Cerebral embolism
434.9	Cerebral artery occlusion, unspecified
325	Phlebitis and thrombophlebitis of intracranial venous sinuses
437.6	Nonpyogenic thrombosis of intracranial venous sinus
Myocardial infarction	
410	Acute myocardial infarction

Table 8: ICD-9 CM codes for anaphylactic reactions

ICD CODE	ICD TERM
995.0	Other anaphylactic shock
999.4	Anaphylactic shock due to serum
999.8	Other transfusion reaction (Septic shock due to transfusion, Transfusion reaction NOS)

Table 9: ICD-9 CM codes for acute renal failure

ICD CODE	ICD TERM
584	Acute renal failure
584.5	With lesion of tubular necrosis
584.6	With lesion of renal cortical necrosis
584.7	With lesion of renal medullary [papillary] necrosis (Necrotizing renal papillitis)
584.8	With other specified pathological lesion in kidney
584.9	Acute renal failure, unspecified

Table 10: Intravenous immune globulin indications in the US

[<http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm133691.htm>]

Product	Manufacturer	Indications
Gammagard Liquid	Baxter Healthcare Corporation	<ul style="list-style-type: none"> • Treatment of primary immunodeficiency disorders associated with defects in humoral immunity • Multifocal motor neuropathy
Gammagard S/D	Baxter Healthcare Corporation	<ul style="list-style-type: none"> • Prevention of bacterial infections in patients with hypogammaglobulinemia and/or recurrent bacterial infections associated with B-cell chronic lymphocytic leukemia. • Prevention of coronary artery aneurysms associated with Kawasaki Syndrome. • To induce rapid rise in platelet count when needed to prevent and/or to control bleeding in a patient with idiopathic thrombocytopenic purpura.
Iveegam E/N	Baxter Healthcare Corporation	<ul style="list-style-type: none"> • Replacement therapy in patients with primary immunodeficiency syndromes • Kawasaki syndrome
Polygam S/D	Baxter Healthcare Corporation	<ul style="list-style-type: none"> • Primary humoral immunodeficiency • Immune mediated thrombocytopenia
Carimune NF	CSL Behring AG	<ul style="list-style-type: none"> • Primary humoral immunodeficiency • Immune thrombocytopenic purpura
Gammar-P I.V.	CSL Behring AG	<ul style="list-style-type: none"> • Primary humoral immunodeficiency
Panglobulin NF	CSL Behring AG	<ul style="list-style-type: none"> • Primary humoral immunodeficiency • Immune Thrombocytopenic Purpura
Privigen	CSL Behring AG	<ul style="list-style-type: none"> • Primary immunodeficiency • Chronic Immune Thrombocytopenic Purpura
Flebogamma DIF 5%	Grifols	<ul style="list-style-type: none"> • Replacement therapy in primary (inherited) humoral immune deficiency disorders
Venoglobulin-S	Grifols Biologicals, Inc.	<ul style="list-style-type: none"> • Primary humoral immunodeficiency • Immune mediated thrombocytopenia • Kawasaki syndrome
Octagam	Octapharma	<ul style="list-style-type: none"> • Treatment of primary humoral Immunodeficiency
Gamimune N	Talecris Biotherapeutics, Inc.	<ul style="list-style-type: none"> • Primary humoral immunodeficiency • Immune Mediated Thrombocytopenia • Bone marrow transplantation • Pediatric HIV-1
Gamunex	Talecris Biotherapeutics, Inc	<ul style="list-style-type: none"> • Primary humoral immunodeficiency • Idiopathic thrombocytopenic purpura • Chronic inflammatory demyelinating polyneuropathy (CIDP)