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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
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Product reference	EU numbers: EU/1/08/446/001 - 007
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Joint PASS?	No
Research question and objectives	The research questions are: 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: 1. Measure and compare the incidence of 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" 2. Evaluate the safety profile of Privigen® in children (0-18 years) with CIDP
Country(-ies) of study	United States
Author (and Principal Investigator)	Carlos Martinez, MD MSc Institute for Epidemiology, Statistics and Informatics GmbH Im Dinkelfeld 32 60388 Frankfurt Germany Tel +49 6109 3777551 Fax +49 6109 3777552 carlos.martinez@pharmaepi.com

Marketing authorisation holder(s)

Marketing authorisation holder(s)	CSL Behring GmbH Emil-von-Behring-Strasse 76 35041 Marburg Germany
MAH contact person	Dr. Nina Walser CSL Behring AG Wankdorfstrasse 10, 3000 Bern 22 Switzerland Tel: +41 31 344 5505 Fax: +41 31 344 4920 E-mail: nina.walser@cslbehring.com

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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.

IgPro10_5003, Version 2.0 (21-Sep-15).

PI: Carlos Martinez, MD MSc. Institute for Epidemiology, Statistics and Informatics GmbH. 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 using a US database with objectives (Part 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 (Part 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 ascertained using ICD-9 CM codes and HA-specific lab tests in temporal relationship with Privigen exposure. The outcome variables to be assessed in children with CIDP in Part 2 of the study, in addition to HA, include diagnosis codes for aseptic meningitis, acute renal failure, thromboembolic events and anaphylactic reactions. A medical review

of the database records of all patients with a presumed study outcome will be conducted to confirm the correct application of the case finding algorithm.

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

Study size: As of the writing of the first interim report for this study dated 3 November 2014, the Premier database contained data on 8,993 adult and paediatric patients administered Privigen between 1 January 2008 and 31 December 2012 (Period 1: baseline). Three patients aged <18 were treated with Privigen® for CIDP.

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", has been available since 3 November 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
V2.0	21-Sep-15	Multiple – see specific changes in Appendix 4	Multiple – see specific changes in **Annex 4**	Due to patient privacy concerns on the part of Premier, Inc., the data provider for the study, the information from the planned chart review is not able to be provided to the study investigators or sponsor. Therefore, the chart review component of the study is cancelled at this time. As a result validated HA outcomes diagnoses, and information about Privigen lot numbers, patient blood group, exact time and dose of Privigen administered, and other detailed information will not be available for analysis. Expert medical assessment of the database records was used to further refine and finalise the algorithm for ascertainment of potential HA cases and their categorisation in the analysis of period 1. The final algorithm will be applied to all study periods. In addition, the protocol is updated with information from Interim Report 1 dated 3 Nov 2014

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	Actual / Planned date
Start of data collection	Actual 25 February 2014
End of data collection	Planned 15 April 2019
Interim report 1	Actual 3 Nov 2014
Interim report 2	Planned 1 Nov 2016
Registration in the EU PAS register	Actual 12 Mar 2014
Final report of study results	Planned1 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]

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 isohaemagglutinins 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 approximately14,000 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, in April 2015 CSL Behring implemented 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 full implementation of this manufacturing step for the US market is expected by Q4 2015 / Q1 2016.

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] However, since the Premier database does not contain the date of diagnosis for in-hospital acquired diseases, and since the onset of HA may occur on a date before the date the diagnosis is recorded, we have used an at-risk period of 30 days after. 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 30 days after the last infusion assuming no subsequent infusion was given. If subsequent infusions are given within 30 days, the treatment episode continues until no infusion is given for 30 consecutive days or the patient switches to another IV-IG. If Privigen® is again administered more than 30 days after the last infusion from the prior treatment episode, such treatment will constitute a new treatment episode.

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 30 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.

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 ascertained as follows: Potential HA will be ascertained using specific ICD-9 CM codes, and from additional nonspecific ICD-9 CM codes including "Other transfusion reaction", "Complication of medical care NEC/NOS" and "Transfusion reaction, unspecified" (**Annex 3, Table 3**) or unstructured text plus a record for a haptoglobin and/or antiglobulin test (**Annex 3, Table 4**). Potential HA cases are to occur during the same hospitalization as the administration of Privigen, or in a subsequent in-hospital encounter or outpatient visit. A 30-day at-risk period for the occurrence of HA following administration of Privigen will be applied to identify potential HA cases in temporal relationship with Privigen use.

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.

Medical review of database records for patients with potential HA and unspecified anaemia

Database record summaries for all patients with potential HA and those with in temporal association with Privigen use will be reviewed by a medical expert. Database record summaries will consist of a chronological listing of all in-hospital dispensed medications, ordered laboratory tests, surgical procedures and medical and diagnostic interventions on a patient-level basis in the 120 days before and 90 days after the date of onset of potential HA. The use of Privigen or of another IVIg will be labelled as "IVIg". The medical expert's assessment will include the presumed indication for IVIg use, the type of anaemia and the likelihood of the anaemia being an HA. The expert's assessment was used to further refine and finalise the algorithm for ascertainment of potential HA cases and their categorisation in the analysis of period 1. The final algorithm will be applied to all study periods.

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

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 not be available in the Premier data extract (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. 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).

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). The AEs of interest will be identified among children with CIDP treated with Privigen® using ICD-9 CM codes.

9.4.3 Observational period

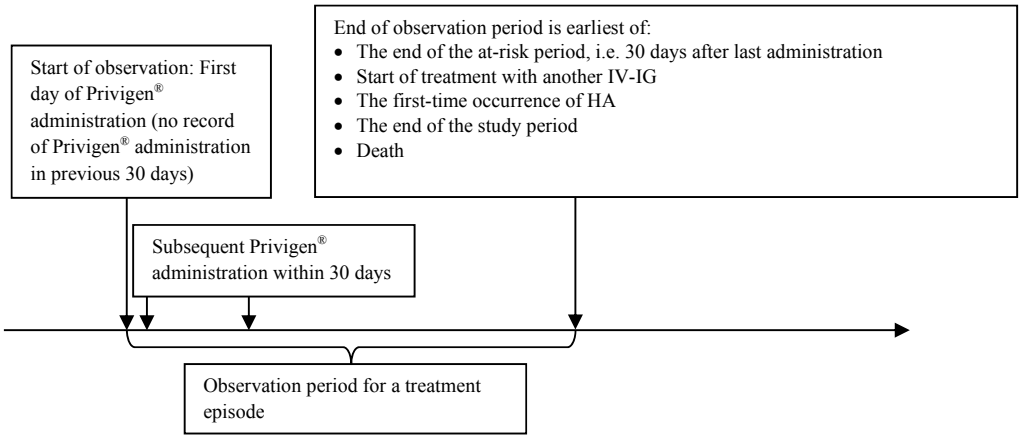
The total study period for Part 1will be from Jan 2008 until ca. Dec 2018, separated into the three defined calendar-time periods. The total study period for Part 2 will be over the whole study period until ca. Dec 2018. The observational period covers the time in which the patient is considered to be 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 30 days after last administration of Privigen®
- Start of treatment with another IV-IG
- The occurrence of the outcome of interest
- The end of the study period
- Death

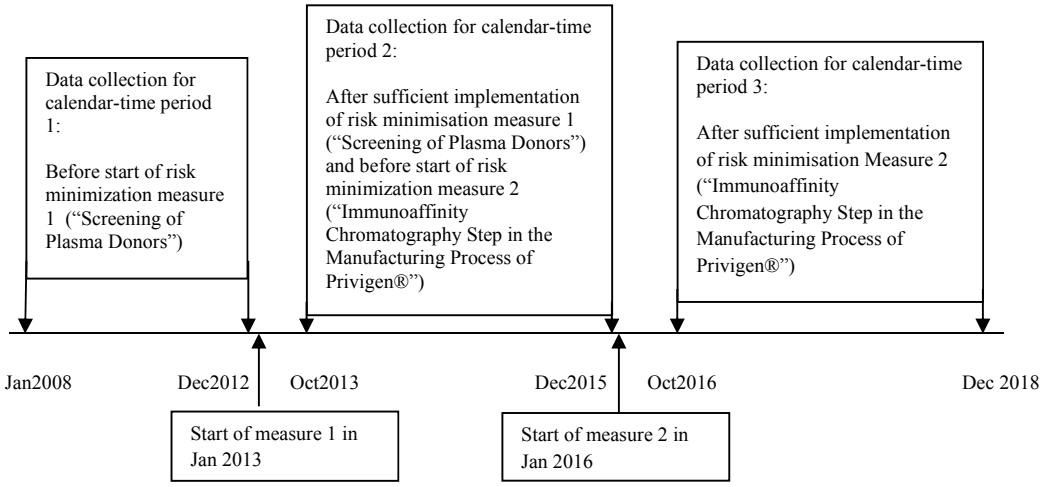
New admissions to hospital with a diagnosis at admission of HA (Part 1) or another study outcome (Part 2) will be identified by an ICD-9 CM code.

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 30 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: Data collection for calendar-time periods for evaluating HA in relation to timing of risk minimization measures



9.5. Study size

The objective of Part 1 of the study is to measure and compare the incidence of HA in adults and children before and after implementation of each of the two risk minimization measures: 1) "Screening of Plasma Donors" and 2) "Introduction of an Immunoaffinity Chromatography Step" in the manufacturing process of Privigen. The study periods for the assessment of the two risk minimization measures are provided below.

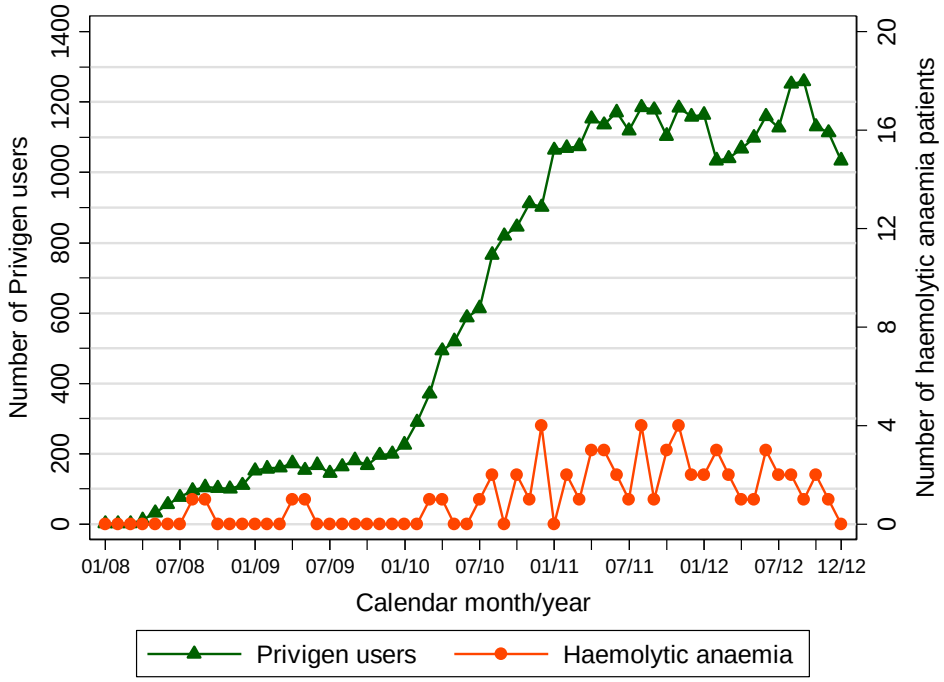
Study period	Measure	Calendar-time Study period	Observation period
Period 1	None (baseline)	Jan 2008 to Dec 2012	60 months
Period 2	1	Oct 2013 to Dec 2015	27 months
Period 3	2	Oct 2016 to Apr 2019	31 months

To evaluate whether the risk minimization measures are effective it is planned to estimate and to separately compare the incidence rate (IR) of HA following Privigen administration in Period 1 (Baseline) with: (i) the IR in Period 2 and (ii) the IR in Period 3. Power calculations have been performed to assess the minimum detectable risk reduction following the implementation of the risk minimization measures.

Observed Privigen use in Period 1 and expected Privigen use in Periods 2 and 3

As of the writing of Interim report 1 dated 3 November, 2014 for this study, there were 8,993 patients meeting the criterion for study entry i.e. with at least one Privigen administration during Jan 2008-Dec 2012 (Period 1). The number of patients treated over time increased between Jan 2008 and Dec 2010 and stabilized thereafter (**Figure 3**). Therefore, the total observed use of Privigen between Jan 2011 and Dec 2012 (24 months) was used to project the number of new Privigen users in Period 2 and 3. During those 24 months there were 6,684 current Privigen users, with approximately 440,000 person days of at-risk time for HA in association with Privigen use.

Figure 3: Time trend of Privigen users and potential HA patients in Premier during Period 1



For Period 2 it is assumed there will be 7,519 users of Privigen with approximately 495,000 person-days at risk for HA in Period 2 (assuming the same rate of new patients as in the last 24 months of Period 1 and accounting for the longer duration of Period 2 (i.e. 27 months/24 months times 6,684 patients, and 27 months/24 months times 440,000 person-days).

For Period 3 it is assumed there will be 8,633 patients with approximately 570,000 person-days of at risk time in Period 3 (multiplication factor 31 months/24 months).

Power calculation

Since the degree of risk reduction in the incidence of HA following introduction of each of the risk minimization measures is unknown the statistical power of the study to detect different assumed reductions in the incidence of HA from Period 1 (baseline) to Period 3 following implementation of risk minimization measures 1 and 2 was estimated using the asymptotic power of the one-sided Wald test for Poisson regression (Lyles et al., 2007). As noted above, it is assumed there will be 7,519 users

of Privigen with approximately 495,000 person-days at risk for potential HA in Period 2 and 8,633 patients with 570,000 person-days of at risk time in Period 3. Under these assumptions, the study is estimated to have the statistical power (with one-sided alpha = 0.025) shown in **Table 1** for different reductions of Privigen-associated incidence rates of HA in Periods 2 and 3 compared to Period 1.

Table 1: Estimated statistical power to detect HA incidence rate reduction from Period 1 to Period 2 and Period 3

Reduction[1] (%)	Period 1 vs Period 2 Power[2] (%)	Period 1 vs Period 3 Power[2] (%)
10	7.2	7.5
15	11.6	12.1
20	17.6	18.6
25	25.7	27.3
30	35.5	37.8
35	46.8	49.8
40	58.6	62.0
45	69.9	73.4
49	77.9	**81.3**
50	79.7	83.0
51	**81.5**	84.6
55	87.4	90.2
60	92.9	94.8
65	96.3	97.6
70	98.2	99.0
75	99.2	99.6
80	99.6	99.8
85	99.8	99.9
90	99.8	99.9

HA: Haemolytic anaemia.
[1] Assumed true reduction of incidence rate for Privigen-associated HA between period 1 and period 2/3.
[2] Using one-sided Wald test (α = 0.025) for Poisson regression (Lyles et al., 2007).

Interpretation

As shown in **Table 1** the study will have sufficient power (one-sided alpha=0.025 and beta=0.8) to detect a reduction in the rate of Privigen-associated HA from Period 1 (baseline) to Period 2 (following the implementation of the first risk minimization measure) of at least 51% and from Period 1 to Period 3 (following the implementation of the second risk minimization measure) of at least 49%.

The calculations are obviously very sensitive to the baseline number of HA cases. A positive caveat is that the ability of the study to detect change in the incidence of HA will increase if the number of patients treated with Privigen increases in the Premier database in Period 2 and/or Period 3, leading to more Privigen-treated patients at risk and more cases from those periods.

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 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 person-days on exposure.

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 person-days on corresponding exposure. The corresponding crude incidence rate 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, and assumed body weight. 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 person-days of treatment exposure.

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 30 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. 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 not be available. 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

In this study the actual dose of Privigen® expressed as mg per kilogram bodyweight administered to the patient will not be available. 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 estimating 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.

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 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). Information about all the released lots in the US in each of the study periods will be collected from the relevant CSLB department(s) including information about the relevant Anti-A and Anti-B titers. The titer information of the released lots will be calculated for each study period (mean titer of anti-A and anti-B). A comparison of the mean titers per study period will provide an estimate of the titers before and after implementation of each of the 2 risk minimisation measures in the US, which will be evaluated in the context of the HA rates after implementation of these measures.

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 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 submitted for publication to a peer-reviewed journal. The final study report will be posted on the EU PAS Register.

13. References

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SIGNATURES ON BEHALF OF SPONSOR

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 Number: IgPro10_5003, Version 2.0

I have read the protocol IgPro10_5003, Version 2.0 titled "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" and confirm that, to the best of my knowledge, the protocol accurately describes the design and conduct of the study.

Douglas Watson

Douglas Watson, PhD
Director, Clinical Epidemiology
CSL Behring

21 Sep 2015
Date
(DD MMM YYYY)

A. Mallick

Dr. Anngret Mallick
Sr. Director, Safety Risk Management, GCSP
Deputy EU QPPV
CSL Behring

21 Sep 2015
Date
(DD MMM YYYY)

SIGNATURE OF INVESTIGATOR

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 Number: IgPro10_5003, Version 2.0

I have read the protocol IgPro10_5003, Version 2.0 titled "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".

By signing this protocol, I agree to conduct the study in accordance with the protocol and applicable regulatory requirements.

Changes to the protocol will only be implemented after written approval is received from CSL Behring (CSL).

I will ensure that study staff fully understand and follow the protocol.

21 Sep 2015

Carlos Martinez, MD MSc
Institute for Epidemiology, Statistics and Informatics GmbH

Date
(DD MMM YYYY)

Annex 1. List of stand-alone documents*

Number	Document reference number	Date	Title
1	IgPro10_5003, Document 1	21-Sep-15	List of study investigators
* Available upon request			

Annex 2. ENCePP Checklist for Study Protocols

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:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	8
1.1.2 End of data collection[2]	☒	☐	☐	8
1.1.3 Study progress report(s)	☒	☐	☐	8
1.1.4 Interim progress report(s)	☒	☐	☐	8
1.1.5 Registration in the EU PAS register	☐	☐	☒	
1.1.6 Final report of study results.	☒	☐	☐	8

Comments:

Section 2: Research question	**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)	☒	☐	☐	8-10
2.1.2 The objective(s) of the study?	☒	☐	☐	10-11
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	11
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?				

[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.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
	☐	☐	☒	

Comments:

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

Section 3: Study design	**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)	☒	☐	☐	11-12
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	13
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)	☒	☐	☐	21-23

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	11-12
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	11-12
4.2.2 Age and sex?	☒	☐	☐	16-17
4.2.3 Country of origin?	☒	☐	☐	12
4.2.4 Disease/indication?	☒	☐	☐	8
4.2.5 Co-morbidity?	☐	☐	☒	
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)	☒	☐	☐	11-12, 16-18

Comments:

Age applicable to Part 2 of the study

Section 5: Exposure definition and measurement	**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)	☒	☐	☐	12-13,17
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)	☒	☐	☐	27
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	17-18
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	12
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	22-23

Comments:

At-risk period for exposure time is derived from the literature and the likely clinical manifestation and the recording of a study outcome in Premier

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	13
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)	☒	☐	☐	13

Comments:

Section 7: Confounders and effect modifiers	**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				

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
known confounders)	☒	☐	☐	13-14
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	28

Comments:

Effects modifiers addressed for Part 1

Section 8: Data sources	**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.)	☒	☐	☐	12-13
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.)	☒	☐	☐	13
8.1.3 Covariates?	☒	☐	☐	13-14
8.2 Does the protocol describe the information 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)	☒	☐	☐	15
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	14-15
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	14-15
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	15-16
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	15-16
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☒	☐	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)				

Section 8: Data sources	Yes	No	N/A	Page Number(s)
	☒	☐	☐	15

Comments:

Section 9: Study size and power	Yes	No	N/A	Page Number(s)
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	18-20

Comments:

Section 10: Analysis plan	Yes	No	N/A	Page Number(s)
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	21-24
10.3 Are descriptive analyses included?	☒	☐	☐	21-22
10.4 Are stratified analyses included?	☒	☐	☐	22, 26, 28
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	22
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	23

Comments:

10.5 and 10.6 addressed for Part 1

Section 11: Data management and quality control	Yes	No	N/A	Page Number(s)
11.1 Is information provided on the management of missing data?	☐	☐	☒	
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	24-25
11.3 Are methods of quality assurance described?	☒	☐	☐	24-25

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	24-26
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☐	☐	☒	
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)	☒	☐	☐	27-28
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	18-20
12.3 Does the protocol address other limitations?	☒	☐	☐	25-28

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☐	☐	☒	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	28-29

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Page Number(s)
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	7

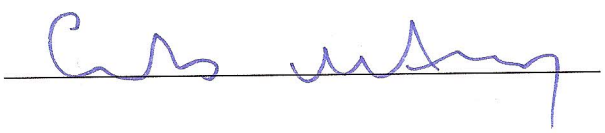
Comments:

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)?	☒	☐	☐	8, 29
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	29

Comments:

Name of the main author of the protocol: Carlos Martinez, MD MSc

Date: 21-Sep-15

Signature: 

Annex 3. Additional information

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

	Dose	Frequency of injections
Replacement therapy		
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
Immunomodulation:		
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 Thereafter: 1 g/kg bw	In divided doses over 2-5 days 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
Specific codes	
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
Unspecific codes	
999.8	Other transfusion reaction NEC
999.80	Transfusion reaction, unspecified
999.88	Other infusion reaction
999.89	Other transfusion reaction
999.9	Complication of med care NEC/NOS

Table 4: CPT-4 codes supporting haemolytic anaemia

CPT-4 codes	CPT-4 Procedure
Antiglobulin test	
86880	Coombs test direct
86885	Coombs test indirect qual
86886	Coombs test indirect titer
86922	Compatibility test antiglob
Haptoglobin test	
83010	Assay of haptoglobin quant
83012	Assay of haptoglobins

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	• Treatment of primary immunodeficiency disorders associated with defects in humoral immunity • Multifocal motor neuropathy
Gammagard S/D	Baxter Healthcare Corporation	• 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	• Replacement therapy in patients with primary immunodeficiency syndromes • Kawasaki syndrome
Polygam S/D	Baxter Healthcare Corporation	• Primary humoral immunodeficiency • Immune mediated thrombocytopenia
Carimune NF	CSL Behring AG	• Primary humoral immunodeficiency • Immune thrombocytopenic purpura
Gammar-P I.V.	CSL Behring AG	• Primary humoral immunodeficiency
Panglobulin NF	CSL Behring AG	• Primary humoral immunodeficiency • Immune Thrombocytopenic Purpura
Privigen	CSL Behring AG	• Primary immunodeficiency • Chronic Immune Thrombocytopenic Purpura
Flebogamma DIF 5%	Grifols	• Replacement therapy in primary (inherited) humoral immune deficiency disorders
Venoglobulin-S	Grifols Biologicals, Inc.	• Primary humoral immunodeficiency • Immune mediated thrombocytopenia • Kawasaki syndrome
Octagam	Octapharma	• Treatment of primary humoral Immunodeficiency
Gamimune N	Talecris Biotherapeutics, Inc.	• Primary humoral immunodeficiency • Immune Mediated Thrombocytopenia • Bone marrow transplantation • Pediatric HIV-1
Gamunex	Talecris Biotherapeutics, Inc	• Primary humoral immunodeficiency • Idiopathic thrombocytopenic purpura • Chronic inflammatory demyelinating polyneuropathy (CIDP)

Annex 4. Specific changes to protocol version 2.0

Number	Section of study protocol	Amendment or update	Reason
1.	4. Abstract, *Variables:*	**Previous Text:** "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 ascertained using ICD-9 CM codes and HA-specific lab tests. 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." **Changed to read:** "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 ascertained using ICD-9 CM codes and HA-specific lab tests in temporal relationship with Privigen exposure. The outcome variables to be assessed in children with CIDP in Part 2 of the study, in addition to HA, include diagnosis codes for aseptic meningitis, acute renal failure, thromboembolic events and anaphylactic reactions. A review of the database records for all patients with a presumed study outcome will be conducted to confirm the correct application of the case finding algorithm."	Revised to update HA outcome variable
2.	4. Abstract, *Study Size*	**Previous tex**t: "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)."	Text updated with Information from Interim Report 1 dated 03-Nov-2014.

Number	Section of study protocol	Amendment or update	Reason
		Changed to read: "As of the writing of the first interim report for this study dated 3 November 2014, the Premier database contained data on 8,993 adult and paediatric patients administered Privigen between 1 January 2008 and 31 December 2012 (Period 1: baseline). Three patients aged <18 were treated with Privigen® for CIDP."	
3.	4. Abstract, *Study Size*	**Previous tex**t: "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." **Changed to read:** **"**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", has been available since 3 November 2014."	Information no longer current
4.	6. Milestones	**Updated table:** Table with milestone dates updated to revise planned dates and include actual dates as available	Information no longer current
5.	7. Rationale and Background	**Deleted text**: '[redacted]	Information no longer current

Number	Section of study protocol	Amendment or update	Reason
		[redacted]"	
6.	7. Rationale and Background	**Previous text**: "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." C**hanged to read**: "Furthermore, in April 2015 CSL Behring implemented 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 full implementation of this manufacturing step for the US market is expected by Q4 2015 / Q1 2016."	Text / information updated
7.		**Previous text:** "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®	Since the Premier database does not contain the date of diagnosis for in-hospital acquired diseases, and since the onset of HA may occur on a date before the date the diagnosis is recorded, for Interim Report 1 and henceforth an at-risk period of 30 days after

Number	Section of study protocol	Amendment or update	Reason
		is again administered more than 10 days after the last infusion from the prior treatment episode, such treatment will constitute a new treatment episode." **Changed to read:** "However, since the Premier database does not contain the date of diagnosis for in-hospital acquired diseases, and since the onset of HA may occur on a date before the date the diagnosis is recorded, we have used an at-risk period of 30 days after. 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 30 days after the last infusion assuming no subsequent infusion was given. If subsequent infusions are given within 30 days, the treatment episode continues until no infusion is given for 30 consecutive days or the patient switches to another IV-IG. If Privigen® is again administered more than 30 days after the last infusion from the prior treatment episode, such treatment will constitute a new treatment episode."	Privigen administration (rather than the 10 days specified in the original protocol) is used to increase the sensitivity of our case-ascertainment algorithm.
8.	9.3 Variables, Exposure	**Deleted text:** "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."	Chart review will not be performed. As a result validated HA outcomes diagnoses, and information about Privigen lot numbers, patient blood group, exact time and dose of Privigen administered, and other detailed information will not be available for analysis.
9.	9.3 Variables, Exposure	**Previous text:** **"**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®……" **Changed to read:** **"**However, patients may still be regarded as potential cases after hospital discharge if there is	The analysis in the interim report was based on an at-risk period of 30 days, since the Premier database does not contain the date of diagnosis for in-hospital acquired diseases, and since the onset of HA may occur on a date before the date the diagnosis is recorded,

Number	Section of study protocol	Amendment or update	Reason
		subsequent evidence of HA within 30 days of the last administration of Privigen®……"	we have used an at-risk period of 30 days after Privigen administration to increase the sensitivity of our case-ascertainment algorithm.
10.	9.3 Variables, Exposure	**Deleted text:** "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."	The text was deleted as it was incorrect.. The correct information is included in the revised text shown in item number 7 above ("If subsequent infusions are given within 30 days, the treatment episode continues until no infusion is given for 30 consecutive days or the patient switches to another IV-IG.").
11.	9.3 Variables, Outcomes	**Previous text:** "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	Corrected incomplete sentence and revised to update definitions of outcome variables and to describe database records review by a medical expert.

Number	Section of study protocol	Amendment or update	Reason
		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." **Changed to read**: "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 ascertained as follows: Potential HA will be ascertained using specific ICD-9 CM codes, and from additional nonspecific ICD-9 CM codes including "Other transfusion reaction", "Complication of medical care NEC/NOS" and "Transfusion reaction, unspecified" (**Annex 3, Table 3**) or unstructured text plus a record for a haptoglobin and/or antiglobulin test (**Annex 3, Table 4**). Potential HA cases are to occur during the same hospitalization as the administration of Privigen, or in a subsequent in-hospital encounter or outpatient visit. A 30-day at-risk period for the occurrence of HA following administration of Privigen will be applied to identify potential HA cases in temporal relationship with Privigen use. Database record summaries for all patients with potential HA and those with unspecified anaemia in temporal association with Privigen use will be reviewed by a medical expert. Database record summaries will consist of a chronological listing of all in-hospital dispensed medications, ordered laboratory tests, surgical procedures and medical and diagnostic interventions on a patient-level basis in the 120 days before and 90 days after the date of onset of potential HA. The use of Privigen or of another IVIg will be labelled as "IVIg". The medical expert's assessment will include the presumed indication for IVIg use, the type of anaemia and the likelihood of the anaemia being an HA. The expert's assessment was used to further refine and finalise the algorithm for ascertainment of potential HA cases and their categorisation in the analysis of period 1. The final algorithm will be applied to all study	

Number	Section of study protocol	Amendment or update	Reason
		periods."	
12.	9.3 Variables, Outcomes	**Deleted text:** **"***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 / validation of study outcomes in Part 1 will not be performed. As a result validated HA outcomes diagnoses will not be available for analysis. The expert medical assessment of the database records will be performed in lieu of chart review. *See Item 13 below* .

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		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	

Number	Section of study protocol	Amendment or update	Reason
		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).	
13.	9.3 Variables, Outcomes	**Inserted text:** *Medical review of database records for patients with potential HA and unspecified anaemia* Database record summaries for all patients with potential HA and those with in temporal association with Privigen use will be reviewed by a medical expert. Database record summaries will consist of a chronological listing of all in-hospital dispensed medications, ordered laboratory tests, surgical procedures and medical and diagnostic interventions on a patient-level basis in the 120 days before and 90 days after the date of onset of potential HA. The use of Privigen or of another IVIg will be labelled as "IVIg". The medical expert's assessment will include the presumed indication for IVIg use, the type of anaemia and the likelihood of the anaemia being an HA. The expert's assessment was used to further refine and finalise the algorithm for ascertainment of potential HA cases and their categorisation in the analysis of period 1. The final algorithm will be applied to all study periods.	Medical review of database records for patients with potential HA and unspecified anaemia will be performed in lieu of medical chart review
14.	9.3 Variables, Outcomes	**Previous text:** **"**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	Chart review will not be performed. As a result validated HA outcomes diagnoses, and information about Privigen lot numbers, patient blood group, exact time and dose of

Number	Section of study protocol	Amendment or update	Reason
		are not identified." C**hanged to read:** "Blood group will not be available in the Premier data extract (see Section 9.9 Limitations of the Research Methods)."	Privigen administered, and other detailed information will not be available for analysis.
15.	9.4.1 Databases	**Deleted text:** **"**Premier can access hospital charts for additional clinical data not coded but found in patient medical records, including laboratory data."	Chart review will not be performed. As a result validated HA outcomes diagnoses, and information about Privigen lot numbers, patient blood group, exact time and dose of Privigen administered, and other detailed information will not be available for analysis.
16.	9.4.1 Databases	**Deleted text:** **"**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."**	Chart review will not be performed. As a result validated HA outcomes diagnoses, and information about Privigen lot numbers, patient blood group, exact time and dose of Privigen administered, and other detailed information will not be available for analysis.
17.	9.4.2 Study Cohort (Part 2)	**Previous text:** "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	Chart review will not be performed. As a result validated HA outcomes diagnoses, and information about Privigen lot numbers, patient blood group, exact time and dose of Privigen administered, and other detailed information will not be available for analysis.

Number	Section of study protocol	Amendment or update	Reason
		AE." **Changed to read:** "The AEs of interest will be identified among children with CIDP treated with Privigen® using ICD-9 CM codes.	
18.	9.4.3 Observational Period	**Previous text:** "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)" **Changed to read:** "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 30 days after last administration of Privigen® • Start of treatment with another IV-IG"	The at-risk period definition has been changed from 10 days to 30 days. Reference to Annex 3 no longer relevant.
19.	9.4.3 Observational Period	**Revised Figure:** Figure 1 revised to show at-risk period of 30 days rather than 10 days	The at-risk period definition has been changed from 10 days to 30 days.
20.	9.4.3 Observational Period	**Previous text:** **"**The at-risk period of 30 days will be the same as for patients in Part 1,…."	The at-risk period definition has been changed from 10 days to 30 days.

Number	Section of study protocol	Amendment or update	Reason
		Changed to read: **"**The at-risk period of 10 days will be the same as for patients in Part 1….."	
21.	9.4.3 Observational period	**Revised Figure 2**	To clarify the information in the Figure
22.	9.4.3 Observational period	**Deleted text below Figure 2:** **"**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. "	The dates referred to are confirmed.
23.	9.5 Study Size	**Updated entire section** using more current information included in Interim Report 1.	More current information available from Interim Report 1 dated 03-Nov-2014.
24.	9.7.1 Part 1 – incidence of HA before and after implementation of the risk minimisation measures	**Deleted text:** "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."	Lot numbers for Privigen received by patients will not be available. The titer information of the released lots will be calculated for each study period (mean titer of anti-A and anti-B). *See item 34 below.*
25.	9.7.1 Part 1 – incidence of HA before and after implementation of the risk minimisation measures	**Previous text:** **"**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.**"**	Crude incidence rate calculations revised to use person-time in the denominator

Number	Section of study protocol	Amendment or update	Reason
		Changed to read: "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 person-days on exposure."	
26.	9.7.1 Part 1 – incidence of HA before and after implementation of the risk minimisation measures	**Deleted text:** 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.	For Interim Report 1 the analysis was not performed due to small numbers. We assume that the mechanism of HA is dependent on isoagglutinin titer levels. Therefore, the risk of HA should be independent from the number of previous administrations and therefore a restriction to the first IVIG application not needed. Incidence rates rather than cumulative incidence estimates are preferred.
27.	9.7.1 Part 1 – incidence of HA before and after implementation of the risk minimisation measures	**Previous text:** **"**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®." **Changed to read:**	Crude incidence rate calculations revised to use person-time in the denominator

Number	Section of study protocol	Amendment or update	Reason
		"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 person-days on corresponding exposure. The corresponding crude incidence rate will be calculated for the treatment episodes with a low cumulative dose of Privigen®."	
28.	9.7.1 Part 1 – incidence of HA before and after implementation of the risk minimisation measures	**Previous text:** "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**." **Changed to read:** "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, and assumed body weight."	Chart review will not be performed. As a result validated HA outcomes diagnoses, and information about Privigen lot numbers, patient blood group, exact time and dose of Privigen administered, and other detailed information will not be available for analysis.
29.	9.7.2 *Part 2 – safety profile in children with CIDP*	**Previous text:** **"**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."	Crude incidence rate calculations revised to use person-time in the denominator

Number	Section of study protocol	Amendment or update	Reason
		Changed to read: "For these rates, the numerator will be the number of episodes with the outcome event and the denominator will be person-days of treatment exposure."	
30.	9.9 Limitations of the Research methods - *Evaluation of severity of HA in Part 1*	**Text deleted:** "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."	Chart review will not be performed. As a result validated HA outcomes diagnoses, and information about Privigen lot numbers, patient blood group, exact time and dose of Privigen administered, and other detailed information will not be available for analysis.
31.	9.9 Limitations of the Research methods - *Potential for variability among patients in risk of outcomes*	**Previous text:** "In this study, data on blood group will only be obtained for patients with potential HA and in whom medical chart review is possible." **Changed to read:** "In this study, data on blood group will not be available."	Chart review will not be performed. As a result validated HA outcomes diagnoses, and information about Privigen lot numbers, patient blood group, exact time and dose of Privigen administered, and other detailed information will not be available for analysis.
32.	9.9 Limitations of the Research methods – *Exposure details*	**Previous text:** "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." **Changed to read:** "In this study, the actual dose of Privigen® expressed as mg per kilogram bodyweight administered to the patient will not be available."	Chart review will not be performed. As a result validated HA outcomes diagnoses, and information about Privigen lot numbers, patient blood group, exact time and dose of Privigen administered, and other detailed information will not be available for analysis.

Number	Section of study protocol	Amendment or update	Reason
33.	9.9 Limitations of the Research methods – *Potential for information bias due to changes in the ascertainment, classification and recording of HA over time in Part 1*	**Previous text:** "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. **Changed to read:** "Information bias will be addressed by estimating 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."	Chart review will not be performed. As a result validated HA outcomes diagnoses, and information about Privigen lot numbers, patient blood group, exact time and dose of Privigen administered, and other detailed information will not be available for analysis.

Number	Section of study protocol	Amendment or update	Reason
34.	9.9 Limitations of the Research methods – *Collection of Privigen lot numbers in patients with HA*	**Previous text:** "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)." **Changed to read:** "The Premier database does not contain information about Privigen lot numbers. 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). Information about released lots in the US in each of the study periods will be collected. The titer information of the released lots will be calculated for each study period (mean titer of anti-A and anti-B). A comparison of the mean titers per study period will provide an "estimate" of the titers before and after implementation of the Immunoaffinity chromatography step in the US."	Chart review will not be performed. As a result validated HA outcomes diagnoses, and information about Privigen lot numbers, patient blood group, exact time and dose of Privigen administered, and other detailed information will not be available for analysis.
35.	10.0 Protection of human subjects	**Deleted text:** "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	Chart review will not be performed. As a result validated HA outcomes diagnoses, and information about Privigen lot numbers, patient blood group, exact time and dose of Privigen administered, and other detailed

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		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.	information will not be available for analysis.
36.	Annex 1 . List of stand-alone documents	**Deleted entry from Table:** 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"	Chart review will not be performed. As a result validated HA outcomes diagnoses, and information about Privigen lot numbers, patient blood group, exact time and dose of Privigen administered, and other detailed information will not be available for analysis.
37.	Annex 1 . List of stand-alone documents	**Added entry to Table:** "List of study investigators"	Previously omitted by mistake
38.	Annex 2 . ENCePP Checklist for Study Protocols (Section 5 comment)	**Previous text:** "At-risk period for exposure time is derived from the literature" **Changed to read:** "At-risk period for exposure time is derived from the literature and the likely clinical manifestation and the recording of a study outcome in Premier"	Justification for change in at-risk period for HA following Privigen® exposure
39.	Annex 2 . ENCePP Checklist for Study Protocols (Section 13 comment)	**Deleted text:** "Ethical review will only be applicable to chart review of selected cases and will follow procedures already established by Premier"	Chart review will not be performed. As a result validated HA outcomes diagnoses, and information about Privigen lot numbers, patient blood group, exact time and dose of

Number	Section of study protocol	Amendment or update	Reason
			Privigen administered, and other detailed information will not be available for analysis.
40.	Annex 3. Additional information	**Deleted text:** Procedures for validation and grading of HA and HA severity 1. Definition of HA for potential HA cases with access to medical charts; and 2. Severity Grade for HA in the presence of haemoglobin concentration results	Chart review will not be performed. As a result validated HA outcomes diagnoses, and information about Privigen lot numbers, patient blood group, exact time and dose of Privigen administered, and other detailed information will not be available for analysis.
41.	Annex 3. Additional information (Table 3)	**Revised Table 3**	Table updated to include ICD-9 codes for non-specific anemias
42.	12. Plans for disseminating and communicating study results	**Previous text:** "The results of the study will be published in a peer-reviewed journal. " **Changed to read:** "The results of the study will be submitted for publication to a peer-reviewed journal.."	Results will be submitted but publication is not certain.