Postmarketing Requirement (PMR)
Non-Interventional 2-armed Study to Evaluate the Safety of *octagam*® *Immune Globulin Intravenous (Human) 5% Liquid Preparation*, with a Special Emphasis on Monitoring, Analysis and Reporting of Thromboembolic Events (TEEs)

Study ID:	GAM5-28
Development Phase:	Post-Authorization
Marketing Authorization Holder	Octapharma Pharmazeutika Produktionsges.m.b.H. Oberlaaer Str. 235 1100 Vienna Austria
Version Number:	Version 08
Release Date:	August 6, 2015

PROTOCOL AUTHORIZATION

This observational study will be conducted in compliance with the protocol, and applicable regulatory requirements.

Sponsor Representatives:

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
CDSU	Central Drug Safety Unit
CFR	Code of Federal Regulations
ECG	Electrocardiogram
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capturing
FXIa	Activated Coagulation Factor XI
HAV	Hepatitis A Virus
HBc	Hepatitis B Core Antigen
HBV	Hepatitis B Virus
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis B Virus
HIV	Human Immunodeficiency Virus
IgG	Immunoglobulin G
IVIG	Intravenous Immunoglobulin
IRB	Institutional Review Board
ISRB	Independent Safety Review Board
MaxSPRT	Maximized Sequential Probability Ratio TEST
MedDRA	Medical Dictionary for Regulatory Activities
PMR	Postmarketing Requirement
PI	Primary Humoral Immunodeficiency
SMQ	Standardized MedDRA Query
TEE(s)	Thromboembolic Event(s)

PROTOCOL SYNOPSIS

Name of Sponsor/Company: Octapharma AG Seidenstrasse 2 8853 Lachen, Switzerland	
Name of Investigational Product: Octagam 5%	Protocol Identification Code: GAM5-28
Name of Active Ingredient: Human immunoglobulin	Version / Date of Protocol: Version 08/ August 6, 2015
Title of Study: Postmarketing Requirement (PMR) Non-Interventional 2-armed Study to Evaluate the Safety of octagam® Immune Globulin Intravenous (Human) 5% Liquid Preparation, with a Special Emphasis on Monitoring, Analysis and Reporting of Thromboembolic Events (TEEs)	
Indication: Primary Immunodeficiency Diseases	
Number of Study Centre(s): At least 10 study sites in the US.	
Study Duration: 2013 to 2019	**Development Phase:** Postmarketing
Objectives: **Primary:** The primary objective is to assess and evaluate the safety profile of *octagam® 5%* during or after administration under routine clinical use for all labeled indications, with a special emphasis on the occurrence of TEEs. The incidence of TEEs in patients receiving *octagam® 5%* will be compared with the incidence rate in a matching concurrent control group of patients receiving other IVIGs for routine clinical use. **Secondary:** Secondary objectives are to characterize TEE frequency in *octagam® 5%* patients and in the patients of the concurrent control group by patients' key characteristics.	
Study Design: This PMR Study is a prospective, 2-armed, multicenter, non-interventional study as defined in Title IX. Patients will either be administered the brand of IVIG therapy ordered by their prescribing physician, or for patients issued unspecified or generic prescriptions of IVIG therapy, *octagam® 5%* or another brand of IVIG therapy will be provided by the Investigator according to federal, state and local regulations and good clinical practice (GCP) guidelines.	
Number of Patients: This PMR Study will observe a minimum of 500 patients (250 per group) under regular treatment with *octagam® 5%* or other brands of IVIG. Having in mind that the observation period should cover 4 infusions for a single patient, this would result in 2,000 documented infusions.	
Patient Selection Criteria:	

<table>
<tr><td colspan="2">Name of Sponsor/Company:

Octapharma AG
Seidenstrasse 2
8853 Lachen, Switzerland</td></tr>
<tr><td>Name of Investigational Product:
Octagam 5%</td><td>Protocol Identification Code:
GAM5-28</td></tr>
<tr><td>Name of Active Ingredient:
Human immunoglobulin</td><td>Version / Date of Protocol:
Version 08/ August 6, 2015</td></tr>
<tr><td colspan="2">Inclusion Criteria:
Patients who meet all of the following criteria are eligible for the PMR study:
1. Male and female patients aged ≥ 18 years.
2. Patients with confirmed diagnosis of Primary Humoral Immunodeficiency (PI) as stated by the World Health Organization and requiring immunoglobulin replacement therapy due to hypogammaglobulinemia or agammaglobulinemia.
3. Patients on regular treatment (every 3 to 4 weeks) with IVIG dose ≤ 1 g/kg for a period of at least 6 months, not changing the brand for at least 60 days prior to enrollment and planning to remain on the same product until the end of the study.

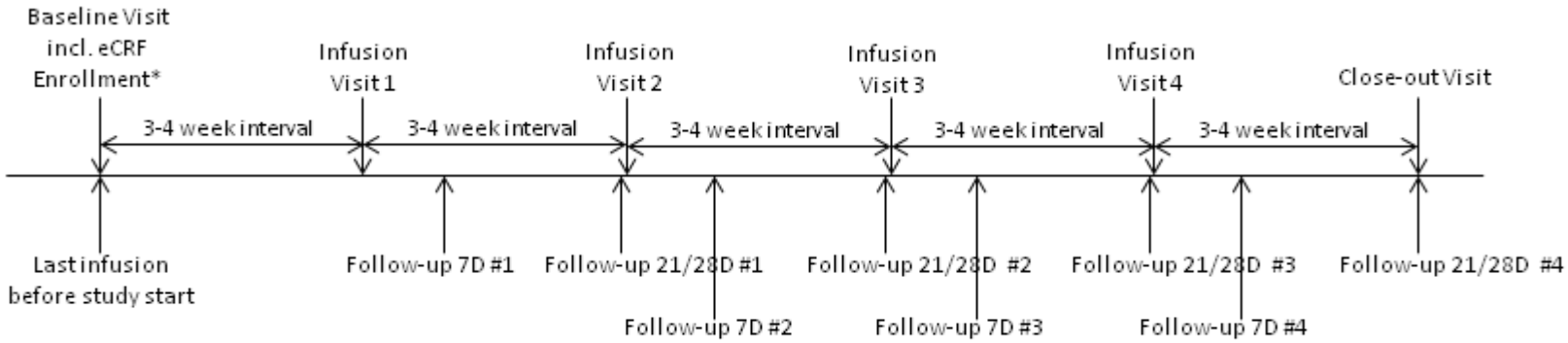
Exclusion Criteria:
Patients who meet any of the following criteria are not eligible for the PMR study:
1. Patients with a history of TEEs* within the previous 24 months.
2. Patients with a regular treatment frequency of more than once every 3 to 4 weeks.
* This includes: ischemic stroke, transient ischemic attack, cerebral infarction, cerebrovascular accident, cerebral thrombosis, embolic infarctions, (acute) myocardial infarction, deep vein thrombosis, pulmonary embolism, venous thrombosis.</td></tr>
<tr><td colspan="2">Test Product, Dose, Mode of Administration, and Batch Number(s):
<u>octagam 5%</u>
octagam® 5% contains 50 mg protein per mL of solution of which ≥ 95% is IgG; the IgA content is ≤0.2 mg/mL and IgM content is ≤0.1 mg/mL. All four IgG subclasses are present in proportions corresponding to the normal physiological distribution. The product is liquid, contains maltose for regulating osmolality and has undergone multiple virus inactivation procedures including S/D treatment.
octagam® 5% can be stored for 2 years at a temperature of +2°C (36°F) to +25°C (77°F). Detailed information on indications, dosages, the side-effect profile and other parameters of octagam® 5% can be found in the Package Insert.

<u>Comparator Drugs</u>
IVIG therapies, other than octagam® 5%, that are available in the US for administration.</td></tr>
<tr><td colspan="2">Duration of Treatment:

The regular duration of observation for an individual patient will be the period of administering 4 infusions, adding up to 12 or 16 weeks (incl. Close-Out Visit) depending on the patient’s 3- or 4-week infusion schedule.</td></tr>
<tr><td colspan="2">Reference Therapy, Dose, Mode of Administration, and Batch Number(s):</td></tr>
</table>

Name of Sponsor/Company: Octapharma AG Seidenstrasse 2 8853 Lachen, Switzerland	
Name of Investigational Product: Octagam 5%	Protocol Identification Code: GAM5-28
Name of Active Ingredient: Human immunoglobulin	Version / Date of Protocol: Version 08/ August 6, 2015
Only patients on regular treatment (every 3 to 4 weeks) with IVIG dose ≤ 1 g/kg for a period of at least 6 months will be enrolled.	
Study Outcome Parameters (Primary and Secondary Endpoints): The incidence of TEEs in patients receiving *octagam® 5%* will be compared with the incidence rate in a matching concurrent control group of patients receiving other IVIGs for routine clinical use; this comparison will be implemented by use of a Maximized Sequential Probability Ratio TEST (MaxSPRT) for Binomial data.	
Summary of Study Procedures and Statistical Analysis Plan: Study Procedures: See Figure 1 and Table 1. Statistical Analysis: The primary objective of this study is the close monitoring of the occurrence of TEEs. This statistical monitoring will be carried out by means of the Maximized Sequential Probability Ratio TEST (MaxSPRT) for Binomial data, cf. Kulldorff et. al. 2011. This procedure is especially suited for the early detection of excess risks of events of special interest and has already shown good properties in vaccine trials. The study will use a 2-armed study design, in which patients treated with *octagam®* 5% will be compared with a prospective control group of patients treated with other brands of IVIG. To ensure accurate case counts in each group, two time windows for the occurrence of TEEs are defined: within seven days of infusion (to capture primarily arterial events) and within 21 days (to capture both arterial and venous events).	

Figure 1 Flow Chart of Study Events



*: The Baseline Visit may be performed up to one infusion interval before Study Infusion Visit 1, however it may take place on the same day prior to Study Infusion 1.

Table 1: Assessment schedule

Parameters/Assessments/Activities	Baseline Visit		Infusion Visit 1	Infusion Visit 2		Infusion Visit 3		Infusion Visit 4		Close-Out
		Enroll-ment	↓ **Infusion 1**	pre-infusion	↓ **Infusion 2**	pre-infusion	↓ **Infusion 3**	pre-infusion	↓ **Infusion 4**	Visit
Obtaining Informed Consent	X									
Patient demographics	X									
Medical history[1]	X									
TEE risk factor evaluation	X									
Blood viscosity[2]	X									
Concomitant diseases	X									
Previous medications	X									
Previous IVIG treatment details[3]	X									
Viral status[4] and vaccination status[5]	X									X
Concomitant medications	X			X		X		X		X
Laboratory[6]	X			X		X		X		X
eCRF Enrollment		X								
IVIG infusion details			X		X		X		X	
Body weight			X		X		X		X	
Vital signs			X	X	X	X	X	X	X	
Adverse Drug Reactions and all TEEs			<---------- X ---------->							
Safety follow-up questionnaire										
7 days (+2 days) after previous infusion			X		X		X		X	
3-4 weeks after previous infusion				X		X		X		X
Overall efficacy assessment										X
Medical Record Review[7]										X
Measles Antibody Testing (select sites only)[8]										

[1] Including all medication taken within the last infusion interval (3-4 weeks) before PMR Study entry. Only relevant medical history and medications should be entered in the CRF [2] Testing recommended in patients at a known risk of hyperviscosity [3] During the last 6 months. [4] If available.
[5] Changes in vaccination status to be documented. [6] Clinically relevant lab test results should be collected if routinely done/available. [7] Within 12 weeks after Study End. [8] Measles antibody testing will be performed only on patients receiving *octagam® 5%* before and during the study at select site(s) after appropriate written informed consent is provided.

1. INTRODUCTION

1.1. BACKGROUND

1.1.1. octagam® 5%

octagam® 5% is a liquid intravenous polyvalent immunoglobulin (IVIG) preparation, which has undergone a three-stage viral inactivation. The product is prepared from human plasma and mainly contains human normal immunoglobulin G (IgG). The IgG molecules are present in their native form which is necessary for their biological activity.

octagam® *5%* is produced from a pool of at least 3500 donations of human fresh frozen plasma per batch. The large donor pool ensures that the product contains a broad range of antibodies directed against pathogens and foreign antigens and one that is far more diverse than that of plasma from an individual donor. Donor plasma sampling, the manufacture of the product and the measures to ensure the product's viral safety are subject to strict regulations laid down by regulatory authorities. Octapharma uses exclusively plasma which has been tested by nucleic acid amplification testing techniques. The production process contains three validated virus inactivation steps (modified ethanol fractionation, pH storage, solvent/detergent virus inactivation).

IVIG is FDA-approved for primary humoral immunodeficiency (PI), such as congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome and severe combined immunodeficiency.

octagam® *5%* was introduced in the European market in 1993 and in the US in 2004. A total of almost 70 tons of *octagam*® has been used worldwide since its first introduction. It was recognized as being effective and well tolerated. Data on its tolerability in long-term use- has also been published (1).

Analysis of Octapharma's pharmacovigilance data revealed a critical increase of thromboembolic events (TEEs) in the 3rd Quarter of 2010. A complete voluntary market withdrawal was initiated in September of 2010. Octapharma believes that an unexpected increase in activated coagulation factor XI (FXIa) in the final product was the cause for the increase of TEEs. Additional purification steps have been implemented to remove FXIa and this new product will be evaluated in this study.

No other safety issues have been identified.

1.1.2. Primary Humoral Immunodeficiency

The PI diseases are a heterogeneous group of disorders with an intrinsic defect of the tissues, cells, or proteins of the immune system resulting in immune deficiency. Many of these disorders are characterized by hypogammaglobulinemia with or without defective antibody production. Children and adults with PI have an increased risk of getting recurrent bacterial and viral infections that typically attack the respiratory tract (sinusitis, bronchitis, pneumonia) but can also affect the gastrointestinal tract (gastroenteritis). They can be severe and can lead

to substantial morbidity. Responses to antibacterial therapy are often poor. At present, most PI diseases are not curable, but IVIGs have been shown to decrease the total number of severe infections and the duration of hospitalization.

Therapeutic indications for replacement therapy with IVIG are PI syndromes such as:

- Congenital agammaglobulinemia and hypogammaglobulinemia.
- Common variable immunodeficiency.
- Wiskott-Aldrich syndrome.
- Severe combined immunodeficiency.

Replacement therapy with immunoglobulin purified from pools of plasma from multiple donors has been used since the early 1950s. The initial products were administered intramuscularly, and were of limited efficacy because of the relatively small quantities that could be administered by that route. Beginning in the 1980s, IVIG became available in the United States, and these are now the treatment of choice for patients with PI in which humoral immunity is impaired.

Patients suffering from PI usually need lifelong replacement therapy.

Post-dose peak levels of IgG are reached immediately after infusion of IVIG. It has been shown that after infusion, exogenous IgG is distributed relatively rapidly between plasma and extravascular fluid until approximately half is partitioned in the extravascular space. Therefore a rapid initial drop in serum IgG is to be expected. Several factors such as the endogenous production, the actual catabolism rate, the underlying disease or inter-patient variability help to explain the wide range observed for terminal half-lives. Pharmacokinetic data are required for each new product to ensure that it will not behave differently from existing preparations, in terms of appropriate dose and timing of the infusions.

1.1.3. Rationale for Conducting the Study

This Postmarketing Requirement (PMR) Study is deemed to be necessary to document the positive risk/benefit ratio of *octagam® 5%* in patients with PI with a special emphasis on monitoring, analysis and reporting of TEEs.

2. OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective is to assess and evaluate the safety profile of *octagam® 5%* during or after administration under routine clinical use for all labeled indications, with a special emphasis on the occurrence of TEEs. The incidence of TEEs in patients receiving *octagam® 5%* will be compared with the incidence rate in a matching concurrent control group of patients receiving other IVIGs for routine clinical use.

2.2. SECONDARY OBJECTIVES

Secondary objectives are to characterize TEE frequency in *octagam® 5%* patients and in the patients of the concurrent control group by patients' key characteristics.

3. INVESTIGATIONAL PLAN

3.1. PRIMARY AND SECONDARY ENDPOINTS

3.1.1. Primary Endpoint

The incidence of TEEs in patients receiving *octagam® 5%* will be compared with the incidence rate in a matching concurrent control group of patients receiving other IVIGs for routine clinical use; this comparison will be implemented by use of a Maximized Sequential Probability Ratio TEST (MaxSPRT) for Binomial data.

For the evaluation of the primary endpoint all confirmed TEEs that occurred within 7 days after the last IVIG administration will be considered. Please refer to Section 9.1 for a formal definition of this endpoint.

3.1.2. Secondary Endpoints

Characterization of incidence of TEEs in *octagam® 5%* and in the concurrent control group patients by demographics (age, sex), dose, infusion rate and known TEE risk factors.

3.1.3. Adjudication of TEEs

To determine/confirm a TEE the following adjudicators will be involved:

Adjudicator 1 (Investigator)

On the corresponding adverse drug reaction (ADR)/TEE reporting form of the eCRF, the Investigator is specifically asked if the reported event is a TEE in his/her opinion.

The Investigator will not be blinded with respect to actual treatment.

Adjudicator 2 (Octapharma Central Drug Safety Unit)

Once an ADR/TEE is entered into the eCRF system, it automatically generates adverse event reports that are forwarded to Octapharma's Central Drug Safety Unit (CDSU). CDSU is processing the cases in routine manner (including assessments of expectedness, causality, seriousness, TEE classification of event).

Octapharma's CDSU will not be blinded with respect to actual treatment.

Adjudicator 3 (Independent Safety Review Board, ISRB)

The ISRB will receive anonymized case reports and/or lists of all reported adverse reactions. Serious cases and suspected TEEs (as determined by Adjudicator 1 and/or Adjudicator 2) will be reviewed on an ad-hoc basis; other cases (non-serious non-TEEs) will be reviewed on a

quarterly basis. The ISRB will then vote on all new cases (simple majority), record their judgment and return their decisions back to data management.

The ISRB will be blinded with respect to actual treatment.

In case, the adjudicators disagree, the following scheme will be applied:

Determined as TEE by Adjudicator 1?	Determined as TEE by Adjudicator 2	Determined as TEE by Adjudicator 3	Determined as TEE in database?
Yes	No	No	yes
Yes	Yes	No	yes
No	Yes	No	yes
No	No	Yes	yes
No	Yes	Yes	yes
Yes	No	Yes	yes

In addition, the standardized MedDRA Query (SMQs) for TEEs will be applied. In the unlikely event that a case is identified by the SMQ that was not yet classified as a TEE by Adjudicators 1, 2 or 3, the case will be included as a TEE in the monthly report.

In the sequential/monthly reports, all cases marked as TEE as specified above will be included.

3.2. OVERALL PMR STUDY DESIGN AND PLAN

This PMR study is a prospective, 2-armed, multicenter, non-interventional study as defined in Title IX. Patients will either be administered the brand of IVIG therapy ordered by their prescribing physician, or for patients issued unspecified or generic prescriptions of IVIG therapy, *octagam® 5%* or another brand of IVIG therapy will be provided by the Investigator according to federal, state and local regulations and good clinical practice (GCP) guidelines. For data analyses, patients will be analyzed in two groups: One group who has received *octagam® 5%* and the other who was treated with other brands of IVIG. Depending on the patient's insurance provider, the IVIG infusions may be administered at study site, or outside the study site, e.g. in an outpatient infusion center, a physician's office or at the patient's home. For patients treated outside the study site, the Investigator is responsible for discussing and collecting of informed consent, as well as for providing a Patient Diary and appropriate training on its completion... Moreover, the Investigator needs to ensure that contact details for the follow-up calls are provided. Patients have to be informed that this information will be provided to an external contract partner involved in the follow-up. For home treatment, contracted nursing services will be utilized to administer the infusion according to established regional clinical practice guidelines.

All patients will receive a 7-day (+2 days) follow-up call to evaluate and record any safety issues that may have arisen. All data related to ADRs, or lack thereof, during the infusion and the 7-day (+2 days) follow-up period will be recorded in the eCRF. In order to ensure that all

follow-ups are performed thoroughly and consistently, a standardized safety questionnaire will be used (Appendix 1). In addition, a 3- to 4-week follow-up will be performed, usually before the next infusion is administered. In total, 4 IVIG infusions are to be administered in 3 to 4 week intervals. Three (3) to 4 weeks after the 4th infusion a Close-Out Visit will occur. The Investigator should ensure that any previously dispensed diaries are collected at the Close-Out Visit or after premature termination of the patient's study participation.

No randomization of patients to one of the two treatment groups will be performed. However, a matched pairs approach will be set up to achieve a good match between the two study groups with respect to confounding variables and baseline characteristics, and to avoid bias while ensuring a maximum of statistical power. With this approach it can be ensured that the enrollment ratio between groups is approximately 1:1 without systematically privileging any particular competitor product or disease pattern. Please refer to Section 8.2 for details on the enrollment procedure.

4. PMR STUDY POPULATION

4.1. POPULATION BASE

This PMR study will observe a minimum of 500 patients (250 per group) under regular treatment with *octagam® 5%* or other brands of IVIG. Having in mind that the observation period should cover 4 infusions, this would result in 2,000 documented infusions.

4.1.1. Patient Inclusion Criteria

Patients who meet all of the following criteria are eligible for the PMR study:

1. Male and female patients aged ≥ 18 years.
2. Patients with confirmed diagnosis of PI as stated by the World Health Organization and requiring immunoglobulin replacement therapy due to hypogammaglobulinemia or agammaglobulinemia.
3. Patients on regular treatment (every 3 to 4 weeks) with IVIG dose ≤ 1 g/kg for a period of at least 6 months, not changing the brand for at least 60 days prior to enrollment and planning to remain on the same product until the end of the study.

4.1.2. Patient Exclusion Criteria

Patients who meet any of the following criteria are not eligible for the PMR study:

1. Patients with a history of TEEs* within the previous 24 months.
2. Patients with a regular treatment frequency of more than once every 3 to 4 weeks.

* This includes: ischemic stroke, transient ischemic attack, cerebral infarction, cerebrovascular accident, cerebral thrombosis, embolic infarctions, (acute) myocardial infarction, deep vein thrombosis, pulmonary embolism, venous thrombosis.

4.2. PRIOR AND CONCOMITANT THERAPY

Relevant concomitant medications the patient is taking at baseline and given during the course of this PMR study will be documented at the Baseline Visit and the Infusion Visits with the generic name, dosage, indication, frequency and mode of administration, including start and end dates.

Any concomitant treatment is at the treating physician's discretion, taking into account the interactions mentioned in the respective IVIG Package Inserts.

The responsible Investigator should instruct the patient to notify them and their treating physician/health care professional (if applicable) regarding any new prescriptions or over the counter medication(s), he/she takes after enrollment into the study. Patients not treated at the study site, will be instructed to capture all concomitant medications in their diaries. All medications (including blood transfusions and vaccinations) administered and considered to be relevant to this trial by the Investigator should be listed on the corresponding eCRF page.

4.3. PREMATURE TERMINATION

If, for any reason, the Investigator, treating physician or the patient decides to discontinue or change the observed IVIG brand within the observation period of 4 infusions, the observation of this patient will be terminated. The Sponsor may choose to discontinue a patient in the event that significant protocol violations are identified. In the event that a patient is discontinued from the trial, the study site still should record all data up to the termination. If possible, a close-out visit should be performed. The reason for premature termination must be documented in the eCRF.

If the reason for discontinuing IVIG therapy is a TEE (independent of being rated as ‘related’ or ‘unrelated’) or another ADR, the specific reaction has to be recorded. It is recommended that the Investigator makes thorough efforts to clearly document the outcome and notify the treating physician (if applicable).

If the patient is lost to follow-up, the reason(s) why the patient was lost to follow-up should be documented as well as any attempt made to contact the patient.

4.4. ASSIGNMENT OF PATIENTS TO TREATMENT GROUPS

Due to the non-interventional character of this PMR study, patients are not randomized to a specific treatment and treatment is not allocated experimentally by the Investigator.

In this PMR, the *octagam*® 5% treatment group and the comparator group will receive treatment as prescribed by their physicians and will be observed for the health outcomes of interest.

5. TREATMENT

This is a PMR non-interventional study. Patients documented in this PMR study will receive commercially available IVIG therapy.

5.1. CHARACTERIZATION OF OBSERVATIONAL DRUGS

5.1.1. octagam 5%

octagam® 5% contains 50 mg protein per mL of solution of which ≥ 95% is IgG; the IgA content is ≤ 0.2 mg/mL and IgM content is ≤ 0.1 mg/mL. All 4 IgG subclasses are present in proportions corresponding to the normal physiological distribution. The product is liquid, contains maltose for regulating osmolality and has undergone multiple virus inactivation procedures including S/D treatment.

octagam® 5% can be stored for 2 years at a temperature of +2°C (36°F) to +25°C (77°F).

Detailed information on indications, dosages, the side-effect profile and other parameters of *octagam® 5%* can be found in the Package Insert.

5.1.2. Comparator Drugs

IVIG therapies, other than *octagam® 5%*, available in the US for administration as part of this protocol are detailed in Table 2.

The internet pages with the current links to the package inserts were accessed in September 2013.

Table 2: List of Comparator IVIGs

Product	Product Details
BIVIGAM™ Immune Globulin Intravenous (Human), 10% Liquid	http://www.bivigam.com/clientuploads/pdfs/Prescribing_Information.pdf
Carimune® NF	http://www.cslbehring-us.com/docs/374/33/Privigen-Prescribing-Information%20(1),0.pdf
Flebogamma® DIF 5%	http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM172599.pdf
Flebogamma® DIF 10%	http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM221606.pdf
Gammagard Liquid® 10%	http://www.baxter.com/products/biopharmaceuticals/downloads/gamliquid_PI.pdf
Gammagard S/D®	http://www.baxter.com/products/biopharmaceuticals/downloads/GGSD_Low_IgA_PI.pdf

Gammaked® 10%	http://www.gammaked.com/filebin/pdf/gammaked-prescribing-information.pdf
Gammaplex® 5%	http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM182963.pdf
Gamunex®-C 10%	http://www.talecris-pi.info/inserts/gamunex.pdf
Privigen® 10%	http://www.cslbehring-us.com/docs/374/33/Privigen-Prescribing-Information%20(1),0.pdf

5.2. TREATMENT DETAILS

Patients will either be administered the brand of IVIG therapy ordered by their prescribing physician, or for patients issued unspecified or generic prescriptions of IVIG therapy, *octagam® 5%* or another brand of IVIG therapy will be provided by the Investigator according to federal, state and local regulations and GCP guidelines. For dosage recommendations, refer to the respective product Package Inserts.

Depending on the patient's insurance provider, IVIG infusions may be administered at study site, or outside the study site, e.g. in outpatient infusion center, physician's office or at the patient's home. Established regional clinical guidelines apply for the treatment of patients outside the study side by health care professionals. The Investigator is responsible for providing and instructing the patients on the completion of a Patient Diary (Appendix 2), where patients are asked to collect the treatment details.

All dosages of IVIG that the patient received during this PMR Study as well as the maximum infusion rate for each infusion should be recorded on the corresponding eCRF page.

Any drug dose-adjustment and interruptions are at the treating physician's discretion according to the patient's clinical condition.

6. STUDY CONDUCT

6.1. OBSERVATIONS BY VISIT

6.1.1. Baseline Visit

The following assessments and activities will be performed during the Baseline Visit:

- Obtaining written informed consent.
- Patient demographics.
- Medical history including concomitant diseases. Only clinically relevant medical history and concomitant diseases should be entered into the CRF.
- Concomitant medications. Only clinically relevant concomitant medication should be entered into the CRF.
- Infectious episodes within the last 12 months.
- Previous IVIG treatment details (during the last 6 months).

- TEE risk factor evaluation.
- Blood viscosity (in patients at risk of hyperviscosity, if available).
- Laboratory tests (last available results that are clinically relevant).
- Viral status and vaccination status.
- Perform enrollment in the eCRF.

Before a patient can be enrolled into the study, the Investigator must confirm that the patient meets all inclusion/exclusion criteria, and enter the baseline data into the eCRF. The eCRF might (temporarily) deny enrollment of patients with particular characteristics and/or treatment assignment in case there is a pronounced misbalance between the treatment groups overall or with respect to the key parameters used for the matching of patients required; see section 8.2 for details.

The Baseline Visit may take place at the same day when Infusion Visit 1 takes place; however, it is also permitted to perform baseline activities up to one infusion interval in advance. In any case the EDC enrollment must take place before the first infusion for documentation at Infusion Visit 1 takes place. If a patient cannot be enrolled at the planned time because of obstructions due to balancing procedures (see Section 8.2), the Investigator can enroll the patient as soon as the obstructions will be lifted; however the baseline visit needs to be updated or done completely again.

For patients treated outside the study site, the Investigator is responsible for providing a Patient Diary (Appendix 2). Patients must be instructed how to use the diary and to collect the data properly. The Investigator must ensure that the appropriate patient contact details for the follow-up calls are provided to the external contract partner who will be performing these calls. Patients must be informed that this contact information will be provided to an external contract partner involved in the follow-up.

6.1.2. Infusion Visits

The first infusion visit (Infusion Visit 1) may be at the same day when the Baseline Visit takes place or up to one infusion interval in advance; however, in any case the baseline activities have to be completed before the first infusion. Visits 2 through 4 will take place in 3–4 week intervals.

The following assessments and activities will be documented at Infusion Visits 1 through 4:

- Body weight (if available).
- Infusion details (date, duration, lot number/s, dose, maximum infusion rate).
- Vital signs (before infusion and during infusion or after the end of infusion – as available).
- Laboratory tests (if available).
- Changes in relevant concomitant medications.

- ADRs (if applicable).

6.1.3. Follow-up

To evaluate and record any safety issues that may have arisen, follow-ups will be performed in a thorough and consistent manner. In order to achieve this purpose, a standardized questionnaire will be used (see Appendix 1). Data fields in the eCRF will correspond with the data fields of the questionnaire.

Patients will receive a follow-up telephone call 7-day (+2 days) after each IVIG infusion to administer the patient questionnaire. In addition, 3–4 week follow-ups will be performed either at the study site, or again by phone if the patient is treated outside the study site on the same day as and prior to the next infusion. The contract research organization performing the follow-ups will enter all data directly into the eCRF.

For infusion 4, the follow-up will be performed at the Close–Out Visit at the study site or as a telephone follow-up performed by the study site to patients who do not receive their infusions at the study site.

6.1.4. Close-Out Visit

The Close-Out Visit will take place 3–4 weeks after the 4th Infusion Visit. Patients who have received a Patient Diary will return the completed diary. If the Close-Out Visit cannot take place at the study site, the Investigator is responsible to receive all required information via telephone and must make sure to receive any previously dispensed Patient Diaries.

The following assessments and activities will be documented at the Close-Out Visit:

- Safety follow-up questionnaire (see Appendix 1)
- ADRs occurring since previous infusion (if applicable).
- Changes in relevant concomitant medications.
- Changes in vaccination status.
- Overall efficacy assessment.
- Available clinically relevant laboratory results
- Measles antibody testing only in certain patients as defined in section 7.2.5.
- Transfer of new information from the Patient Diary (if applicable).

Within 12 weeks after study end, a review of medical records will be performed at the study site by the study monitor. In order to ensure that this review is performed thoroughly and consistently, a data monitoring plan will be developed by the responsible contract research organization.

6.2. DURATION OF PMR STUDY

It is planned that this PMR will start within 10 months after protocol finalization (i.e. acceptance of protocol by FDA).

The regular duration of observation for an individual patient will be the period of administering 4 infusions, what adds up to 12 or 16 weeks (incl. Close-Out Visit) depending on the patient's 3- or 4-week infusion schedule.

According to the sequential analysis design, the study will be continued until either the value of the log-likelihood ratio test statistic is > 2.77259, a total of 8 TEEs have been recorded or the total of 2000 infusions has been reached; please refer to Section 9.2 for further details.

7. ASSESSMENTS AND METHODS

7.1. BASELINE ASSESSMENTS

The following information will be captured at the Baseline Visit:

- Patient Demographics: year of birth, sex, ethnic origin, height, diagnosis and grading of diagnosis (physician's assessment).
- Medical history: date of diagnosis of PI, previous and ongoing relevant concomitant diseases; obtained by interviewing the patient.
- Previous IVIG treatments during the last 6 months including product name, dose, and frequency; obtained by interviewing the patient
- Ongoing medications considered relevant by the Investigator: generic name, dosage, frequency and mode of administration, including start date; obtained by interviewing the patient.
- TEE risk factor evaluation: smoking habits, history of previous TEEs, cardiovascular risk factors such as coronary artery disease, impaired cardiac output, known or suspected hyperviscosity, obesity, diabetes, hypertension, hyperlipidemia, advanced age, coagulation disorders, oral estrogen use, in-dwelling catheters or devices, and prolonged periods of immobilization.
- Whole blood viscosity testing: is strongly recommended to be performed for known risk patients, i.e. those with cryoglobulins, fasting chylomicronemia / markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. Test should include the complete blood count and both systolic and diastolic blood viscosity parameters when possible.
- Laboratory test results: only if routinely done and available.
- Viral status and vaccination history if known.

7.2. SAFETY ASSESSMENTS

To allow continuous monitoring of the product's safety, all treatment-related ADRs, all TEEs (regardless of causality) and other safety information as defined below must be documented and reported to Octapharma. Any ADR (regardless of administered product) indicated by signs and symptoms must be documented using specific forms. All TEEs will be reported regardless of administered product, severity or relatedness to the product.

7.2.1. Thromboembolic Events

The following list includes diagnoses and symptoms of possible TEEs that could be expected to be reported:

Acute myocardial infarction
Increased heart enzymes*
ECG signs of myocardial infarction*
Angina pectoris*
Acute coronary syndrome*
Chest pain or pressure*
Cardiac arrest**

(Ischemic) Stroke

Transient ischemic attack

Cerebrovascular accident
Vision or speech disorders*
Unilateral paresis/weakness
Movement disorders*
Dysphasia*
Sudden severe headache*

Deep vein thrombosis
Pain or tenderness in leg(s)*
Pain in calf/calves*
Swelling calf/calves/lower legs*

Pulmonary embolism
Unexplained shortness of breath*
Sudden chest pain getting worse with a deep breath, coughing, or chest movement*
Cyanosis*

Thrombophlebitis

Infusion site thrombosis

* Possible sign or symptom of TEE
** May be outcome of TEE

In case of a TEE, the Adverse Drug Reaction/TEE Reporting Form in the eCRF should be filled out. The question "Suspected TEE case" should be ticked yes. The definitions as in chapter 7.2.2 apply, but additionally the causality may be "unrelated" to the product, as all TEEs regardless of causality must be documented.

7.2.2. Adverse Drug Reactions

Adverse drug reaction (ADR):

An ADR is any noxious and unintended response to a study drug which occurs at doses normally used in humans for the prophylaxis or therapy of disease or for the restoration, correction or modification of physiological function. A response in this context means that a causal relationship between the study drug and an adverse event is at least a reasonable possibility.

The following causality definitions should be used for classification of each ADR:

Definite: Event or laboratory test abnormality, with plausible time relationship to drug intake

Cannot be explained by disease or other drugs

Response to withdrawal plausible (pharmacologically, pathologically)

Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon)

Re-challenge satisfactory, if necessary.

Probable: Event or laboratory test abnormality, with reasonable time relationship to drug intake

Unlikely to be attributed to disease or other drugs

Response to withdrawal clinically reasonable

Re-challenge not required.

Possible: Event or laboratory test abnormality, with reasonable time relationship to drug intake

Could also be explained by disease or other drugs

Information on drug withdrawal may be lacking or unclear.

Unlikely: Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)

Disease or other drugs provide plausible explanations

The following 3-point rating scale should be used to rate the intensity of each ADR:

Mild: Experience that is usually transient, which causes discomfort but does not interfere with the patient's routine activities.

Moderate: Experience is sufficiently discomforting to interfere with the patient's routine activities.

Severe: Experience is incapacitating and prevents the pursuit of the patient's routine activities.

Serious adverse drug reaction (SADR):

A **serious ADR** is any untoward medical occurrence that is considered related to study drug and that at any dose:

- results in death
- is life-threatening (this implies that the patient was at an immediate risk of death at the time of the event, and not a hypothetical situation of what could or would have happened if, for example, no treatment had been administered)
- requires in-patient hospitalization or prolongation of existing in-patient hospitalization (hospitalization does not refer to the treatment of an ADR on an out-patient status or to hospitalization because of study-related procedures (e.g., infusion at two consecutive days) or because of an elective surgical procedure for which the date had been scheduled earlier)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is another important medical event (e.g. suspected transmission of an infectious agent, or other reactions that should be reported in an expedited manner although they did not immediately result in one of the above seriousness criteria, e.g. symptoms of TEEs)

Medical judgment should be exercised in deciding whether an adverse drug reaction is serious in other situations: Important ADRs that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definitions above, should also be considered serious.

7.2.3. Other Relevant Drug Safety Information

Any safety information relating to

- pregnancies/breastfeeding,
- drug abuse (persistent, sporadic or intentional excessive use of a medicinal product inconsistent with the Package Insert or acceptable medical practice),
- overdose (treatment exceeding the medically recommended dose),
- medication errors (prescribing or dispensing error),

- interactions with other medicinal products or devices,

associated with IVIG treatment, even if no ADR occurred, should be reported.

Post study related safety reports:

If a patient dies within 4 weeks after the last IVIG administration documented in this PMR study, this should be reported even if the death is considered unrelated to IVIG therapy.

Pregnancies:

Pregnancies occurring during the study (fetal exposure to IVIG treatment) need to be reported. A pregnancy notification form should be completed for pregnant women who will be included into the study as well as for women who get pregnant during the study. If it is determined after the study has ended that a patient became pregnant during the study period, the information should be reported subsequently. Follow-up information on the outcome of both mother and fetus will be requested by Octapharma.

Overdose, interaction, misuse, and medication error

The following safety relevant information should be reported irrespective whether an ADR occurred. If no ADR occurred, the information should be forwarded within the same timelines as non-serious ADRs. If one report with safety relevant information also fulfills one of the criteria for seriousness, the reporting timelines for serious ADRs apply (see Section 7.2.4).

Drug overdose:

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than that specified in the protocol, and higher than the known therapeutic dose and of clinical relevance. The reaction must be clearly identified as an overdose.

Interaction:

A drug interaction is a situation in which a substance/medicinal product affects the activity of IVIG, i.e., the effects are increased or decreased, or they produce an effect that none of the products exhibits on its own. The reaction must be clearly identified as drug interaction.

Misuse:

Misuse is the deliberate administration or use of the medicinal product outside its described indication or outside the current state of the art medical practice (off-label use). The reaction must be clearly identified as misuse.

Medication error:

Medication error involves the inadvertent administration or unintended use of a medicinal product which may be caused by the naming, presentation of pharmaceutical form/packaging, instructions for use/labeling. The reaction must be clearly identified as a medication error.

7.2.4. Reporting of ADRs and Other Safety Information

If one or more questions in the safety follow-up questionnaire (Appendix 1) are answered with "yes", an automatically generated message will be sent to the responsible monitor who in turn must forward it immediately (within the same working day) to the corresponding Investigator. The Investigator has to contact the patient within 24 hours after having received the message in order to verify and validate the reported event. As soon as the investigator becomes aware of an ADR or TEE (regardless of causality), he must enter that information into the eCRF according to the timelines as defined below.

Once an ADR has been entered into the eCRF system, an automatically generated message will be sent to Octapharma's CDSU who will process the case in routine manner.

ADR reporting timelines:

Serious ADRs and all TEEs (irrespective of seriousness and relatedness) must be reported by the Investigator immediately (within 24 hours) via the EDC.

Non-serious ADRs and other safety information should be reported by the Investigator no later than 10 working days via the EDC.

More information about possible ADRs and other safety information can be found in the Package Insert.

Serious ADRs and all TEEs (irrespective of seriousness and relatedness) reported in association with *octagam 5%* will be reported by Octapharma in expedited manner to the FDA.

Serious ADRs and all TEEs (irrespective of seriousness and relatedness) reported in association with other IVIG brands will be reported by Octapharma to the responsible manufacturer for further processing and reporting. All the cases will be included in the monthly analyses.

All **serious unexpected** ADRs which have a reasonable possibility of being product-related and all **TEEs** (which have a reasonable possibility of being product-related) in association with a non-Octapharma product will be forwarded by Octapharma to the FDA.

All non-serious ADRs reported in association with other IVIG brands will be reported by Octapharma to the responsible manufacturer for further processing and reporting.

7.2.5. Laboratory Evaluations

The timing of blood or urine sampling for laboratory evaluations is at the discretion of the treating physician. If such blood or urine sampling takes place routinely, the following laboratory parameters should be documented, if available: hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet, count, ALAT, ASAT, bilirubin, creatinine, CRP, and whole blood viscosity.

At select sites only, patients who have received at least 4 infusions of *octagam® 5%* before study start as well as 4 infusions of *octagam® 5%* during the study and who are willing and

provide written informed consent will be tested for trough levels of specific antibodies against measles at the close out visit. A total of 25 patients will be tested at sponsor selected centers.

7.2.6. Vital Signs

Vital signs (temperature, heart rate, respiratory rate, blood pressure) are recommended to be taken before, during or no later than 1 hour after the end of each infusion. Available results have to be documented in the eCRF.

7.3. EFFICACY ASSESSMENTS

Infectious episodes since baseline visit will be asked and documented. The effect of IVIG therapy on infections will be assessed.

8. DATA HANDLING AND RECORD KEEPING

8.1. ELECTRONIC CASE REPORT FORMS (ECRF)

A web-based secure system will be utilized for remote data entry. Each patient is uniquely identified in the study by an ID number that will be allocated automatically. Once assigned to a patient, a patient number will not be reused.

An eCRF will be completed for every study patient and signed by the investigator or designee. All forms will be filled out electronically via a web-based system and will capture all infusions and follow-up communications, including any ADR or TEE (regardless of causality) or lack thereof. All persons allowed entering or changing eCRF data are documented in the user list.

Missing or non-plausible data will be completed and/or corrected in accordance with specific operating instructions by telephone inquiries, fax, emails or visits at the site.

The eCRF pages that have been locked will be printed by the responsible Data Management Group and stored at the participating sites' archives for at least as long as required by regulatory authorities after completion or discontinuation of the trial, together with the original informed consent forms and the patient identification list. The Sponsor will archive the eCRF database.

Data will be cleaned in accordance with the Data Management Plan and the Data Validation Plan periodically before the EDC system is locked and released for statistical analysis.

8.2. ENROLLMENT PROCEDURE

The enrollment procedure is to ensure that the evaluation of TEE occurrence can be evaluated statistically on basis of a matched pairs approach, but also to minimize patient exclusion as this could introduce bias and prolong the study duration unnecessarily. To achieve these goals the patient characteristics that will be used to match the patients into pairs for the analysis will be monitored monthly. A report on the exact composition of the current patient cohort with respect to these parameters will be made available on a daily basis. These reports will be monitored by the project manager, and appropriate measures will be implemented into the

EDC system to deny enrollment of patients once the imbalance between treatment groups becomes too pronounced. There will however be no immediate and automated denial of patient enrollment as this could lead to a situation where the possibility to enroll a particular patient changes incessantly. The project manager will take any such decision on basis of the available reports and the current prospect of patient enrollment, using the following balancing algorithm as the guiding principle.

The following data will be used to establish matched pairs for the patient enrollment and are therefore mandatory items in the tracking system and part of the balancing algorithm and report:

- [Treatment (*octagam® 5%* | competitor IVIG)]
- Age groups (18–43 years | 44–68 years | >68 years)
- Sex (male | female)
- Dose groups (low: <0.3 g/kg | medium: 0.3–0.7 g/kg | high: >0.7–1.0 g/kg)
- TEE risk (Low | Medium | High) defined as follows:
  Low TEE risk: less than 2 of the 11 risk factors listed below
  Medium TEE risk: 2–4 of the 11 risk factors listed below
  High TEE risk: more than 4 of the 11 risk factors listed below
  - Cardiovascular risk factors
  - Occurrence of any TEE(s) > 2 year prior to study enrollment
  - Diabetes mellitus
  - Hyperlipidemia
  - Hypertension
  - Obesity (Body Mass Index >30)
  - Smoking currently or within last 2 years
  - Oral estrogen use
  - Coagulation disorders
  - In-dwelling catheters or devices
  - Prolonged periods of immobilization

Whenever a patient is enrolled, the balancing algorithm will evaluate the relative difference between the number of patients treated with *octagam® 5%* and the number of patients treated with a comparable IVIG in the same patient stratum:

$$r_S = \left| \frac{[Number\ of\ Octagam\ pts.\ in\ stratum\ S] - [Number\ of\ Other\ pts.\ in\ stratum\ S]}{[Total\ number\ of\ pts.\ in\ stratum\ S]} \right|$$

where ‘S’ is any stratum defined by the categories used for matching pairs as defined above.

The goal is to have comparable numbers of patients in each stratum as well as overall; these relative differences and the absolute number of patients per treatment group in each stratum

will be used by the project manager to steer enrollment.To also control the overall balance with regard to the treatment arms a dynamic tolerance margin is defined in the following way:

Let $n_{50\_octagam}$ be the number of patients enrolled under octagam® 5% and n_{50_other} be the number of patients enrolled under a competing IVIG when $n_{total} = 50$. Define

$$R50_{rel} = \max\left(\text{abs}\left(\frac{n_{50\_octagam} - n_{50\_other}}{50}\right),\ 0.5\right)$$

and

$$a = (0.05 - R50_{rel}) / 350$$

then the dynamic tolerance margin is defined as

$$\text{margin} = \max(R50_{rel} + a*(n\_total - 50),\ 0.05)$$

for $50 \leq n_{total} \leq 400$ and as 0.05 for $n_{total} > 400$. For $n_{total} < 50$ no tolerance margin is defined.

8.3. INVESTIGATOR SITE FILE

The Sponsor or designee is responsible for maintaining all adequate records to enable the conduct of the project to be fully documented. This includes, among others, the observational plan (this study protocol) and any amendments (if applicable), a sample of the eCRF, relevant correspondence pertaining to the conduct of the project, other written information, financial aspects of the project, signed agreement between involved parties, a copy of the notification to competent authorities, and notifications of ADRs/unrelated TEEs to Sponsor.

The EDC system is documenting chronologically screening/enrollment of patients. The participating study sites are responsible for maintaining a confidential patient identification code list which provides the unique link between named source records and eCRF data for the Sponsor. The Sponsor must take care for the retention of this confidential list for the maximum period of time required by local regulations. The participating study sites should take measures to prevent accidental or premature destruction of these documents.

No study document should be destroyed without prior written agreement between the participating study sites and the Sponsor. Should a participating study site elect to assign the study documents to another party, or move them to another location, the Sponsor must be notified in writing.

8.4. INDEPENDENT SAFETY REVIEW BOARD

An Independent Safety Review Board (ISRB) will be established by the Sponsor.

A Charter (see Appendix 3) has been set up for the ISRB overseeing all Octapharma post-authorization safety studies with *octagam*® 5% and/or *octagam*® *10%* as defined in the Plan for an Integrated Safety Analysis provided earlier. The ISRB is a group of independent external medical experts not actively involved in any of the concerned post-authorization safety studies. The ISRB has been set up in order to review the safety data deriving from the

post-authorization safety studies and, based on their review, provide Octapharma with assessments, opinions or recommendations.

The ISRB has the following specific responsibilities:

- to review all suspected serious adverse drug reactions on a case by case basis;
- to review all suspected TEE cases on a case by case basis;
- to provide an opinion on the causality assessments of the reported TEE cases;
- to review all reported cases on a quarterly basis (both related and unrelated cases, if any) with the objective to detect "hidden" cases of TEEs.

9. STATISTICAL METHODS AND SAMPLE SIZE

9.1. STATISTICAL ANALYSIS

The primary objective of this study is the close monitoring of the occurrence of TEEs. This statistical monitoring will be carried out by means of the Maximized Sequential Probability Ratio TEST (MaxSPRT) for Binomial data, cf. Kulldorff et. al. 2011 (2). This procedure is especially suited for the early detection of excess risks of events of special interest and has already shown good properties in vaccine trials.

The study will use a 2-armed study design, in which patients treated with *octagam*® 5% will be compared with a prospective control group of patients treated with other brands of IVIG.

To ensure accurate case counts in each cohort, two time windows for the occurrence of TEEs are defined: within seven days of infusion (to capture primarily arterial events) and within 21 days (to capture both arterial and venous events).

The following TEE endpoints are defined:

TEE_7 = yes, if a candidate thromboembolic event is reported within 7 days after the last IVIG administration and this event is confirmed as a TEE.

= no, otherwise.

TEE_{21} = yes, if a candidate thromboembolic event is reported within 21 days after the last IVIG administration and this event was confirmed as a TEE.

= no, otherwise.

TEE_7 will be considered as the primary endpoint while TEE_{21} will be considered as secondary.

The procedure for adjudication of candidate TEEs is described in Section 3.1.3.

The proposed method will provide a sequential comparison of the hypothesis

$$H_0: RR \leq 1 \text{ versus the alternative } H_A: RR > 1,$$

where RR denotes the relative risk of occurrence of TEEs within 7 days after the last IVIG administration (i.e. RR = Prob(TEE_7 | *octagam*® *5%*) / Prob(TEE_7 | other IVIG).

This will be done on a monthly basis for the duration of the study in order to detect a potential excess risk for TEEs.
Furthermore, the relationship of the following patient and treatment characteristics with the occurrence of TEEs (TEE_7 and TEE_{21}) will be assessed in the context of a conditional logistic regression model (see SAP for further details):

- IVIG treatment group (octagam® 5%, other brand),
- Cardiovascular risk group (Low / High),
- Presence of coagulation disorders (yes, no),

- Presence of in-dwelling catheters or devices (yes, no),
- Presence of prolonged periods of immobilization (yes, no),
- Use of estrogens (yes, no)

For the purpose of this analysis, the study population will be considered to be matched by age group at enrollment (18-43, 44-68, > 68 years) and gender (male, female) as described in section 8.2 of the study protocol; these two parameters will be used as strata in the conditional logistic regression.

Statistical analysis of the other parameters will be descriptive. Validated software will be used for the statistical analysis. All data will be listed in their entirety and will be presented in summary tables.

In general, all study parameters will be described using the following standard statistical parameters: arithmetic means, standard deviation, median, minimum and maximum. Frequency tables (absolute and relative frequencies) will be produced for the qualitative assessment of data.

The demographic data, indications for use, baseline values, and number of doses will be summarized descriptively. Safety assessments will be presented by frequency tables and corresponding figures.

If sufficient laboratory or other test data are available, these will be presented as mean values before and after treatment with scatter diagrams and the corresponding regression lines.
The measles antibodies will be measured by a validated bioassay and the results will be analyzed with respect to the amount of antibody administered in octagam and trough levels obtained. Raw data will be provided. Analysis will include modeling by proportional shrinking of results to simulate trough titers in each patient as if the product administered had an anti-measles antibody level of 0.15 X CBER standard. Octapharma will calculate hypothetical serum antibody levels by dividing the minimum potency acceptable (0.15 X CBER standard) by the actual potency of the lot(s) given to each patient, and using this factor times the actual trough level to predict the trough level that would occur in the setting of the proposed minimum product potency.

9.2. QUANTITATIVE DETERMINATION OF THE PMR STUDY POPULATION

The proposed MaxSPRT method for Binomial data requires monitoring of the two study cohorts until the procedure either detects a possible excess risk (by comparing the test statistic with a pre-determined critical value) or until the end of the surveillance period is reached (expressed as the expected total number of TEE_7 events in both cohorts).

For the determination of the upper limit of the surveillance period a rate of occurrence of a TEE_7 between 1% and 1.5% per treated patient is assumed. Based on a total of 500 patients with 4 documented administrations the expected number of TEE_7 events would be 5–8.

It is planned to ensure that both treatment groups will be about the same size and hence the ratio of the exposure times will be close to 1. This will be achieved by an enrollment process

that prohibits that the study population becomes to imbalanced with respect to any parameter of interest; the tolerance margins for such imbalances will be reduced as the study progresses and the total number of patients enrolled increases. Please refer to Section 8.2 for further details.

If the type I error probability is fixed at $\alpha = 0.05$ then the study will be continued until either

- the value of the log-likelihood ratio test statistic is > 2.77259

or

- a total of 8 TEE events have been recorded.

For details see the cited reference (2).

9.3. INTERIM ANALYSIS

Descriptive interim analyses are planned every 3 months as part of PSURs until completion of this study.

In addition to the ongoing monitoring and evaluation of TEE occurrences throughout the whole study, it is planned to prepare monthly reports on the TEE analysis as described in Section 9.1. These reports will be submitted to the FDA within 21 days of the last data lock point. In addition to the statistics and figures associated with the MaxSPRT, these reports will include the number of patients enrolled to date in each arm, the number, type, and rate of TEEs within 7 and 21 days after the last IVIG administration in each study arm, the number of patients lost to follow-up, the sponsor's assessment of the data to date and the sponsor's assessment of whether any difficulties in completing the observational study were encountered.

9.4. FINALANALYSIS

The patient enrollment process is designed to ensure that major imbalances in known and suspected confounding factors are minimized to facilitate the use of a conditional logistic regression model to study the relative risk of TEEs between treatment groups. For the evaluation of the relative risk all factors identified in Section 9.1 above will be assessed in the context of a conditional logistic regression model, using age and sex as strata.

10. ETHICAL/REGULATORY, LEGAL AND ADMINISTRATIVE ASPECTS

10.1. ETHICAL / REGULATORY FRAMEWORK

The study documentation will be submitted to the appropriate Institutional Review Boards (IRBs).

10.1.1. Institutional Review Board Approval

The protocol for this study has been designed in accordance with the general ethical principles. The review of this protocol by the IRBs and the performance of all aspects of the

study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the ICH Guidelines as well as in Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards.

The Investigator will be responsible for preparing documents for submission to the IRB and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.

The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number.

Any amendments to the protocol (see Section 10.4) after receipt of IRB approval must be submitted by the Investigator to the IRB for approval. The Investigator is also responsible for notifying the IRB of any serious deviations from the protocol, or anything that may involve added risk to patients.

10.1.2. Informed Consent

The Investigator must obtain written informed consent of a patient prior to any study related procedures as per GCP as set forth in the CFR and ICH guidelines.

Documentation that written informed consent occurred prior to the patient's entry into the study and the informed consent process should be recorded in the patient's source documents. The original consent form signed and dated by the patient and by the person consenting the patient prior to the patient's entry into the study, must be maintained in the Investigator's study files.

Patients agreeing to participate in the measles antibody testing must sign an addendum to the informed consent explaining this testing prior to the patient testing before study infusion 3.

10.1.3. Patient Confidentiality

Octapharma affirms the patient's right to protection against invasion of privacy. In compliance with US federal regulations, Octapharma requires the Investigator to permit Octapharma representatives and, when necessary, representatives of the FDA or other regulatory authorities to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the patient's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

10.1.4. Premature Discontinuation of Study

The Investigator and Octapharma have the right to discontinue this study at any time for reasonable medical or administrative reasons. Possible reasons for termination of the study could be but are not limited to:

- Unsatisfactory enrollment with respect to quantity or quality.
- Inaccurate or incomplete data collection.
- Falsification of records.
- Failure to adhere to the study protocol.

Any possible premature discontinuation would be documented adequately with reasons being stated, and information must be issued according to local requirements (e.g., IRB, regulatory authorities, etc.).

10.2. APPROVAL OF STUDY DOCUMENTS

The study protocol, a sample of the patient information and informed consent form, any other materials provided to the patients, and further requested information will be submitted by the Sponsor or the Investigator to the appropriate IRB and the FDA.

10.3. PATIENT INFORMATION AND INFORMED CONSENT

Prior to receiving their first IVIG treatment in the context of this PMR, patients will be informed about the scope of the study and the use of their data. After consenting to study participation they will sign an informed consent form on paper that will be kept at the study site. Date of signature will be recorded in the eCRF.

10.4. PROTOCOL AMENDMENTS

Any prospective change to the protocol will be agreed between the Sponsor and the FDA. Any such amendments will be submitted to the IRB as required by applicable regulations. IRB approval will at a minimum be requested for any change to this protocol which could affect the safety of the patients, any increase in the number of patients treated, the addition of a new test or procedure, or the dropping of a test intended to monitor safety.

10.5. CONFIDENTIALITY OF PATIENTS' DATA

All patient data documented on the eCRF will be pseudo-anonymized by the participating study site. Only the Investigator, or a person authorized by the Investigator will be able to decode the patient identity using an internal patient allocation list.

11. REPORTING AND PUBLICATION

11.1. INTERIM AND FINAL REPORT

Throughout the entire period of the observational study, the relevant data from the interim and final analyses will be reported in the Periodic Safety Update Reports.

11.2. REPORTING OF PMR STUDY RESULTS

The Sponsor will compile a Final Report within 6 months after the final statistical analysis is available.

11.3. PUBLICATION OF DATA

The results of this project may be published or presented at scientific meetings.

12. REFERENCES

(1) Debes A, Bauer M, Kremer S. Tolerability and safety of the intravenous immunoglobulin Octagam(R): a 10-year prospective observational study. Pharmacoepidemiol Drug Saf 2007 Jul 18;16:1038-47.

(2) Kulldorff M, et. al. A Maximized Sequential Probability Ratio Test for Drug and Vaccine Safety Surveillance, Sequential Analysis 2011; 30: 58-78

13. APPENDICES

Appendix 1 Safety Follow-up Questionnaire

Appendix 2 Patient Diary

Appendix 3 DMC Charter