octapharma

# OBSERVATIONAL PLAN

## NON-INTERVENTIONAL STUDY ON THE TOLERABILITY OF IVIG AND SCIG

## GAM10-06

## "GammaTrack"

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PROTOCOL AUTHORIZATION

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

**Sponsor Representatives:**

[redacted]

Qualified Person for Pharmacovigilance
Octapharma Pharmazeutika Produktionsges.m.b.H.
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**LIST OF ABBREVIATIONS**

| | |
|---|---|
| ADR | Adverse Drug Reaction |
| eCRF | Electronic Case Report/Record Form |
| EDC | Electronic Data Capturing |
| EMA | European Medicines Agency |
| IVIG | Intravenous Immunoglobulin |
| NIS | Non-Interventional Study |
| PASS | Post-Authorisation Safety Surveillance |
| PID | Primary Immunodeficiencies |
| SCIG | Subcutaneous Immunoglobulin |
| S/D | Solvent/Detergent |
| SID | Secondary Immunodeficiencies |
| SmPC | Summary of Product Characteristics |
| TNBP | |

# 1 INTRODUCTION

## 1.1 BACKGROUND

Since more than six decades immunoglobulins have been used to provide antibodies for the prevention of viral and bacterial diseases (replacement therapy) in immunocompromised patients. In the earlier years (around 1950), the IgG preparations were administered intramuscularly. This route of administration causes substantial discomfort, and restricts the amount of IgG that can be given to the patients. Since its use as a replacement therapy for patients with primary (PID) and secondary (SID) immunodeficiencies, the clinical use of intravenous immunoglobulin (IVIG) has expanded and has become an important treatment option in a wide spectrum of diseases. IVIG is used routinely in autoimmune and acute inflammatory conditions due to IVIG's immune-modulatory and anti-inflammatory properties. During the last 25 years, the use of subcutaneously administered immunoglobulins (SCIG) has further contributed to the successful treatment of PID and SID patients. Administration via the SC route offers several advantages over IV infusion from a patient's and a physician's perspective and therefore became an alternative treatment option to IV treatment. After introduction of small, portable syringe drivers, SCIG products have gained even more popularity in Europe, USA, and Canada as a practical, effective and safe treatment, as they can be safely self-administered at home or even when travelling.

octagam® 5% and octagam® 10% are liquid polyvalent IVIG preparations, which are subject to a three-stage viral inactivation. The products are prepared from human plasma and mainly contain human normal immunoglobulin G. The molecules are present in their native form which is essential for the biological activity. octagam® 5%, has been approved in 83 countries worldwide since 1995; octagam® 10% has been approved in 58 countries worldwide since 2008.

octagam® is produced from a pool of at least 3,500 donations of human fresh frozen plasma per batch.[1] The large donor pool ensures that the product contains a broad range of antibodies directed against pathogens and foreign antigens, which is far more diverse than that of plasma from an individual donor. Donor plasma sampling, the manufacturing of the product and the measures to ensure the product's viral safety are subject to strict regulations laid down by regulatory authorities. Octapharma exclusively uses plasma that has been tested by nucleic acid testing (NAT) techniques. The production process contains three validated virus inactivation steps (modified ethanol fractionation, pH treatment, and solvent/detergent (S/D) virus inactivation).

panzyga® (Immune Globulin Intravenous (Human), 10%) is a sterile liquid preparation of highly purified immunoglobulin G (IgG) derived from large pools of human plasma. The panzyga® manufacturing process achieves a significant viral reduction through a combination of two dedicated manufacturing process steps: S/D treatment and nanofiltration (20 nm). The Source Q chromatography (ion-exchange chromatography) step in the panzyga® process also contributes significantly to the viral safety of panzyga®. The efficacy of the virus inactivation procedures has been extensively validated. panzyga® has been approved in 29 countries worldwide since 2016.

cutaquig® is a sterile solution of human normal immunoglobulin containing 16.5% (165 mg/mL) protein for SC administration, prepared from at least 3500 donations of human fresh-frozen plasma. Effective viral reduction is obtained via a combination of 3 validated manufacturing steps: cold-ethanol fractionation, S/D treatment with TNBP (Tri-n-butyl phosphate) and Octoxynol, and pH 4 treatment. cutaquig® has been approved in Canada.

This post-marketing surveillance study is designed to ensure long-term consistency between data from the pre-licensure clinical studies and clinical use. Documentation of the administration of Octapharma's IVIG products (octagam®, panzyga®) and the newly licensed SCIG product (cutaquig®) in clinical practice will not only improve the efficacy and tolerability knowledge database, but will produce findings that cannot be obtained in the same way in controlled clinical studies. This surveillance study will support the optimal use of octagam®, panzyga®, and cutaquig®, thus bringing benefit for both physicians and patients.

# 2 OBJECTIVES

1) The primary objective is to document the safety and tolerability of octagam®, panzyga® and cutaquig® in any indication, age group or treatment regimen.
2) The secondary objective is to document their efficacy in patients receiving treatment.

[1] For simplicity, the term octagam® refers in this document, to both strengths (5% and 10%) unless noted otherwise.

# 3 INVESTIGATIONAL PLAN

## 3.1 OVERALL DESIGN AND PLAN

This is a prospective, multicentre, non-interventional study (NIS).

The treating physician decides whether, how and for how long a patient is to be treated with octagam®, panzyga®, and/or cutaquig®.

### 3.1.1 Population

octagam®, panzyga®, and/or cutaquig® will be prescribed regularly to any patient who needs to be treated with an IgG product because of their medical condition and whom the treating physician wants to include in this observational study, after the decision has been made to prescribe IVIG or SCIG treatment.

This study will observe 300–500 patients treated with octagam®, panzyga® and/or cutaquig® in any indication, age group, gender or treatment regimen. It is not possible to specify the exact number of doses per patient that are to be documented because of the different indications for use.

All patients who are eligible to enter the study will be informed by the physician before study entry about the conduct, implication and goal of this Post-Authorisation safety Surveillance. This will be done following center internal procedures. Each patient is uniquely identified in the study by an ID number that will be provided by the study centre to ensure patient confidentiality. Once assigned to a patient, a patient number will not be reused nor will the patient be allowed to re-enter the study after completion or discontinuation.

### 3.1.2 Centres

This observational study is conducted in outpatient and inpatient centres globally.

### 3.1.3 Flowchart of Study Events

Due to its non-interventional and observational nature, this study will strictly exclude pre-defined visits or time schedules (except that a close-out visit should take place before a patient leaves the NIS). However, it is recommended to perform subsequent visits on regular intervals according to standard treatment procedures for the respective disease.

Table 1 lists all assessments recommended by this protocol.

*Table 1: Assessment schedule*

| Assessments | Baseline or Entry Visit | Subsequent Infusion Visits | Close-Out Visit |
|---|---|---|---|
| Baseline assessments | ✓ | | |
| Previous IVIG and SCIG treatments | ✓ | | |
| Concomitant medication(s) | ✓ | ✓ | ✓ |

| | | | |
|---|---|---|---|
| octagam®/panzyga® /cutaquig® treatment details | | ✓[1] | |
| Information on efficacy | | ✓ | ✓ |
| Adverse drug reactions (ADRs) | | ✓[1] | ✓ |
| Checking of patient diary for patients doing cutaquig® home treatment | | ✓ | ✓ |

[1] May take place at the same day as baseline/entry visit.

Data obtained during the study will be recorded, for this purposeElectronic case report forms (eCRF), namely a secure web-based data entry system (see Section 7.1), will be used.

The eCRF will consist of 4 main sections:

1) Baseline documentation: Must be completed when a new patient is enrolled. The patient's demographic data (year of birth or age, gender, weight, general condition, risk factors), medical history, basic disease (including date of diagnosis and details on previous treatments), and concomitant medications and diseases are to be documented.
2) Treatment record: Treatment details with octagam®/panzyga®/cutaquig® are to be documented, including date of administration, method of administration, infusion speed, dosage, batch number, concomitant medications incl. treatment details, if applicable. In case of home treatment with cutaquig®, patients will be asked to fill in a study diary to carefully document information (ie. including date and method of administration, infusion speed, dosage, batch number; concomitant medications incl. treatment details, if applicable).
3) Suspected ADRs occurring during or after administration of octagam®/panzyga®/cutaquig® are to be recorded on separate ADR forms. Patients are to be advised to document in their diaries every ADR they experience at home, also in case they do not need any medical treatment.
4) Efficacy assessment: Available efficacy data are to be documented.

### 3.1.4 Study Duration

This study started in August 2011 in 4 European countries and was then extended to Canada. The European centres are now closed or being closed and the study will continue in Canada. Planned study end is 2022.

The duration of observation for an individual patient will be as long as any of the described IVIGs or the SCIG will be prescribed by the treating physician and until the next regularly scheduled visit of the patient after last infusion. For patients with PID or SID the observation period should last at least 12 months, if possible.

### 3.1.5 Premature Termination

If, for any reason, the physician or the patient decides to discontinue treatment with octagam®, panzyga® or cutaquig®, the observation period of this patient is to be

terminated and a close-out visit should take place. The physician should make efforts to complete and document all available observations. The reason for termination is to be documented.

If the reason for discontinuing octagam®, panzyga® or cutaquig®therapy is the occurrence of an ADR, the specific reaction must be recorded and the outcome is to be documented.

# 4 TREATMENT

## 4.1 OBSERVATIONAL DRUGS

Subjects documented in this NIS will receive commercially available octagam®, panzyga® or cutaquig® prescribed by a physician.

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. octagam® 10% contains 100 mg protein per mL of solution of which ≥ 95% is IgG; the IgA content is ≤0.4 mg/mL and IgM content is ≤0.3 mg/mL. All four IgG subclasses are present in proportions corresponding to the normal physiological distribution. The product is liquid, contains maltose and has undergone multiple virus inactivation procedures.

panzyga® is a 10% solution ready for intravenous administration. panzyga® is made from a pool of at least 1000 donations of human fresh-frozen plasma per batch. During the manufacturing process of panzyga®, significant viral reduction is obtained via a combination of different validated steps during the manufacturing process. The efficacy of the virus inactivation procedures has been extensively validated according to relevant international guidelines in place.

cutaquig® is a sterile solution of human normal immunoglobulin containing 16.5% (165 mg/mL) protein, prepared from at least 3,500 donations of human fresh-frozen plasma per batch. Effective viral reduction is obtained via a combination of three validated manufacturing steps. The manufacture of cutaquig® is based on the octagam® manufacturing process including an additional adsorption step onto a commercially available and widely used chromatography column for the removal of coagulation factor XI (FXI). The process is identical up to the step of diafiltration.

octagam® 5% can be stored for 2 years at a temperature of +2 °C to +25 °C. octagam® 10% can be kept refrigerated at +2 °C to +8 °C for 2 years but can also alternatively be stored for 9 months at room temperature, in which case the end date automatically becomes the expiry date. panzyga® can be stored at +2 °C to +8 °C for 24 months from the date of manufacture. Within this shelf-life the product may be stored up to 9 months at ≤ 25°C. After the storage at ≤ 25°C the product must be used or discarded. cutaquig® can be stored for 2 years at +2 °C to +8 °C. Within this shelf-life the product may be stored up to 6 months at ≤ 25°C and must be used or discarded within that period.

Patients are treated with octagam®, panzyga® or cutaquig®according to the Investigator's prescription. For dosage recommendations please refer to the local octagam®, panzyga® or cutaquig®package leaflets.

Dosage and duration of treatment is at the sole discretion of the Investigator and will depend on the type and/or severity of the disease and the patient's clinical condition.

In case of SCIG home treatment the Investigator should promote compliance by instructing the patient to take cutaquig® exactly as prescribed and by stating that compliance is necessary for the patient's safety. The patient should be instructed to contact the Investigator if he/she is unable for any reason to administer cutaquig® as prescribed.

All dosages of octagam®, panzyga® or cutaquig® that a patient received during the observation period at the study center are to be recorded on the corresponding eCRF pages. Dosages of cutaquig® that a patient administered during the observation period at home are to be recorded in the patient diary and will be entered into the eCRF later. It is of utter importance that all data entered into the diary are checked by the Investigator for completeness and any safety-relevant issues (including infusion site reactions) during each patient's visit to the study center.

Any drug dose adjustment and interruptions should be recorded on the corresponding eCRF page.

If, for any reason, the Investigator or the patient decide to discontinue the treatment with octagam®, panzyga® or cutaquig®, the observation period of this patient will be terminated. Efforts should be made to arrange a close-out visit. The reason(s) for termination in the eCRF is to be documented. Switching from one Octapharma Ig product to another Octapharma Ig product is possible without termination of the study but should be documented.

### 4.2 CONCOMITANT TREATMENTS

Any other concomitant treatments are at the Investigator's discretion and need to be documented in the eCRF or the patient diary and transferred later into the eCRF.

The Investigator should instruct the patient to notify the site about any new medications he/she takes after starting this observation.

## 5 SAFETY MONITORING

To allow continuous monitoring of the product safety all adverse drug reactions (ADRs) and other safety-relevant information as defined below are to be documented.

### 5.1 ADVERSE DRUG REACTION

An ADR is any noxious and unintended response to the 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. Response in this context means that a causal relationship between the study drug and an adverse event (AE) is at least a reasonable possibility.

**Serious ADR**

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

- is resulting in death;

- is life-threatening ("life-threatening" means that the patient was at an immediate risk of death at the time of the event; it does not mean a hypothetical situation of what could or would have happened if, for example, no treatment had been administered);
- requiring hospitalisation or prolongation of existing hospitalisation (hospitalisation does not refer to the treatment of an ADR on an out-patient status);
- resulting in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is any other 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).

Medical judgment should be exercised in deciding whether an ADR 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.

Causality assessment of cases should follow the WHO-UMC causality categories: https://www.who-umc.org/media/2768/standardised-case-causality-assessment.pdf

## 5.2 OTHER RELEVANT DRUG SAFETY INFORMATION

The following events should also be reported:

a) pregnancies/breastfeeding;
b) drug abuse (persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects), misuse;
c) overdose (treatment exceeding the medically recommended dose);
d) medication errors (prescribing or dispensing error);
e) interaction(s) with other medicinal product or device;
f) suspected transmission of infectious agent;
g) off-label use;
h) occupational exposure;
i) lack of efficacy;
j) quality complaints with harm (or potential harm) of the patient.

This information should be reported if associated with the use of octagam®, panzyga® and/or cutaquig®or – in case of pregnancy/breastfeeding – if observed during treatment with octagam®, panzyga® and/or cutaquig®.

Above mentioned events should also be recorded if no ADR occurred.

In the eCRF specific pages are included for data entry for ADRs and infusions site reactions.

### 5.3 REPORTING OF ADRS AND OTHER SAFETY INFORMATION

All ADRs and other safety information as defined above have to be documented on the specific electronic forms of the electronic data capturing (EDC) system.

*Serious* ADRs have to be entered *immediately* (within 24 hours) into the eCRF and should be transferred electronically to Octapharma.

Non-serious ADRs and other safety information should be reported upon recognition but no later than 10 days.

Patients undergoing home treatment should be asked to inform their treating physician immediately of any ADR, or other relevant safety information. The treating physician will assess the causal relationship for ADR and report the event as described above.

Octapharma will handle all ADRs as post-marketing safety reports and will report the cases in compliance with applicable regulations for pharmacovigilance.

### 5.4 LABORATORY INVESTIGATIONS

The type and timing of blood sampling for laboratory evaluations are at the full discretion of the responsible physician. If such blood sampling takes place, only abnormal and clinically significant abnormal parameters should be documented in the eCRF.

## 6 STATISTICAL CONSIDERATIONS

Statistical analysis of all parameters will be descriptive. SAS 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 categorical parameters.

The demographic data, indications for use, baseline values, and number of doses will be summarised descriptively. Tolerability and efficacy assessments made by the treating physicians will be presented by frequency tables and corresponding figures.

## 7 DATA HANDLING AND RECORD KEEPING

### 7.1 ELECTRONIC CASE REPORT FORMS

An electronic case report form (eCRF) at the sites via a web-based secure and validated EDC system will be used for each patient enrolled. Investigators and study nurses are allowed to enter or change data in the eCRF as long as they are registered on a Delegation of Authority Log. Access to the eCRF is made only via a compatible web browser (Internet Explorer or Firefox). Internet is required. All safety relevant information will be transferred electronically to Octapharma's Corporate Drug Safety Unit.

Monitors and data management will have access to the data in the eCRF without the possibility to modify data. They are able to create queries. Investigators need to reply to given queries in the eCRF. Data will be checked for plausibility and completeness. Investigators must provide missing or non-plausible data in the eCRF.

At the end, the Principle Investigator will electronically sign the eCRF. The eCRF pages that have been locked will be printed and stored in the Investigator's archives for at least as long as required by regulatory constraints after completion or discontinuation of the trial, together with the original informed consent forms (if applicable) and the patient identification list. The Sponsor will archive the whole eCRF database.

## 7.2 INVESTIGATOR SITE FILE

The Investigator is responsible for maintaining all adequate records to enable the conduct of the project to be fully documented. This includes, among others, this protocol and any subsequent amendments, a sample of the eCRF, all 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, ethics committees or hospital administration, if applicable.

The Investigator is responsible for maintaining a confidential patient identification code list which provides the unique link between named source records and eCRF data. The Investigator must arrange for the retention of this confidential list for the maximum period of time required by local regulations.

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

## 7.3 DATA PROTECTION

In accordance with applicable regulations, all patient data documented on the eCRFs are to be pseudo-anonymised by the treating physician. Only the treating physician, or a person authorised by the treating physician, will be able to decode the patient identity using an internal patient allocation list.

Informed consent for the inclusion of a patient into this non-interventional study may or may not be required depending on the country; signing of a data privacy statement maybe sufficient for most countries. However, the treating physician is advised to always inform the participating patient about their inclusion in this NIS and the use of their pseudo-anonymised data in reports. This process should be documented in the patients' records.

If requested by national regulations governing the performance of non-interventional clinical studies, this NIS protocol (and any other documentation to be provided to patients, like patient diaries) has to be submitted to the Ethics Committee in charge for the hospital/institution where the NIS is conducted.

## 7.4 FINAL REPORT

At the end of the NIS, a final report will be compiled within 1 year.

# 8 GENERAL INFORMATION

The observational study is registered on clinicaltrial.gov under number NCT02303093.

For any questions relating to the observational study please contact:

Local Octapharma contact and/or central study team in Vienna:

[redacted]

Local Canadian Octapharma contact:

[redacted]