8 Summary

Name of Sponsor: Octapharma GmbH, Elisabeth-Selbert-Str. 11, 40764 Langenfeld, Germany	
Name of Investigational Product: octagam® 5%, octagam® 10%, panzyga®	**Study number:** GAM-33

Title of Study:

Non-interventional safety study on the tolerability and safety of octagam® 5%, octagam® 10% or panzyga®

Indications:

Replacement therapy in patients with primary and secondary immunodeficiencies, immunomoduation in patients with autoimmune diseases.

Study Design:

Open, prospective, multicentre non-interventional safety study (§63f AMG).

Setting:

The study was conducted between 01/2014 – 12/2019 in 229 in- and outpatient centres throughout Germany.

Rationale and Background:

octagam® 5%, octagam® 10% and panzyga® are polyvalent human immunoglobulins for intravenous use. They are approved for replacement therapy in patients with primary or secondary immunodeficiencies or for immunomodulation in patients with autoimmune diseases. The scope of the NIS was to collect and systematicallly document the tolerability and safety of these products in routine clinical practice and to gain more extensive insightin dosing schemes, additional therapies and other parameters which could have an influence on the tolerability or efficacy. Furthermore it was intended to directly compare the tolerability of octagam® with the recently approved 10% intravenous immunoglobulin panzyga®. As systematically documented data on quality of life of patients treated with octagam® were rare, data on HRQL were collected using validated questionnaires.

Objectives:

The main objective of the NIS was to collect data on the tolerability and safety of octagam® 5%, octagam® 10% or panzyga® in a broad spectrum of patients treated for replacement therapy in primary or secondary immunodeficiencies or for immunomodulation in various autoimmune diseases in routine clinical practice.

Further objectives were to assess efficacy data by disease specific clinical and laboratory parameters, if available. Furthermore patients' health-related quality of life was documented.

Subjects / Study Size:

It was planned to document the treatment of 5,000 patients. Patients of both genders and all ages who receive octagam® 5%, octagam® 10% or panzyga® for replacement therapy or immunomodulation as recommended by the corresponding SmPC could be enrolled. There

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were no additional formal inclusion or exclusion criteria defined.

Study treatment:

Patients were treated with octagam® 5% or octagam® 10% following the recommendations of the corresponding SmPC. Dosing and treatment schedule was at the discretion of the treating physician and depend on the type and severity of the disease.

During the time of the study panzyga® was not brought into the German market. Thus, no patient received panzyga® and no data of panzyga® could be analysed accordingly.

Statistical Methods:

In general, only descriptive statistical analyses were performed. There were two distinct analyses depending on the indication: for patients with antibody deficiencies and for patients with autoimmune diseases.

Quantitative data (e.g., age) were analysed by the statistical parameters valid N, missing N, mean, standard deviation, minimum, maximum, 25% quantile, median and 75% quantile.

Qualitative data (e.g., gender) were presented by means of absolute and relative frequency distributions. The calculation of percentages was based on the valid data per parameter, excluding patients with missing values. The absolute number of missing values was presented. Not coded open text entries were listed.

Results & Conclusion:

Patients:

A total of 5,473 patients were enrolled, of which 5,452 were included in the safety analysis set (SAF) and 5,188 in the full analysis set (FAS). 4,479 of the patients were diagnosed with antibody defciencies (SAF-AD) and 973 with autoimmune diseases (SAF-IM). 47.8% of the patients with immunodeficiencies (SAF-AD) received octagam® 5%, 47.3% octagam® 10% and 4.9% received both. More than half of the IM patients (56.3%) were treated with octagam® 10%, 39.2% with octagam® 5%, and 4.5% with both products.

Most patients with antibody deficiencies (85.9%) suffered from secondary immunodeficiencies (SID) and 14.1% from primary immunodeficiencies (PID). In the SID subgroup, the most common malignancies were chronic lymphocytic leukemia (CLL, 36.1%), non-hodgkin-lymphoma (NHL, 21.9%), bone marrow (stem cell) transplantation (BMT, 20.7%) and multiple myeloma (MM, 12.8%). In the PID subgroup, most patients were diagnosed with common variable immunodeficiency (CVID, 62.0%) and IgG subclass deficiency (IgGSD, 29.6%).

51.3% of the IM patients were diagnosed with immune thrombocytopenia (ITP), 22.3% with multiple sclerosis (MS), 7.5% with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), 6.2% with myasthenia gravis (MG), 2.6% with Guillain-Barré syndrome (GBS), 2.0% with myositis and 1.6% with multifocal motor neuropathy (MMN).

Treatment:

In total, 87,378 infusions were documented for patients with immunodeficiencies, 18,058 (20.7%) for PID and 69,320 (79.3%) for SID patients. PID patients received on average 27.5

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infusions per patient, SID patients 17.6 infusions per patient. The mean doses per treatment cycle were comparable between PID and SID patients (0.26 g/kg and 0,24 g/kg BW). On average 1.0 and 1.2 infusions per treatment cycle were administered. The mean dose for PID and SID was higher for patients treated with octagam® 10% (PID: 0.30 g/kg and SID: 0.25 g/kg) than with octagam® 5% (PID: 0.20 g/kg and SID: 0.23 g/kg), primarily for PID patients. The mean treatment interval between infusions was 29.2 days for PID and 27.0 days for SID.

IM patients received a total of 20,075 infusions, the mean numbers of infusions per patient ranged from 9.1 for ITP patients to 157.4 for MMN patients. The number of treatment cycles varied strongly between the indications. The mean number of treatment cycles were lowest for patients with ITP (mean: 5.4) and myasthenia gravis (mean: 4.8), but higher for patients with GBS, CIDP, MMN or myositis (range: 19.9 - 75.5 treatment cycles). The mean number of infusions per treatment cycle was 2.1 (range: 1.0 - 2.6). The mean dose per treatment cycle varied dependent on the indication (0.21 g/kg - 0.89 g/kg). Thus, the mean dose was 0.80 g/kg for ITP and CIDP, 0.89 g/kg for MMN and 0.21 g/kg for MS patients. In total, the mean dose per infusion and per treatment cycle was slightly higher in infusions with octagam® 10% than with octagam® 5%.

Safety results:

In the antibody deficiency group, a total number of 540 ICSRs (0.62% of infusions) were reported, of which 57 (0.07% of infusions) were classified as serious. A total of 909 ADRs were observed, which occurred in 15.8% of PID and 9.4% of SID patients. The ADR rates were higher in PID and SID patients treated with octagam® 10% (PID: 17.1%, SID: 11.5%) than with octagam® 5% (PID: 13.6%, SID: 7.5%). The most frequent ADRs in PID were chills (0.172% of infusions), nausea (0.105% of infusions) and dizziness (0.083% of infusions), in SID patients chills (0.244% of infusions), nausea and headache (each 0.042% of infusions). The frequency of ADRs showed some differences between octagam® 5% and octagam® 10%.

In the IM group the overall ADR rate was slightly lower. A total number of 77 ICSRs (0.38% of infusions) were reported, of which 9 (0.04% of infusion) were serious. In this patient group, a total of 136 ADRs were observed in 6.5% of patients. The ADR rates of octagam® 5% and octagam® 10% were similar. The most frequent ADRs in IM patients were headache (0.070% of infusions), chills (0.060% of infusions) and nausea (0.055% of infusions). There were only minor differences between both products regarding the ADR freqency.

Efficacy:

For patients with antibody deficiencies efficacy was assessed by analysing the infection rate and the IgG levels before und during octagam® treatment. For ITP patients, the number of thrombocytes before and during treatment was analysed.

Throughout the study the number of PID and SID patients with infection was reduced compared to the time before start of treatment (from 76.2% to 45.8% for PID, from 66.9% to 40.8% for SID). This effect is more pronounced in patients receiving immunosuppressants or antimicrobial agents without IVIG pre-treatment. The annual infection rate decreased for PID from 2.3 to 1.2 infections per year and for SID from 1.8 to 1.0 infections per year.

The mean total IgG values increased from 649 mg/dl at baseline to 730 mg/dl within the first 3 months for PID and from 647 mg/dl to 742 mg/dl in SID. In PID and SID subgroups based on pre-treatment the mean baseline values were lowest for PID patients pre-treated only with

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antimicrobial agents (560 mg/dl) and lowest for SID patients pre-treated with rituximab with or without other immunosuppressants (441 mg/dl). In all subgroups the IgG values increased within the first 3 months and remained increased at later time points up to 12 months.

These results are consistent with the physician's general assessment that revealed an overall favourable influence of octagam® therapy on infection frequency, intensity, duration and on antibiotic consumption in the vast majority (>70%) of PID and SID patients throughout the observation period.

The platelet counts for ITP patients increased during the first 7 days after start of octagam® therapy to values carrying a low risk of bleeding, from baseline mean values of 24,151 /µl up to mean values of 48,729 /µl.

The general assessment of the octagam® therapy for the IM patient subgroup showed an overall favourable influence on the course of disease, e.g. for more than two thirds of ITP and CIDP patients the influence was rated favourable by the treating physician.

Health-related quality of life (HRQL) as measured by using the SF-36 questionnaire showed some improvements in specific domains for PID as physical role functioning or emotional role functioning, but remained nearly unchanged for SID patients. Due to the small number of IM patients with available HRQL data, the analysis is limited in this patient group.

Conclusion:

This open prospective multicentre non-interventional safety study shows that both, octagam® 5% and octagam® 10%, have a good saftey profile in the therapy of a broad spectrum of indications and age groups.

Appendix

A Study protocol

B Case report forms

C Source tables – AD

D Source tables – IM