



Final Analysis Statistical Analysis Plan (SAP)

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“GammaTrack”

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1.0/14 Apr 2020	FINAL 1.0		N/A (Initial version of this SAP)

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LIST OF ABBREVIATIONS

The following abbreviations will be used within this SAP.

Abbreviation or special term	Explanation
ADR	Adverse Drug Reaction
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CIDP	Chronic Inflammatory Demyelinating Polyradiculoneuropathy
cm	Centimetre
CSR	Clinical Study Report
DM	Dermatomyositis
eCRF	Electronic Case Report Form
g	Gram
GBS	Guillain-Barré Syndrome
hr	Hours
ICH	International Conference on Harmonization
ICSR	Individual Case Safety Report
ITP	Immune Thrombocytopenic Purpura
IVIG	Intravenous Immunoglobulin
kg	Kilogram
MedDRA	Medical Dictionary for Regulatory Activities
MG	Myasthenia gravis
min	Minutes
mL	Millilitre
MMN	Multifocal Motor Neuropathy
MS	Multiple Sclerosis
NIS	Non-Interventional Study
PID	Primary Immunodeficiency
PM	Polymyositis
PT	Preferred Term
PV	Pemphigus Vulgaris
SAP	Statistical Analysis Plan



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SCIG	Subcutaneous Immunoglobulin
SID	Secondary Immunodeficiency
SD	Standard Deviation
SOC	System Organ Class
TEN	Toxic Epidermal Necrolysis
TFLs	Tables, Figures and Listings

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1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide detailed descriptions of the statistical methods, data derivations and data displays for study protocol GAM10-06 Version 06 “Non-Interventional Study on the Tolerability of IVIG and SCIG” dated 27-Jun-2018 for the final analysis. The table of contents and templates for the tables, figures and listings (TFLs) will be produced in a separate document.

Any deviations from this SAP will be described and justified in the Clinical Study Report (CSR).

The preparation of this SAP has been based on International Conference on Harmonization (ICH) E9 guideline.

All data analyses and generation of TFLs will be performed using SAS 9.4® or higher.

2 STUDY OBJECTIVES

2.1 Primary objective(s)

The primary objective is to document the safety and tolerability of octagam®, panzyga® and cutaquig® in any indication, age group or treatment regimen.

2.2 Secondary objective(s)

The secondary objective is to document their efficacy in patients receiving treatment.

2.3 Exploratory objective(s)

Not Applicable

2.4 Safety objective(s)

This is the primary objective in this observational study

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3 STUDY DESIGN

3.1 General study design

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®.

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.

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

3.2 Randomization and blinding

This is a non-randomized open-label observational study.

3.3 Study treatments and assessments

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

Due to its non-interventional and observational nature, this study will strictly exclude predefined 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 the 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)		✓	✓
Checking of patient diary for patients doing cutaquig® home treatment		✓	✓

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

3.4 Primary endpoint(s)

The primary endpoint of this study is the incidence (count and frequency) of ADRs.

3.5 Secondary endpoint(s)

Secondary endpoint in this study is the efficacy of the IVIG/SCIG measured as:

For patients with diagnosis primary immunodeficiency (PID) or secondary immunodeficiency (SID):

- For each fourth infusion visit (starting with infusion visit 4) and the close-out visit: Influence of the treatment with IVIG/SCIG on the frequency, intensity and duration of infections and the consumption of antibiotics since the last visit.
- For each fourth infusion visit (starting with infusion visit 4) and the close-out visit: Occurrence of infectious episodes since the last visit.

For patients with other diagnoses than PID or SID:

- For each infusion visit and the close-out visit: Development of the clinical appearance of disease since the last visit.

-
- At the close-out visit: Influence of IVIG or SCIG treatment on the course of the disease.

3.6 Exploratory endpoint(s)

Not Applicable

3.7 Safety endpoint(s)

In this study, the safety endpoint is equal to the primary endpoint.

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4 SAMPLE SIZE AND POWER

No formal sample size calculation was conducted for this study. This study will observe 300-500 patients.

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5 ANALYSIS POPULATIONS

No analysis populations have been defined in the study protocol. For the purpose of the statistical analysis the following two populations will be considered:

5.1 Enrolled population

The Enrolled population will consist of all patients for whom baseline assessments are available, irrespective whether these patients were treated with any study drug.

The Enrolled population will be used in the summary of patient disposition.

5.2 Safety population (Safety)

The Safety population will consist of all patients who had at least one infusion of any study drug.

The Safety population will be used for all analyses except the analysis of disposition. Patients will be included in the analysis according to the actual treatment received. As patients are allowed to change the study drug during the course of the study, treatment groups can be defined that are composed of more than one treatment depending on which patterns of treatment change will be actually observed.

5.3 Protocol deviations/violations and exclusions from analysis sets

In this NIS, no protocol deviations/violations have been collected and no per-protocol population will be defined.

6 STATISTICAL CONSIDERATIONS AND ANALYSIS

6.1 Derived Variables

The below table provides the list of derived variables for demographic and baseline characteristics, various duration derivations and other important derivations applicable for this study.

Variables	Formula
Demographic and baseline characteristics	
Age at baseline (in years)	Year of the baseline visit – year of birth
Body mass index (BMI) (kg/m ²)	Baseline weight (kg)/[height (m)] ² . Round to two decimal places.
Derivation of durations	
Study day at any visit	Date of interest – date of first IGIV/SCIG infusion. One day is added if this difference is ≥ 0 .
Treatment duration (in months)	(Date of last infusion with IVIG/SCIG – Date of first infusion with IVIG/SCIG + 1)/30.4375. Round to one decimal place.
Study duration (in months)	(Maximum(Date of close-out visit, date of last infusion with IVIG/SCIG) - Date of first infusion with IVIG/SCIG + 1)/30.4375. Round to one decimal place.
Derivation of exposure related measures	
Dose per infusion (g)	Infusion volume (mL) x <i>strength</i> where <i>strength</i> = 0.05 for octagam® 5% <i>strength</i> = 0.1 for octagam® 10% and panzyga® <i>strength</i> = 0.165 for cutaquir®
Dose per infusion (g/kg body weight)	Dose per infusion (g)/weight (kg), weight as measured at the respective infusion visit. Round to two decimal places.
Maximum infusion rate (mL /kg body weight/hr)	See section 7.4.2 for necessary transformations. Round to two decimal places.

6.2 Handling of missing data and outliers

6.2.1 Missing data analysis methods

For the handling of missing numbers of infections, see sections 7.3.2 and 7.5.2. Missing values of body weight in the calculation of measures of exposure will be handled as described in section 7.4.2. Otherwise, missing data will not be imputed for any analysis. For the handling of missing or incomplete start and end dates of Individual Case Safety Reports and medications, see section 6.2.2.

6.2.2 Handling of missing or incomplete dates

For the determination whether an Individual Case Safety Report (ICSR, see section 7.6.1 for the definition) as denoted on the ADR form that has a missing or incomplete start date might not qualify as on-study-case the following rules will be applied:

If only the day of ICSR start date is missing:

If the ICSR start year and month are the same as that for the first infusion date, then:

- If the full (or partial) ICSR end date is not before the first dose date or ICSR end date is missing, then impute the ICSR start day as the day of first dose date; otherwise, impute the ICSR start day as 1.
- Otherwise, if the full (or partial) ICSR end date is before the first dose date, then impute the ICSR start day as 1.

Compare the imputed ICSR start date with the first infusion date to determine whether the ICSR actually occurred before the first dose or can be evaluated as on-study ICSR.

If day and month of ICSR start date are missing:

If ICSR start year = first dose year, then:

- If the full (or partial) ICSR end date is not before the first infusion date or the ICSR end date is missing, then impute the ICSR start month and day as the month and day of the first infusion date; otherwise, impute the ICSR start month as January and the start day as 1.
- Otherwise, if the full (or partial) ICSR end date is before the first dose date, then impute the ICSR start month as January and the start day as 1.

Compare the imputed ICSR start date with the first infusion date to determine whether the ICSR actually occurred before the first dose or can be evaluated as on-study ICSR.

If the year of ICSR start date is missing:

If the year of the ICSR start date is missing or the ICSR start date is completely missing, then compare the full (or partial) ICSR end date to the first infusion date. If the ICSR end date is before the first dose date, then the ICSR will not be considered as on-study ICSR. Otherwise, the ICSR will be considered as on-study ICSR.

Imputation rules for missing or partial medication start/stop dates are defined below:

Missing or partial medication start date:

- If only the day is missing, use the first day of the month.
- If day and month are both missing, use the first day of the year.

- If day, month and year are all missing, use a date before the minimum of the first infusion date and the medication stop date.

Missing or partial medication stop date:

- If only the day is missing, use the last day of the month.
- If day and month are both missing, use the last day of the year.
- If day, month and year are all missing, assign 'continuing' status to stop date

Note that these imputation rules are only applied to determine the status of an ICSR or medication in relation to the treatment phase of the study. Imputed dates are not to be used in any patient listings.

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7 STATISTICAL METHODS

7.1 General statistical conventions

All statistical procedures will be completed using SAS version 9.4 or higher.

Continuous variables will be summarized using descriptive statistics, including number of subjects (n), mean, median, standard deviation (SD), minimum and maximum.

For categorical variables, summaries will include counts of patients and percentages. Percentages will be rounded to one decimal place.

All summaries will be presented by treatment group and overall, unless otherwise specified. As patients are allowed to change the study drug during the course of the study, treatment groups can be defined that are composed of more than one treatment depending on which patterns of treatment change will actually be observed. In case that such treatment groups are defined, summary tables by visit or summary tables for events that occur within the study will contain more than one column for these composed treatment groups. A patient will be summarized in the column that belongs to the actual treatment that the patient received at the respective visit or at the onset of the respective event.

All patient data, including those derived, will be presented in individual patient data listings. Unless otherwise stated, unscheduled visit results will be included in date/time chronological order, within patient listings only. All listings will be sorted by centre, patient number, date/time and visit (if applicable). The treatment group as well as patient's sex, age and diagnosis will be stated on each listing. Unless otherwise stated, data listings will be based on the Safety population.

7.2 Patient disposition

Patient disposition information will be summarized by treatment group and overall. The number of patients who were enrolled will be shown in the overall summary, further the number and percentage of patients who received at least one infusion with study drug, who ended the study but continued treatment with study IVIG/SCIG and who terminated treatment with study IVIG/SCIG will be presented. The primary reason for early withdrawal will also be tabulated. The number of patients treated will be used as the denominator for the percentage calculation.

A table of patient disposition will also be generated by study centre and country.

The study duration (in months) of an individual patient will be calculated as $(\text{Maximum}(\text{Date of close-out visit, date of last infusion with IVIG/SCIG}) - \text{Date of first infusion with IVIG/SCIG} + 1)/30.4375$ and will be summarized by treatment group and overall in the Safety population.

Patient disposition will be listed.

7.3 Demographics and baseline characteristics

7.3.1 Demographics

Age (years), height (cm), weight (kg) and BMI (kg/m^2) at baseline will be summarized descriptively by treatment group and overall in the Safety population. The baseline weight will be defined as the weight measured before the first IVIG/SCIG infusion. Age category (categorized by age groups < 18, 18-43, 44-68, and > 68 years), race and sex will be summarized by counts and frequencies.

In addition, demographic characteristics will also be presented by diagnosis.

7.3.2 Baseline and disease characteristics

The underlying diagnosis and its severity as assessed by the investigator will be summarized by treatment group and overall in the Safety population. For the diagnosis the following pre-specified categories will be considered if at least one patient with this diagnosis is included in the Safety population:

- Primary Immunodeficiency (PID)
- Secondary Immunodeficiency (SID)
- Immune Thrombocytopenic Purpura (ITP)
- Guillain-Barré Syndrome (GBS)
- Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)
- Multifocal Motor Neuropathy (MMN)
- Myasthenia Gravis (MG)
- Multiple Sclerosis (MS)
- Dermatomyositis (DM)
- Polymyositis (PM)
- Pemphigus Vulgaris (PV)
- Toxic Epidermal Necrolysis (TEN)
- Other.

The presence of pre-specified concomitant diseases/risk factors at baseline will be summarized descriptively by treatment group and overall in the Safety population. The following concomitant diseases/risk factors will be considered:

- History of previous thromboembolic events (yes/no)
- Atherosclerosis (yes/no)
- Coronary artery disease (yes/no)
- Impaired cardiac output (yes/no)
- Obesity (yes/no)
- Diabetes (yes/no)
- Hypertension (yes/no)

- Hyperlipidemia (yes/no)
- Coagulation disorders (yes/no)
- In-dwelling catheters or devices (yes/no)
- Immobilization (yes/no)
- Known or suspected blood hyperviscosity (yes/no)
- Other cardiovascular risk factor(s) (yes/no)
- Other relevant concomitant diseases (yes/no).

Previous thromboembolic events and other relevant concomitant diseases will be coded by MedDRA Version 23.0 or higher and summarized by System Organ Class (SOC) and Preferred Term (PT) in the Safety population. The sort order will be by decreasing frequency in the overall group by SOC and then by PT within SOC. These summaries will also be generated by diagnosis.

For patients with diagnosis PID or SID the history of recent infectious episodes within the last 12 months before study observation start is recorded in the eCRF. In case any recent infectious episodes have been observed, patients are asked regarding the infected area and the number of infectious episodes in this area using the following pre-specified categories:

- Serious infections of the upper respiratory tract
- Serious infections of the lower respiratory tract
- Urinary tract infections
- Bacteremia/sepsis
- Bacterial meningitis
- Osteomyelitis/septic arthritis
- Bacterial pneumonia
- Visceral abscesses
- Other infectious diseases.

The occurrence of any recent infectious episodes, the occurrence of any recent infectious episodes in each of the above categories, the total number of recent infectious episodes and the total number of recent infectious episodes in each of the above categories will be summarized by treatment group and overall in the Safety population. These summaries will be generated for the pool of PID/SID patients and for each of the two diagnoses separately.

As cases of bacterial pneumonia actually are always recorded as cases of serious infections of the lower respiratory tract as well, the former will not be counted in the calculation of the total number of recent infectious episodes.

In case that a certain type of infection has occurred but the pertaining number of infectious episodes is missing this number will be set to one.

All baseline and disease characteristics will be listed.

7.3.3 Previous and concomitant medications

Previous and concomitant medications will be coded according to WHO Drug Dictionary, version 19.1 (B3 format). Concomitant medications will be summarized by preferred name and ATC level 2 in the Safety population. For this analysis a medication will be considered as concomitant if it cannot be excluded that it is given after the first IGIV/SCIV infusion in the study up to the close-out visit. That is, only medications with a stop date before the first IGIV infusion or a start date after the close-out visit will be excluded from the summary of concomitant medications. All previous and concomitant medications will be listed.

Details for imputing missing or partial start and/or stop dates of medications for the purpose of determination of the status as previous/concomitant are described in Section 7.2.2.

Previous treatment for the underlying primary diagnosis will be summarized by preferred name and ATC level 2 separately for (i) patients with PID and SID and (ii) patients with any other diagnosis in the Safety population.

For patients with PID/SID the previous treatment with immunoglobulins (within 6 months before study start) will be summarized by drug name, treatment group and overall.

For patients with other diagnoses than PID or SID any previous treatment (within 6 months before study start) will be summarized by drug name and ATC level 2.

These summaries will also be generated by diagnosis.

All previous treatments for the underlying diagnosis - including also non-drug therapies and other blood products - will be listed.

7.4 Extent of exposure

7.4.1 Treatment duration

Treatment duration (in months) will be calculated as (last infusion date – first infusion date + 1)/30.4375, regardless of study drug interruptions.

Treatment duration will be summarised by treatment group and overall in the Safety population using descriptive statistics. A summary of treatment duration will also be provided by diagnosis.

7.4.2 Exposure to study drug

For each patient the following measures will be calculated and summarized with descriptive statistics by treatment group and overall in the Safety population:

- Number of IVIG/SCIG infusions.
- Number of IVIG/SCIG infusion courses. An infusion course is defined as a sequence of infusions that are given over consecutive days with allowed gaps of 3 days without

documented infusions, i.e. a new course starts when there are at least 4 days without documented infusions.

- Complete dose (in g and g/kg body weight).
- Mean dose per infusion (in g and g/kg body weight).
- Mean dose per infusion course (in g and g/kg body weight).
- Average infusion rate (in mL/kg body weight/hr).
- Maximum infusion rate (in mL/kg body weight/hr).

In the eCRF only the volume (in mL) of an infusion is captured. To calculate doses in grams the following transformations will be applied:

For octagam® 5% the dose in grams per infusion will be calculated as infusion volume (mL) x 0.05 as octagam® 5% contains 50 mg protein per mL of solution. For octagam® 10% the dose in grams per infusion will be calculated as infusion volume (mL) x 0.1 as octagam® 10% contains 100 mg protein per mL of solution. Panzyga® comes as a 10% solution ready for intravenous administration; hence the dose in grams per infusion will also be calculated as infusion volume (mL) x 0.1. Cutaquig® is a sterile solution of human normal immunoglobulin containing 16.5% (165 mg/mL) protein, hence the dose in grams per infusion will be calculated as infusion volume (mL) x 0.165. To get the dose per kg body weight the dose in grams will be divided by the body weight (in kg) as determined at the respective infusion visit. In case the weight is missing the following rules will be applied:

- (i) Use the weight measured at the latest preceding infusion visit.
- (ii) If no weight measurements are made at any preceding infusion visit use the weight from the first visit on which weight was measured.

For each patient the complete dose (in g or g/kg body weight) is calculated as sum of the doses (in g or g/kg body weight) over all infusions and the mean dose per infusion (in g or g/kg body weight) as arithmetic mean of the doses (in g or g/kg body weight) over all infusions. The mean dose per infusion course (in g or g/kg body weight) is defined by (i) summing up all doses (in g or g/kg body weight) over an infusion course and then (ii) calculating the arithmetic mean of these summed-up doses over all infusion courses.

The infusion rate (in mL /kg body weight/hr) per single infusion will be calculated as infusion volume (mL)/(duration of infusion (hr) x weight (kg)), missing weights will be imputed as described above. The average infusion rate for a patient will be determined as the arithmetic mean of the infusion rates over all infusions.

For each infusion visit, the maximum infusion rate is recorded in the eCRF. Maximum infusion rates can be reported in four different units: mL/min, mL/hr, mL/kg body weight/min, and mL/kg body weight/hr. The following transformations will be applied to get the maximum infusion rate in mL/

kg body weight/hr:

Original Unit	Transformation
mL/min	x 60 / weight (kg)
mL/hr	/ weight (kg)
mL/kg body weight/min	x 60
mL/kg body weight/hr	No transformation necessary

Missing weights will be imputed as described above. For the tabulation the maximum of the maximum infusion rate over all infusions will be determined for each patient.

All summaries of exposure measures will also be generated by diagnosis.

All infusion details as recorded in the eCRF will be listed.

7.5 Efficacy analyses

This section addresses separately the analyses to be conducted on the efficacy variables measured in this study.

7.5.1 Analysis methods

All efficacy outcomes will be analysed by descriptive statistics only. No statistical tests will be performed.

7.5.2 Analysis of efficacy endpoint(s)

For patients with diagnosis PID or SID:

For each fourth infusion visit (starting with infusion visit 4) and the close-out visit the influence of the treatment with IVIG/SCIG on the frequency, intensity and duration of infections and the consumption of antibiotics since the last visit is recorded. Possible outcomes are beneficial, unchanged and unfavorable. Counts and percentages of these outcomes will be summarized by infusion visit and for the close-out visit by treatment group and overall in the Safety population. In addition, the patient's last available assessments will be summarized. These summaries will be generated for the pool of PID/SID patients and for each of the two diagnoses separately.

For each fourth infusion visit (starting with infusion visit 4) and the close-out visit the occurrence of new infectious episodes (yes/no) since the last visit is recorded. In case of the occurrence of new infectious episodes patients are asked regarding the infected area and the number of infectious episodes in this area using the following pre-specified categories:

- Serious infections of the upper respiratory tract

- Serious infections of the lower respiratory tract
- Urinary tract infections
- Bacteremia/sepsis
- Bacterial meningitis
- Osteomyelitis/septic arthritis
- Bacterial pneumonia
- Visceral abscesses
- Other infectious diseases

The number and percentage of patients with new infectious episodes since the last visit and the number and percentage of patients with new infectious episodes in each of the above categories will be summarized by infusion visit and for the close-out visit by treatment group and overall in the Safety population. In addition, this summary will be generated for the patient's last available assessment.

Further the occurrence of any infectious episodes during the course of the study, the occurrence of any infectious episodes in each of the above categories during the course of the study, the total number of infectious episodes and the total number of infectious episodes in each of the above categories will be summarized by treatment group and overall in the Safety population. These summaries will be generated for the pool of PID/SID patients and for each of the two diagnoses separately.

As cases of bacterial pneumonia actually are always recorded as cases of serious infections of the lower respiratory tract as well, the former will not be counted in the calculation of the total number of infectious episodes.

In case that a certain type of infection has occurred but the pertaining number of infectious episodes is missing this number will be set to one.

According to the study protocol (section 3.1.4) the individual duration of the study should be at least 12 months for patients with diagnosis PID or SID. To evaluate the efficacy for patients who fulfill this condition the analyses described above will be repeated in this subgroup. To evaluate the efficacy for patients who do not fulfill this condition but are at least 6 months in the study the analysis will also be repeated for patients with a study duration of at least 6 months but less than 12 months.

For patients with diagnoses different from PID or SID:

At each infusion visit and the close-out visit patients with diagnoses other than PID or SID are asked regarding the development of the disease since the last visit. Possible outcomes are improved, not changed and deteriorated. The number and percentage of patients with these outcomes at each infusion visit and the close-out visit will be summarized by treatment group and overall in the Safety population. In addition, this summary will be generated for the patient's last available assessment.

At the close-out visit, patients with diagnoses other than PID or SID are also asked regarding the influence of IVIG/SCIG treatment on the course of the disease. Possible outcomes are beneficial, unchanged and unfavorable. The number and percentage of patients with these outcomes will be summarized by treatment group and overall in the Safety population.

These summaries will be generated for the pool of non-PID/SID patients and for each of the pre-specified diagnoses (see section 7.3.2) separately.

All efficacy outcomes will be listed.

7.6 Safety analysis

This section describes the safety analyses that will be conducted on the treatment period, i.e., the safety analyses on all data collected during the treatment period and all data collected in patients who dropped-out during the treatment period.

Safety analyses will be conducted on the Safety population and will be performed for all safety variables specified below.

All safety data will be summarized by treatment group and overall.

No statistical tests will be performed.

7.6.1 Individual Case Safety Reports (ICSRs) and Adverse Drug Reactions (ADRs)

There will be a clear differentiation between ‘cases’ and the individual symptoms reported. This distinction is reflected in the eCRF by the possibility to enter several symptoms on a single ADR form. The following terminology is used in this document to clearly reflect this differentiation:

ADR = A single symptom or term reported; always coded to an individual MedDRA preferred term (PT).

Individual Case Safety Report (ICSR) = All reported symptoms or terms that are related to one and the same infusion (except re-challenges – to be counted also as one ICSR).

The assessment of severity and relatedness to study drug will be done on the case level.

For all analyses (except the listing of ICSRs leading to death), cases recorded on the ADR form of the eCRF but rated as “not related” will be excluded. Further, cases recorded on the ADR form but with a start date before the first IVIG/SCIG infusion will be excluded from all summaries as well but will be included in the listings if not rated as “not related”.

An overview table will show the count and percentage as well as the number of ICSRs regarding the occurrence of any ICSR, any serious ICSR, and any ICSR leading to withdrawal of study drug by treatment group and overall. Percentages will be calculated with two different denominators:

- Number of patients in the respective treatment group

- Number of infusions in the respective treatment group.

This overview table will also be presented by diagnosis.

The tabulation of count and percentage of ADRs and serious ADRs will be based on PTs and SOC's of the MedDRA thesaurus. MedDRA version 23.0 will be used for coding. Percentages again will be calculated based on the number of patients and on the number of infusions by treatment group and overall.

These summaries of ADRs will also be presented by diagnosis, by country (Austria, Spain, France, UK and Canada) and by age group (age categories < 18, 18-43, 44-68, and > 68 years).

All ICSRs will be listed, in addition, there will be separate listings for

- ICSRs leading to death (this listing will also include cases rated as “not related”).
- Serious ICSRs
- ICSRs leading to withdrawal of study drug.

In summaries by SOC and PT, ADRs will be sorted by decreasing frequency in the overall group by SOC and then by PT within SOC.

7.6.2 Clinical laboratory evaluations

Clinically relevant laboratory results were collected when available and will be presented in listings but will not be tabulated.

7.6.3 Vital signs

Body weight is measured at each infusion visit. The body weight measured before the first infusion will be summarized as baseline weight (in kg), measurements from the other infusion visits will be listed only.

7.6.4 Other safety assessments

At the close-out visit patients are asked how the study IVIG/SCIG treatment was tolerated in comparison to previous IVIG/SCIG treatment. The outcome of this survey (Not applicable, good, moderate, bad) will be summarized by counts and percentages by treatment group and overall in the Safety population. This summary will also be generated by diagnosis.

In case of a pregnancy the respective form in the eCRF has to be completed. The entries from the pregnancy form will only be listed.

7.7 Other analyses

7.7.1 Subgroup analysis

All summaries will also be generated by the underlying diagnosis. In addition, summaries of ICSRs and ADRs will also be generated by country (Austria, Spain, France, UK and Canada) and by age group (age categories < 18, 18-43, 44-68, and > 68 years).

7.8 Interim analysis

Not applicable.

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8 CHANGES TO PLANNED ANALYSIS FROM STUDY PROTOCOL

According to the protocol tolerability and efficacy assessments made by the treating physicians will be presented by frequency tables and corresponding figures. However, no figures will be generated for the final analysis.

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9 REFERENCES

1. ICH Topic E9: Statistical Principles for Clinical Trials (CPMP/ICH/363/96 – adopted March 1998).

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