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Statistical Analysis Plan

Study ID	SCGAM-01
Study title	Clinical Phase 3 Study to Evaluate the Pharmacokinetics, Efficacy, Tolerability and Safety of Subcutaneous Human Immunoglobulin (*octanorm 16.5%*) in Patients with Primary Immunodeficiency Diseases
Study phase	III

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Document History

Version	Date	Author	Description
Final v1	31 -May-2013	███████	New document
Final v2	25-Nov-2013	███████	Formula in section 8.4 updated with the correct z value to reflect the 99% confidence interval.
Final v3	14-May-2014	███████	Updated to reflect changes in protocol, in particular the change in inclusion criteria regarding previous IVIG treatment
Final v4	27-Jun-2014	███████	Clarification that the upper limit of a 2-sided 98% CI will be used for evaluation of the primary endpoint. Formula in section 8.4 adjusted accordingly.
Final v5	19-Aug-2014	███████	Correction of the critical value used in the formula for the 2-sided 98% CI corrected to 2.33
Final v6	21-Apr-2016	███████	Minor clarification to section 4.2 (age groups) Minor revision of laboratory details: HIV test methods used, blood urea Increase of patients in age group ≥16 years and ≤75 years New interim analysis according to the PSP (section 11, request for deferral of pediatric studies)
Final v7	22-JAN-2019	███████, ██████	SAP version 7.0 contains all updates planned for final analysis: • Incorporation of revised age groups (according to protocol version 9.0) 2 to <6 | ≥6 to <12 | ≥12 to <17 | ≥17 to ≤75 • Overview about interim analyses performed and clarifications/updates resulting from the interim analyses, now planned to be applied for final analysis as well (see section 5.1)

Abbreviations

AE	Adverse Event	ITT	Intention-To-Treat
ALAT	Alanine Aminotransferase	IVIG	Intravenous Immunoglobulin
ASAT	Aspartate Aminotransferase	Λz	Elimination Rate Constant
AUC	Area Under the concentration-time Curve	LDH	Lactate Dehydrogenase
BMI	Body Mass Index	MedDRA	Medical Dictionary for Regulatory Activities
CBC	Complete Blood Count	MRT	Mean Residence Time
CHQ-PF50	Child Health Questionnaire - Parent Form	NAT	Nucleic Acid Test
CI	Confidence Interval	PI	Primary Immunodeficiency
C_{max}	Maximum plasma Concentration	PK	Pharmacokinetic
C_{min}	Minimum plasma Concentration	PP	Per Protocol
CMV	Cytomegalovirus	PSP	Pediatric Study Plan
CoA	Certificate of Analysis	PT	Preferred Term
CSR	Clinical Study Report	QoL	Quality of Life
DCF	Dose Conversion Factor	$T_{\frac{1}{2}}$	Elimination Half-Life
(e)CRF	(Electronic) Case Report Form	T_{max}	Time to Maximum Plasma Concentration
FAS	Full Analysis Set	TEAE	Treatment Emergent Adverse Event
FDA	Food and Drug Administration	TEE	Thromboembolic Event
GCP	Good Clinical Practice	TOST	Two One-Sided Tests
HBV	Hepatitis B Virus	Vss, Vz	Volume of Distribution
HCV	Hepatitis C Virus	WBC	White Blood Cell
HIV	Human Immunodeficiency Virus	SAP	Statistical Analysis Plan
ICH	International Conference on Harmonisation	SAR	Suspected Adverse Reactions
IgG	Immunoglobulin G	SBI	Serious Bacterial Infections
IMP	Investigational Medicinal Product	SOC	System Organ Class

Table of Contents

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1. Preface

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Octapharma protocol SCGAM-01: *Clinical Phase III Study to Evaluate the Pharmacokinetics, Efficacy, Tolerability and Safety of Subcutaneous Human Immunoglobulin (octanorm 16.5%) in Patients with Primary Immunodeficiency Diseases.*

This phase III study is conducted to assess efficacy, safety and tolerability, and the pharmacokinetic (PK) properties of *octanorm* in patients with a confirmed diagnosis of Primary Immunodeficiency (PI) Disease as defined by the WHO and requiring immunoglobulin replacement therapy due to hypogammaglobulinaemia or agammaglobulinaemia.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the FDA and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials[1].

The following documents were reviewed in preparation of this SAP:

- Clinical Study Protocol SCGAM-01, Version 9.0, dated 16-Jan-2019

The reader of this SAP is encouraged to also read the clinical protocol for details on the planned conduct of this study. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analyses.

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[1] International Conference on Harmonization. (1998). Guidance on Statistical Principles. ICH Topic E9 (Statistical Principles for Clinical Trials) (p. 37). London: International Conference on Harmonization.

2. Purpose

This SAP outlines all statistical analyses to be performed on data collected in study SCGAM-01, and the resulting output that will be compiled to support the completion of the Clinical Study Report (CSR).

The planned analyses identified in this SAP will be included in regulatory submissions and/or future manuscripts. Exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc or unplanned analyses performed that are not identified in this SAP will be clearly identified in the respective CSR.

The statistical output provided to the medical writer of the CSR will closely follow the ICH guideline for industry on topic E3 (Structure and Content of Clinical Study Reports[2]) to facilitate the subsequent compilation of the CSR.

This statistical output will consist of tables, figures and listings, including

- Tables, figures and listings used or referenced in, or appended to the CSR as detailed in the remainder of this SAP (section 14 of the CSR)
  - Demographic data summary figures and tables
  - Efficacy data summary figures and tables
  - Safety data summary figures and tables
  - Pharmacokinetic results summary figures and tables
- Listings provided as appendices to the CSR
  - Patient data listings (section 16.2 of the CSR)
  - Individual patient data listings (section 16.4 of the CSR) will be covered by inclusion of SAS datasets into the electronic submission to the authorities

A detailed list of all tables, figures and listings will be supplied in a separate document later when all feedback from authorities will be available.

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[2] International Conference on Harmonization. (1996). Structure and Content of Clinical Study Reports. Structure and Content of Clinical Study Reports (Guideline for Industry) (S. 37). London: International Conference on Harmonization.

3. Study Objectives and Endpoints

3.1.   Study Objectives

3.1.1.   Primary Objectives

The first primary objective of the study is to assess the efficacy of *octanorm* in preventing serious bacterial infections (SBI) compared with historical control data.

The second primary objective is to evaluate the PKs of *octanorm* and to compare the area under the curve (AUC) with that of intravenous immunoglobulin (IVIG) treatment.

3.1.2.   Secondary Objectives

Secondary objectives are

- to evaluate the tolerability and safety of *octanorm*
- to determine the PK profile of *octanorm*
- to assess the dose conversion factor (DCF) when switching patients from intravenous immunoglobulin (IVIG) treatment
- to develop guidance and recommendations to support further adjustments of the dosing of octanorm based on the total IgG trough level
- to assess the effect of *octanorm* on quality of life (QoL) measures

3.2.   Study Endpoints (Target Variables)

3.2.1.   Primary Target Variables

The primary (efficacy) endpoint is the rate of SBI (defined as bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess) per person-year on treatment.

The SBI rate will be calculated as (number of SBI) / (person-years) on basis of the observation period after completion of the 12-week wash-in/wash-out phase to ensure that any occurring infection can be attributed to steady-state treatment with *octanorm* unambiguously; this observation period is hereinafter referred to as 'primary observation period' or 'primary treatment period'. A two-sided 98% confidence interval will be calculated that accounts for intra-patient correlation in incidents following a compound Poisson process model. The null hypothesis of an SBI rate ≥ 1.0 per person year (see section 10.1) will be rejected if the upper limit of this CI, that corresponds to the upper 1-sided 99% confidence limit, is less than 1.0.

The primary endpoint with respect to the PK investigations is the area under the concentration-time curve from time 0 (start of infusion) to the end of the nominal dosing period, standardized to 1 week (AUCτ), at steady-state.

3.2.2.   Secondary Target Variables

- Efficacy
  - The annual rate of all infections of any kind or seriousness
  - Non-serious infections (total and by category)
  - Time to resolution of infections
  - Use of antibiotics (number of days and annual rate)
  - Hospitalizations due to infection (number of days and annual rate)

- o Episodes of fever
- o Days missed from work/school/kindergarten/day care due to infections and their treatment
- o QoL assessments using the Child Health Questionnaire-Parent Form (CHQ-PF50) from parent or guardian of patients <14 years of age and the SF-36 Health Survey in patients ≥14 years of age

- Safety:
  - o Occurrence of all treatment emergent adverse events (TEAEs) throughout the entire 65-week treatment period starting with the first administration of investigational medicinal product (IMP)
  - o Occurrence of temporally associated TEAEs
  - o Proportion of infusions with at least 1 temporally associated AE
  - o Occurrence of suspected adverse reactions (SARs)
  - o TEAEs by speed of infusion
  - o Infusion site reactions
  - o Vital signs (blood pressure, pulse, body temperature, respiratory rate)
  - o Laboratory parameters (hematology, clinical chemistry, markers for intravascular hemolysis, and tests for viral safety)

- Pharmacokinetic (PK):
  - o PK profiles of total IgG, of IgG subclasses (IgG1, IgG2, IgG3, IgG4), and of antigen-specific antibodies against Haemophilus influenzae, Streptococcus pneumoniae (types 4, 6B, 9V, 14, 18C, 19F, 23F), cytomegalovirus (CMV), tetanus, and measles.
  - o Trough levels of serum IgG (total and subclasses) throughout the study
  - o Trough levels of specific antibodies against Haemophilus influenzae, Streptococcus pneumoniae (types 4, 6B, 9V, 14, 18C, 19F, 23F), CMV, tetanus, and measles throughout the study
  - o IVIG to *octanorm* DCF (based on the area under the concentration-time curve [$AUC\tau$])

The following PK parameters will be calculated for each PK profile, reported in individual data listings, and summarized by means of descriptive statistics:

Remark: For octanorm profiles the actual potencies of the batches will be used for all dose-dependent PK calculations. For the IVIG batches the actual potencies will not be known in general, and thus the nominal IgG content will be used for dose-dependent PK parameters concerning total IgG. No dose-dependent PK parameters will be calculated for IVIG profiles of IgG sub-classes and the antigen-specific antibodies.

- Dose per kg
- Maximum concentration [C_{max}]
- Time to maximum concentration [T_{max}]
- Minimum concentration [C_{min}]
- Time to minimum concentration [T_{min}]
- Elimination rate constant [λz]
- Half-life [$T_{\frac{1}{2}}$]
- Specification of the data points used for determination of λz and, by extension, $T_{\frac{1}{2}}$

- Area under the concentration-time curve from time 0 [start of the infusion] to the time point of the last non-zero concentration [AUC_{0-last}]
- Area under the concentration-time curve from time 0 [start of the infusion] to the end of the nominal dosing period, standardized to 1 week [$AUC\tau$]
- Volume of distribution at steady-state (V_{SS}) and terminal exponential volume of distribution (V_Z) will be calculated for total IgG and IgG subclasses only
- Clearance [CL]
- Mean residence time (MRT) will be calculated for total IgG and IgG subclasses only

Further objectives of the PK analysis:

- Calculation of the DCF for switching patients from IVIG to *octanorm* 16.5% SCIG treatment will be done on basis of the $AUC\tau$ as a measure for the bioavailability of total IgG
- Development of algorithms to determine the target trough level and titration recommendations to individually adjust the octanorm dosing if necessary.

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4. Study Methods

4.1. Overall Study Design and Plan

Study SCGAM-01 is designed as a prospective, open-label, non-controlled, single-arm, multicentre phase III clinical study. Therefore no randomization or blinding procedures are performed.

The study design comprises a 12-week wash-in/wash-out period followed by a 12-month efficacy period, and a PK substudy that will include at least 20 evaluable patients. Patients participating in the PK substudy will undergo 3 PK assessments.

The PK substudy comprises a full PK profile after the last administration of the previously used IVIG product before a patient is switched to *octanorm* (PK_{IV}), a full PK profile at the end of the wash-in/wash-out phase (PK_{SC1}), and a final PK profile after 28 administrations of *octanorm* to assess the bioavailability of total IgG with respect to the two administration methods (PK_{SC2}). A PK interim analysis will be conducted after all PK_{SC1} data are available to revise the initial conversion factor of 1.5 to the corrected value according to the AUCτ, and to obtain a titration scheme to be used by the investigator to achieve the associated target trough levels.
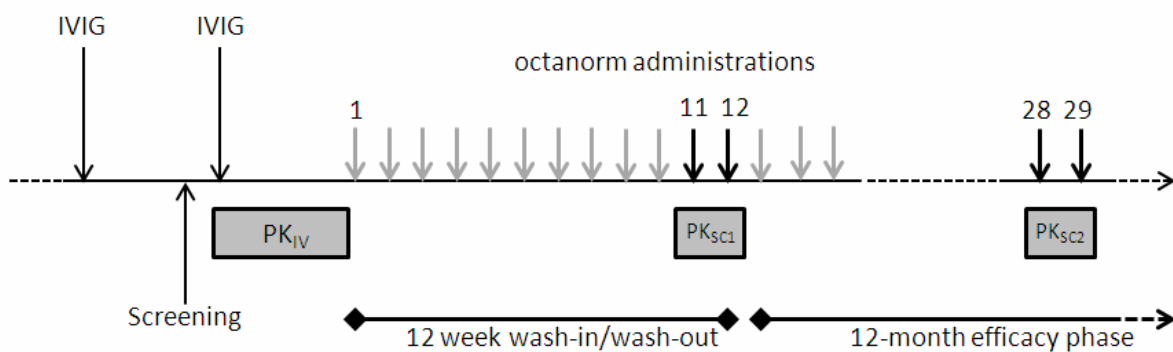
Only patients participating in the PK substudy will have an infusion of their previously used IVIG product during the course of the study; all other patients will receive *octanorm* only, starting from the first time the next regular treatment is due.

Because the interim PK evaluation will have an impact on the initial dose conversion factor of newly enrolled subject and the subsequent titration, it is useful to differentiate between 3 groups of patients, depending on the time of enrollment :
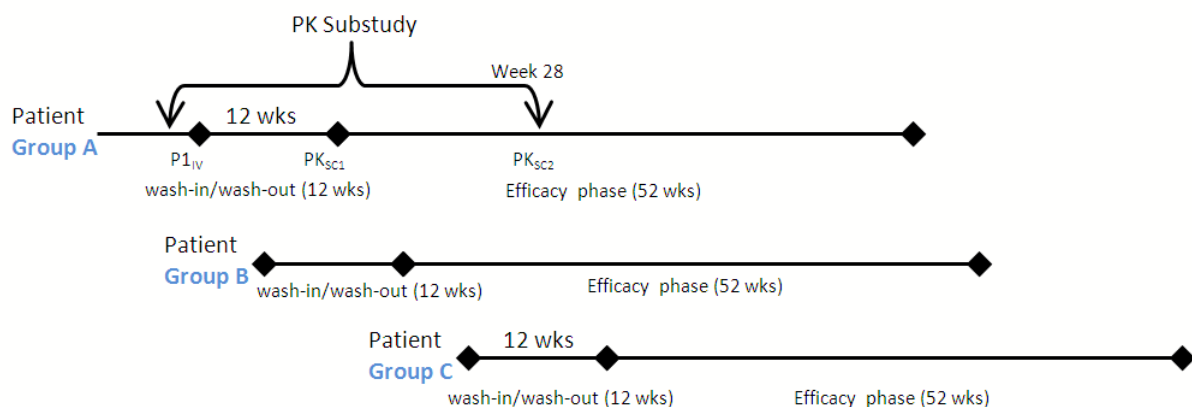
All patients must be on regular, steady-state IVIG treatment before entering the study, with constant dosing and IgG trough levels above 5.0 g/L.

All patients enrolled (in any of these groups) have to undergo a 12 week wash-in/wash-out period.

Each patient will be treated with *octanorm* over a period of 15 months (3 months wash-in/wash-out phase and 12 months efficacy phase). Each patient who stays in the study for the whole period will receive 64 *octanorm* administrations. The final examinations will be performed 1 week after the end of the last infusion, or 1 week after premature withdrawal of the patient from the study.

The total duration of the study for an individual patient will be approximately 70 weeks (depending on the IVIG treatment schedule before enrollment and on whether the patient participates in the PK substudy or not).

4.2.   Age groups

According to protocol version 9.0, at least 50 (and up to 78) patients who comply with the inclusion and exclusion criteria will be enrolled into 4 age groups as follows (age at time of informed consent):

- ≥2 to <6 years: at least 4 patients
- ≥6 to <12 years: at least 10 patients
- ≥12 to <17 years: at least 6 patients
- ≥17 to ≤75 years: at least 25 to a maximum of 39 patients

To collect sufficient PK data for each age group, at least 20 patients, but not more than 34 patients, will be enrolled in the PK substudy of the study as follows:

- ≥2 to <6 years: at least 2 evaluable patients.
- ≥6 to <12 years: at least 6 evaluable patients.
- ≥12 to <17 years: at least 4 evaluable patients.
- ≥17 to ≤75 years: at least 6 evaluable patients.

Additional recruitment into the PK study will ensure that at least 12 paediatric PK patients will be available for the final analysis.

Enrollment will be centrally coordinated to ensure that these distributions of patients in the four age groups (2 to <6 | ≥6 to <12 | ≥12 to <17 | ≥17 to ≤75) will be achieved, overall and in the PK substudy.

4.3.   PK substudy

One goal of study SCGAM-01 is to develop guidance and recommendations for dose adjustments when patients are switched from regular IVIG treatment to treatment with *octanorm* 16.5%. The underlying basic idea to derive such recommendations is to ensure that the overall bioavailability of total IgG for a patient on steady-state SCIG treatment ought to be the same as it was for the preceding steady-state IVIG treatment. The areas under the time-concentration curves, normalized to a 1 week time period (AUC_T), will be used as the measure of bioavailability.

Because full PK profiles are not determined within the usual clinical routine, it is impractical to base an algorithm for dose adjustments on a target AUC itself; thus dose recommendations will be developed on basis of the data obtained at the interim PK analysis based on PK_{IV} and PK_{SC1} to provide

investigators with a tool to base initial dosing of new patients and dose titration on the trough total IgG levels that will be determined in the local labs.

Please refer to section 12 for further details on the PK interim- and final analysis.

4.4.   Selection of Study Population

The study population consists of patients of both sexes with a confirmed diagnosis of PI who require immunoglobulin replacement therapy due to hypogammaglobulinaemia or agammaglobulinaemia, and who are on a stable treatment with any marketed IVIG product. 'Stable' in this context means that patients must have been on regular IVIG treatment for at least 6 infusions with a minimum of 2 months on the same product prior to entering the study, at a constant dose between 200 and 800 mg/kg body weight (±20% of the mean dose for the last 6 infusions). In addition a trough IgG level of at least 5.0 g/L in 2 previous treatments must have been achieved and documented.

To ensure that the study results are optimal applicable to standard Immunoglobulin therapy in PI patients and not distorted by foreseeable confounders, specific exclusion criteria are deployed, including acute infections requiring intravenous antibiotic treatment, severe liver or renal impairment, and the use of prohibited medication like immunosuppressive or immunomodulatory drugs; please refer to the study protocol for a detailed list of all in- and exclusion criteria.

To ensure a meaningful age distribution of the patients, overall as well as in the PK substudy, a centrally coordinated enrollment procedure will be applied with respect to four predefined age groups as detailed in section 4.2 above.

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5. Sequence of Planned Analyses

5.1. Interim Analyses

Once the 20 to 24 patients enrolled into the PK substudy have had the first two PK assessments (PK$_{IV}$ and PK$_{SC1}$), the corrected dose conversion factor and the dose adjustment recommendations table was determined as described in section 12.2. According to study protocol it was planned that these results would be used to adjust the dose regimens of the study participants as follows:

- Patients participating in the PK substudy: once the corrected DCF is known and if the corrected DCF is > 1.5, the further *octanorm* doses should be calculated with the corrected DCF
- Patients not participating in the PK part who were enrolled before the interim results were available: if the corrected DCF is > 1.5, the dose (of initially 1.5 times their IVIG dose) will be adjusted to match the corrected DCF
- New patients enrolled after completion of the PK interim analysis: the corrected DCF will be used to calculate the dosing of *octanorm*

However, no such adjustment was realized during the course of the study, but all newly enrolled patients were dosed with 1.5 times their IVIG dose and no dose adjustments were made on basis of the interim DCF results. As was initially planned, this PK interim assessment did not have any impact on the study proceedings and did not result in any change of the sample size or study design.

Because of the low recruitment rate of pediatric patients, Octapharma has requested a deferral for the completion of the pediatric subset (children and adolescents 2-16 years) of SCGAM-01 at the time of initial Biologics License Application; to this effect, data obtained from all adult patients (and meaningful available data of pediatric patients) was evaluated in aninterim analysis and was included in the initial Biologics License Application of octanorm in adult patients.

As soon as the pediatric subset will have completed the study and results are available, an amendment will be submitted in order to obtain marketing authorization for the use of octanorm in pediatric patients.

All standard procedures related to data review, disposition of patients, and database lock were followed for all interim analyses.

In detail, the following interim analyses were conducted for submission in different countries:

- Submission in Czech republic in Apr 2015 - safety analysis
- Submission in Canada in Feb 2017– complete analysis of all patients with cut-off date 15NOV2016
- Submission to PEI in June 2017- complete analysis of all patients with same cut-off date (15NOV2016)
- Submission to FDA in Dec 2017- complete analysis of all patients with cut-off date 27OCT2017
- Second submission to PEI in Jun 2018 - complete analysis of all patients (including 20 paediatric patients, 4 of them PK-patients) who had already finished study

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All major interim analyses were conducted based on SAP version 6.0, dated 21-Apr-2016. During the interim analyses a few inconsistencies were noted in the SAP, which are corrected in current SAP version. The current version contains clarifications and additional details concerning the following:

- definition and use of primary treatment period
- definition of suspected adverse reaction
- separate analysis of infusion site reactions
- additional details of exposure analysis

Moreover during interim analysis data review, a few minor updates were made to the planned analysis, which are now reflected in current SAP version:

- For most of the AE tables, it was decided to present systemic AEs excluding infections and infections only in separate AE tables
- For the secondary efficacy endpoint use of antibiotics it was decided to present two versions of the tables, for all antibiotics and systemic antibiotics only

Finally, based on the review of the interim analyses by the regulatory authorities, a few more additional analyses were added to the current SAP version which were completed as post-hoc analysis on the interim data but shall again be included for final analyses. These are clearly identified in further sections of the SAP by referring to a regulatory request.

5.2. Final Analyses and Reporting

As stated in section 4.1, each patient is treated with *octanorm* over a total period of approximately 70 weeks; one week after the last infusion a follow-up visit is performed, and the patient will be switched to a commercially available immunoglobulin product at the discretion of the investigator. Once the last patient has completed the study, data validation will be completed and the database will be locked according to the applicable standard operating procedures. This process includes a data review, the identification and classification of any protocol violations as detailed in section 7, and thus the patient disposition with respect to the analysis populations. All final, planned, analyses identified in the protocol and in this SAP will be performed only after the last patient has completed the study, the subject disposition has been agreed and documented, and the final SAP has been approved.

Key statistics and study results will be made available to the study team following database lock and prior to completion of the final CSR by means of tables, figures and listings.

Any additional, post-hoc, exploratory analyses completed to support planned study analyses, which were not identified in the final SAP, will be documented and reported in appendices to the CSR. Any results from these unplanned analyses will also be clearly identified in the text of the CSR.

6. Sample Size Determination

It is known that the observed serious infection frequency is less than 0.5 per year during periods of regular (generally every 3 to 4 weeks) administration of IVIG (FDA 2008[3]) and should be similar for SCIG treated patients (Chapel et al., 2000, [1]). Therefore, using STPLAN v4.3 software, it is calculated that 42 evaluable patient-years would be sufficient to test the null hypothesis that the serious infection rate is greater than or equal to 1.0 per person-year at the 1% level of significance with 90% power (Brown et al., 2006, [2]).

The study will enroll at least 50 subjects, each treated with *octanorm* over a period of 15 months. Since all patients have to undergo a 12-week wash-in/wash-out phase during which any occurring infection cannot be attributed unambiguously to a steady-state treatment with *octanorm*, each patient who completes the study will contribute one person-year of observation to the evaluation of the primary endpoint. Assuming a drop-out rate of 15%, the number of evaluable person-years would still be at least 42.5 and thus satisfy above sample size consideration.

The maximum number of patients in each age group and study phase is determined by the minimum numbers required as described in section 4.2 above; it is not possible for all groups to recruit the maximum number if the total number is to remain between 50 and 78 patients. Recruitment will be monitored centrally, ensuring that the minimum enrolment targets are met in each age group.

The PK substudy will include at least 20 patients who will contribute to the analysis of bioavailability described in section 12.3. Assuming that the intrasubject variability, expressed as coefficient of variation, does not exceed 0.25 and that the correlation between $AUC\tau_{SC}$ and $AUC\tau_{IV}$ is at least 0.4, the equivalence test for the paired geometric mean ration will have a power of 87.5%.

6.1. Patient Replacement Policy

Patients withdrawn from the study because of safety or efficacy reasons will not be replaced. Patients withdrawn from the study for any other reason, e.g. major protocol violation, pregnancy or administrative reasons will also not be replaced. However, if the number of withdrawals exceeds the limit of 15%, the sponsor and the coordinating investigator will assess the situation and decide on a possible replacement policy.

6.2. Premature Termination of the Study

If early termination of the study becomes necessary, the sponsor and the investigator will ensure that adequate consideration is given to the protection of the patients' interests. Premature termination will be notified in accordance with applicable regulatory requirements.

Early termination of the study as a whole or centre-wise may apply for the following reasons:

Clinical Study: At any time the study as a whole will be terminated prematurely if e.g.:

- New toxicological or pharmacological findings or serious AEs invalidate the earlier positive benefit-risk-assessment

- If more than 2 thromboembolic events (TEEs) are observed fulfilling the following criteria:

  o assessed as probably or possibly related to *octanorm* treatment by investigator and/or sponsor

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[3] Guidance for Industry - Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency. 2008.

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- o confirmed by IDMC

- If more than 2 cases of clinically significant hemolysis are observed fulfilling the following criteria:

  - o assessed as probably or possibly related to octanorm treatment by investigator and/or sponsor

  - o confirmed by IDMC

- If the corrected DCF obtained after the 2nd PK analysis at the end of the wash-in/wash-out phase (PK$_{SC1}$) turns out to be ≥2.0.

- Any other reason rendering the continuation of the study impossible for the Sponsor

Study Centre: At any time the study can be terminated at an individual centre if e.g.:

- The centre cannot comply with the requirements of the protocol.

- The centre cannot comply with applicable standards.

- The centre's first patient is not recruited by 10 weeks after initiation of the centre.

- The required recruitment rate is not met.

- Should the study be prematurely terminated, all study materials (completed, partially completed and blank forms, IMPs etc.) must be returned to the Sponsor.

7. Analysis Populations

The following populations will be considered for the statistical analysis:

The **safety analysis set (SAF)** consists of all patients who received at least part of one infusion of *octanorm*.

The **full analysis set (FAS)** is defined according to the intention-to-treat (ITT) principle and consists of all patients of the SAF who satisfy all major eligibility criteria and for whom any post-baseline data is available; it is the set of eligible patients with treatment effects measured.

The **per-protocol (PP) set** consists of all patients of the FAS excluding those with major protocol violations which may have an impact on the analysis of the primary efficacy endpoint. This is the set of patients who participated in the study as intended and for whom the primary efficacy endpoint can be evaluated as planned.

All protocol violations documented during the conduct of the study or identified at the data review process prior to DB lock will be reviewed and classified as minor or major and with respect to its effect on the planned analysis. Only major protocol violations with the potential to significantly affect the study results or to invalidate the interpretation of the data obtained will lead to exclusion of patients from the PP set. This classification of protocol violations is the joint responsibility of the clinical study manager, the study statistician, and Octapharma's responsible medical expert, and will be performed and documented before the database is locked and the statistical analyses are performed.

Protocol violations to be considered will include (but not be limited to):

- Violations of the study entry criteria
- Administration of any other blood or plasma-derived product or of any other immunoglobulin preparations
- Any prohibited concomitant medication (including long term corticosteroids, daily, ≥ 0.15 mg of prednisone or equivalent/kg/day, immunosuppressive and immunomodulatory drugs)
- Failure to attend two scheduled consecutive visits OR three or more scheduled visits during the study for reasons other than clinical reasons

The **PK evaluable set for the interim analysis (PK1)** will consist of all patients who have concentration data for the pre-infusion trough levels and the $AUC\tau_{IV}$ and $AUC\tau_{SC}$ determinations prior to the switch to *octanorm* (PK_{IV}) and after the 11th infusion of *octanorm* (PK_{SC1}). Patients with protocol violations or particular medical conditions likely to influence the trough levels and/or the AUC values will be excluded from PK1 to ensure the accuracy of the calculation of the corrected dose conversion factor.

The **PK evaluable set for the assessment of bioavailability (PK2)** will consist of all patients who have sufficient concentration data to determine $AUC\tau_{IV}$ and $AUC\tau_{SC}$ prior to the switch to *octanorm* (PK_{IV}) and after the 28th infusion of *octanorm* (PK_{SC2}) respectively. Patients with protocol violations or particular medical conditions likely to influence these AUC values will be excluded from PK2 to ensure the accuracy of the assessment of bioavailability.

Note: As a consequence of these definitions it is possible that a subject is included in PK1 but not in PK2 and vice versa.

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All efficacy endpoints will be analyzed on the basis of both, the FAS and the PP analysis sets, to allow for an assessment of the robustness of the results with respect to protocol violations.

Analysis of the safety endpoints will be based on the safety set.

The PK analyses will be based on the PK evaluable analysis sets.

Whenever appropriate, the analyses will be stratified according to the predefined age groups (2 to <6 | ≥6 to <12 | ≥12 to <17 | ≥17 to ≤75).

Additionally, for primary and secondary endpoints, the following subgroups will be investigated based on regulatory request:

- Male vs female subjects
- A different definition of age groups: 2 to < 12, 12 to < 17, 17 to 65, and > 65 years

8. General Issues for Statistical Analysis

Descriptive summaries will be presented for each of the primary and secondary variables. In general, summaries will be completed for all patients overall and by age group. .

Continuous, quantitative variable summaries will include the number of patients with non-missing values (N), mean, standard deviation, median, minimum and maximum, 1st and 3rd quartile.

Categorical, qualitative variable summaries will include the frequency and percentage of patients who are in the particular category. In general the denominator for the percentage calculation will be based upon the total number of patients in the analysis population unless otherwise specified.

8.1. Analysis Software

Statistical analyses will be performed using SAS Software version 9.1 or later; for the pharmacokinetic analysis specialized software Phoenix WinNonlin Professional (version 6.2 or later) will be used for the calculation of non-compartmental pharmacokinetic parameters.

8.2. Withdrawals

Patients who withdraw from the study prematurely will be considered in all data presentations for which they contribute data; in particular for the analysis of the rate of serious bacterial infections they will be considered with their actual observation period as defined in section 8.4 below.

8.3. Handling of Missing Data

In general, missing data will not be imputed: calculations pertaining to person-year computations will be based on observed values only.

For missing weight measurements the last available body weight will be used for all calculations related to dosing and PK parameters; in individual patient data listings missing data will however not be replaced by imputed values.

No analyses of the patterns of missing data will be done.

For adverse events the following will be applied:

An Adverse Event (AE) is defined as treatment-emergent, if first onset or worsening is after start of the first infusion of *octanorm*.

If the start date and time of an AE are partially or completely missing, the AE will be assumed to be treatment-emergent if it cannot be definitely shown that the AE did not occur or worsen during the treatment emergent period (worst case approach). Missing dates and times will not be replaced.

For medications the following will be applied: A medication will be assumed to be concomitant if it cannot be definitely shown that the medication was not administered during the *octanorm* treatment period as defined in section 8.4 below. Missing dates will not be replaced.

8.4. Derived and Computed Variables

The following derived and computed variables have been initially identified as important for the analysis of the primary and secondary target variables. It is expected that additional variables will be required. The SAP will not be amended for additional variables that are not related to the primary target or key secondary target variables. Any additional derived or computed variables will be identified and documented in the SAS programs that create the analysis files. If the SAP is not

amended, further derivations related to primary and secondary target variables will be described in the CSR.

- **Age** will be derived according to the usual definition that a person is n years old until she or he has completed her or his $(n+1)^{th}$ year of life, using the date of informed consent as the reference date. This is also the definition that will be applied for evaluation of the age related inclusion criteria, and the stratification into the four predefined age groups   [Unit: years]
- **Body Mass Index**: BMI = (Body weight) / Height^2 [Unit: kg/m^2]
- The *octanorm* **treatment period** is defined as the period between the day of first treatment with study drug to the end of the observation period. This will usually be the termination visit.

  If the patient is lost to follow-up and no termination visit is performed, the last patient contact that is not more than 6 weeks after the last administration of study product will be considered as the end of the treatment with *octanorm* (even if the patient received an infusion with *octanorm* on this day)   [Unit: years]

- Because the *octanorm* treatment period also includes the wash-in/wash-out phase it is necessary to also define a **primary treatment period**, which starts on the date of the 12th infusion of *octanorm* and ends together with the *octanorm* treatment period defined above. This ensures that any occurring infection can be attributed to a steady-state treatment with *octanorm* unambiguously.   [Unit: years]
- The **rate of serious bacterial infections** per year during regularly repeated treatment with *octanorm* will be calculated as r = (Total number of serious bacterial infections occurring in the primary treatment periods) / (Sum of primary treatment periods)   [Unit: 1/years]
- The **rate of other infections** will be derived using the same method

Calculation of the confidence intervals of these rates will account for intra-patient correlation in incidents following a compound Poisson process model.[3]

With C_i infections for the ith patient, and C total infections, the adjusted 2-sided 98% CI is calculated by:

$$\left[e^{\ln(r)-2.33\cdot\sqrt{\frac{\sum C_i^2}{C^2}}} \; ; \; e^{\ln(r)+2.33\cdot\sqrt{\frac{\sum C_i^2}{C^2}}} \right]$$

- The **rate of infusions with one or more temporally associated AEs** will be calculated for each patient as r = (Number of infusions with one or more temporally associated AEs) / (Number of infusions started). An AE is defined as a temporally associated if, and only if, the onset (or worsening) is either during an infusion of study medication or within 72 hours of the end of the infusion.   [Unit: N/A]
- The **rate of absence from work or school** will be based on the assumption of 200 working/school days per year, i.e. the rate is to be calculated as R = (1/200)*(Number of days absent from work or school) / (Patient years on *octanorm* treatment)   [Unit: 1/years]
- The **pharmacokinetic endpoints** of this study will be analyzed by use of non-compartmental methods and is based on the assumption that steady-state conditions are observed at the time the PK profile is assessed; please refer to Section 12 for further details. The **elapsed**

time is computed as the difference in time from the start of the infusion to the sampling time and is presented in uniform units (hours).

9. Study Subjects and Demographics

9.1. Disposition of Subjects and Withdrawals

All patients enrolled in the study will be accounted for. Descriptive summaries of population data will be provided overall and by age group; these will include

- The frequency and percent of patients in each analysis population, age strata and enrollment group (with respect to the time of inclusion in relation to the progress of the PK substudy as detailed in section 4.3)
- The disposition of patients (including number of patients enrolled, number of patients treated, number of completers)
- study withdrawals by reason of withdrawal

9.2. Protocol Violations

Protocol violations will be checked on complete data for all relevant patients prior to defining the analysis populations. Relevant in this context means:

- All patients of the PK substudy for the PK1 population and the PK interim analysis
- All patients for the final analysis

The final decision regarding inclusion/exclusion of patients from the analysis sets will be taken based on protocol adherence reports during data review meetings before database lock, data release and analysis (interim and final), applying the definitions in section 7.

Major protocol violations will be summarized by type of violation and by age group. Individual patients with these protocol violations will be listed.

9.3. Demographics and Other Baseline Characteristics

Descriptive summaries of the demographic and other baseline characteristics will be completed for the populations specified below, overall and by age group; these include:

- Demographics (Age, Gender, Race/Ethnicity, Height, Weight, BMI (calculated), ABO Rhesus blood type)

  (SAF, FAS, PP, PK1, PK2)

- Medical History (SAF)

  Medical history will be coded with the Medical Dictionary for Regulatory Activities (MedDRA, according to the version specified in the Data Management Plan). Incidences of findings in medical history will be summarized by MedDRA system organ class (SOC) and preferred term (PT)

- Previous IVIG Therapies (SAF)
- Prior and Concomitant Medications (SAF)

  Medications will be coded using the WHO Drug Dictionary (according to the version specified in the Data Management Plan). Incidences of prior and concomitant medications will be summarized by ATC level 2 and ATC level 4

- Baseline Physical Examination, including vital signs (SAF)
- Chest X-ray (posterior-anterior and lateral)

9.4. Measurement of Treatment Compliance and Exposure

The following parameters will be listed and summarized per patient and/or per infusion:

- Body weight
- Actual dose (total and per kg body weight, based on the latest available weight measurement)
- Total dose of *octanorm* administered
- Total number of infusions administered
- Total volume of solution administered
- Infusion times
- Overall amount of product administered (only included in data listings)
- Maximal volume administered (in total and per kg body weight, overall and per site)
- Infusion sites
- Infusion flow rates (overall and per site)
- Number of infusion parts administered per infusion
- Number of needles used

For some of the exposure variables listed above, further summaries will be prepared by patient and time period (infusions 1- 6, infusions 7- 24, infusions 25 - 39, after the 40th infusion), as the maximum allowed flow rates and volume given in study protocol increase over time.

Based on regulatory request, an analysis of realized flow rates (overall and per site) and realized volume administered per site will additionally be performed, comparing actual flow rates and volumes to maximum allowed flow rates and volumes that are given in the study protocol.

Moreover, deviations from the planned treatment schedule will be summarized by counting the number of infusions that deviate from the scheduled intervals by more than 2 days, and by listing all cases with more than two days deviation individually.

10. Efficacy Analysis

This study will examine the efficacy of *octanorm*. Formal planned analyses are described below. It may be necessary for additional exploratory analyses to be performed after the results from the planned analysis are completed; in this case full details of additional analyses will be given in the CSR.

All efficacy endpoints will be analyzed on the basis of both, the FAS and the PP analysis sets, to allow for an assessment of the robustness of the results with respect to protocol violations. The FAS analysis is considered to be the primary assessment of efficacy, and will be presented first in the report.

10.1. Primary Efficacy Variable Analysis

The primary efficacy variable is the rate of SBIs per person-year, where SBIs are defined as bacterial pneumonia, bacteremia/sepsis, osteomyelitis/septic arthritis, visceral abscess, or bacterial meningitis.

The rate of SBIs per person-year during the primary treatment period with *octanorm* as defined in section 8.4 will be presented as point estimate of the rate along with a two-sided 98% confidence interval (CI). Calculation of this CI will account for intra-patient correlation in incidents following a compound Poisson process model. Furthermore, all observed serious bacterial infections will be listed individually and in full detail.

The null hypothesis to be tested is that the serious infection rate is greater than or equal to 1.0 per person-year, tested at the 1% level of significance. The null hypothesis will be rejected if the upper two-sided 98% confidence limit – which is the upper one-sided 99% confidence limit – is less than 1.0.

The numbers of patients with SBIs, and the number of such infections, will be tabulated in a frequency table, by type of infection and severity and in total. Because of the limited number of infections expected, no further rates will be presented and no sub-analysis for specific infections will be carried out.

The analysis of the primary efficacy variable will be repeated for the total treatment period.

Moreover, for the interim analyses two sensitivity analyses were added based on regulatory request, because at the time of the interim analyses 0 serious bacterial infections were observed. In that case, it is not possible to calculate a confidence interval with the originally planned method using compound Poisson process model. Thus, as first sensitivity analysis, the originally planned two sided 98% confidence interval was calculated for the worse case that one bacterial infections would have been observed. As second sensitivity analysis, the confidence interval was calculated using standard Poisson distribution.

These two sensitivity analyses will be repeated for final analysis if still 0 serious bacterial infections are observed. The second model will also be used as a sensitivity analysis if a very small number of serious bacterial infections is observed, as within patient correlations are negligible for small number of serious bacterial infections.

10.2. Secondary Efficacy Variable Analysis

All secondary efficacy variables described in sections 10.2.1 to 10.2.6 will be analyzed in the primary treatment period as well as additionally in the total treatment period.

10.2.1. Rate of Other Infections

The rate of other infections will be analyzed and presented using the same method as the rate of serious bacterial infections. However, the upper limit of a one sided 95% confidence interval will be calculated.

As the originally planned method of CI calculation using compound Poisson process model is not very common, an alternative method for CI calculation will be used as sensitivity analysis, based on regulatory request. The alternative method will be based on overdispersed Poisson regression model using PROC GENMOD.

Overdispersed Poisson regression does account for within-patient correlations as the original model, but uses different underlying assumptions than the originally planned model.

Two different versions of the overdispersed Poisson regression will be applied, the first basic model without any additional factor to calculate the CI in the total group, the 2nd model with age group as factor to calculate the CI within the age groups.

Other infections include acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, acute bronchitis, infectious diarrhea, etc. All such infections will be listed and tabulated according to type and severity.

10.2.2. Time to resolution of infections

The duration of infection will be summarized by standard descriptive statistics (N, mean, SD, median, Q1, Q3, Min, Max) by type of infection and by severity. The individual characteristics of each infection, including the time to resolution will be listed.

10.2.3. Use of Antibiotics

All antibiotic treatment administered to a patient during the course of the study will be listed in full detail, including type, trade- and/or generic name, dosing, duration and the indication for the use of the antibiotic (Verbatim and MedDRA term).

The numbers of patients treated with antibiotics, the number of treatment episodes per person-year and the number of treatment days per person-year will be tabulated. Moreover, based on regulatory request for additional confidence interval calculation, the upper limit of a one-sided 95% confidence interval will be calculated for number of treatment days per person-year using the compound Poisson process model.

The analysis of antibiotics will be performed including all antibiotics and will be repeated including systemic antibiotics only.

10.2.4. Hospitalizations

All hospitalizations due to infection during the course of the study will be listed together with duration and reason for the hospitalization. The numbers of patients hospitalized due to infections at least once during the study, the number of such hospitalizations per person-year and the number of days in hospital per person-year will be tabulated. Moreover, based on regulatory request for

additional confidence interval calculation, the upper limit of a one-sided 95% confidence interval will be calculated for number of days in hospital per person-year using the compound Poisson process model.

10.2.5.   Episodes of Fever

All episodes of fever will be listed. The numbers of patients with at least one episode of fever during the course of the study and the number of episodes per person-year will be presented.

10.2.6.   Absences from Work or School

All absences from work or school will be listed with duration and reason for absence. The individual absence rates per person-year will calculated as detailed in section 8.4 and summarized by descriptive statistics. Moreover, based on regulatory request for additional confidence interval calculation, the upper limit of a one-sided 95% confidence interval will be calculated for number of days absent from work/school per person-year using the compound Poisson process model.

10.2.7.   Quality of Life

Quality of life (QoL) assessments will be made using the Child Health Questionnaire-Parent Form (CHQ-PF50) from parent or guardian of patients < 14 years of age and the SF-36 Health Survey in patients ≥ 14 years of age.

The applicable questionnaire will be chosen on basis of the patient's age on the date of informed consent and will not be changed thereafter.

The QoL assessments will take place before the first infusion, at week 28, and at the (early) termination visit.

Data from each QoL will be presented descriptively by visit, along with the change from baseline (defined as the first infusion).

11. Safety and Tolerability Analyses

The analysis of safety assessments in this study will be presented for the Safety Population.

11.1. Adverse Events

All reported AEs will be coded according to MedDRA.

An Adverse Event (AE) is defined as **treatment-emergent**, if first onset or worsening is after start of the first infusion of *octanorm*. Only treatment-emergent AEs **(TEAE)** are accounted for in the analysis.

Adverse events that occur between informed consent and the start of the first infusion of *octanorm* will be documented and flagged as pre-treatment AEs.

For each TEAE, the time relative to the start of the infusion will be calculated and the TEAE will be classified as **temporally associated** if the onset is during the infusion or within 72 hours after the end of the infusion.

In addition **suspected adverse reactions (SARs)** are defined as all adverse events that are temporally associated (as defined above) or were determined to be at least possibly related to administration of *octanorm* by the investigator or by Octapharma's medical expert, or that have a missing or indeterminate causality assessment.

All treatment-emergent AEs for each patient, including multiple occurrences of the same event, will be listed in full detail, including reported term, MedDRA preferred term and system organ class, onset, duration, time to the AE occurrence from last dose, causality, dosage, severity, seriousness and actions taken. The listing will include the number of the last infusion prior to each AE and the relative time. An evaluation to identify any AE with increased frequency over time will be performed.

Treatment-emergent adverse events will be summarized by age group and for the study as a whole as described in subsequent paragraphs. Most of the AE tables will be split analyzing infections separately from all other AEs.

The following will be presented in AE summary tables:

- Total number of TEAEs reported
- Number of temporally associated TEAEs
- Number of SARs
- Number and percentage of infusions temporally associated with one or more TEAE
- Number of temporally associated TEAEs divided by the total number of infusions
- Number of SARs divided by the total number of infusions
- Infusion rate at the onset of temporally associated TEAEs (frequencies and percentages)

On a per patient basis the incidence of TEAEs will be summarized by system organ class, preferred term and maximum severity. If a patient experiences an adverse event more than once the event at the most severe occurrence will be considered. Patients will be included only once under each system organ class and only once in the overall totals under the most severe event occurrence.

TEAEs will be summarized by strongest relationship to study medication by system organ class and preferred term. If a patient experiences an adverse event more than once the event most related to study medication will be considered. Patients will be included only once under each system organ class and only once in the overall totals under the most related to study medication occurrence.

Incidences of TEAEs (given as the number and percentage of patients) will be summarized overall and for each age group as follows:

- Temporally associated TEAEs by system organ class, preferred term and time relative to infusion (grouped as before)
- TEAEs by system organ class, preferred term and maximum severity
- TEAEs by system organ class, preferred term and strongest relationship
- Serious TEAEs by system organ class and preferred term
- TEAEs leading to withdrawal by system organ class and preferred term
- TEAEs leading to death by system organ class and preferred term
- Other significant TEAE by system organ class and preferred term*

* Other significant TEAEs include any non-serious AE or marked laboratory abnormalities that lead to withdrawal of IMP treatment, and/or dose reduction and/or significant additional concomitant therapy (i.e. medications given intravenously).

Narratives will be prepared describing each death, each other serious AE and those of the other significant AEs that are judged to be of special interest because of clinical importance. The narrative will address the following: nature and severity of event, clinical course leading up to event, indication of timing relevant to investigational medicinal product administration, relevant laboratory measurements, whether the drug was stopped, countermeasures or post-mortem findings, if any, and a causality assessment.

11.2. Infusions with One or More Temporally Associated AEs

The number of infusions with at least one temporally associated adverse event (including AEs judged not to be related to *octanorm* by the investigator) over the total number of infusions will be calculated for each patient, and the ratio will be presented, including the associated upper one-sided 95% confidence limit. The calculation of this confidence interval will take into account the observed intra-patient correlation - this is necessary because each patient may experience more than one infusion with an associated AE; it can therefore not be assumed that the observed events are statistically independent. This analysis will be performed for the primary as well as for the total treatment period.

11.3. Infusion Site Reactions

Infusion Site Reactions are captured on a separate eCRF page. Summaries will be prepared for

- Number of patients with infusion site reactions by severity and by type of reaction
- Number of infusions with infusion site reactions by severity, by type of reaction and by week

11.4. Clinical Laboratory Evaluations

The following laboratory tests will be performed during the course of the study to investigate the safety and tolerability of *octanorm*; for the timing of these lab panels and tests please refer to the flow chart of study events and sections 6.1 (Observations by Visit) and 7.3.4 (Laboratory Safety Tests) of the protocol:

- Standard hematology
    - Complete blood count [CBC]
    - WBC differential
    - Hematocrit

- o Hemoglobin
- Clinical chemistry
    - o Sodium
    - o Potassium
    - o Glucose
    - o Alanine aminotransferase [ALAT]
    - o Aspartate aminotransferase [ASAT]
    - o Lactate dehydrogenase [LDH]
    - o Total bilirubin
    - o Blood urea nitrogen or blood urea
    - o Creatinine
- Coombs' test
    - o Direct Coombs' test (if positive, the antibodies responsible for the positive direct Coombs' test will be eluted to investigate their specificity [anti-A, anti-B or anti-D])
    - o indirect Coombs' test
- Extended laboratory tests in case of confirmed Coombs' test together with drop in hemoglobin of ≥2g/dL
    - o Plasma-free hemoglobin
    - o Haptoglobin
    - o Reticulocyte count
    - o Unconjugated bilirubin
    - o Blood smear
- Urinalysis
    - o Protein
    - o pH
    - o Glucose
    - o Ketones
    - o Leukocytes
    - o Hemoglobin
    - o Hemosiderin
    - o Urine pregnancy test (women of childbearing potential)

All laboratory assessments, with the exception of the serum concentrations used for the PK profiles, will be done at the local laboratories (or at central laboratory if required) according to the site's standard procedures.

The serum concentrations used for the PK profiles of total serum IgG, IgG subclasses and antigen-specific antibodies against Haemophilus influenzae, Streptococcus pneumoniae (types 4, 6B, 9V, 14, 18C, 19F, 23F), CMV, tetanus and measles will be determined at the central laboratory.

Total serum IgG trough levels will be determined by both laboratories, local and central. Because the local results will be available more quickly and correspond to the data available during everyday local clinical praxis, these values should be used as a basis for dose changes if required. The corresponding trough levels determined in the central laboratory will be used for all PK evaluations, including the calculation of the corrected DCF and the derivation of dose recommendations based on target trough levels. Both sets of trough values will be listed and compared to verify that there are no major and systematic differences between the central and any of the local labs, which could affect an effective dosing regimen.

All laboratory data will be converted to standard units during the Data Management process. The laboratory data will be listed with suitable flags indicating abnormal values (L=Lower than reference range, H=Higher than reference range).

Summary statistics for the laboratory values as well as their changes from baseline at each time will be tabulated for all laboratory parameters.

11.5.   Viral Markers

Virology markers will be assessed prior to 1st infusion, at visit 11 and at the (early) termination visit, and will include:

- o   HBsAg
- o   HIV–1/2
- o   NAT: HBV
- o   NAT: HCV
- o   NAT: HIV–1
- o   NAT: Parvovirus B19
- o   NAT: HAV

These data will be listed as well with suitable flags indicating positive results. Furthermore shift tables will be presented to show any changes in the viral status during the study.

11.6.   Vital Signs

To evaluate short-term tolerance, vital signs (blood pressure, body temperature, pulse and respiratory rate) will be monitored at screening, at weeks 1, 4, 16, 28 40, 52, and finally at the (early) termination visit. Measurements will be carried out before, at least once during, and within 1 hour after the infusion of *octanorm*. The same will be applied for the infusion of IVIG products in the PK substudy.

Vital signs parameters will be summarized by visit and measurement time, using the standard set of summary statistics for both absolute values and changes from baseline, where the baseline value is the pre-infusion measurement.

11.7.   Further Safety Evaluations

11.7.1   Physical Examination

A general physical examination will be performed at the screening visit, and relevant findings will be documented; the physical examination will be repeated at weeks 1, 4, 16, 28 40, 52, and finally at the (early) termination visit.

Changes in results of physical examination will be summarized by body system and visit. Any clinically relevant worsening from the baseline status will be documented as an AE.

11.7.2.   Thromboembolic Events and Clinically Significant Hemolysis

All TEEs and all clinically significant cases of hemolysis that were assessed as probably or possibly related to *octanorm* (by investigator and/or sponsor and confirmed by the IDMC) will be listed in full detail, together with all relevant lab parameters.

12. Pharmacokinetic Analysis

12.1. PK Sampling

Patients participating in the PK substudy will undergo 3 PK assessments:

- After the last administration of the previously used IVIG product (PK$_{IV}$)
- At the end of the wash-in/wash-out phase (PK$_{SC1}$)
- After 28 administrations of *octanorm* (PK$_{SC2}$)

Blood samples will be taken for the measurement of total IgG, IgG subclasses, and selected antigen-specific antibody levels at the following eight time-points for each PK profile; all time points (unless otherwise specified in the lists below) are specified in relation to the **end** of infusion.

- For the PK$_{IV}$ profile:
    1. Before the start of the IVIG infusion
    2. 15 minutes (±5 minutes)
    3. 60 minutes (±10 minutes)
    4. 24 hours (±3 hours)
    5. 3 days (±6 hours)
    6. 7 days (± 6 hours)
    7. 14 days (±3 days)
    8. 21 days (±3 days) (for patients on 3-week infusion schedule) or 28 days (±3 days) (for patients on 4-week infusion schedule)
- For the PK$_{SC1}$ and the PK$_{SC2}$ profiles:
    1. Before the start of the *octanorm* infusion
    2. 10 minutes before the anticipated end of the infusion
    3. 2 hours (± 30 minutes)
    4. 1 day (±6 hours)
    5. 2 days (±6 hours)
    6. 3 days (±6 hours)
    7. 4 days (±6 hours)
    8. 7 days (± 6 hours)

For all PK assessments, in case any of the PK blood draws are not done within these time windows, the sample should be obtained as soon as possible afterwards. The actual exact sampling time point must always be recorded and will be used for the calculation of the PK parameters.

All PK sampling times and concentrations, including all trough- and profile samples, will be listed for each analyte and for each patient along with times for the start of infusion, nominal times, actual times and elapsed times (actual time difference from time of infusion start). There will be separate listings for the sampling time characterization, for the total IgG along with the 4 IgG subtypes, for the 7 *Streptococcus pneumoniae* antibody subtypes and for the remaining 5 antibody data.

12.1.1. PK Profile Concentrations

PK profile concentrations for each analyte will be summarized for each treatment frequency (for the IVIG profile) and by nominal sampling time and presented according to the general principles given in section 8. There will be separate summaries for the total IgG along with the 4 IgG subtypes, for the 7 Streptococcus pneumonia antibody subtypes and for the remaining 5 antibody data.

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Individual PK profiles will be presented graphically in Trellis plots (i.e. several plots featuring the same pairs of variables on one page). There will be three figures produced for each patient (each figure presented as rectilinear and semi-logarithmic plots) with one figure containing the total IgG along with the 4 IgG subtypes, another figure with the Streptococcus pneumonia antibody subtypes and the last figure with the remaining antibody data.

12.1.2. PK Trough Concentrations

All available trough concentration data for all PK analytes will be presented per patient and summarized according to the general principles given in section 8 by age group, in total, and for the PK substudy alone; these data will include the pre-study trough levels, the pre-dose concentrations for each infusion of *octanorm*, and the concentrations measured at follow-up.

Trough levels of total IgG as well as for the IgG subclasses (PK substudy only) will be presented graphically by infusion on a time scale. In addition, the frequency of total IgG trough levels below 5.0 g/L will be presented for each infusion.

Trough concentration data for the antibodies will include data collected prior to the first infusion and at follow-up, and will be available for patients in the PK substudy only. This data will be summarized by age group and by treatment frequency and presented according to the general principles given in section 8. Trough levels of all antigen specific parameters will be summarized separately by infusion and presented graphically on a time scale.

12.2. Dose Conversion Factor and Target Trough Levels

The following procedure will be applied at the PK interim analysis to obtain the best possible estimates for a dose adjustment policy to achieve and maintain the same constant bioavailabilities patients had on their preceding steady-state IVIG treatment after the transition to a steady-state treatment with *octanorm* is completed:

I.   After enrollment into the PK part of this study, each patient is to be treated once more with his regular infusion of IVIG, according to his normal treatment schedule (3 or 4 weeks) and standard product and dose regimen. This will be the last IVIG treatment, and the regular time period (3 or 4 weeks) following this infusion will be used to obtain a full PK profile of each patient on IVIG steady-state treatment (PK$_{IV}$).

II.   At the end of this interval, the patient will receive his first infusion of *octanorm*, and will thus be switched to a weekly, subcutaneous treatment schedule. The initial dose for this treatment will be 1.5 times the corresponding dose of IVIG the patient received previously (standardized to 1 week).

III.   In the final week of the wash-in/wash-out period (following the 11th infusion of *octanorm*) the patient is considered to be on a steady-state treatment with *octanorm* for several treatment cycles, and a full PK profile for this subcutaneous treatment regimen will be performed (PK$_{SC1}$).

IV.   The comparison of the initial PK$_{IV}$ profile and the PK$_{SC1}$ profile after completion of the wash-in/wash-out period will be used to calculate the corrected dose conversion factor as well as algorithms for the determination of target trough levels and dose adjustments during the subsequent 4 months of weekly *octanorm* infusions, with the aim to achieve a similar bioavailability associated with subcutaneous infusions, expressed as AUC$_\tau$.

V.   Details on the derivation of the corrected conversion factor, the target trough levels and the dose adjustment recommendations:

a.   Abbreviations used:

PK$_{IV}$:

AUCτ$_{IV}$ = Area Under the Concentration-time curve from 0 to the end of the dosing period (i.e. 21 or 28 days), standardized to 1 week for comparability.

T$_{IV}$ = Trough level associated with the current steady-state IVIG treatment; to level out short-term fluctuations, the average of the two last available trough levels – i.e. the start and the end-point of the IVIG PK cycle – will be used as T$_{IV}$.

Dose$_{IV}$ = Dose of IgG administered intravenously, in IU/L per kg body weight (actual weight), standardized to 1 week.

PK$_{SC}$:

AUCτ$_{SC}$ = Area Under the Concentration-time curve from 0 to the end of the dosing period (i.e. 1 week)

T$_{SC}$ = Trough level associated with the steady-state SCIG treatment; to level out short-term fluctuations, the average of the two last available trough levels – i.e. the start and the end-point of the PK$_{SC}$ profile – will be used as T$_{SC}$.

Dose$_{SC}$ = Dose of IgG administered subcutaneously, in IU/L per kg body weight (actual weight).

b. Firstly, a least-squares regression will be performed, modeling AUCτ$_{SC}$ as a linear function of Dose$_{SC}$; to account for patients with hypogammaglobulinaemia, the intercept will not be set to 0, but forced not to exceed the equivalence of a constant endogenous total IgG level of 2 g/L. This regression model will be used to determine the Dose$_{SC}$ levels associated with the original AUCτ$_{IV}$ values. Dividing these calculated Dose$_{SC}$ values by the actual Dose$_{IV}$ values results in individual ratios for all patients in the PK1 population; the average of these ratios will be used as the **corrected dose conversion factor**.

c. Because full PK profiles are not determined within the usual clinical routine, it is impractical to base an algorithm for dose adjustments on a target AUC itself; thus the target trough and the titration recommendations will be based on the trough levels. Whereas the algorithms detailed in this section will be derived from the trough levels determined by the central lab, the actual usage of the recommendations obtained will be based on results from the local labs.

d. The relation between the steady-state trough levels and the associated AUCτ will be modeled by linear regression for both PK profiles, PK$_{IV}$ and PK$_{SC}$. By combination of these two linear functions, it is possible to derive a **target trough level** as the Trough$_{SC}$ associated with the Trough$_{IV}$ reported by a newly enrolled patient. The eCRF system will set up in a way that allows incorporation of this algorithm upon completion of the PK interim analysis, so that the target trough level will be displayed to the investigator whenever a new patient is enrolled and the Trough$_{IV}$ is available.

e. Finally, Trough$_{SC}$ will be modeled as a linear function of Dose$_{SC}$ with no intercept; this yields a slope for the total IgG trough level response to *octanorm* dose increments; this slope will be used to derive an easy to use dose adjustment tabulation featuring body weight and the desired change in trough level function according to the following table shell:

	Body Weight (kg)				
	10	15	20	…	120

Difference from target IgG trough level (g/L)	Dose adjustment (mL per Week)				
1					
1,5					
…	The entries in this table will be calculated as (<Body Weight>*<Desired Change>) / (165*<Slope obtained by lin. regression>)				
5					

VI.   After availability of these interim PK analysis results, the investigators will apply the following:

- For patients in the PK substudy (group A): if the corrected DCF is > 1.5, the further *octanorm* doses should be calculated with the corrected DCF.
- For patients already enrolled who are not participating in the PK substudy (group B): if the corrected DCF is > 1.5, the further *octanorm* doses should be calculated with the corrected DCF.
- Newly enrolled patients (group C) will start their subcutaneous treatment according to the corrected DCF without further adjustments (unless medically indicated).
- The investigators will be provided with a dose adjustment table to be used for further titration based on the desired target trough level for each individual patient if required. All further dose changes are at the discretion of the treating physician, and the individualization of dosing should take precedence over applying the corrected DCF.

12.3.   Bioavailability

Patients in the PK substudy will undergo a final PK profiling (PK$_{SC2}$) after their 28th treatment with *octanorm* to verify whether the aim to achieve comparable bioavailability has been met. This will be evaluated by a two one-sided tests (TOST) analysis of the mean AUC$_T$ ratio associated with the final adjusted subcutaneous versus the intravenous doses; this TOST analysis for multiplicative equivalence of paired lognormal geometric means with bounds 0.8 and 1.2 will be performed on the α=0.05 confidence level.

12.4.   Pharmacokinetic Parameter Estimates

Individual PK parameters for each analyte will be derived by non-compartmental analysis, using the Phoenix WinNonlin Professional software (version 6.2 or later), applying a steady-state data model. These parameters will be listed by patient, analyte and PK profile. Standard summary statistics of PK parameters will be tabulated for IgG total, each IgG subclass and antibody assay, for PK$_{IV}$ stratified per treatment interval of the intravenous treatment (3 or 4 weeks), by age group and in total.

The following PK parameters will be calculated:

C$_{max}$	Maximum concentration observed (between 0 and τ)	
T$_{max}$	Time when C$_{max}$ is observed	timing starts at begin of infusion
C$_{min}$	the minimum concentration between 0 and Tau (at Tmin).	
T$_{min}$	Time when C$_{min}$ is observed	

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λz	Elimination rate constant	determined by linear regression on the terminal[4] phase of the logarithm of the concentration.
$T_{1/2}$	Half-life	derived from the elimination rate constant as $T_{1/2}=\ln(2) / \lambda z$
AUC_{0-last}	Area under the concentration-time curve	from time 0 [start of the infusion] to the time point of the last non-zero concentration, calculated by use of the linear trapezoidal rule
AUCτ	Area under the concentration time-curve from 0 to the end of the dosing interval	standardized to 1 week
CL	Clearance (at steady state)	CL=Dose / AUCτ [dose normalized]
Vz	Volume of distribution based on the terminal phase (for steady state data)	Vz=Dose / (λz*AUCτ) [weight adjusted]
MRT	Mean residence time	Extrapolated to infinity
Vss	Volume of distribution at steady-state	Vss=MRT*CL [weight adjusted]

12.4.1. Potencies

All PK calculations related to infusions of octanorm that involve dosing or the amount of a specific compound (e.g. a specific IGg subclass) administered, will be based on the actual potencies, i.e. on the amount of the compound present in the actually used batch according to the certificate of analysis. In case more than one batch of octanorm is used in a single administration, the actual potency will be calculated as the correctly weighted average of the individual batch potencies.

Because the actual potencies of the various IVIG products and batches used for the PK_IV profiles will not be available in general, the corresponding calculations for these profiles will be based on the nominal potencies as far as total IgG is concerned. The effect of this difference will however be negligible as the total IgG content is expected to be very close to 100% in any IVIG product on the market.

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[4] The noncompartmental approach does not presume that the plasma concentration follows a mono-exponential decay during the complete elimination phase (t ≥ Tmax). The appropriate time point when the terminal elimination phase starts will be determined automatically by the software WinNonlin. At least 3 valid measurements will be used for the determination of λz, and the number of points used will be reported as well.

13. Reporting Conventions

The following reporting conventions will be adopted for the presentation of study data. These conventions will enhance the review process and help to standardize presentation with common notations.

13.1. General Reporting Conventions

- All tables and data listings will be developed in landscape orientation, unless presented as part of the text in a CSR.
- Figures will in general also be presented in landscape orientation, unless presented as part of the text in a CSR. Exceptions are the Trellis plots that will be presented in portrait orientation.
- Legends will be used for all figures with more than one variable or item displayed.
- Figures will be in black and white, unless color figures have been identified as useful for discriminating presentation in the figure. Lines in figures should be wide enough to view the line after being photocopied.
- Specialized text styles, such as bolding, italics, borders, shading, superscripted and subscripted text will not be used in tables, figures and data listings unless they add significant value to the table, figure, or data listing.
- Only standard keyboard characters should be used in tables and data listings. Special characters, such as non-printable control characters, printer specific, or font specific characters, will not be used on a table, figure, or data listing. Hexadecimal character representations are allowed (e.g., µ, α, β).
- The ICH numbering convention is to be used for all tables, figures and data listings.
- All footnotes will be left justified and placed at the bottom of a page. Footnotes must be present on the page where they are first referenced. Footnotes should be used sparingly and must add value to the table, figure, or data listing. If more than four footnote lines are planned then a cover page may be used to display footnotes.
- Missing values for both numeric and character variables will be presented as blanks in a table or data listing. A zero (0) may be used if appropriate to identify when the frequency of a variable is not observed.
- All date values will be presented as DDMMMYYYY (e.g., 29AUG2001) format.
- All observed time values will be presented using a 24-hour clock HH:MM format (e.g. 15:26).
- Time durations will be reported in HH:MM notation. The use of decimal notation to present (display) time durations should be avoided (e.g. 0.083h = 5min) unless it is necessary to show the computation of time differences in a table, figure, or data listing, in which case both notations may be used to display the time duration.
- All tables, figures and data listings will have the name of the program, and a date stamp on the bottom of each output.

13.2. Population Summary Conventions

- Population(s) represented on the tables or data listings will be clearly identified in the title as "Population: <name of population>" where <name of population> is any of the analysis population names or abbreviations defined in section 7 (safety analysis set (SAF), full analysis set (FAS or ITT), per-protocol set (PP), PK evaluable sets (PK1, PK2).

- Sub-population(s) or special population(s) descriptions will provide sufficient detail to ensure comprehension of the population (e.g., ITT Females, Per-Protocol Males >60 years of age) used for analysis in a table or figure.
- Population sizes may be presented for each treatment or dosing category as totals in the column header as (N=xxx), where appropriate.
- Population sizes shown with summary statistics are the samples sizes (n) of patients with non-missing values.
- All population summaries for continuous variables will include: N, mean, SD, median, Q1, Q3, minimum and maximum.
- All percentages are rounded and reported to a single decimal point (xx.x%).

14. References

[1] Chapel HM, Spickett GP, Ericson D, Engl W, Eibl MM, and Bjorkander J (2000) The comparison of the efficacy and safety of intravenous versus subcutaneous immunoglobulin replacement therapy. J Clin Immunol, 20, 94-100.

[2] Brown BW, Brauner C, Chan A, Gutierrez D, Herson J, Lovato J, Polsley J, Russell K, and Venier J (2006) STPLAN Version 4.3, Calculations for Sample Sizes and Related Problems. n a, 1-184.

[3] Kegler SR (2007) Applying the compound Poisson process model to the reporting of injury-related mortality rates. Epidemiologic Perspectives & Innovations 2007, 4:1

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15. Tables, Listings and Figures

To be supplied in a separate document later when all feedback from authorities will be available.