octapharma

CLINICAL STUDY PROTOCOL

CLINICAL PHASE III STUDY TO EVALUATE THE PHARMACOKINETICS, EFFICACY, TOLERABILITY AND SAFETY OF SUBCUTANEOUS HUMAN IMMUNOGLOBULIN (OCTANORM 16.5%) ISARN PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES

Investigational Product:	*octanorm 16.5%*
Indication:	Primary Immunodeficiency Diseases
Study Design:	Prospective, open-label, non-controlled, single-arm, multicenter phase III study
Sponsor:	OCTAPHARMA Pharmazeutika Prod.Ges.m.b.H., Oberlaaer Strasse 235, 1100 Vienna, Austria
Study Number:	SCGAM-01
BB-IND Number:	15617
EudraCT Number:	2013-003877-87
ClinicalTrials.gov ID:	NCT 01888484
Development Phase:	Phase III
Planned Clinical Start:	2014
Planned Clinical End:	2020
Date of Protocol:	January 16, 2019
Version:	09
Coordinating Investigator:	[redacted] St. Anne´s University Hospital in Brno Institute of clinical imunology a alergology Pekařská 53 656 91 Brno, Czech Republic

STUDY OUTLINE

Name of Sponsor/Company: OCTAPHARMA Pharmazeutika Prod.Ges.m.b.H., Oberlaaer Strasse 235, 1100 Vienna, Austria	
Name of Investigational Product: *octanorm 16.5%*	**Protocol Identification Code:** SCGAM-01
Name of Active Ingredient: Human Normal Immunoglobulin	**Edition / Date of Protocol:** 09 / January 16, 2019
Title of Study: 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.	
Indication: Primary immunodeficiency (PI) diseases.	
Number of Study Center(s): 10–22 selected study sites in the United States, Europe and Russia.	
Study Duration: 2014 to 2020	**Development Phase:** III

Objectives:

Primary:

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 pharmacokinetic (PK) characteristics of *octanorm* and to compare the area under the curve (AUC) with that of IVIG.

Secondary:

The secondary objectives of the study are:

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

Study Design:

The study is a prospective, open-label, non-controlled, single-arm, multicenter phase III study with a 12-week wash-in/wash-out period followed by a 12-month efficacy period.

Number of Subjects/Patients:

At least 50 (and up to 78) patients who comply with the inclusion and exclusion criteria will be enrolled into the study. Numbers of patients to be enrolled per age group will be as follows (age at time of informed consent):

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

Subject/Patient Selection Criteria:

Inclusion Criteria:

1. Age of ≥2 years and ≤75 years.
2. Confirmed diagnosis of PI as defined by ESID and PAGID and requiring immunoglobulin replacement therapy due to hypogammaglobulinaemia or agammaglobulinaemia. The exact type of PI should be recorded.

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3. Patients with at least 6 infusions on regular treatment with any IVIG, thereof a minimum of the last 2 months on the same product prior to entering the study. Constant IVIG dose between 200 and 800 mg/kg body weight (±20% of the mean dose for the last 6 infusions).
4. Availability of the IgG trough levels of 2 previous IVIG infusions before enrolment, and maintenance of ≥5.0 g/L in the trough levels of these 2 previous infusions.
5. Negative result on a pregnancy test (HCG-based assay in urine) for women of childbearing potential and use of a reliable method of contraception for the duration of the study.
6. For adult patients: freely given written informed consent. For minor patients: freely given written informed consent from parents/legal guardians and written informed assent from the child/adolescent in accordance with the applicable regulatory requirements.
7. Willingness to comply with all aspects of the protocol, including blood sampling, for the duration of the study.

Exclusion Criteria:

1. Acute infection requiring intravenous antibiotic treatment within 2 weeks prior to and during the screening period.
2. Known history of adverse reactions to IgA in other products.
3. Patients with body mass index >40 kg/m^2.
4. Exposure to blood or any blood product or plasma derivatives, other than IVIG treatment for PID, within the past 3 months prior to first infusion of *octanorm.*
5. Ongoing history of hypersensitivity or persistent reactions to blood or plasma derived products, or any component of the investigational product (such as Polysorbate 80).
6. Requirement of any routine premedication for IgG administration.
7. History of malignancies of lymphoid cells and immunodeficiency with lymphoma.
8. Severe liver function impairment (ALAT 3 times above upper limit of normal).
9. Known protein-losing enteropathies or proteinuria.
10. Presence of renal function impairment (creatinine >120 µM/L or creatinine >1.35 mg/dL), or predisposition for acute renal failure (e.g., any degree of pre-existing renal insufficiency or routine treatment with known nephritic drugs).
11. Treatment with oral or parenteral steroids for ≥30 days or when given intermittently or as bolus at daily doses ≥0.15 mg/kg.
12. Treatment with immunosuppressive or immunomodulatory drugs.
13. Live viral vaccination (such as measles, rubella, mumps and varicella) within the last 2 months prior to first infusion of *octanorm.*
14. Treatment with any investigational medicinal product within 3 months prior to first infusion of *octanorm.*
15. Presence of any condition, that is likely to interfere with the evaluation of study medication or satisfactory conduct of the trial.
16. Known or suspected to abuse alcohol, drugs, psychotropic agents or other chemicals within the past 12 months prior to first infusion of *octanorm.*
17. Known or suspected HIV, HCV, or HBV infection.
18. Pregnant or nursing women.
19. Planned pregnancy during course of the study.

Test Product, Dose, Mode of Administration, and Batch Number(s):

octanorm 16.5%, human normal immunoglobulin for subcutaneous (SC) administration.

octanorm has to be administered subcutaneously every week (±2 days). If, during the study, the **body weight changes by > 5%,** the dose is to be adjusted to keep the dose constant on a milligram

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per kilogram body weight basis. For patients participating in the PK substudy, the *octanorm* dose during the wash-in/wash-out phase is to be calculated as follows:

$$\frac{\text{previous IVIG dose (in grams) times 1.5}}{\text{number of weeks between IVIG doses}}$$

After the analysis of PK data obtained at the end of the wash-in/wash-out phase ("PK_{SC1}"), the "corrected" DCF will be calculated. If the corrected DCF is >1.5, the *octanorm* dose should be revised in accordance with the corrected DCF for all patients.

During the efficacy phase of the study, the patients' *octanorm* dose should be individualized by titrating upward based on the difference between each subject's measured serum total IgG trough levels while on *octanorm* and each subject's *target* serum total IgG trough level as determined below. This individualization of dosing should take precedence over applying the corrected DCF.

Batch (lot) numbers will be reported in the final report of the study.

Duration of Treatment:

Each patient who stays in the study for the whole period will receive 64 weekly SC infusions of *octanorm*.

Reference Therapy, Dose, Mode of Administration, and Batch Number(s):

Not applicable.

Study Outcome Parameters (Primary and Secondary Endpoints):

Primary endpoints:

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

Secondary **efficacy** endpoints:

- 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).
- Episodes of fever.
- Days missed from work/school/kindergarten/day care due to infections and their treatment.
- QoL assessments using the CHQ-PF50.

Secondary **pharmacokinetic** (PK) endpoints:

- 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.
- Trough levels of serum total IgG (total and subclasses) throughout the study.
- 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.
- IVIG to *octanorm* DCF (based on the area under the concentration-time curve [AUCτ]).

Secondary **safety** endpoints:

- Occurrence of all treatment emergent adverse events (TEAEs) throughout the entire 65-week treatment period starting with the first infusion of *octanorm*.

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- Occurrence of temporally associated TEAEs.
- Proportion of infusions with at least 1 temporally associated adverse event (AE).
- Occurrence of suspected adverse reactions (SARs).
- TEAEs by speed of infusion.
- Local injection site reactions.
- Vital signs (blood pressure, pulse, body temperature, respiratory rate).
- Laboratory parameters (hematology, clinical chemistry, markers for intravascular hemolysis, and tests for viral safety).

Summary of Study Procedures and Statistical Analysis Plan:

Study Procedures:

The study consists of a 12-week wash-in/wash-out period followed by a 12-month efficacy period. Patients participating in the PK substudy will undergo 3 PK assessments (see figure below).

Only patients previously on IVIG may be enrolled. All patients have to undergo the 12-week wash-in/wash-out period.

Each patient will be treated with *octanorm* over a period of about 15 months (12-week 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* SC weekly infusions. 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.

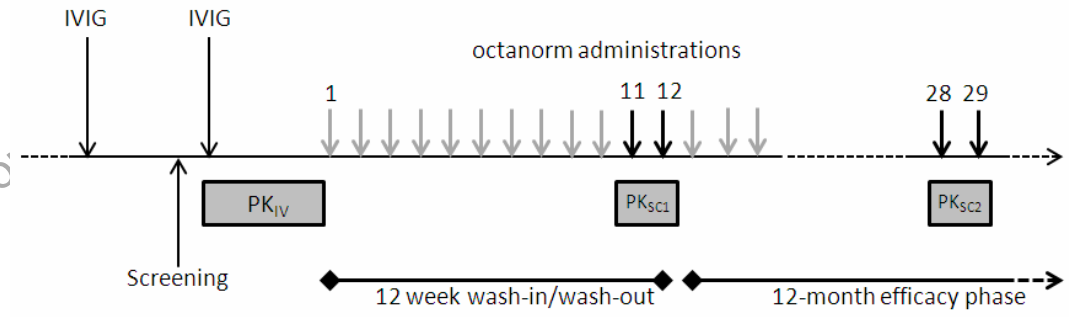
The total duration of the study for an individual patient will be about 70 weeks (depending on the IVIG treatment schedule before enrollment and on whether the patient participates in the PK substudy, or not).

At least 50 (and up to 78) patients who comply with the inclusion and exclusion criteria will be enrolled into the study.

An Independent Data Monitoring Committee will periodically review relevant data with emphasis on thromboembolic events (TEEs) and clinically significant hemolysis.

PK substudy:

Figure 1



The aim is to achieve at least 20 evaluable patients with complete PK profiles. The dosage regimen of IVIG treatment must have been constant for at least 6 infusions with a minimum of 2 months on the same product prior to entering the study (between 200 and 800 mg/kg body weight, ±20% of the mean dose for the last 6 infusions). IgG trough levels must be documented for 2 previous infusions to demonstrate that treatment is at steady-state, and must be ≥5.0 g/L. The Screening Visit must be performed before the last pre-study IVIG infusion. Screening results must be known before the first IMP administration.

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The **first PK evaluation ("PK_{IV}")** (see figure above) will take place before and after the last IV administration of IVIG, according to the patient's regular treatment schedule. Blood samples will be taken for the measurement of total IgG, IgG subclasses, and selected antigen-specific antibody levels, and the calculation of PK parameters at predefined intervals.

In the following 12-week wash-in/wash-out phase, weekly SC doses of *octanorm* will be given, at 1.5 times the previous IVIG dose adjusted for weekly dosing.

After training of the patient or his/her relative or caregiver at the study site (for at least 4 SC infusions), SCIG infusions may be (self-) administered at home. Every 4 weeks the infusion is to be given at the study site (latest after 6 weeks, exceptionally). Before starting home treatment, a diary will be provided to the patients for documenting the date, volume and speed of infusion, occurrence of infections, AEs and local tissue reactions at injection sites, body temperature around 1 hour after the end of the infusion, missed days from work/school/kindergarten/day care, inpatient hospital stays, and any changes in concomitant therapies between visits.

At the end of the wash-in/wash-out phase namely between Week 11 and Week 12, all patients participating in the PK substudy have to undergo the **second PK evaluation ("PK_{SC1}")** to determine the "corrected" DCF. Blood samples will be taken for the measurement of total IgG, IgG subclasses, and selected antigen-specific antibody levels, and calculation of PK parameters at predefined intervals.

The PK data will be subjected to an interim analysis. The "corrected" DCF will be derived from PK data by comparing the AUC under IVIG treatment with the AUC under *octanorm* treatment. The data for AUC IVIG will be taken from the first PK evaluation described above.

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.

Between Week 28 and Week 29, **the third PK evaluation ("PK_{SC2}")** will take place to determine the PK characteristics of *octanorm* under steady–state conditions and to verify whether the aim to achieve comparable bioavailability has been met. This will be evaluated by a *two one-sided test* (TOST) analysis of the mean AUC_T ratio associated with the applied *octanorm 16.5%* dose versus the IVIG doses.

Efficacy Phase:

The efficacy phase of the trial starts after completion of the 12-week wash-in/wash-out phase.

Patients who did not participate in the PK substudy have to be trained at the study site (for at least 4 infusions). Thereafter, the patient or his/her relative or caregiver may continue with *octanorm* infusions at home. Every 4 weeks the infusion is to be given at the study site. A 6-week interval may be acceptable exceptionally (e.g. in case of vacation). Before starting home treatment, a diary will be provided to the patients for documenting the date, volume and speed of infusion, occurrence of infections, AEs and local tissue reactions at injection sites, body temperature around 1 hour after the end of the infusion, missed days from work/school/ kindergarten/day care, inpatient hospital stays, and any changes in concomitant therapies between visits.

At the visits taking place at the study site, the following interventions and activities will be performed at pre-defined time points: Drawing of blood samples, determination of body weight, review of the patient diary, physical examination including vital sign assessments, QoL assessments, assessments of local injection site reactions, urine sampling, and urine pregnancy tests.

AEs and any changes in concomitant medications will be recorded throughout the study period.

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Statistical Analysis:

A formal statistical analysis plan describing all details of the analyses to be performed will be prepared by the study statistician and approved by the Sponsor prior to start of the statistical analysis.

The following populations will be considered for the statistical analysis:

The *safety analysis set* consisting 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 safety analysis set 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.

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.

The PK evaluable set for the interim analysis 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 this population to ensure the accuracy of the calculation of the corrected DCF.

The PK evaluable set for the assessment of bioavailability 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* respectively. Patients with protocol violations or particular medical conditions likely to influence these AUC values will be excluded from this population to ensure the accuracy of the assessment of bioavailability.

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 analysis will be based on the PK evaluable analysis sets.

The membership of each patient in the respective analysis populations will be determined prior to statistical analysis in a data review meeting by a panel consisting of a medical expert from the Sponsor, the clinical study manager, the data manager and the study statistician.

A descriptive efficacy and safety assessment after 100 SC infusions were given to patients is planned in order to obtain first impression of the performance of *octanorm* in the treatment of PID with respect to efficacy and safety.

Efficacy analysis plan:

The rate of SBI per person-year (bacterial pneumonia, bacteremia/sepsis, osteomyelitis/ septic arthritis, visceral abscess, bacterial meningitis) during the treatment period with *octanorm* will be presented as point estimates of the rate along with a 99% CI. Calculation of this CI will account for intra-patient correlation in incidents following a compound Poisson process model. Furthermore, all observed SBI will be listed individually and in full detail.

The FDA Guidance for Industry suggests that, based on historical data, a statistical demonstration of a serious infection rate per person-year less than 1.0 is adequate to provide substantial evidence of efficacy. Therefore, 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 1-sided 99% confidence limit is less than 1.0.

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The rate of other infections will also be calculated per person-year and presented with the appropriate 95% CI.
The duration of infection will be summarized by standard descriptive statistics by type of infection and by severity. The individual characteristics of each infection, including the time to resolution will be listed.
The use of antibiotics will be reported as a detailed list of all such medications, and the number of patients treated with antibiotics, the number of treatment episodes and the number of treatment days will be tabulated.
All absences from work or school will be listed with duration and reason; the individual absence rates will be summarized descriptively.
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.
All hospitalizations due to infections during the course of the study will be listed with duration and reason; the numbers of patients hospitalized, the number of hospitalizations and the number of days in hospital will be tabulated and summarized descriptively.
The QoL data will be presented descriptively by visit, along with the change from baseline (defined as the first infusion).

PK analysis plan:

The PK analysis will be done by use of non-compartmental methods using actual elapsed time from the start of the infusion and based on the assumption that steady-state conditions are observed at the time of PK assessments. The PK results for IVIG treatment will be compared with the PK results for SCIG treatment.
The following PK parameters will be analyzed descriptively for all IgG (total and subtypes) and antigen specific antibody assays:

- 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 [$T_{½}$]
- Specification of the data points used for determination of λz and, by extension, $T_{½}$
- Area under the concentration-time curve from time 0 [start of the infusion] to the time point of the last non-zero concentration [$AUC_{0\text{-last}}$]
- 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

Individual PK profiles will be presented graphically in Trellis plots (i.e. several plots with the same pairs of variables on 1 page) using a linear scale as well as a logarithmic scale for the plasma concentrations.
Trough levels of all monitored IgG and antigen specific parameters will be summarized by infusion number and presented graphically as time profiles. In addition, the frequency of total IgG trough levels below 5.0 g/L will be presented for each infusion.

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The corrected DSF will be derived from the observed $AUC\tau_{IV}$ and $AUC\tau_{SC}$ and the actual doses administered intravenously (at PK_{IV}) and subcutaneously (at PK_{SC1}) respectively, based on a linear least-square regression between $AUC\tau_{SC}$ and $Dose_{SC}$.

In addition, an easy-to-use dose adjustment tabulation will be derived to provide the investigators with guidance on dose adjustments based on the actual- and target trough levels and the body weight of each individual patient.

Safety analysis plan:

The safety analysis will comprise descriptive statistics, tabulations and listings of all TEAEs, safety laboratory results, viral markers, vital signs and physical examination findings.

All reported AEs will be coded according to MedDRA.

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

AEs that occur between informed consent and the start of the first infusion of *octanorm* will also be documented and will be 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 SARs are defined as all AEs that are either 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 reported events will be listed and tabulated in full detail, in particular the following key figures will be presented for each age group and for the study as a whole:

- 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).

Narratives will be prepared describing each death, other SAEs, and other significant AEs that are judged to be of special interest because of clinical importance.

Interim analysis:

Upon completion of the second PK assessments (PK_{SC1}), the conversion factor will be determined. This factor will then be used to calculate the initial dosing for any patient newly enrolled. Beside this use of the conversion factor for the dose calculation, this interim assessment will have no impact on the study proceedings and will not result in any change of the sample size or study design.

FLOW CHART OF STUDY EVENTS *(for PK Substudy see Figure 1)*

Assessments: Patients not participating in the PK study	**Screening**	***octanorm 16.5 %* Infusions**																			**Termination**
		Wash-in/Wash-out Phase						*Efficacy Phase*													
Site visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Week	-	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**28A**	**32**	**36**	**40**	**44**	**48**	**52**	**52A**	**56**	**60**	65
Informed consent In-/exclusion criteria Demog.; MedHx & pre-treatments; Chest x-ray[1]	☒																					
Body weight	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒	☒		☒	☒	☒	☒	☒	☒		☒	☒	
Physical examination	☒	☒			☒			☒			☒				☒			☒				☒
Vital signs	☒	☒			☒			☒			☒				☒			☒				☒
IgG trough levels	☒	☒[6]	☒[6]	☒[6]	☒[6]	☒[6]	☒[6]	☒[6]	☒[6]	☒[6]	☒[6]		☒[6]	☒[6]	☒[6]	☒[6]	☒[6]	☒[6]		☒[6]	☒[6]	☒
Hematology (CBC, WBC differential, haematokrit, hemoglobin)	☒	☒[6]			☒[6]			☒[6]			☒[6]				☒[6]			☒[6]				☒
Clinical Chemistry (sodium, potassium, glucose, ALAT, ASAT, LDH, total bilirubin, blood urea nitrogen or blood urea, creatinine)	☒	☒[6]			☒[6]			☒[6]			☒[6]				☒[6]			☒[6]				☒
Direct Coomb´s test[3];	☒	☒[6,7]			☒[6,7]						☒[6]	☒						☒[6]	☒			☒
Safety lab[4]: reticulocyte count, haptoglobin, plasma-free hemoglobin, unconjugated bilirubin, blood smear	☒	☒			☒						☒	☒						☒	☒			☒
Urine analysis: pH, glucose, ketones, leukocytes, hemoglobin and hemosiderin	☒	☒[6]			☒[6]			☒[6]			☒[6]				☒[6]			☒[6]				☒
Viral markers[5]: HBsAG, HIV-1/2; NAT: HBV, HCV, HIV, parvovirus B19, HAV	☒										☒											☒
Urine pregnancy test[2]	☒							☒			☒				☒			☒				☒
Infusion of IMP (on site) [8]		☒[8]	☒	☒[8]	☒	☒	☒	☒[8]	☒	☒	☒[8]		☒	☒	☒[8]	☒	☒	☒[8]		☒	☒	
Local injection site reaction		☒	☒	☒	☒	☒	☒	☒	☒	☒	☒		☒	☒	☒	☒	☒	☒		☒	☒	
Patient diary check						☒	☒	☒	☒	☒	☒		☒	☒	☒	☒	☒	☒		☒	☒	☒
QoL questionnaire		☒									☒											☒
Concomitant medication		←																			→	☒
Adverse events	☒	←																			→	☒

[1] Only if last available chest X-ray is older than 12 months [2] In females with childbearing potential [3] If positive, the antibodies responsible for the direct Coombs' test will be eluted to investigate their specificity [anti-A, anti-B or anti-D]; [4] Sample assessed if Coombs' test was positive [5] Additional retention samples will be drawn and shipped to central laboratory only at Screening and Termination visit [6] Pre-Infusion [7] Post-infusion

[8] Measurements of the vital signs will be carried out before, at least once during, and within 1 hour after the infusion of IMP.

PROTOCOL SIGNATURES

Signature of the Sponsor's Representative

This study is intended to be conducted in compliance with the protocol, Good Clinical Practice and the applicable regulatory requirements.

[redacted]

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Signature of the Principal Coordinating Investigator

This study is intended to be conducted in compliance with the protocol,
Good Clinical Practice and the applicable regulatory requirements.

[redacted]

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Description
ADR	Adverse Drug Reaction
AE	Adverse Event
ALAT	Alanine Aminotransferase
AUC	Area Under the Concentration-Time Curve
CHQ-PF50	Child Health Questionnaire-Parent Form
CI	Confidence Interval
C_{max}	Maximum Plasma Concentration
C_{min}	Minimum Plasma Concentration
CMV	Cytomegalovirus
CRO	Contract Research Organization
CSF	Cerebrospinal Fluid
DCF	Dosing Conversion Factor
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBV	Hepatitis B Virus
HCG	Human Chorionic Gonadotrophin
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intention-To-Treat
IV	Intravenous
IVIG	Intravenous Immunoglobulin
MedDRA	Medical Dictionary for Regulatory Activities
PI	Primary Immunodeficiency
PK	Pharmacokinetic
PP	Per Protocol
QoL	Quality of Life
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAR	Suspected Adverse Reaction
SBI	Serious Bacterial Infection(s)
SC	Subcutaneous
SCIG	Subcutaneous Immunoglobulin
TEAE	Treatment Emergent Adverse Event
TEE(s)	Thromboembolic Event(s)
T_{max}	Time to Maximum Plasma Concentration
T_{min}	Time to Minimum Plasma Concentration
WBC	White Blood Cell

1 INTRODUCTION

1.1 Background

The primary therapeutic use of γ-immunoglobulins (IgG) is to provide antibodies to prevent viral and bacterial diseases (replacement therapy) in patients with primary immunodeficiency (PI) syndromes who have significant defects of antibody formation (humoral immunity).

The PI syndromes are a heterogeneous group of disorders with an intrinsic defect of the tissues, cells, or proteins of the immune system resulting in immune deficiency. Many of these disorders are characterized by hypogammaglobulinaemia with or without defective antibody production. Children and adults with PI have an increased risk of recurrent bacterial and viral infections that typically attack the respiratory tract (sinusitis, bronchitis, pneumonia) but can also affect the gastrointestinal tract (gastroenteritis). They can be severe and can lead to substantial morbidity. Responses to antibacterial therapy are often poor. At present, most PIs are not curable, but immunoglobulins have shown to decrease the total number of severe infections and the duration of hospitalization.

In the earlier years (around 1950), the IgG preparations were administered intramuscularly. This route of administration causes substantial discomfort, and restricts the amount of IgG that can be given to the patients. During the last 20 years, several IgG preparations have been developed for intravenous (IV) and subcutaneous (SC) administration, and their use has further contributed to the successful treatment of patients with PI disorders.

The administration via the SC route offers some advantages over IV infusion from a patient's and a physician's perspective and therefore become an alternative treatment option to the IV treatment. After the introduction of small, portable syringe drivers, this route of administration has gained even more popularity in Europe and the US as a practical, effective and safe treatment, because home therapy can also be recommended with this kind of administration.

There are two major differences in the pharmacokinetic (PK) characteristics of intravenously administered immunoglobulins (IVIG) and subcutaneously administered immunoglobulins (SCIG): delayed absorption and reduced bioavailability.

Following IV administration, the plasma concentration peaks immediately upon termination of the infusion, frequently reaching concentrations more than twice as high as the trough level. After SC administration, the absorption of IgG into the subcutaneous tissue is slower; the IgG must be delivered into the blood stream by the lymphatic system. Thus, with SCIG, the intravascular IgG concentration increases gradually, peaking at 48–72 hours. Most other features of SCIG treatment are consequences of these fundamental differences.[1]

Studies of the PKs of SCIG have shown a lower bioavailability than IVIG. This decreased bioavailability may involve degradation in the tissues and/or local binding in the intercellular matrix. Because of this expectation, several studies were designed to directly determine the bioavailability of SCIG as compared to IVIG.[2]

On converting from IVIG to SCIG replacement therapy for PI, the equivalent monthly dose of IgG is usually determined in one of two ways:

- 1:1 dosing: The 3 to 4 weekly IVIG dose is split into 3 to 4 equal weekly SCIG infusions.
- Dosing based on the area under the curve (AUC). The SCIG dose is calculated from PK data to provide a monthly exposure to IgG equivalent to that with IVIG.

The former is common in Europe, while the latter is a requirement of the US Food and Drug Administration (FDA) for SCIG labeling studies.[3]

No differences have been reported in the half-life of SCIG and IVIG. With modern IgG preparations, half-lives have generally been reported to be about 30–35 days. Thus, there is no clinically significant difference in the half-life of IgG between the two administration routes.[1]

However, SCIGs are usually given weekly, compared with IVIG regimens in which a large dose is given every 3rd or 4th week. The use of smaller doses at more frequent intervals results in stable, higher trough IgG serum concentrations which remain constant between consecutive SCIG infusions.[4]

In 3 recent studies comparing IVIG and SCIG in PI patients, the mean peak serum IgG level immediately after IV infusions was 2303 mg/dL.[5-7] In contrast, the mean peak with SCIG was 1410 mg/dL and the time for the peak IgG concentration (T_{max}) was 62.6 h (2.6 days).[8]

With weekly SCIG administrations, only about 4.5 days elapse between the T_{max} of one dose and the administration of the next dose. Given the half-life of 30 days this means that the IgG plasma concentration has dropped by only about 10 to 20% before the serum level starts to rise again. In contrast, with IVIG dosing intervals of 3–4 weeks (about one half-life), the drop in plasma concentration will be about 40 to 50% by the time the next dose is due. These differences in the dosing intervals used in most SCIG vs. IVIG regimens result in more stable serum IgG levels with SCIG.[1,8]

Pooled data from 7 studies in which equivalent monthly SC IgG doses were given weekly vs. IVIG every 21–28 days showed that trough serum IgG levels were 10 to 20% higher with weekly SC doses than with the same total monthly IVIG dose. After 6 to 12 weekly infusions, near-steady-state IgG levels were achieved with differences between minimum and peak concentrations of only 5 to 10% of the overall mean.[1,8]

No clinical data are available that would allow comparison of the long-term efficacy of SCIG versus IVIG administration on the development of bronchiectasis or other changes on lung scans, nor on deterioration of pulmonary function in patients who have PI. Similarly, no data are available comparing the efficacy of SC versus IVIG on the persistence or progression of chronic sinus disease in PI patients with that problem, or on other complications of PI.[9]

Orange et al (2012) reviewed the clinical efficacy of SCIG and identified 13 clinical studies in a total of 482 patients representing more than 27,500 infusions. The rate of serious bacterial infections (SBI) was the most common primary efficacy endpoint in these studies. Secondary endpoints included overall infections (i.e. infections not meeting SBI criteria), missed days at work or school, days in hospital and days on antibiotics. Definitions of overall infections and SBI were not standardized across studies. In 6 studies, SBI were defined by FDA criteria and included bacterial pneumonia, meningitis, sepsis, osteomyelitis or visceral abscess. In 2 studies, a SBI was defined as an infection requiring hospitalization.[3]

The rate of SBI was reported in 11 studies and varied from 0 to 0.09 events per patient and year. Infections were reported in 11 studies and varied from 2 to 5.18 patient and year. These figures are overall at least as good as those reported for IVIG studies.

To provide adequate protection from infection, a serum IgG concentration of >5 g/L following IgG therapy has been recommended. Several retrospective studies and one prospective study, however, have shown that higher serum IgG concentrations, resulting from higher doses of IVIG, are associated with a decreased incidence of infections.[3]

A recent meta-analysis in 16 individual studies of IVIG focused on the diagnosis of pneumonia, the most comparable endpoint, and demonstrated a statistically significant inverse correlation between higher IgG dose and a lower incidence of pneumonia, with a 27% decrease in incidence of pneumonia for every 100 mg/kg increase in dose.[10]

Despite its well-established safety profile, IVIG often leads to undesired symptoms, ranging from mild systemic adverse reactions, such as flushing, fever, muscle aches, tiredness, headache and dizziness, to severe reactions, manifesting as chest pain, tachycardia, and changes in blood pressure, aseptic meningitis, thrombosis or renal failure.[4]

The slower rate of rise towards the peak and the truncation of its height are believed to be responsible for the much lower incidence of systemic adverse events (AEs) with SCIG. This is consistent with observations that many AEs of IVIG infusions are rate-related, and has been repeatedly confirmed.[9]

On the other hand local reactions at SC injection sites are common. These reactions are rarely severe, and are accepted by most patients. In the meta-analysis by Orange et al. the reporting rate varied from 0.028 to 0.697 per infusion demonstrating that the majority of patients tolerate SCIG well.[3]

octanorm, the investigational product (IMP) in this study, is an immunoglobulin preparation from human normal plasma and is manufactured by Octapharma. It contains 16.5% (165 mg/mL) protein. The product is aimed for SC infusion by pump or syringe.

Further information on the IMP can be found in the Investigator's Brochure.

1.2 Rationale for Conducting the Study

The administration of immunoglobulins via the SC route offers several advantages over IV infusion from a patient's and a physician's perspective. Replacement therapy by rapid SC infusion with a pump was introduced during the late 1980s. Several reports have shown that the SC method is feasible, safe, efficient, cost-effective and highly appreciated by the patients.[11-19]

Self-administration at home with small portable pumps or syringes can easily be learned by the patients, which is another advantage of SC administered immunoglobulins (SCIG). It may remarkably improve the patient's quality of life and compliance as it reduces the frequency of hospitalizations and the need for home care. Administration of IgG via the SC route provides more stable and well-balanced IgG plasma levels until the end of the treatment interval, in contrast with the peak IgG plasma concentrations attained with IVIG solutions which weaken at the end of dose. When effective IVIG therapy cannot be continued because of the lack of peripheral and central vein access, SCIG might also be an alternative treatment option.

Experience has shown that replacement therapy with immunoglobulins is life saving. If replacement is started early, and if appropriate amounts are given with sufficient frequency, the cycle of recurrent infections and progressive lung damage can be arrested. Near to normal serum IgG levels can be easily maintained.

Post-dose peak levels of SCIG are reached usually 3–6 days after infusion. It has been shown that after infusion, exogenous IgG is distributed relatively rapidly between plasma and extravascular fluid until approximately half is partitioned in the extravascular space. Therefore, a rapid initial drop in serum IgG is to be expected. Several factors such as the endogenous production, the actual catabolism rate, the underlying disease or inter-patient variability help to explain the wide range observed for terminal half-lives. PK data are required for each new

product to ensure that it will not behave differently from existing preparations, in terms of appropriate dose and timing of the infusions.

The rationale for conducting the present clinical study is to investigate the PK characteristics, efficacy, and safety of *octanorm*, and to provide guidance on the dosing when switching patients from IV to SC treatment in patients suffering from PI.

1.3 Benefit-Risk Statement

Patients with PI need life-long treatment with immunoglobulins. Replacement therapy is expected to achieve protective trough levels of 5–6 g/L.

Standard measures are taken to prevent infections resulting from the use of medicinal products prepared from human blood or plasma. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot totally be excluded. The virus inactivation methods for *octanorm* are described in the Investigator's Brochure.

The safety profile of SCIG is well characterized. For *octanorm 16.5%*, the same type of adverse reactions may be expected. No new or unknown safety problems are expected to emerge for *octanorm 16.5%*, which are not already described in the Investigator's Brochure.

In terms of efficacy, it can reasonably be assumed that *octanorm* exhibits the same effectiveness as other SCIG brands.

2 STUDY OBJECTIVES

2.1 Primary Objective

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

The second primary objective is to evaluate the PKs of *octanorm* and to compare the AUC with that of IVIG.

2.2 Secondary Objective(s)

The secondary objectives of the study are:

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

3 INVESTIGATIONAL PLAN

3.1 Primary and Secondary Endpoints

3.1.1 Primary Endpoint

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

3.1.2 Secondary Endpoint(s)

Secondary **efficacy** endpoints are:

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

Secondary **pharmacokinetic** (PK) endpoints are:

- 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.
- Trough levels of serum total IgG (total and subclasses) throughout the study.
- 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.
- IVIG to *octanorm* DCF (based on the area under the concentration-time curve [AUCτ]).

Secondary **safety** endpoints are:

- Occurrence of all treatment emergent AEs (TEAEs) throughout the entire 65-week treatment period starting with the first infusion of IMP.
- Occurrence of temporally associated TEAEs.
- Proportion of infusions with at least 1 temporally associated AE.
- Occurrence of suspected adverse reactions (SARs).
- TEAEs by speed of infusion.
- Local injection site reactions.
- Vital signs (blood pressure, pulse, body temperature, respiratory rate).

- Laboratory parameters (hematology, clinical chemistry, markers for intravascular hemolysis, and tests for viral safety).

3.2 Overall Study Design and Plan

3.2.1 Study in General

The study is a prospective, open-label, non-controlled, single-arm, multicenter phase III study with a 12-week wash-in/wash-out period followed by a 12-month efficacy period. Patients participating in the PK substudy will undergo 3 PK assessments.

The study will be conducted at approximately 10–22 selected study sites in the United States and/or in Europe.

Only patients previously on IVIG may be enrolled. All patients have to undergo the 12-week wash-in/wash-out period.

Each patient will be treated with *octanorm* over a period of about 15 months (12-week 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* SC infusions. 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 about 70 weeks (depending on the IVIG treatment schedule before enrollment, and on whether the patient participates in the PK substudy or not).

At least 50 (and up to 78) patients who comply with the inclusion and exclusion criteria will be enrolled into the study. Study-related procedures will begin only after written informed consent has been obtained from the patient. For minor patients, written consent must be obtained from the parents or legal guardians. In addition, when required by the local regulatory authorities, Independent Ethics Committee (IEC) or Institutional Review Board (IRB), written assent must be obtained from children and adolescents based upon the age requirements established by those institutions.

Numbers of patients to be enrolled per age group will be as follows (age at time of informed consent):

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

An Independent Data Monitoring Committee will periodically review relevant data with emphasis on thromboembolic events (TEEs) and clinically significant hemolysis.

3.2.2 Pharmacokinetic Substudy

In the PK substudy (group A), the aim is to achieve at least 20 evaluable patients with complete PK profiles, grouped by age as follows:

- ≥2 to <6 years of age: at least 2 patients.
- ≥6 to <12 years of age: at least 6 patients.
- ≥12 to <17 years of age: at least 4 patients.

- ≥17 to ≤75 years of age: at least 6 patients.

To achieve this, at least 20 patients but not more than 40 patients will be enrolled in the PK substudy; additional patients might be asked to participate in the PK substudy if more than one patient in an age group are not evaluable for whatever reason.

All patients must be on regular IVIG treatment before entering the study. The dosage regimen of IVIG treatment must have been constant for at least 6 infusions with a minimum of 2 months on the same product prior to entering the study (dose between 200 and 800 mg/kg body weight, ±20% of the mean dose for the last 6 infusions). IgG trough levels must be documented for 2 previous infusions to demonstrate that treatment is at steady-state, and must be ≥5.0 g/L. If, during the study, the body weight changes by > 5%, the dose is to be adjusted to keep the dose constant on a milligram per kilogram body weight basis.

The Screening Visit must be performed before the last pre-study IVIG IV infusion. Screening results must be known before the first IMP administration.

The **first PK evaluation ("PK_{IV}")** (see *Figure 1*) will take place before and after the last administration of IVIG, according to the patient's regular treatment schedule. Blood samples will be taken (in total 8 times) for the measurement of total IgG, IgG subclasses, and selected antigen-specific antibody levels, and the calculation of PK parameters at predefined intervals (see Section 6.1.2).

In the following 12-week wash-in/wash-out phase, weekly (±2 days) SC doses of *octanorm* will be given, at 1.5 times the previous IVIG dose adjusted for weekly dosing.

After training of the patient or his/her relative or caregiver at the study site (for at least 4 SC infusions), SCIG infusions may be (self-) administered at home. Every 4 weeks the infusion is to be given at the study site (latest after 6 weeks, exceptionally). Before starting home treatment, a patient diary will be provided to the patients for documenting the date, volume and speed of infusion, occurrence of infections, all AEs, local tissue reactions at injection sites, body temperature around 1 hour after the end of the infusion, missed days from work/school/kindergarten/day care, inpatient hospital stays, and any changes in concomitant therapies between visits.

For the study-related interventions taking place during the wash-in/wash-out phase, see Section 6.1.3 below.

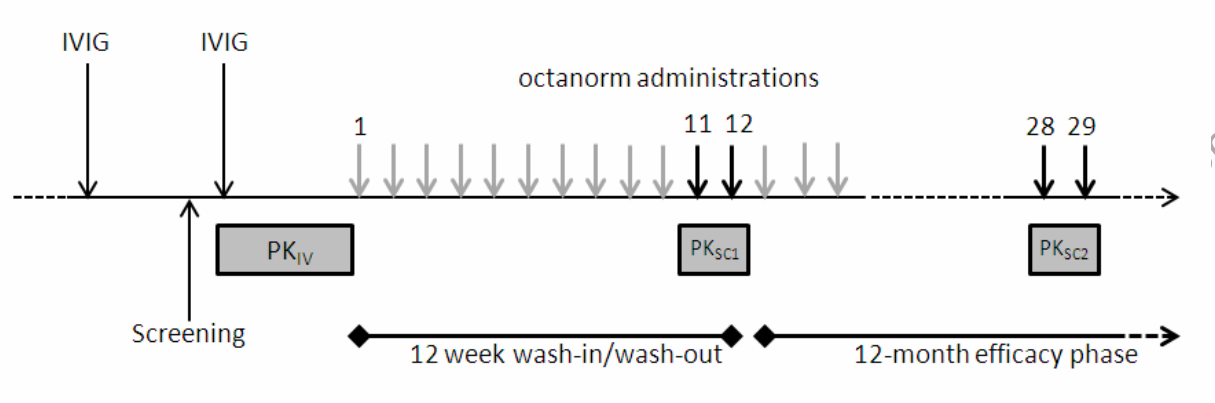
At the end of the wash-in/wash-out phase namely between Week 11 and Week 12, all patients participating in the PK substudy have to undergo the **second PK evaluation ("PK_{SC1}")** to determine the "corrected" DCF. Blood samples will be taken (in total 8 times) for the measurement of total IgG, IgG subclasses, and selected antigen-specific antibody levels, and calculation of PK parameters at predefined intervals.

The PK data will be subjected to an interim analysis (see Section 9.2.3 and 9.4). The "corrected" DCF will be derived from PK data by comparing the AUC under IVIG treatment with the AUC under *octanorm* treatment. The data for AUC IVIG will be taken from the first PK evaluation described above.

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.

Between Week 28 and Week 29, **the third PK evaluation ("PK_{SC2}")** will take place to determine the PK characteristics of *octanorm* under steady–state conditions and to verify whether the aim to achieve comparable bioavailability has been met. This will be evaluated by a *two one-sided test* (TOST) analysis of the mean AUC_T ratio associated with the applied *octanorm 16.5%* dose versus the IVIG doses.

Figure 1 PK Substudy



3.2.3 Efficacy Phase

The efficacy phase of the trial starts after completion of the 12-week wash-in/wash-out phase and will comprise the following groups of patients (see *Figure 2*):

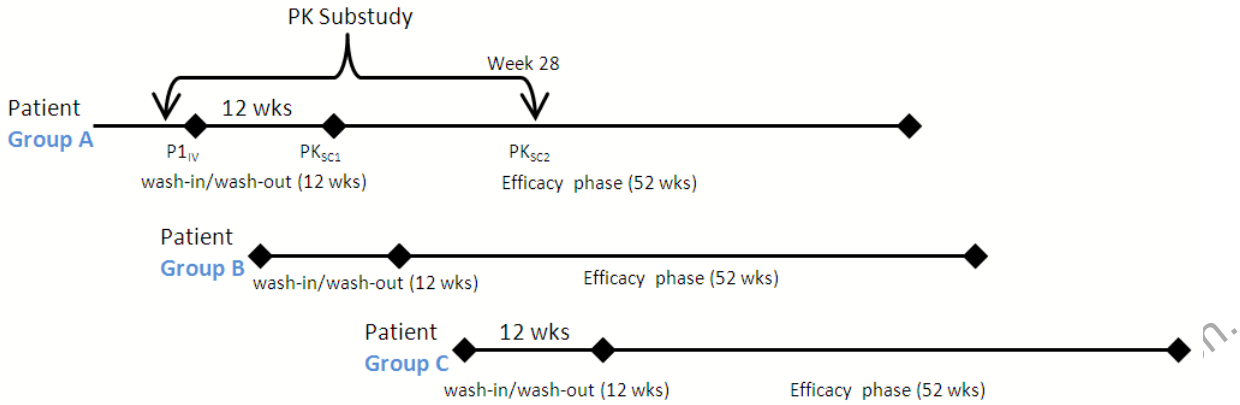
Group A. At least 20 but not more than 40 patients who underwent the PK substudy (PK_{IV} and PK_{SC1}). Once the corrected DCF is known and if the corrected DCF is >1.5, the further *octanorm* doses should be calculated with the corrected DCF. See also dosing recommendations in Section 5.4. Patients will be treated and observed for a period of 12 months.

Group B. Patients of any age group* who do not participate in the PK substudy but who are enrolled in parallel to the ongoing PK substudy. All patients have to undergo a 12-week wash-in/wash-out phase. Patients will receive 1.5 times the previous IVIG dose adjusted for weekly dosing and will stay on this dose until the corrected DCF is known. If the corrected DCF is >1.5, the further *octanorm* doses should be calculated with the corrected DCF. See also dosing recommendations in Section 5.4. Patients will be treated and observed for a period of 12 months.

Group C. Patients of any age group* who did not participate in the PK substudy and who are enrolled *after* the corrected DCF is known. All patients have to undergo a 12-week wash-in/wash-out phase. Patients will receive a SC dose adjusted by the corrected DCF. See also dosing recommendations in Section 5.4. Patients will be treated and observed for a period of 12 months.

* Enrolled in a centrally administrated fashion to ensure the overall distribution of patients in the 4 age groups as defined in Section 3.2.1.

Figure 2 Efficacy Phase – Groups of Patients



For patients of Groups B and C, screening must be performed between the last pre-study IVIG infusion and the first infusion of *octanorm*, i.e. at the time when the patients' next treatment with IVIG would be due. All results necessary to check the patients' eligibility must be available before the first IMP administration.

Patients who will not participate in the PK substudy have to be trained at the study site (for at least 4 infusions). Thereafter, the patient or his/her relative or caregiver may continue with *octanorm* infusions at home. Every 4 weeks the infusion is to be given at the study site. A 6-week interval may be acceptable exceptionally (e.g. in case of vacation). Before starting home treatment, a diary will be provided to the patients for documenting the date, volume and speed of infusion, occurrence of infections, AEs and local tissue reactions at injection sites, body temperature around 1 hour after the end of the infusion, missed days from work/school/kindergarten/day care, inpatient hospital stays, and any changes in concomitant therapies between visits.

At the visits taking place at the study site, the following interventions and activities will be performed at pre-defined time points (see Section 6.1.3): Drawing of blood samples, determination of body weight, review of the patient diary, physical examination including vital sign assessments, QoL assessments, assessments of local injection site reactions, urine sampling, and urine pregnancy tests.

AEs and any changes in concomitant medications will be recorded throughout the study period.

3.3 Discussion of Study Design and Choice of Control Group(s)

3.3.1 Study Design

The inclusion and exclusion criteria chosen are considered adequate to ensure that the study population will be representative of patients suffering from PI.

The study design takes into account FDA's comments and requests included in the clinical hold letter (dated April 27, 2012) for IND 15019 for another SCIG of Octapharma (*gammanorm 16.5%*).

The study design is also in line with similar study protocols conducted with other SCIG brands.[18,20]

3.3.2 Dosing

On converting from IVIG to SCIG replacement therapy for PI, the equivalent monthly dose of IgG is usually determined in one of two ways:

- 1:1 dosing, wherein the monthly IVIG dose is split into four equal weekly SCIG infusions;
- AUC dosing, in which the SCIG dose is calculated from PK data to provide a monthly exposure to IgG equivalent to that with IVIG.

The former is common in Europe, while the latter is a requirement of the US FDA for SCIG labeling studies. For AUC dosing, the SCIG dose has been 1.3 or 1.5 times higher than the previous IVIG dose.[3,18,21]

Therefore, the proposed study design with respect to dosing is acceptable, having in mind that a corrected DCF will be applied once available. During the wash-in/wash-out phase, appropriate dose levels will be maintained by regular monitoring of IgG trough levels.

3.3.3 Control Group(s)

Introduction of a placebo group would not be justified for ethical reasons. An active control group is not considered relevant, as the efficacy of treatment with SCIG has been demonstrated for this indication.

3.3.4 Target Parameters

The outcome measures in this study are consistent with previous studies of other IVIG or SCIG products and are also in compliance with the FDA Guidance for Industry.[22]

The QoL questionnaires are standardized, validated instruments that have been widely used in clinical studies, including PI.

3.3.5 Statistical Considerations

The FDA Guidance for Industry suggests that, based on historical data, a statistical demonstration of a serious infection rate per person-year less than 1.0 is adequate to provide substantial evidence of efficacy.[22] Therefore, 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 1-sided 99% CI is less than 1.0.

Because a single patient may experience more than one SBI, the calculation of this confidence interval will take into account such intra-patient correlation, following a compound Poisson process model.

The PK substudy will provide at least 20 pairs of PK profiles; this gives adequate statistical power for a comparison of the total IgG bioavailability (expressed as AUCτ) associated with the two administration methods (SC and IV), under reasonable conservative assumptions with respect to the intra-subject variability and the correlation between $AUC\tau_{SC}$ and $AUC\tau_{IV}$.

The calculation of the corrected dose conversion factor will be based on at least the same number of pairs of AUC values; in addition the PK interim analysis will include a full set of descriptive statistics and graphical representations to facilitate in depth review of individual deviations from the overall relation between $AUC\tau_{SC1}$ and $AUC\tau_{IV}$. The trough levels associated with these pairs of AUC values will be used to develop dose adjustment recommendations based on trough levels rather than the AUC itself; this derivation will be based on the assumption that the relation between dose per kg body weight and steady-state

trough levels, as well as the relation between steady-state trough level and AUCτ, can be modeled by linear regression.

4 STUDY POPULATION

4.1 Population Base

At least 50 male or female patients suffering from PI will be eligible for inclusion to this clinical study.

4.1.1 Inclusion Criteria

Patients who meet all of the following criteria may be enrolled:

1. Age of ≥2 years and ≤75 years.
2. Confirmed diagnosis of PI as defined by ESID and PAGID and requiring immunoglobulin replacement therapy due to hypogammaglobulinaemia or agammaglobulinaemia. The exact type of PI should be recorded.
3. Patients with at least 6 infusions on regular treatment with any IVIG, thereof a minimum of the last 2 months on the same product prior to entering the study. Constant IVIG dose between 200 and 800 mg/kg body weight (±20% of the mean dose for the last 6 infusions).
4. Availability of the IgG trough levels of 2 previous IVIG infusions before enrolment, and maintenance of ≥5.0 g/L in the trough levels of these 2 previous infusions.
5. Negative result on a pregnancy test (HCG-based assay in urine) for women of childbearing potential and use of a reliable method of contraception for the duration of the study.
6. For adult patients: freely given written informed consent. For minor patients: freely given written informed consent from parents/legal guardians and written informed assent from the child/adolescent in accordance with the applicable regulatory requirements.
7. Willingness to comply with all aspects of the protocol, including blood sampling, for the duration of the study.

4.1.2 Exclusion Criteria

Patients who meet one (or more) of the following criteria are excluded from the study:

1. Acute infection requiring intravenous antibiotic treatment within 2 weeks prior to and during the screening period.
2. Known history of adverse reactions to IgA in other products.
3. Patients with body mass index >40 kg/m^2.
4. Exposure to blood or any blood product or plasma derivatives, other than IVIG treatment of PID, within the past 3 months prior to first infusion of *octanorm.*
5. Ongoing history of hypersensitivity or persistent reactions to blood or plasma derived products, or any component of the investigational product (such as Polysorbate 80).
6. Requirement of any routine premedication for IgG administration.
7. History of malignancies of lymphoid cells and immunodeficiency with lymphoma.
8. Severe liver function impairment (ALAT 3 times above upper limit of normal).

9. Known protein-losing enteropathies or proteinuria.
10. Presence of renal function impairment (creatinine >120 µM/L or creatinine >1.35 mg/dL), or predisposition for acute renal failure (e.g., any degree of pre-existing renal insufficiency or routine treatment with known nephritic drugs).
11. Treatment with oral or parenteral steroids for ≥30 days or when given intermittently or as bolus at daily doses ≥0.15 mg/kg.
12. Treatment with immunosuppressive or immunomodulatory drugs.
13. Live viral vaccination (such as measles, rubella, mumps and varicella) within the last 2 months prior to first infusion of *octanorm.*
14. Treatment with any investigational medicinal product within 3 months prior to first infusion of *octanorm.*
15. Presence of any condition, that is likely to interfere with the evaluation of study medication or satisfactory conduct of the trial.
16. Known or suspected to abuse alcohol, drugs, psychotropic agents or other chemicals within the past 12 months prior to first infusion of *octanorm.*
17. Known or suspected HIV, HCV, or HBV infection.
18. Pregnant or nursing women.
19. Planned pregnancy during course of the study.

4.2 Prior and Concomitant Therapy

Details of any prior and concomitant medication must be recorded in the electronic case report form (eCRF).

4.2.1 Permitted Concomitant Therapy

Routine premedication to alleviate potential tolerability problems is not allowed during the study. However, patients who experience 2 consecutive TEAEs that are likely to be prevented by premedication are permitted to receive antipyretics, antihistamines, or antiemetic drugs. Non-steroidal anti-inflammatory drugs can affect renal function and should be avoided. Local anesthetics to reduce pain associated with needle insertion are allowed. The use of such medication(s) must be recorded.

Any prior and concomitant therapy (medication and non-drug therapy, such as physiotherapy) taken within 30 days prior to screening, throughout the study and for 1 week after the end of the last infusion, will be documented in the eCRF

4.2.2 Forbidden Concomitant Therapy

Treatment with any IMP within 3 months prior to first infusion of *octanorm* is forbidden.

Exposure to blood or any blood product or derivative, other than IVIG used for regular PID treatment, within the past 3 months prior to the first infusion of *octanorm* is forbidden. Administration of any blood or plasma derived product is forbidden during the study and should only be given for emergency reasons. Patients will be withdrawn from the study if IgG preparations other than *octanorm* are administered.

Premedication for the study SCIG infusions shall not be given, with the exception of permitted therapy as stated above (for patients with 2 consecutive TEAEs). Corticosteroids shall not be given as a pre-treatment to alleviate potential tolerability problems.

Treatment with oral or parenteral steroids for ≥30 days or when given intermittently or as bolus, at daily doses ≥0.15 mg/kg of prednisone or equivalent is forbidden.

Immunosuppressive and immunomodulatory drugs are also forbidden.

Live viral vaccines are forbidden in the 2 months prior to first infusion of *octanorm*.

octanorm must not be mixed with other medicinal products.

4.3 Withdrawal and Replacement of Patients

4.3.1 Premature Patient Withdrawal

Patients have the right to withdraw from the study at any time for any reason, without the need to justify. The responsible Investigator also has the right to withdraw patients from the study in case of AEs, protocol violations, or administrative reasons. An excessive rate of withdrawals can render the study un-interpretable. Therefore, unnecessary withdrawal of patients should be avoided.

Reasons for premature patient withdrawal can be the following:

- Patient's decision: Should a patient decide to withdraw, the Investigator will make the best efforts to complete and report all information available at time of withdrawal. The Investigator will document the reason(s) for withdrawal of each patient in the eCRF.
- Withdrawal for safety reason: If the reason for removal of a patient from the study is an AE or an abnormal laboratory test result, this specific event or test will also be recorded. If a patient is withdrawn from the study because of an AE, the Investigator will make thorough efforts to clearly document the outcome.
- Administration of other immunoglobulin preparation: If for any reason a patient's therapy is changed to another IVIG or SCIG preparation within this study, the patient will be withdrawn from the study.
- Pregnancy: Pregnant patients may not be included in the study. A pregnancy test is mandatory at the Screening Visit and at Weeks 16, 28, 40, and 52 (and at the Termination Visit). All female patients of childbearing potential are responsible for using effective contraception during their study participation. If a pregnancy occurs, treatment with the IMP must be stopped immediately and Octapharma's Central Drug Safety Unit must be informed.

If a patient is withdrawn, the Investigator will organize a Termination Visit. At this visit, all investigations including laboratory tests should be performed to allow the patient to be included in both safety and efficacy evaluations. This Termination Visit is identical to the follow-up visit of the last IgG administration.

4.3.2 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.

4.4 Assignment of Patients to Treatment Groups

The patients will be recruited into 4 age strata: ≥2 years to <6 years, ≥6 years to <12 years, ≥12 years and <17 years, and ≥17 and ≤75 years.

Enrolment in each age group will stop when the maximum number allowed for that age group has been achieved. Recruitment will be monitored centrally to ensure that the minimum enrolment targets are met in each age group. The patient numbers will be allocated sequentially in the order in which the patients are enrolled. The fact that a patient has been enrolled will be reported immediately and automatically by the electronic data capture system to the Investigator, the contract research organization (CRO) and the Sponsor.

All patients enrolled in this study will be treated with *octanorm*.

Each patient will be identified by the previously assigned patient number throughout the trial; no additional patient or randomization number will be used.

Under no circumstances are patients who participate in the study permitted to re-enroll for a second time.

4.5 Relevant Protocol Violations

In the case of any major protocol violation, the Investigator and Octapharma will decide on the further participation of the patient in this study, after having discussed all relevant aspects.

A list of all included patients with all violations from the intended study procedures and other criteria that may affect the validity of patient data for statistical analysis will be prepared after the clinical phase of the study is completed. The list will be discussed by a panel consisting of the clinical study manager, a medical expert of the Sponsor, the data manager and the study statistician. This panel will decide upon the inclusion of each patient in the analysis populations.

4.6 Subsequent Therapy

In case a patient decides to withdraw from the study or is withdrawn by the Investigator, he/she may be switched back to the treatment he/she has received before study participation or to another commercially available IVIG or SCIG.

5 INVESTIGATIONAL MEDICINAL PRODUCT(S)

5.1 Characterization of Investigational Product(s)

Name of Medicinal Product: *octanorm*

Active ingredient of *octanorm*: Human normal immunoglobulin

Table 1 Biochemical Characteristics of octanorm 16.5%

Parameter	
Total protein (of which * ≥96% is human IgG)	150 – 180 mg per mL
Maltose	70 – 90 mg per mL
Octoxynol	≤5 µg per mL
TNBP	≤1 µg per mL
IgA	≤0.6 mg per mL
Polysorbate 80	10 – 60 µg per mL
pH	5.0 – 5.8
Osmolality	310 – 380 mosmol/kg
Polymers + Aggregates	≤5% of the total chromatogram area
Monomers + Dimers	≥90% of the total chromatogram area
Fragments	≤5% of the total chromatogram area
Sodium	≤30 mMol/L

* ≥96% applicable for the USA and Canada; ≥95% applicable for Europe

Each batch (lot) of *octanorm* is prepared from at least 3,500 donations of human fresh frozen plasma. Effective viral reduction is obtained via a combination of 3 validated manufacturing steps: cold-ethanol fractionation, solvent/detergent treatment with TNBP and Octoxynol, and pH 4 treatment. The manufacture of *octanorm* is based on the *Octagam* manufacturing process including an additional adsorption step onto commercially available and widely used chromatography column for the removal of coagulation factor XI. The process is identical up to the step of diafiltration. After this step the product solution is concentrated to a target concentration of 200 g/L. Polysorbate 80 and maltose are added during final formulation to final concentrations of 10-60 µg/mL and 70-90 mg/mL, respectively.

5.2 Packaging and Labeling

octanorm is delivered in glass vials.

Each *octanorm* vial will be labeled as follows:

US, Canada Master Label

Caution: New Drug - Limited by Federal (or United States) Law to Investigational Use
octanorm 16.5% Study: **SCGAM-01** Unit size: ____ **mL**
1 mL contains: 165 mg protein of which ≥96% is human normal immunoglobulin G.
Solution for subcutaneous injection.
To be stored at 36 °F to 46 °F, protected from light. Must not be frozen. Keep out of the reach and sight of children.
Must be inspected visually for particulate matter and discoloration prior to administration. Solutions that are cloudy or have a deposit must not be used.
To be warmed up to room or body temperature before use. After first opening, use immediately.
Patient No.: |___|___|___|___|
Dosage: Please refer to the handling instruction provided.
BB-IND number: 15617
Investigator: _____
Sponsor: OCTAPHARMA Pharmazeutika Prod.Ges.m.b.H.; Oberlaaerstr. 235, 1100 Vienna, Austria, Tel: [redacted]
Batch No.: _____ Expiry date: _____

Europe Master Label

FOR CLINICAL TRIAL USE ONLY Study: **SCGAM-01**
octanorm 16.5% Unit size: ____ **mL**
1 mL contains: 165 mg protein of which ≥95% is human normal immunoglobulin G.
Solution for subcutaneous injection.
To be stored at +2 °C to +8 °C**,** protected from light. Must not be frozen. Keep out of the reach and sight of children.
Must be inspected visually for particulate matter and discoloration prior to administration. Solutions that are cloudy or have a deposit must not be used.
To be warmed up to room or body temperature before use.
Dosage: Please refer to the handling instruction provided.
Patient No.: |___|___|___|___|
EudraCT number: 2013-003877-87
Sponsor: OCTAPHARMA Pharmazeutika Prod.Ges.m.b.H.; Oberlaaerstr. 235, 1100 Vienna, Austria, Tel: [redacted]
Investigator: _____
Batch No.: _____ Expiry date: _____

Final labeling will comply with the national requirements of each country where the study is to be conducted.

5.3 Conditions for Storage and Use

octanorm must be stored and transported light-protected at 2 °C to +8 °C (36 °F to 46 °F) and must not be frozen.

octanorm must not be used after its expiration date.

Authorized personnel at the individual study centers will ensure that the investigational product is stored in appropriate conditions in a secure refrigerator with restricted access.

5.4 Dose and Dosing Schedule

octanorm has to be administered subcutaneously every week (±2 days). Minimum time of 4 days must be kept in between two single subcutaneous infusions. If, during the study, the body weight changes by >5%, the dose is to be adjusted to keep the dose constant on a milligram per kilogram body weight basis.

For patients participating in the PK substudy, the *octanorm* dose during the wash-in/wash-out phase is to be calculated as follows:

$$\frac{\text{previous IVIG dose (in grams) times 1.5}}{\text{number of weeks between IVIG doses}}$$

After the analysis of PK data obtained at the end of the wash-in/wash-out phase ("PK_{SC1}"), the "corrected" DCF will be calculated. If the corrected DCF is >1.5, the *octanorm* dose should be revised in accordance with the corrected DCF for all patients (i.e. patients of Groups A, B, and C, see Section 3.2.3).

During the efficacy phase of the study, the patients' *octanorm* dose should be individualized by titrating upward based on the difference between each subject's measured serum total IgG trough levels while on *octanorm* and each subject's *target* serum total IgG trough level as determined below. This individualization of dosing should take precedence over applying the corrected DCF.

The calculation of the corrected DCF will be based on the AUCτ as the measure for bioavailability. However, because in clinical routine no PK profiles are determined, the actual dose adjustment for individual patients cannot be based on the AUC. To overcome this issue, an algorithm will be developed that allows adjusting individual dose regimens on basis of the total IgG trough levels rather than on AUC. This algorithm will be derived from at least 20 pairs of PK_{IV} and PK_{SC1} profiles available for the PK interim analysis, and will be based on the assumption of linear relationships between the dose per kg body weight and the steady-state trough levels, as well as between the steady-state trough level and AUCτ. Please refer to Section 9.2.3.2 and the SAP for further details on these derivations.

5.5 Preparation and Method of Administration

Vials of *octanorm* must be allowed to warm to room or body temperature prior to infusion. Thereafter, *octanorm* should be infused subcutaneously using a syringe driver for precise infusion rates and standard infusion materials provided to the patients by the site. The correct amount of IgG taken from 12 or 48 mL vials of *octanorm* will be infused with the aid of a syringe driver. The content of the vials will have to be transferred into the syringes suitable for the syringe driver selected. Remaining solution in a vial must be discharged.

octanorm must not be mixed with other medicinal products. An aseptic technique must be used throughout the procedure.

Each vial must be examined visually for particulate matter and discoloration prior to administration. The solution should be clear or slightly opalescent. Solutions that are cloudy or have a deposit must not be used.

The patient or his/her relative or caregiver will be instructed at the clinic/doctor’s office or at the infusion center in the use of the following:

- syringe driver,

- infusion techniques,
- keeping of a patient diary and
- measures to be taken in case of severe AEs.

After training of the patient or his/her relative or caregiver at the study site (for at least 4 SC administrations), SCIG infusions may be (self-)administered at home. Every 4 weeks the infusion is to be given at the study site (latest after 6 weeks exceptionally).

Patients must be monitored at the study site for at least one hour after the first dose of *octanorm*.

Infusion sites: The maximal number of infusion sites used simultaneously should not exceed 6. Infusion sites should be at least 2 inches (approx. 5 cm) apart. The actual sites of infusion should be changed with each weekly administration.

Volume:

- *Adults*: For the first administration, 15 mL per infusion site should not be exceeded. After the 6th administration, this may be gradually increased to 25 mL/site, if tolerated, to 35 mL/site after the 24th administration. Starting with the 40th administration and when the previous volumes were well tolerated, the volume can be increased to a maximum of 40 mL/site.
- *Children* (≥5 years of age): For the first administration, 10-15 mL per infusion site should not be exceeded. After the 6th administration, this may be gradually increased to 25 mL/site and, if tolerated, to a maximum of 30-35 mL/site after the 24th administration.
- *Small children* (<5 years of age): For the first administration, 10 mL per infusion site should not be exceeded. After the 6th administration, and, if tolerated, this may be gradually increased to a maximum of 10-15 mL/site. After the 24th administration, this may be gradually increased to 20 mL/site.

Infusion rate: For the first 6 administrations of *octanorm*, the maximum recommended flow rate is 15 mL per hour per site. For subsequent infusions, the flow rate may be gradually increased to a maximum of 25 mL per hour per site as tolerated. The maximum flow rate is, however, not to exceed a total of 30 mL per hour for all sites for the first 6 infusions and 50 mL per hour for all sites up to infusion no. 24 and, if tolerated, 80 mL per hour for all infusion sites thereafter.

For adult patients only: starting with the infusion no.40 (site visit no.15) the maximum flow rate can be (gradually) increased up to 100 mL per hour for all infusion sites - if the previous rates are well tolerated.

5.6 Blinding, Emergency Envelopes and Breaking the Study Blind

Not applicable for this open-label study.

5.7 Treatment Compliance

5.7.1 Drug Dispensing and Accountability

Sponsor or designee will deliver *octanorm* to the participating investigators. Investigator will keep current drug inventory and dispensing log, detailing the dates, batch (lot) numbers, and quantities of IMP dispensed to each patient.

The inventory will be available to the monitor to verify drug accountability during the study. The study monitor will review all empty and partially used vials of IMP and will cross-check versus the patient source documentation (records), eCRF, and drug dispensing log. After this check, empty or partially used vials should be destroyed at the study site following local policies. The destruction must be documented.

For their home treatment, sufficient amount of *octanorm* will be handed out to the patients. The Investigator or his designee has to document the date, quantities and batch (lot) number(s) of IMP handed out including the corresponding patient number. The patients will be advised to return used or expired vials to the study site at their on-site visits, and to return used and unused vials at the (early) Termination Visit.

5.7.2 Assessment of Treatment Compliance

Patients will receive infusions at the study site under the surveillance of authorized study personnel the first 4 weeks and then every 4 weeks. Infusion details will be documented together with the batch number(s) in the eCRF.

After training at the study site (for at least 4 infusions), the patient or his/her relative or caregiver will continue with SCIG infusions at home. Every 4th week the infusion will be given at the study site.

Throughout the study, patients will be asked to document on a diary the date, batch (lot) numbers, number of vials, speed of infusion, injection site(s), occurrence of infections, TEAEs and local tissue reactions at injection sites, missed days from work/school/kindergarten/day care, inpatient hospital stays, and any changes in concomitant therapy between visits. The diary will be reviewed during the patient's infusion visit at the study site.

6 STUDY CONDUCT

6.1 Observations by Visit

6.1.1 Screening Visit

The Screening Visit must be performed before the last pre-study IVIG IV infusion. Screening results must be known before the first IMP administration.

Study-related procedures will begin only after written informed consent has been obtained by the patient or their legal guardian. At the Screening Visit the following activities will be performed:

- Written informed consent.
- Check of inclusion and exclusion criteria.
- Documentation of demographic data.
- Documentation of medical history including all adverse conditions that have occurred during the last 60 days.
- Recording of all previous drug and non-drug therapies during the last 60 days.
- General physical examination, including body weight and vital signs.
- Chest X-ray (only if last available chest X-ray is older than 12 months).
- Drawing of blood samples for total IgG trough level.

- Drawing of blood samples for safety laboratory parameters including viral markers and Coombs' test.
- Urine sampling including urine pregnancy test (in females of childbearing potential only).

6.1.2 Pharmacokinetic Visits

Patients participating in the PK substudy will undergo 3 PK assessments: one together with the last IV infusion of IVIG (PK_{IV}), one at the end of the 12-week wash-in/wash-out phase (PK_{SC1}); and one after 28 weeks on *octanorm* SC treatment (PK_{SC2}, see *Figure 1*).

1st PK Evaluation (PK_{IV})

Blood samples will be taken at the following intervals before and after the IV infusion of IVIG:

1. one sample before the start of the IVIG IV infusion

   and then at the following intervals after the end of IV 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), and
8. 21 days (±3 days) for patients on 3-week infusion schedule or 28 days (±3 days) for patients on 4-week infusion schedule.

In case any of the PK blood draws are not done within these time windows, the sample should be obtained as soon as possible after the missed time-point in order to keep the total number of PK samples equal. The exact sampling time point must always be recorded.

2nd PK Evaluation (PK_{SC1})

The second PK evaluation should start together with the 11th *octanorm* SC infusion.

Blood samples will be taken at the following intervals before and after the SC infusion:

1. one sample before start of the *octanorm* SC infusion,
2. one sample approximately 10 minutes before the anticipated end of the SC infusion,

   and then at the following intervals after the end of the SC 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).

In case any of the PK blood draws are not done within these time windows, the sample should be obtained as soon as possible after the missed time-point in order to keep the total number of PK samples equal. The exact sampling time point must always be recorded.

3rd PK Evaluation (PK_{SC2})

The third PK evaluation should start together with the 28th *octanorm* SC infusion.

Blood samples will be taken at the following intervals before and after the SC infusion:

1. one sample before start of the *octanorm* SC infusion,
2. one sample 10 minutes before the anticipated end of the SC infusion,

   and then at the following intervals after the end of the SC 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).

In case any of the PK blood draws are not done within these time windows, the sample should be obtained as soon as possible after the missed time-point in order to keep the total number of PK samples equal. The exact sampling time point must always be recorded.

6.1.3 Treatment Visits

Each patient who stays in the study for the whole period will receive 64 *octanorm* SC weekly infusions. The first 4 infusions must be given at the study site. After having received training at the study site (i.e. earliest after at least 4 infusions), the patient or his/her relative or caregiver may continue with weekly *octanorm* SC infusions at home. However, every 4 weeks (latest after 6 weeks exceptionally) the infusion is to be given at the study site.

At each of these visits at the study site, the following activities will be performed *before* IMP administration:

- Drawing of blood samples for total IgG trough level (within 30 minutes before IMP administration).
- Determination of body weight.
- Assessment of local injection site reactions.
- Collection and review of the patient diary (only if visit is preceded by home treatment phase). The Investigator will evaluate the patient's diary and will ask the patient about the occurrence of any AEs and any changes in concomitant therapies (medication and non-drug therapy). Relevant data will be transcribed onto the eCRF. Discrepancies between patient diary entries and eCRF entries must be explained by the Investigator.

The following activities will be performed before IMP administration at Weeks 1, 4, 16, 28, 40, and 52:

- Physical examination including vital signs.
- Drawing of blood samples for safety laboratory parameters. Urine sampling.

The following activities will be performed at other time points:

- Drawing of blood sample for direct Coombs' test:
  - Week 1 and 4: before and after IMP infusion;
  - Week 28 and 52: before IMP infusion.
  - At the visit Week 28A and 52A (2–3 days after IMP infusion) blood sample for extended lab tests will be taken (blood smear and testing of the samples will be done only in case of confirmed positive direct Coombs' test together with drop in hemoglobin of ≥2g/dL)
- Blood sample for viral markers will be taken before the start of infusion given at the study site at Week 28 (±4 weeks).
- QoL assessments will take place before the first infusion, at Week 28, and at the (early) termination visit.
- A urine pregnancy test (females of childbearing potential only) will be at Weeks 16, 28, 40, and 52 (and at other times if indicated).

AEs and any changes in concomitant medications will be recorded throughout the study period.

6.1.4 Termination Visit

One week after the last infusion, or sooner if a patient withdraws prematurely from the study, a Termination Visit will be performed including the following assessments:

- Physical examination (including vital signs).
- Drawing of blood samples for total IgG trough level.
- Drawing of blood samples for safety laboratory parameters including viral markers and Coombs' test.
- Urine sampling including urine pregnancy test (in females of childbearing potential only).
- QoL assessments.
- Collection and review of the patient diary.
- Changes in concomitant medications.
- AE monitoring including assessment of local infusion site reactions.

After the final examination, the clinical study is considered completed for the patient. No further study-related assessments may be performed, unless safety concerns (e.g. ongoing AEs) require follow-up.

6.2 Duration of Study

6.2.1 Planned Duration for an Individual Patient

The total study duration per 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.

6.2.2 Planned Duration for the Study as a Whole

The study is planned to start enrolling in 2014. The study is planned to be completed by 2020. The investigators have to inform the monitors of any recruitment difficulties or delays in the anticipated completion date.

6.2.3 Premature Termination of the Study

Both the responsible Investigators and the Sponsor reserve the right to terminate the study at any time. Should this be necessary, the procedures will be arranged on an individual study basis after review and consultation by both parties. In terminating the study, 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.

Furthermore, the Investigator should promptly inform the IEC/IRB and provide a detailed written explanation. The pertinent regulatory authorities should be informed according to national regulations.

Early termination of the study as a whole or center-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 TEEs (i.e. ischemic stroke, transient ischemic attack, cerebral infarction, cerebrovascular accident, cerebral thrombosis, embolic infarctions, [acute] myocardial infarction, deep vein thrombosis, pulmonary embolism, venous thrombosis excluding thrombophlebitis) are observed fulfilling the following criteria:
        - assessed as probably or possibly related to *octanorm* treatment by Investigator and/or Sponsor;
        - confirmed by the Independent Data Monitoring Committee (IDMC).
    - If more than 2 cases of clinically significant hemolysis are observed (for definition see Section 7.3.1.1) fulfilling the following criteria:
        - assessed as probably or possibly related to *octanorm* treatment by Investigator and/or Sponsor;
        - 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 Center

- At any time the study can be terminated at an individual center if e.g.:
    - The center cannot comply with the requirements of the protocol.
    - The center cannot comply with applicable standards.
    - The center's first patient is not recruited by 10 weeks after initiation of the center.

- The required recruitment rate is not met.

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

7 ASSESSMENTS AND METHODS

7.1 Background / Baseline Information

The following general or background assessments will be performed during the study at predefined time points:

Demographic data: Sex, age, weight and height (calculated Body Mass Index), ethnic origin, ABO Rhesus blood type (to be obtained if unknown).

Medical history: All previous medical conditions and surgeries, the exact type of PI, all adverse conditions that have occurred during the last 60 days (with special emphasis on, but not restricted to, infections). Obtained by interviewing the patient.

Previous and ongoing therapies: All previous drug and non-drug therapies (e.g. physiotherapy) during the last 60 days. Obtained by interviewing the patient.

General physical examination, including vital signs. The physical examination will be performed according to study site's routine procedures and will be as comprehensive as necessary to detect relevant somatic or neurological diseases

Chest X-ray (posterior-anterior and lateral). Obtained only if last available chest X-ray is older than 12 months.

7.2 Efficacy Assessments

To study the effectiveness of *octanorm* in the prevention of infections, the following measurements will be recorded throughout the study:

- Number of episodes of SBI, per person-year on treatment, along with type and severity of infection, and time to resolution (primary endpoint).
- Number of episodes of any other infections (including acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, acute bronchitis, infectious diarrhea etc), along with type and severity of infection, and time to resolution.
- Number of days of use and annual rate of antibiotics (oral, parenteral, oral plus parenteral, prophylactic and therapeutic), along with type and dosage of antibiotic.
- Absence and number of days of absence from work/school/kindergarten/day care.
- Hospitalizations due to infections and number of days and annual rate of hospitalization, along with reason.
- Number of episodes of fever.
- QoL assessments.

For the collection of the above measurements, each patient will be provided with an individual diary to be filled in by the patient during the time in between 2 *octanorm* infusion visits at the site (approximately every 4 weeks). The patient's diary will be checked for accuracy of the data by the Investigator and collected at each visit. The data will be then transferred into the eCRF. A new diary will be handed out to the patient for the following period until the next infusion visit at the site.

For the purpose of this study the following events will be considered as SBI to be included in the primary efficacy analysis:

- Bacterial pneumonia.
- Bacteremia/sepsis.
- Osteomyelitis/septic arthritis.
- Visceral abscess.
- Bacterial meningitis.

The presence of any of these infections should be verified by the following specific differentiated diagnostic examinations [22]:

Table 2 Diagnostic Criteria for Serious Infection Types (cont.)

Infection: Bacteremia/sepsis [a] • *Symptoms:* chills, rigors. • *Physical findings:* fever, hypothermia, tachycardia, tachypnea, hypocarbia, hypotension (systolic blood pressure <90 mm Hg or a reduction of ≥40 mm Hg from baseline in the absence of other causes of hypotension), altered mental status, petechiae, purpura, oligouria, cutaneous vasodilation/vasoconstriction. • *Laboratory tests*: **positive blood culture [b]**, leukocytosis (white blood cell (WBC) count >12,000/mm^3), differential WBC count demonstrating >10% immature (band) neutrophils, leukopenia, thrombocytopenia, coagulopathy, lactic acidosis.
Infection: Bacterial Meningitis • *Symptoms*: headache, stiff neck, mental status changes, irritability, decreased feeding (infants), photophobia, nausea/vomiting, rigors, seizures. • *Physical findings*: Kernig's sign, Brudzinski's sign, meningococcal rash, fever of >38°C oral or >39°C rectal. • *Laboratory tests:* **positive cerebrospinal fluid (CSF) Gram stain and/or culture and/or positive CSF bacterial antigen assay,** positive blood culture [c], CSF leukocytosis with neutrophil predominance, decrease in CSF glucose.
Infection: Osteomyelitis/Septic Arthritis • *Symptoms*: pain, decreased range of motion, tenderness, edema, redness, warmth over the involved site (local inflammatory symptoms/signs may be lacking in adults). • *Physical findings*: evidence of soft tissue infection adjacent to the involved bone/joint, drainage from sinus tract from involved bone, fever of >38°C oral or >39°C rectal. • *Laboratory tests*: positive blood culture, positive probe to bone, positive bone aspirate culture, positive bone biopsy culture, positive bone histopathology, positive joint fluid Gram stain and culture. • *Imaging studies*: **positive X-ray, nuclear medicine bone scan, magnetic resonance imaging scan, or computed tomography scan showing bony destruction with radiolucent areas; for chronic osteomyelitis: sequestra, involucra.**

Note: Items in bold are considered essential diagnostic features.

[a] Two of the following should be present to make the diagnosis of sepsis in adults: temperature >38°C oral/ >39°C rectal or <36°C oral or <37°C rectal; heart rate >90 beats/min; respiratory rate >20 breaths/min, or $PaCO_2$ <32 mm Hg; WBC count >12,000/mm^3, <4,000/mm^3, or >10% immature (band) forms. For pediatric subjects, the definition of sepsis using age-specific criteria as recommended by the International Consensus Conference on Pediatric Sepsis should be employed.[23]

[b] Indwelling catheter- or vascular access device-related blood-borne infections are not included because evidence is lacking that these are preventable with IVIG replacement therapy. For subjects without indwelling catheters or vascular access devices, a single blood culture positive for a pathogenic organism will meet the diagnostic criteria for bacteremia. Subjects meeting criteria for positive blood culture but without 2 or more of the sepsis criteria listed above will be classified as having bacteremia.

[c] A blood culture positive for growth of *Streptococcus pneumoniae*, *Neisseria meningitides*, or *Haemophilus influenzae*, in combination with CSF leukocytosis and/or decrease in CSF glucose, can serve to confirm the diagnosis of acute bacterial meningitis.

Continued: Diagnostic Criteria for Serious Infection Types

Infection: Bacterial Pneumonia [d]

- *Symptoms*: productive cough/change in character of sputum, dyspnea or tachypnea, chills, chest pain, rigors, headache, fatigue, sweats, anorexia, myalgias.
- *Physical findings*: rales; pulmonary consolidation as reflected by: dullness on percussion, bronchial breath sounds, egophony; fever >38°C oral or >39°C rectal, or <36°C, hypothermia (temperature <36°C oral or <37°C rectal).
- *Laboratory tests*: leukocytosis, differential WBC count of >10% band neutrophils, leukopenia, hypoxemia (PaO_2 <60 mm Hg on room air), positive blood culture, Gram stain and culture of deep expectorated sputum [e], positive culture with or without positive Gram stain of transtracheal aspirate, pleural fluid culture, lung biopsy, bronchoscopy with bronchoalveolar lavage or protected brush sampling.
- *Imaging studies*: **Pulmonary infiltrate with consolidation on chest X-ray** (new in comparison with baseline chest X-ray)

Infection: Visceral Abscess

- *Symptoms:* abdominal pain, anorexia, weight loss, cough/pleuritic chest pain (hepatic abscess), rigors (seldom present).
- *Physical findings:* intermittent fevers (temperature >38°C oral or >39°C rectal), abdominal tenderness, palpable mass, hepatomegaly, jaundice.
- *Laboratory tests:* **positive Gram stain and/or culture from the infected site, with isolation of an appropriate pathogen,** positive blood culture, leukocytosis with accompanying left shift, differential WBC count of >10% immature (band) neutrophils, elevated serum amylase concentration (pancreatic abscess), elevated alkaline phosphatase concentration (hepatic abscess) pyuria in renal abscess.
- *Imaging studies:* **typical findings on ultrasound, computed tomography scan, magnetic resonance imaging scan, or radionuclide scan**

Note: Items in bold are considered essential diagnostic features.

[d] For the diagnosis of pneumonia in adults, commonly at least 2 of the listed symptoms and/or signs should be present in conjunction with at least one laboratory and one imaging studies diagnostic element. However, for the purposes of counting serious infection episodes in a clinical trial of IVIG, the finding of a new pulmonary infiltrate with consolidation on chest X-ray is considered sufficient. To establish the diagnosis of bacterial pneumonia for pediatric patients, most of the same diagnostic criteria listed may be used, with the following exceptions: Because pediatric patients may not produce a sputum specimen for culture, blood cultures or serology may be substituted to identify the etiologic bacterial pathogen. In infants age 3 to 24 months, who tend to have a higher baseline temperature, fever is defined as a rectal temperature >38.3°C (101°F). In children >2 years, fever is more commonly defined as a rectal temperature >38°C (100.4°F). In pediatric patients, elevations of WBC counts >15,000/mm^3 are frequent but could be variable in patients with bacterial pneumonia, or leukopenia with WBC count <5000/mm^3 may be observed, usually associated with severe infection.

[e] It is recommended to obtain a deep expectorated sputum gram stain to demonstrate the presence of microorganisms on examination of 10-20 oil immersion microscopic fields and <10 squamous epithelial cells and >25 polymorphonuclear leukocytes at 10X low power magnification to determine suitability of sputum culture.

7.3 Safety Assessments

7.3.1 Adverse Events

7.3.1.1 Definitions

Adverse event (AE): An AE is any untoward medical occurrence in a study patient receiving an IMP and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not related to the IMP.

An AE is defined as treatment-emergent (TEAE), if the event began or worsened after the start of first infusion of trial medication.

A suspected adverse reaction (SAR) is an AE that fulfills the criteria of a TEAE plus all AEs either the Investigator or the Sponsor determined as possibly or probably related to *octanorm* plus all AEs for which the causality determination is either missing or unclassifiable.

Adverse drug reaction (ADR): An ADR is any noxious and unintended response to an IMP related to any dose. The phrase "response to an IMP" means that a causal relationship between the IMP and an AE carries at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Significant AEs: Any non-serious AE or marked laboratory abnormality that results in:

- withdrawal of IMP treatment,
- and/or dose reduction,
- and/or initiation of significant concomitant therapy (i.e. medications given intravenously).

Withdrawal due to AE: Discontinuation of study participation because of an AE. Any such events will be followed up by the Investigator until the event is resolved or until the medical condition of the patient is stable. All follow-up information collected will be made available to the Sponsor.

Intravascular hemolysis: Will be suspected if the following criteria are fulfilled (modified acc. to [24]):

- Positive direct Coombs' test (confirmed by retesting);
- Drop in hemoglobin of 2 g/dL or greater;
- At least 2 of the following:
  - increase of reticulocyte count
  - increased lactate dehydrogenase level
  - low haptoglobin level
  - unconjugated hyperbilirubinemia
  - hemoglobinemia
  - hemoglobinuria
  - presence of significant spherocytosis.

- Fulfillment of the following exclusion criteria:
  - History or examination consistent with alternate cause of anemia, including blood loss, other drug-induced hemolysis, anemia associated with chemotherapy (excluded by protocol), or hemolysis associated with underlying disease (excluded by protocol).
  - Negative result of direct Coombs' test.
  - Absence of clinical evidence of hemolysis.

7.3.1.2 Collection

The condition of the patient will be monitored throughout the study. At each visit, whether scheduled or unscheduled, AEs will be elicited using a standard non-leading question such as "*How have you been since the last visit / during the previous study period?*" For minor patients not understanding the question, the answer must be obtained from parents or legal guardians. In addition, the patient diaries (if applicable) will be checked by the Investigator for any documented event.

Any AE which occurs during the study will be noted in detail on the appropriate pages of the eCRF. If the patient reports several signs or symptoms, which represent a single syndrome or diagnosis, the latter should be recorded in the eCRF. The Investigator responsible will grade the severity of all AEs (mild, moderate or severe), the seriousness (non-serious or serious) and causality, as defined below (Sections 7.3.1.3, 7.3.1.4, and 7.3.2). The Sponsor is responsible to assess the expectedness of each ADR (expected or unexpected), as defined below (Section 7.3.1.4).

In the event of clinically significant abnormal laboratory findings, the tests will be repeated and followed-up until they have returned to normal and/or an adequate explanation is available.

Diseases, signs and symptoms and/or laboratory abnormalities already existing before the first administration of IMP are not considered as AEs when observed at a later stage unless they represent an exacerbation in intensity or frequency (worsening).

The Investigator responsible should always provide detailed information concerning any abnormalities and the nature of, and reasons for any necessary action(s), as well as any other observations or comments, which are useful for the interpretation and understanding of the patients' AEs.

7.3.1.3 Severity

The intensity/severity of AEs will be graded as follows:

- mild: an AE, usually transient, which causes discomfort but does not interfere with the patient's routine activities;
- moderate: an AE which is sufficiently discomforting to interfere with the patient's routine activities;
- severe: an AE which is incapacitating and prevents the pursuit of the patient's routine activities.

7.3.1.4 Causality

The relationship of AEs to the administered IMP will be assessed by the Investigator responsible:

- probable: reports including good reasons and sufficient documentation to assume a causal relationship, in the sense of plausible, conceivable, likely, but not necessarily highly probable. A reaction that follows a reasonable temporal sequence from administration of the IMP; or that follows a known or expected response pattern to the suspected medicine; or that is confirmed by stopping or reducing the dosage of the medicine and that could not reasonably be explained by known characteristics of the patient's clinical state.
- possible: reports containing sufficient information to accept the possibility of a causal relationship, in the sense of not impossible and not unlikely, although the connection is uncertain or doubtful, for example because of missing data or insufficient evidence. A reaction that follows a reasonable temporal sequence from administration of the IMP; that follows a known or expected response pattern to the suspected medicine; but that could readily have been produced by a number of other factors.
- unlikely: reports not following a reasonable temporal sequence from IMP administration. An event which may have been produced by the patient's clinical state or by environmental factors or other therapies administered.
- not related (unrelated): events for which sufficient information exists to conclude that the etiology is unrelated to the IMP.
- unclassified: reports which for one reason or another are not yet assessable, e.g. because of outstanding information (can only be a temporary assessment).

Classification of ADRs:

ADRs will be classified by the Sponsor as either expected or unexpected:

- expected: an ADR that is listed in the current edition of the Investigator's Brochure.
- unexpected: an ADR that is not listed in the current edition of the Investigator's Brochure, or that differs because of greater severity or greater specificity.

7.3.1.5 Outcome

The outcome of an AE has to be classified as follows:

- recovered, resolved
- recovering, resolving
- not recovered, not resolved
- recovered, resolved with sequelae
- fatal
- unknown

NOTE: A patient's death per se is not an event, but an outcome. The event which resulted into a patient's death must be fully documented and reported, even in case the death occurs within 4 weeks after IMP treatment end, and without respect of being considered treatment-related or not.

7.3.1.6 Action(s) taken

AEs requiring action or therapy must be treated with recognized standards of medical care to protect the health and well-being of the patient. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment of an emergency situation.

The action taken by the Investigator must be documented:

a) in general

- none
- medication (other than IMP) or other (e.g., physical) therapy started
- test performed
- other (to be specified)

b) on IMP

- none
- product withdrawn
- treatment interrupted
- dose reduced
- dose increased

The responsible Investigator will follow-up each AE until it is resolved or until the medical condition of the patient is stable, and all relevant follow-up information will be reported to the Sponsor.

7.3.2 Local Reactions

All infusion site reactions should be captured on eCRF page called 'infusion site reactions'.

Local injection site reactions are to be assessed by both patients and investigators.

Patients have to grade the overall perception of local reactions in their diaries at 24 hours (±3 hours) post-infusion using a 5-point rating scale: 0=none, 1=very slight, 2=slight, 3=moderate, 4=severe).

Investigators have to evaluate local reactions at within approximately 1 hour post-infusion for the first 4 infusions at the study site and at every study site visit thereafter, using a 4-point rating scale: 0=none, 1=mild, 2=moderate, 3=severe.

Note: Possible reactions to plaster (Contact urticaria under plaster, dermatitis in plaster area etc.) do not constitute an injection site reaction, but should be captured as an Adverse Event (AE) on the AE page in eCRF.

7.3.3 Serious Adverse Events

A serious AE (SAE) is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- is another important medical event.

Hospitalization is NOT considered an SAE in case of:

- hospitalization because of study-related procedures; hospitalization due to hospital standard measures (hospitalization for the first infusion of study drug etc.)
- an elective surgical procedure for which the date was scheduled prior to inclusion in the study
- prolongation of the existing hospitalization due to economical or social, but not due to medical reasons.

NOTE: The term "life-threatening" refers to an event in which the patient was — in the view of the reporting Investigator — at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

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

In addition, although not classified under the seriousness criteria, all suspected transmissions of an infectious agent should be reported as SAE. A suspected virus transmission means that virus antigen has been detected in the patient. A passive transmission of antibodies alone does not constitute a suspected virus transmission.

SAE reporting timelines

All SAEs, whether suspected to be related to study treatment or not, are to be reported by telephone, fax or e-mail immediately to the Clinical Project Manager or designee.

Contact details will be communicated at the study initiation visit.

An Octapharma "Serious Adverse Event Report" must be completed and submitted within 24 hours after recognition of the event.

All SAEs should be reported as follows:

- **in Europe to CRO**: [redacted] (Premier Research)

  Octapharma 24 hours Emergency Telephone Number: [redacted]

- **in USA to CRO**: [redacted] (Premier Research)

  Octapharma 24 hours Emergency Telephone Number: [redacted]

7.3.4 Laboratory Safety Tests

For children the trial-related blood loss (including any losses in the maneuver) should not exceed 3% of the total blood volume during a period of 4 weeks (applicable for the PK_{IV} phase) and should not exceed 1% at any single time. The total volume of blood is estimated at 80 mL/kg body weight.

The following laboratory tests will be performed during the course of the study to investigate the efficacy and safety and tolerability of *octanorm*:

Table 3 Laboratory Tests and Time Points

Test	Timing	Laboratory
Total serum IgG trough levels	At Screening, before any infusion given at the study site and at (early) Termination Visit.	Central & Local
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, measles	Only for patients participating in the PK substudy: before and after the last administration of IVIG (PK_{IV}); between Week 11 and 12 (PK_{SC1}) and between Weeks 28 and 29 (PK_{SC2}).	Central
Hematology (complete blood count, WBC differential, haematocrit, hemoglobin)	At Screening, and pre-infusion at Weeks 1, 4, 16, 28, 40, 52, and at (early) Termination Visit.	Local
Clinical chemistry (sodium, potassium, glucose, ALAT, ASAT, LDH, total bilirubin, blood urea nitrogen or blood urea, creatinine)	At Screening, and pre-infusion at Weeks 1, 4, 16, 28, 40, 52, and at (early) Termination Visit.	Local
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],)	At Screening, before and after IMP infusion at Weeks 1 and 4; before and 2-3 days after IMP infusion at Weeks 28 and 52; and at (early) Termination Visit.	Local (or central laboratory if required)
Extended laboratory tests: reticulocyte count, haptoglobin, plasma-free hemoglobin, unconjugated bilirubin, blood smear.	In case of confirmed positive direct Coombs' test together with drop in hemoglobin of ≥2g/dL.	Local (or central laboratory if required)
Urinalysis: protein, pH, glucose, ketones, leukocytes, hemoglobin, and hemosiderin.	At Screening, and pre-infusion at Weeks 1, 4, 16, 28, 40, 52, and at (early) Termination Visit.	Local (or central laboratory if required)
Urine pregnancy test (women of childbearing potential)	At Screening, at Weeks 16, 28, 40, 52 and at (early) Termination Visit; at other times if indicated.	Local
Virology: serology tests: HBsAg, HIV–1/2; (Multiplex) NAT (Technology of Nucleic Acid testing according to local procedures): HBV, HCV, HIV, parvovirus B19, HAV	At Screening, at Week 28 and at (early) Termination Visit.	Local (or central laboratory if required)

CMV (cytomegalovirus); WBC (white blood cell); ALAT (alanine aminotransferase); ASAT (aspartate aminotransferase); lactate dehydrogenase (LDH); HBsAg (Hepatitis B surface antigen); NAT (nucleic acid testing); HBV (hepatitis B virus); HCV (hepatitis C virus); HIV (human immunodeficiency virus); HAV (hepatitis A virus).

Local laboratory determinations will be done at the individual study sites according to local procedures. A laboratory manual detailing the procedures for the central laboratory samples will be distributed to all study sites.

The normal ranges of each determination at each laboratory involved will be provided in the Clinical Report.

7.3.5 Viral Safety Tests

At the Screening Visit, before the first *octanorm* infusion, viral markers will be tested at the local laboratory (or at central laboratory if required) according to the site's standard procedures. A positive result on HIV, HCV or HBV viral markers is an exclusion criterion. For patients positive in parvovirus B19 or Hepatitis A virus at baseline, follow-up samples may be omitted.

Additional viral marker samples will be taken, at Week 28 and at the (early) Termination Visit.

No follow-up virus tests are planned to be done after study termination. Therefore, patients should receive the same batch of IMP for the last 6 months of the study (i.e. from Week 38 onwards).

Additional retention samples drawn at the Screening Visit and at the (early) Termination Visit will be stored frozen at ≤–70°C at the central laboratory for possible future testing. At sites where a freezer of –70°C or below is not readily available, samples can be stored at or below –20°C. In such cases, shipment to the central laboratory should be performed not later than 2 months after the day of collection.

7.3.6 Vital Signs

To evaluate short-term tolerance, monitoring of vital signs including blood pressure, body temperature, pulse and respiratory rate will be performed at visits taking place at the clinic/study site (i.e. Screening Visit, then in 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 IMP. After the first dose of *octanorm*, patients must be monitored at the study site for at least one hour.

7.3.7 Physical Examination

A general physical examination will be performed at the Screening Visit according to routine procedures and will be as comprehensive as necessary to detect relevant abnormalities. If any findings are abnormal, the Investigator will document the start date and whether or not the abnormal finding is still present at the start of treatment. The physical examination will be repeated in Weeks 1, 4, 16, 28, 40, 52, and finally at the (early) Termination Visit). Clinically relevant worsening from the status before IMP treatment will be documented as an AE.

7.3.8 Other Relevant Safety Information

Post study related safety reports:

Any AE with a suspected causal relationship to the IMP (i.e. adverse drug reaction, ADR) which occurs after the completion of the study should be reported by the Investigator. The usual procedure for reporting post-marketing safety information should be followed, but relation to the clinical study should be stated on the report.

If a patient dies within 4 weeks after the last IMP administration, this should be reported as well, without being considered treatment related or not.

Pregnancies:

Every effort will be made to avoid a pregnancy during the use of an IMP. Pregnancies occurring during the study (fetal exposure to the IMP) need to be reported.

In case of pregnancy during the study the Investigator is asked to complete the pregnancy notification form and to send it (by fax or email) to the Sponsor. Follow-up information on the outcome of both mother and fetus will be requested by a Sponsor representative.

Overdose, interaction, misuse, and medication error:

The following safety relevant information should be reported as AE or as SAE, if the reaction fulfils one of the criteria for seriousness (see Section 7.3.3).

Drug overdose:

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

Interaction:

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

Misuse:

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

Medication error:

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

7.4 Other Assessments

7.4.1 Drug Concentration Measurements

Samples for total IgG trough levels measurements will be taken at the Screening Visit, before any infusion given at the study site and at the (early) Termination Visit; these samples will analyzed at the local and the central laboratory.

For patients in the PK substudy additional samples will be drawn as detailed in Section 6.1.2 and analyzed centrally for total IgG, IgG subclasses (IgG1, IgG2, IgG3, IgG4), specific antibodies against *Haemophilus influenzae*, *Streptococcus pneumoniae* (types 4, 6B, 9V, 14, 18C, 19F, 23F), CMV, tetanus and measles. These data will be used for the PK analysis detailed in Section 9.2.3.

7.4.2 Quality of Life Assessment

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 QoL assessments will take place at the first infusion visit, at Week 28, and at the (early) Termination Visit.

7.5 Appropriateness of Measurements

The therapeutic efficacy, defined as the prevention of SBI, is a very important clinical aspect of any IgG replacement therapy and best characterizes benefit to the patient.

Determination of the pre-next-dose trough level of IgG is a standard method for determination of the correct dose for the individual patient.

The QoL questionnaires are standardized, validated instruments that have been widely used in clinical studies, including studies with PI patients.

8 DATA HANDLING AND RECORD KEEPING

To ensure that data in the CRFs are accurate and complete and in accordance with source records, source data verification will be performed in accordance with Octapharma standards. The extent of source data verification will be defined in detail in the monitoring manual.

8.1 Documentation of Data

8.1.1 Source Data and Records

Source data are defined as all of the information related to clinical findings, observations, or other activities in the study, written down in original records or certified copies of original records. The Investigator will permit study-related monitoring, audit(s), IEC/IRB review(s) and regulatory inspection(s), by providing direct access to source data/records.

For each patient enrolled, the Investigator will document the patient's participation in the study in the source record(s). The Investigator will maintain adequate case histories or patient files for each patient enrolled. Source records should be preserved for the maximum period of time permitted by local regulations.

The following data must be verifiable from the source records: patient's inclusion in Study SCGAM-01, patient number, sex, weight, date of birth, written informed consent, medical history, main inclusion and exclusion criteria, chest X-ray, local laboratory test results, concomitant therapies (medication and non-drug therapy), any AE occurring in the course of the study, details of infusions (batch number, number of vials used, date, dose, rate and site(s)), date and reason for premature withdrawal (if applicable). As part of the source records, laboratory data will be reviewed by the Investigator, assessed as to their clinical significance, signed and dated.

8.1.2 Electronic Case Report Forms (eCRF)

For each patient enrolled, an eCRF will be completed within the electronic data capture (EDC) system and approved by the Investigator or an authorized sub-investigator. Monitors must provide a source data verification flag to each of the eCRF pages in addition to the approval flag by the Investigator.

Study site staff will be responsible for entering all of the patient data into the validated EDC system. All site personnel will be trained on the EDC system and study specific eCRF prior to receiving access to the live database for data entry, as defined in applicable SOPs. The site is also provided with the approved eCRF Completion Guidelines which will assist in data entry and data issues/questions. The site will be notified once the database is active to begin data entry. Additional site training may be provided as refreshers throughout the study, if needed. All persons allowed to enter or change eCRF data must appear on the delegation of authority log.

8.1.3 Changes to Case Report Form Data

Errors occurring on the EDC system can only be corrected by the investigator(s) or other site personnel. An audit trail documents all changes to the data over the entire study period. If data is changed as a result of a query, a comment must be supplied within the query's text, stating the reason for the change, prior to closing. In addition, any changes to a previously saved eCRF page that has not had a query generated will need to have a reason specified for the data change.

Once queries have been resolved by the site staff, the resolutions are assessed by Data Management for incomplete or ambiguous resolutions. If the query response provided confirms the data as correct, the discrepancy will be closed. If the response does not adequately address the question raised, a new query will be issued for further clarification.

Manual checks are performed and programs are run throughout the study until the data is clean (all discrepancies resolved) and the database is ready for lock. Source data verification will be confirmed as complete by the monitor, and all eCRFs will be approved by the Investigator prior to database lock.

8.1.4 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. Only in case of missing body weight, the last available weight measurement will be used for calculating the dose per kg bodyweight (last observation carried forward).

8.2 Information of Investigators

An Investigator's Brochure will be handed out to the Investigator before the start of the study. This report contains all information in the Sponsor's possession necessary for the Investigator to be fully and accurately informed about the safety of the IMP under evaluation and the respective benefit-risk ratio.

The Investigator's Brochure will be updated by the Sponsor at regular intervals and in case new information concerning the IMP becomes available.

All participating investigators will be informed about the relevant study procedures, about the methods for rating relevant study outcomes and how to complete the eCRF in order to reduce discrepancies between participating investigators and study sites. At the study initiation visit, the eCRF will be explained to all study site staff entitled to document data in the eCRF.

The investigators will be kept informed of important information related to the safe use of the investigational product as the study proceeds.

8.3 Responsibilities

The Investigator is accountable for the conduct of the clinical study. The Investigator shall maintain a list of appropriately qualified persons to whom he/she has delegated significant study-related duties. This "Delegation of Authority Log" will be filled in and signed by the Investigator responsible. In accordance with this authority log study site staff (e.g., sub-investigators, nurses) is authorized to perform study related tasks and to enter specific data into the eCRF.

The Investigator is responsible for coordinating the study locally.

8.4 Investigator's Site File

At each study site, the Investigator is responsible for maintaining all records to enable the conduct of the study to be fully documented. Essential documents as required by GCP guidelines and regulations (e.g., copies of the protocol, study approval letters, all original informed consent forms, drug dispensing and accountability logs, correspondence pertaining to

the study, etc.) should be filed accurately and kept by the Investigator for the maximum period of time required by local regulations.

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

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

8.5 Provision of Additional Information

On request, the Investigator will supply the Sponsor with additional data relating to the study, or copies of relevant source records, ensuring that the patient's confidentiality is maintained. This is particularly important when source data are illegible or when errors in data transcription are encountered. In case of particular issues or governmental queries, it is also necessary to have access to the complete study records, provided that the patient's confidentiality is protected in accordance with applicable regulations.

8.6 Independent Data Monitoring Committee

The Sponsor will establish an IDMC. During the study, the IDMC will periodically review relevant data and will give advice on the continuation, modification or termination of the study (see Section 6.2.3). A study-specific Charter will define in detail the composition, responsibilities and procedures of the IDMC.

A descriptive efficacy and safety assessment after 100 SC infusions of IMP were given to patients is planned in order to obtain first impression of the performance of *octanorm* in the treatment of PID with respect to efficacy and safety. This will be assessed by IDMC.

9 STATISTICAL METHODS AND SAMPLE SIZE

The statistical analysis will be delegated under an agreement of transfer of responsibilities to an external CRO. All Octapharma procedures and policies have to be met by this CRO. Discrepancies or exceptions are to be approved by the Sponsor's Manager of Biometrics.

9.1 Determination of Sample Size

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 and should be similar for SCIG treated patients.[22,25] Therefore using STPLAN v4.3 software, it was 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.[26]

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 to a steady-state treatment with *octanorm* unambiguously, 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.

9.2 Statistical Analysis

A formal statistical analysis plan describing all details of the analyses to be performed will be prepared by the study statistician and approved by the Sponsor prior to start of the statistical analysis.

9.2.1 Population for Analysis

The following populations will be considered for the statistical analysis:

The safety analysis set 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 safety analysis set 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.

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; protocol violations to be considered will include (but will 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 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 this population to ensure the accuracy of the calculation of the corrected DCF.

The PK evaluable set for the assessment of bioavailability 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 this population to ensure the accuracy of the assessment of bioavailability.

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 analysis will be based on the PK evaluable analysis sets.

The membership of each patient in the respective analysis populations will be determined prior to statistical analysis in a data review meeting by a panel consisting of a medical expert from the Sponsor, the clinical study manager, the data manager and the study statistician.

All data will be summarized for all patients overall and by age group.

9.2.2 Efficacy Analysis Plan

The rate of SBI per person-year (bacterial pneumonia, bacteremia/sepsis, osteomyelitis/septic arthritis, visceral abscess, bacterial meningitis) during the treatment period with *octanorm* will be presented as point estimates of the rate along with a 99% CI. Calculation of this CI will account for intra-patient correlation in incidents following a compound Poisson process model. Furthermore, all observed SBI will be listed individually and in full detail.

The FDA Guidance for Industry suggests that, based on historical data, a statistical demonstration of a serious infection rate per person-year less than 1.0 is adequate to provide substantial evidence of efficacy.[22] Therefore, 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 1-sided 99% confidence limit is less than 1.0.

The rate of other infections will also be calculated per person-year and presented with the appropriate 95% CI.

The duration of infection will be summarized by standard descriptive statistics by type of infection and by severity. The individual characteristics of each infection, including the time to resolution will be listed.

The use of antibiotics will be reported as a detailed list of all such medications, and the number of patients treated with antibiotics, the number of treatment episodes and the number of treatment days will be tabulated.

All absences from work or school will be listed with duration and reason; the individual absence rates will be summarized descriptively.

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.

All hospitalizations due to infections during the course of the study will be listed with duration and reason; the numbers of patients hospitalized, the number of hospitalizations and the number of days in hospital will be tabulated and summarized descriptively.

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

9.2.3 Pharmacokinetic Analysis Plan

9.2.3.1 General Considerations

The PK analysis will be done by use of non-compartmental methods using actual elapsed time from the start of the infusion and based on the assumption that steady-state conditions are observed at the time of PK assessments. The PK results for IVIG treatment will be compared with the PK results for SCIG treatment.

The following PK parameters will be analyzed descriptively for all IgG (total and subtypes) and antigen specific antibody assays:

- 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 [$T_{½}$]
- Specification of the data points used for determination of λz and, by extension, $T_{½}$
- Area under the concentration-time curve from time 0 [start of the infusion] to the time point of the last non-zero concentration [$AUC_{0\text{-}last}$]
- 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 [AUCτ]
- 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

Individual PK profiles will be presented graphically in Trellis plots (i.e. several plots with the same pairs of variables on 1 page) using a linear scale as well as a logarithmic scale for the plasma concentrations.

Trough levels of all monitored IgG and antigen specific parameters will be summarized by infusion number and presented graphically as time profiles. In addition, the frequency of total IgG trough levels below 5.0 g/L will be presented for each infusion.

9.2.3.2 "Corrected" Dose Conversion Factor and Target Trough Levels

For the IVIG PK profile the AUCτ ('$AUC\tau_{IV}$') will be calculated as the area under the concentration-time curve from time t=0 to the end of the dosing period (i.e. 21 or 28 days), standardized to 1 week for comparability. This measure can be interpreted as the total bioavailability of IgG during one treatment cycle at steady state.

For the SCIG PK profile obtained in the final week of the wash-in/wash-out period the AUCτ ('$AUC\tau_{SC}$') will be calculated in full analogy, but with a dosing period of 7 days.

A least-squares regression will be performed, modeling $AUC\tau_{SC}$ 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 doses of IgG administered subcutaneously ($Dose_{SC}$) associated with the original $AUC\tau_{IV}$ values. Dividing these calculated $Dose_{SC}$ values by the actual doses of IgG administered intravenously, standardized to 1 week ($Dose_{IV}$), results in individual ratios for all available patients; the average of these ratios will be used as the corrected dose conversion factor.

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 described below 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.

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.

For the derivation of an easy to use dose adjustment tabulation based on the actual- and target trough levels, $Trough_{SC}$ 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 that will be used to derive a dose adjustment tabulation featuring body weight and the desired change in trough level. This table will be provided to the investigators for dose adjustments in the efficacy phase of the study as described in Section 3.2.3.

9.2.3.3 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 AUCτ 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 1.25 will be performed on the α=0.05 confidence level.

9.2.4 Safety Analysis Plan

The safety analysis will comprise descriptive statistics, tabulations and listings of all TEAEs, safety laboratory results, viral markers, vital signs and physical examination findings.

9.2.4.1 Adverse Events

All reported AEs will be coded according to MedDRA.

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

AEs that occur between informed consent and the start of the first infusion of *octanorm* will also be documented and will be 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 SARs are defined as all AEs that are either 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 reported events will be listed and tabulated in full detail, in particular the following key figures will be presented for each age group and for the study as a whole:

- 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).

Narratives will be prepared describing each death, other SAEs, and other significant AEs that are judged to be of special interest because of clinical importance.

9.3 Randomization / Stratification / Code Release

There is no randomization in this study.

Enrolment in each age group will stop when the maximum number allowed for that age group has been achieved. Recruitment will be monitored centrally to ensure that the minimum enrolment targets are met in each age group.

9.4 Interim Analysis

Upon completion of the second PK assessments (PK_{SC1}), the conversion factor will be determined as described in Section 9.2.3.2. This factor will then be used to calculate the initial dosing for any patient newly enrolled.

Beside this use of the conversion factor for the dose calculation, this interim assessment will have no impact on the study proceedings and will not result in any change of the sample size or study design.

10 ETHICAL / REGULATORY, LEGAL AND ADMINISTRATIVE ASPECTS

10.1 Ethical / Regulatory Framework

This study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

Prior to submission of the study protocol to the IEC/IRB and Competent Authority, the Sponsor will obtain an EudraCT number for this specific clinical study. In addition, the study will be registered in *ClinicalTrials.gov*.

The study protocol and any subsequent substantial amendment(s), as well as a sample of the information sheet and informed consent form, any other materials provided to the patients, and

further requested information will be submitted to the IEC/IRB and the Competent Authority. The study will be conducted in compliance with the protocol, GCP and the applicable regulatory requirements.

In addition, the study will be conducted under a US Investigational New Drug (IND) application, and therefore must meet the applicable FDA requirements including Statement of Investigator Form 1572 and financial disclosure statement.

The regulatory application or submission for regulatory approval will be made by the Sponsor as required by national law. Study approval must be available before any patient is exposed to a study-related procedure.

The Competent Authorities and the IECs/IRBs will be notified of the end of the clinical study in accordance with local regulations.

10.2 Approval of Study Documents

The study protocol, a sample of the patient information and informed consent form, and further requested information will be submitted to the appropriate IEC/IRB and the competent Authority. The study approval letter must be available before any patient is exposed to a study-related procedure.

The Sponsor, the Investigator and any third party (e.g. CRO) involved in obtaining approval, must inform each other in writing that all ethical and legal requirements have been met before the first patient is enrolled in the study.

10.3 Patient Information and Informed Consent

The Investigator will obtain freely given written consent from each patient after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards and any other aspect of the study which is relevant to the patient's decision to participate. The informed consent form must be signed, with name and date and time noted by the patient, before the patient is exposed to any study-related procedure, including screening tests for eligibility.

For minor patients, freely given written consent must be obtained from parents or legal guardians. In addition, when required by the local regulatory authorities, IECs/IRBs, written assent must be obtained from children and adolescents based upon the age requirements established by those institutions.

The Investigator will explain to each single patient that the patients are completely free to refuse to enter the study or to withdraw from it at any time, without any consequences for their further care and without the need to justify their withdrawal. The Investigator will date and sign the informed consent form of each patient enrolled.

Each patient, or his parents/legal guardians, will give written consent that his/her source records may be reviewed by study monitors, quality assurance auditors and/or health authority inspectors, in accordance with applicable regulations. These persons are bound by confidentiality obligations.

10.4 Protocol Amendments

Any prospective change to the protocol will be agreed between the Investigator (Coordinating Investigator in multicenter studies) and the Sponsor prior to its implementation. Any such amendments will be submitted to the IEC(s)/IRB and/or competent authority responsible as

required by applicable regulations. IEC(s)/IRB approval will at a minimum be requested for any change to this protocol which could affect the safety of the subjects/patients, the objective/design of the study, any increase in dosage or duration of exposure to the IMP, an increase in the number of subjects/patients treated, the addition of a new test or procedure, or the dropping of a test intended to monitor safety.

10.5 Confidentiality of Patients' Data

The Investigator will ensure that the patient's confidentiality will be preserved. On eCRFs or any other documents submitted to the Sponsor, the patients will not be identified by their names, but by an identification code, consisting of a center number and a patient number. Documents that are not for submission to the Sponsor, i.e. the confidential patient identification list, original informed consent forms and source records, will be maintained by the responsible Investigator in strict confidence.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Periodic Monitoring

The study monitor will contact and visit the Investigator regularly and will be allowed, on request, to inspect the various records of the study. It will be the monitor's responsibility to inspect the eCRF at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, correctness and accuracy of all eCRF entries. The study monitor should have access to laboratory test reports and any other source records and data needed to verify the entries on the eCRF. The Investigator agrees to co-operate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

A monitoring visit shall be performed shortly after the inclusion of the first patient at each study site. Thereafter, monitoring frequency will depend on the progress, but is expected to be approximately every 6-8 weeks.

A study Initiation Visit and Termination Visit must take place.

11.2 Audit and Inspection

The Investigator will make all study-related source data and records available to a qualified quality assurance auditor mandated by the Sponsor, or to IEC/IRB/regulatory authority inspectors, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and welfare of the subjects/patients have been adequately protected, and that all data relevant for the assessment of safety and effectiveness of the IMP have been reported to the Sponsor.

12 REPORTING AND PUBLICATION

12.1 Clinical Study Report

The Sponsor will prepare a clinical study report (in accordance with relevant guidelines and Octapharma Standard Operating Procedures) timely after the completion of the study. The Coordinating Investigator will approve the final study report after review.

12.2 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is envisaged by an Investigator, the Investigator agrees to inform the Sponsor and to submit all manuscripts or abstracts to the Sponsor prior to submission to an editorial board or scientific review committee. This will allow the Sponsor to protect proprietary information and to provide comments based on information that may not yet be available to the Investigator.

In accordance with standard editorial and ethical practice, the Sponsor will support publication of multicenter studies only in their entirety and not as individual center data. Authorship will be determined by mutual agreement.

13 LIABILITIES AND INSURANCE

To cover any damage or injury occurring to a patient in association with the investigational medicinal product or the participation in the study, OCTAPHARMA Pharmazeutika Prod.Ges.m.b.H. will contract insurance in accordance with local regulations.

All participating investigators are responsible for dispensing the IMP in adherence to this protocol, and for its secure storage and safe handling throughout the study.

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