CLINICAL STUDY PROTOCOL

CLINICAL PHASE 3 STUDY TO EVALUATE THE EFFICACY, TOLERABILITY AND SAFETY OF SUBCUTANEOUS HUMAN IMMUNOGLOBULIN (OCTANORM) IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES

Investigational Product:	*octanorm*
Indication:	Primary Immunodeficiency Diseases
Study Design:	Prospective, open-label, non-controlled, single-arm, multicentre phase 3 study
Sponsor:	OCTAPHARMA Pharmazeutika Prod.Ges.m.b.H., Oberlaaer Strasse 235, 1100 Vienna, Austria
Study Number:	SCGAM-04
EudraCT Number:	2016-003230-24
Development Phase:	Phase 3
Planned Clinical Start:	Q2 2017
Planned Clinical End:	Q3 2018
Date of Protocol:	30-Nov-2016
Version:	02
Co-ordinating Investigator	Not applicable

STUDY OUTLINE

Name of Sponsor/Company: OCTAPHARMA Pharmazeutika Prod.Ges.m.b.H., Oberlaaer Strasse 235, 1100 Vienna, Austria	
Name of Investigational Product: *octanorm*	**Protocol Identification Code:** SCGAM-04
Name of Active Ingredient: Human Normal Immunoglobulin	**Date of Final Protocol:** 30-Nov-2016

Title of Study:

Clinical phase 3 study to evaluate the efficacy, tolerability and safety of subcutaneous human immunoglobulin (*octanorm*) in patients with primary immunodeficiency diseases.

Indication:

Primary immunodeficiency (PI) diseases.

Number of Study Centre(s):

Approximately 5 study sites in Russia.

Objectives:

- To evaluate the efficacy of *octanorm* in preventing serious bacterial infections (SBI) compared with historical control data.
- To evaluate the tolerability and safety of *octanorm*.

Study Design:

The study is a prospective, open-label, non-controlled, single-arm, multicentre phase 3 study with an 8-week wash-in/wash-out period followed by a 6-month efficacy period.

Number of Patients:

Approximately 20 to 25 patients who comply with the inclusion and Non-Inclusion Criteria will be enrolled into the study.

Patient Selection Criteria:

Inclusion Criteria:

1. Age of ≥18 years and ≤70 years.
2. Confirmed diagnosis of PI requiring immunoglobulin replacement therapy due to hypogammaglobulinaemia or agammaglobulinaemia. The type of PI should be recorded.
3. Patients with at least 4 infusions on regular treatment with any Intravenous Immunoglobulin (IVIG) prior to entering the study. Constant IVIG dose between 200 and 800 mg/kg body weight (the individual doses of the last 4 infusions should not

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vary by more than ±25% of the mean dose for the last 4 infusions).

4. Availability of at least 2 IgG trough levels with an IgG level of ≥5.0 g/L from the period of the last 4 IVIG infusions.
5. Negative result on a pregnancy test (Human Chorionic Gonadotrophin [HCG]-based assay in urine) for women of childbearing potential and use of a reliable method of contraception for the duration of the study. Women of non-childbearing potential must be post-menopausal (amenorrhoeic for at least 12 months) or surgically sterile. Examples for medically acceptable methods of birth control for this study include:
   - Oral, implantable, transdermal or injectable contraceptives
   - Intrauterine device
   - Condoms; diaphragm or vaginal ring with spermicidal jellies or cream
   - Sexual abstinence
   - Vasectomised partner
6. Patient must freely give written informed consent.
7. Willingness to comply with all aspects of the protocol, including blood sampling, for the duration of the study.

Non-Inclusion Criteria:

1. Acute infection requiring intravenous (IV) antibiotic treatment within 2 weeks prior to and during the screening period.
2. Known history of adverse reactions to Immunoglobulin A 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 PI, 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 medicinal product (IMP) (such as Polysorbate 80).
6. History of malignancies of lymphoid cells and immunodeficiency with lymphoma.
7. Severe liver function impairment (ALAT 3 times above upper limit of normal).
8. Known protein-losing enteropathies or proteinuria.
9. 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).
10. Treatment with enteral or parenteral steroids for ≥30 days or when given intermittently

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or as bolus, at daily doses ≥0.15 mg/kg. Inhaled corticosteroids are allowed.

11. Patients with chronic obstructive pulmonary disease (COPD) stage Global Initiative for Chronic Obstructive Lung Disease (GOLD) III or IV.
12. Treatment with immunosuppressive 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 IMP 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 human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV) infection.
18. Pregnant or nursing women; planned pregnancy during course of the study.

Test Product, Dose, and Mode of Administration:

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

octanorm has to be administered subcutaneously every week (±2 days).

The dose will be calculated as follows:

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

If, during the study, the **body weight changes by >5% from baseline (Visit 2)**, the dose is to be adjusted to keep the dose constant on a milligram per kilogram body weight basis.

The dose can also be adjusted if trough levels of IgG during the study are <5 g/L or if there is a clinical need for *octanorm* dose adjustment.

Duration of Treatment:

Each patient who stays in the study for the whole period will receive 32 weekly SC infusions of *octanorm*.

Reference Therapy, Dose, Mode of Administration,

Not applicable.

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Study Outcome Parameters (Primary and Secondary Endpoints):

Efficacy Parameters:

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

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).
- Hospitalisations due to infection (number of days and annual rate).
- Episodes of fever.
- Days missed from work/study due to infections and their treatment.
- Quality of life (QoL) assessment using the SF-36 Health Survey.
- Trough levels of serum total IgG throughout the study.

Safety Parameters:

- Occurrence of all treatment emergent AEs (TEAEs) throughout the entire treatment period starting with the first infusion of IMP.
- Proportion of infusions with at least 1 temporally associated AE.
- Occurrence of adverse drug reactions (ADRs).
- Local injection site reactions.
- Vital signs (blood pressure, pulse, body temperature, respiratory rate).
- Laboratory parameters (haematology, clinical chemistry, and viral status).

Study Procedures:

The study consists of a Screening Period (up to 7 weeks) that starts with the signing of the informed consent form, an 8-week wash-in/wash-out period followed by a 6-month efficacy period. Only patients previously on IVIG treatment may be enrolled. Each patient who stays in the study for the whole period will receive 32 *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, with a telephone follow-up 3 weeks later. The total duration of the study for an individual patient will be about 43 weeks (depending on

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the IVIG treatment schedule before enrolment).

Site staff will be trained by the Sponsor in the use of the SC pump. Patients have to be trained at the study site (for at least 4 infusions). Thereafter, the patient 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, missed days from work/study, inpatient hospital stays, and any changes in concomitant therapies between visits.

Refer to Table 1 for the timings of the interventions and activities during the visits taking place at the study site.

Statistical Analysis Plan:

A formal statistical analysis plan (SAP) describing all details of the analyses to be performed will be prepared by the study statistician and approved by the sponsor before the start of the statistical analysis. The following analysis populations will be defined: safety set, full analysis set, and per-protocol set.

Occurrences of SBI and other infections will be presented as absolute numbers and as point estimates of the mean rates per person-year. Days of work/study missed, number and days of hospitalisations due to infections, the use of antibiotics, number of episodes of fever and QoL data will be presented descriptively.

Trough levels of IgG will be summarised by infusion number and presented graphically as time profiles.

AE rates will be calculated with respect to severity and relationship to IMP administration. Short term tolerance parameters (blood pressure, heart rate, temperature, respiratory rate) and safety laboratory parameters (haematology, clinical chemistry, and urinalysis) will be evaluated and presented descriptively. For categorical parameters frequency tables will be presented, whereas appropriate sample statistics will be presented for continuous parameters.

FLOW CHART OF ASSESSMENTS

Table 1: Flow Chart of Assessments Performed Throughout the Study

ASSESSMENTS	Screen-ing	Weekly *octanorm* Infusions											Termin-ation	Follow-up
		Wash-in/wash-out period					Efficacy period							
VISIT	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**Phone call**
WEEK	**up to −7**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**33**	**36**
Informed consent (Screening will start once informed consent is obtained)	x													
Eligibility criteria (see Section 4.1)	x													
Demographic & baseline characteristics (see Section 7.1)	x													
Medical history and prior medication (see Section 7.1)	x													
Chest x-ray[1]	x													
Body weight	x	x	x	x	x	x	x	x	x	x	x	x		
Physical examination (see Section 7.3.7)	x	x			x			x			x		x	
Vital signs(see Section 7.3.7)	x	x			x			x			x		x	
IgG trough levels[2] (pre-infusion during *octanorm* treatment)	x[3]	x	x	x	x	x	x	x	x	x	x	x	x	
Haematology[2](pre-infusion during *octanorm* treatment)	x	x			x			x			x		x	
Clinical Chemistry[2] (pre-infusion during *octanorm* treatment)	x	x			x			x			x		x	
Urine analysis: pH, glucose, ketones, leukocytes[2]	x	x			x			x			x		x	
Viral markers: NAT: HAV, HBV, HCV, HIV, parvovirus B19[4]	x	x											x	
Urine pregnancy test (in females of childbearing potential)	x							x					x	
Infusion of IMP (on site)		**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**		
Local injection site reaction		x	x	x	x	x	x	x	x	x	x	x		
Patient diary check						x	x	x	x	x	x	x	x	
QoL questionnaire		x											x	
Adverse event (AE) monitoring (see Section 7.3.2)		←	—	—	—	—	—	—	—	—	—	—	—	→
Concomitant medication (see Section 4.2)	x	←	—	—	—	—	—	—	—	—	—	—	—	→

[1] Only if last available chest X-ray (or CT or MRI) is older than 12 months.

[2] Local laboratory; see Section 7.3.6.2. **Haematology**: complete blood count, WBC differential, haematocrit, haemoglobin; **Clinical chemistry**: sodium, potassium, glucose, ALAT, ASAT, LDH, total bilirubin, blood urea nitrogen or urea, creatinine

[3] Only for those patients who have their last IVIG infusion during the Screening Period.

[4] Local or central laboratory; see Section 7.3.6.1. Additional retention samples will be drawn and shipped to central laboratory at Visit 2 and Termination visit.

PROTOCOL SIGNATURES

Signature of the Sponsor's Representatives

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

Wolfgang Frenzel, MD FRENZEL 30. NOV. 2016

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LIST OF ABBREVIATIONS

Abbreviation	Description
ADR	Adverse Drug Reaction
AE	Adverse Event
ALAT	Alanine Aminotransferase
ASAT	Aspartate Aminotransferase
AUC	Area Under the Concentration-Time Curve
CRO	Contract Research Organisation
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FA	Full Analysis
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAV	Hepatitis A Virus
HBV	Hepatitis B Virus
HCG	Human Chorionic Gonadotrophin
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intention-To-Treat
IV	Intravenous
IVIG	Intravenous Immunoglobulin
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
PI	Primary Immunodeficiency
PK	Pharmacokinetic
PP	Per-protocol
QoL	Quality of Life
SAE	Serious Adverse Event
SBI	Serious Bacterial Infection(s)
SC	Subcutaneous
SCIG	Subcutaneous Immunoglobulin
T_{max}	Time to Maximum Plasma Concentration
WBC	White blood cell

1 INTRODUCTION

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 characterised 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 hospitalisation.

In 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 became 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 SC 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 labelling 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 from work or school, days in hospital and days on antibiotics. Definitions of overall infections and SBI were not standardised 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 hospitalisation.[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 medicinal product (IMP) in this study, is an immunoglobulin preparation from human normal plasma and is manufactured by Octapharma. It contains around 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.

1.1 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 is simple and can easily be learned by the patients, which is another advantage of SCIG. It may remarkably improve the patient's quality of life (QoL) and compliance as it reduces the frequency of hospitalisations 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.

A clinical study with *octanorm* (SCGAM-01) is currently being conducted in Czech Republic, Slovak Republic, Poland, Hungary, USA and Canada, with the rationale to investigate PK,

efficacy and safety in PI patients. In total, 50 patients have been included in this study (of whom 10 are children); 18 patients already successfully completed the study, 28 patients are ongoing, and 4 patients left the study (none of them due to AEs or SAEs). More than 2200 weekly SC infusions have been given and were very well tolerated by the patients. No SBI occurred. (For more details see the 'Development Safety Update Report'.)

The rationale for conducting this clinical study (SCGAM-04) is to investigate the efficacy and safety of *octanorm* in patients with PI to provide efficacy and safety data in Russian patients for submission to the national authorities to support marketing authorisation in the Russian Federation.

1.2 Dose Rationale

On converting from IVIG to SCIG replacement therapy for PI, the equivalent monthly dose of IgG is usually determined as 1:1 dosing, wherein the 3 to 4 weekly IVIG dose is split into 3 to 4 equal weekly SCIG infusions. This is common practice in Europe.

In this study, the weekly dose of *octanorm* will be 1:1.

Throughout the study, the appropriate dose levels will be maintained by regular monitoring of IgG trough levels. The *octanorm* dose can be adjusted (increased) by the Investigator if needed (see Section 5.4).

The manufacture of *octanorm* is based on the (IVIG) Octagam manufacturing process. The process is identical up to the step of the second diafiltration. After this step the product solution is concentrated to the *octanorm* target concentration of 165 g/L.

The PK characteristics and the safety profile of the IVIG Octagam are well known. Octagam has been extensively investigated over the last 15 years. More than 900 patients have been enrolled in prospective clinical studies with Octagam 5% or 10%.

In the Russian Federation and in the EU, the recommended and approved Octagam dose in PI is 200 to 800 mg/kg body weight, administered every 3 to 4 weeks. Therefore, in this clinical study, the proposed dose of *octanorm* is within those recommended values.

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.

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

In the ongoing SCGAM-01 study, approximately 50 patients have received more than 2200 weekly SC infusions of *octanorm*, and no serious bacterial infections have occurred, indicating that *octanorm* is effective in the treatment of patients with PI syndromes. It can reasonably be assumed that *octanorm* will have at least the same effectiveness as Octagam and other IVIG brands.

The 2200 weekly SC infusions of *octanorm* were very well tolerated by the patients. Adverse events which were assessed by Investigators and sponsor as 'probably' or 'possibly related' to *octanorm,* were mostly mild or moderate in severity. The majority of them were local

reactions just caused by the injected *octanorm* volume (usually reported as a transient 'swelling', transient redness and infusion site pruritus).

Two serious adverse events (SAE) were reported, both were considered as 'not related' by the Investigator:

1. 'Appendicitis with appendectomy': The appendicitis was severe in intensity but considered not related to *octanorm* treatment.
2. 'Tumour of thyroid gland': Histology after surgery confirmed enlargement of the thyroid gland without signs of malignancy. The investigator assessed the SAE as mild in severity and considered it not related to *octanorm*.

No other SAEs were reported until the finalisation of this Protocol. No death occurred.

No unexpected or unknown safety issues have been detected so far for *octanorm*.

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

2 STUDY OBJECTIVES

The study objectives are:

- To evaluate the efficacy of *octanorm* in preventing SBI compared with historical control data.
- To evaluate the tolerability and safety of *octanorm*.
- To assess the effect of *octanorm* on 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 bacteraemia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess) per person-year on treatment.

3.1.2 Secondary Endpoints

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).
- Hospitalisations due to infection (number of days and annual rate).
- Episodes of fever.
- Days missed from work/study due to infections and their treatment.
- QoL assessment using the SF-36 Health Survey.
- Trough levels of serum total IgG throughout the study.

Secondary **safety** endpoints are:

- Occurrence of all treatment emergent AEs (TEAEs) throughout the entire treatment period starting with the first infusion of IMP.
- Proportion of infusions with at least 1 temporally associated AE.
- Occurrence of adverse drug reactions (ADRs).
- Local injection site reactions.
- Vital signs (blood pressure, pulse, body temperature, respiratory rate).
- Laboratory parameters (haematology, clinical chemistry, and viral status).

3.2 Overall Study Design and Plan

The study is a prospective, open-label, non-controlled, single-arm, multicentre phase 3 study with an 8-week wash-in/wash-out period followed by a 6-month (6 × 4 weeks) efficacy period.

The study will be conducted at approximately 5 selected study sites in Russia.

Only patients previously on IVIG treatment may be enrolled. All patients have to undergo the 8-week wash-in/wash-out period.

Each patient will be treated with *octanorm* over a period of about 8 months (8-week wash-in/wash-out phase and 6-month efficacy phase) (see *Figure 1*). Each patient who stays in the study for the whole period will receive 32 *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, with a telephone follow-up 3 weeks later.

The total duration of the study for an individual patient will be up to 43 weeks (depending on the IVIG treatment schedule before enrolment).

Approximately 20 to 25 patients who comply with the inclusion and Non-Inclusion Criteria will be enrolled into the study. Study-related procedures will begin only after written informed consent has been obtained from the patient.

The Screening Period starts with the signing of the informed consent form. Screening can start before or after the last (4th) IVIG infusion, up to 7 weeks before the first infusion of *octanorm*. The first infusion of *octanorm* will be done around the time when the patient's treatment with IVIG is due.

All results necessary to check the patient's eligibility must be available before the first IMP administration.

Site staff will be trained by the Sponsor in the use of the SC pump. Patients have to be trained at the study site (for at least 4 infusions). Thereafter, the patient may continue with *octanorm* infusions at home. Every 4 weeks the infusion is to be given under oversight of the study personnel 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, missed days from work/study, inpatient hospital stays, and any changes in concomitant therapies between visits.

Refer to Table 1 and Section 6.1 for the timings of the interventions and activities during the visits taking place at the study site.

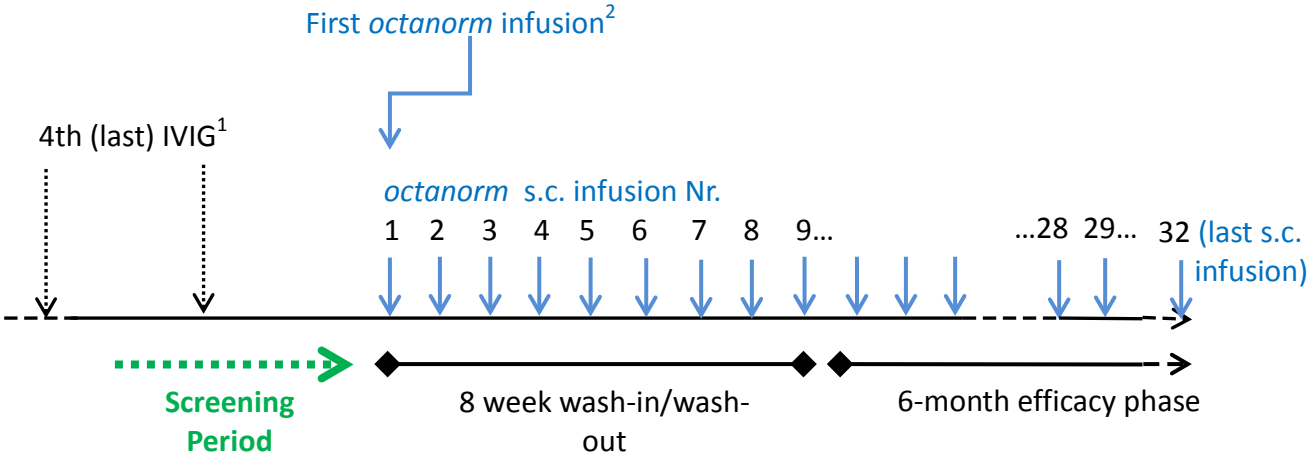

Figure 1 Study Design

1 Patients must have had at least 4 infusions of IVIG to enrol in the study. The last infusion of IVIG can occur before Screening starts or during the Screening Period.

2 The first administration of *octanorm* must take place within 7 weeks of the Screening Visit and around the time when the patient's next treatment with IVIG would have been due.

3.3 Discussion of Study Design and Choice of Control Group

3.3.1 Study Design

The inclusion and Non-Inclusion Criteria chosen are considered adequate to ensure that the study population will be representative of patients suffering from PI.

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

3.3.2 Control Group

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 and with *octanorm* has been demonstrated for this indication.

The historical control data will be based on the standards cited in the Guidance for Industry.[22]

3.3.3 Study Parameters

The outcome measures in this study are consistent with previous studies of other IVIG or SCIG products.

The QoL questionnaire is a standardised, validated instrument that has been widely used in clinical studies, including PI.

4 STUDY POPULATION

4.1 Population Base

Approximately 20 to 25 adult 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 ≥18 years and ≤70 years.
2. Confirmed diagnosis of PI requiring immunoglobulin replacement therapy due to hypogammaglobulinaemia or agammaglobulinaemia. The type of PI should be recorded.
3. Patients with at least 4 infusions on regular treatment with any IVIG prior to entering the study. Constant IVIG dose between 200 and 800 mg/kg body weight (the individual doses of the last 4 infusions should not vary by more than ±25% of the mean dose for the last 4 infusions).
4. Availability of at least 2 IgG trough levels with an IgG level of ≥5.0 g/L from the period of the last 4 IVIG infusions.
5. Negative result on a pregnancy test (Human Chorionic Gonadotrophin [HCG]-based assay in urine) for women of childbearing potential and use of a reliable method of contraception for the duration of the study. Women of non-childbearing potential must be post-menopausal (amenorrhoeic for at least 12 months) or surgically sterile. Examples for medically acceptable methods of birth control for this study include:
   - Oral, implantable, transdermal or injectable contraceptives
   - Intrauterine device
   - Condoms; diaphragm or vaginal ring with spermicidal jellies or cream
   - Sexual abstinence
   - Vasectomised partner
6. Patient must freely give written informed consent.
7. Willingness to comply with all aspects of the protocol, including blood sampling, for the duration of the study.

4.1.2 Non-Inclusion Criteria

Patients who meet one (or more) of the following criteria cannot be included in the study:

1. Acute infection requiring IV antibiotic treatment within 2 weeks prior to and during the screening period.
2. Known history of adverse reactions to Immunoglobulin A 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 PI, 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 IMP (such as Polysorbate 80).

6. History of malignancies of lymphoid cells and immunodeficiency with lymphoma.
7. Severe liver function impairment (alanine aminotransferase [ALAT] 3 times above upper limit of normal).
8. Known protein-losing enteropathies or proteinuria.
9. 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).
10. Treatment with enteral or parenteral steroids for ≥30 days or when given intermittently or as bolus, at daily doses ≥0.15 mg/kg. Inhaled corticosteroids are allowed.
11. Patients with chronic obstructive pulmonary disease (COPD) stage Global Initiative for Chronic Obstructive Lung Disease (GOLD) III or IV.
12. Treatment with immunosuppressive 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 IMP 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 human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV) infection.
18. Pregnant or nursing women; planned pregnancy during course of the study.

4.2 Prior and Concomitant Therapy

Details on medications taken within 30 days prior to screening and any concomitant medications taken during the study and for 4 weeks after the end of the last infusion must be recorded in the CRF. This includes non-drug therapy, such as physiotherapy. Previous IVIG infusions will be recorded as prior therapy (for those infusions given before Screening) and concomitant therapy (if last dose is given within Screening Period), as applicable.

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 anaesthetics (as cream or plaster) to reduce pain associated with needle(s) insertion are allowed. Inhaled corticosteroids are allowed. The use of such medication(s) must be recorded.

4.2.2 Forbidden Concomitant Therapy

Apart from up to one routine IVIG infusion during the Screening Period (see *Figure 1*), 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 during the treatment period.

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 enteral 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 drugs are also forbidden.

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 their decision. The responsible Investigator also has the right to withdraw patients from the study in case of AEs, poor compliance, or administrative reasons. Since an excessive rate of withdrawals can render the study un-interpretable, any 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 electronic case report form (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, at Week 16 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 must be informed: The Pregnancy Notification Form must be completed and sent or faxed to the CRO (see Section 7.3.4 for the contact email and fax number).

If a patient is withdrawn, the Investigator will organise 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 will assess the situation and decide on a possible replacement policy. Patients who do not satisfy specific entry criteria during screening may be rescreened following discussion of the individual case with the Sponsor.

4.4 Assignment of Patients to Treatment Groups

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 (EDC) system to the Investigator, the contract research organisation (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 randomisation number will be used.

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

4.5 Relevant Protocol Deviations

In the case of any critical or major protocol deviation, 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 deviations 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

5.1 Characterisation of Investigational Product

Name of Medicinal Product: *octanorm*

Active ingredient of *octanorm*: Human normal immunoglobulin

Table 2 Biochemical Characteristics of *octanorm*

Parameter	
Total protein (of which ≥95% is human IgG)	150 – 180 mg per mL
Maltose	70 – 90 mg per mL
Octoxynol	≤5 µg per mL
TNBP	≤1 µg per mL
Immunoglobulin A	≤0.6 mg per mL
Polysorbate 80	10 – 60 µg per mL
pH	5.0 – 5.8
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

Each batch (lot) of *octanorm* is prepared from at least 1,000 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 a 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 Labelling

octanorm is delivered in glass vials.

Each *octanorm* vial will be labelled as follows:

FOR CLINICAL TRIAL USE ONLY	Study: **SCGAM-04**
octanorm	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.
INVESTIGATOR NAME: _____ Site No: |___|___|
Patient No.: |___|___|___|___|
Manufacturer: OCTAPHARMA Dessau GmbH; Otto-Reuterstrasse 3, 06847 Dessau-Roßlau, Germany, Tel: +49 340 55080
Sponsor: Octapharma Pharmazeutika Prod.Ges.m.b.H., Oberlaaer Strasse 235, 1100 Vienna, Austria, Tel: +43 (1)61032-0
Batch No.: _____ Expiry date: _____

5.3 Conditions for Storage and Use

octanorm must be stored and transported light-protected at +2 °C to +8 °C and must not be frozen.

octanorm must not be used after its expiration date.

Authorised personnel at the individual study centres 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). There must be a minimum of 4 days between each SC infusion. If, during the study, the body weight changes by >5% from the baseline visit (Visit 2), the dose is to be adjusted to keep the dose constant on a milligram per kilogram body weight basis.

The *octanorm* dose during the wash-in/wash-out phase is to be calculated as follows:

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

The dose can also be adjusted if IgG trough levels during the study are <5 g/L or if there is a clinical need for *octanorm* dose adjustment; in this case any changes should be discussed beforehand with the Octapharma Medical Expert.

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 discarded.

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 will be instructed at the clinic/doctor's office or at the infusion centre 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 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 for at least 1 hour after all doses of *octanorm* given at the study site.

Infusion sites: The maximal number of infusion sites used simultaneously should not exceed 6. Infusion sites should be approximately 5 cm apart. The actual sites of infusion should be changed with each weekly administration.

Volume: For the first administration, 15 mL per infusion site should not be exceeded. After the 4th administration, this may be gradually increased to 25 mL/site, if tolerated, to 35 mL/site after the 16th administration. Starting with the 24th administration and when the previous volumes were well tolerated, the volume can be increased to a maximum of 40 mL/site.

Infusion rate: For the first 4 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 4 infusions and 50 mL per hour for all sites up to infusion no. 16 and, if tolerated, 80 mL per hour for all infusion sites thereafter. Starting with the infusion no.24 (site visit no.10) 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

Any IMP provided to the site will be accounted for. This includes IMP received at the site, IMP dispensed to patients, and IMP returned by the patient.

A Drug Inventory and Dispensing Log will be kept current by the Investigator, detailing the dates and quantities of IMP received and dispensed to each patient and the remaining quantity.

The inventory and dispensing log will be available to the monitor to verify drug accountability during the study.

Unused IMP can be destroyed at the study site or returned to the Sponsor for destruction.

Destruction can be initiated only after accountability has been verified and fully reconciled by the monitor and after the Sponsor has granted written approval of destruction.

For their home treatment, a sufficient amount of *octanorm* will be handed out to the patients. The Investigator or his/her 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. All used and unused IMP returned by the patients **must not** be stored in the secure IMP refrigerator, **must not** be re-used and must be destroyed after drug accountability is completed.

5.7.2 Assessment of Treatment Compliance

After training, for the first 4 weeks patients will receive weekly infusions at the study site under the surveillance of authorised study personnel. The patient will then continue with SCIG infusions at home, with infusions given at the study site every 4th week. Infusion details will be documented together with the batch number(s) in the eCRF.

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/study, 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

The flow chart of assessments by study visit is shown in Table 1, following the study outline.

6.1 Observations by Visit

6.1.1 Screening Visit (Visit 1)

The Screening Period starts with the signing of the informed consent form. The last pre-study IVIG infusion can take place before or after the start of the Screening Period. Screening results must be known before the first IMP administration. The first administration of IMP must take place within 7 weeks of the Screening Visit.

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

- Written informed consent.
- Check of inclusion and Non-Inclusion Criteria.
- Documentation of demographic data.
- Documentation of medical history including all adverse conditions that have occurred during the last 30 days. Documentation of serious infections (for definition see Section 7.2.1) and any IV antibiotics from the previous 12 months.
- Recording of all other previous drug and non-drug therapies during the last 30 days.
- General physical examination, including body weight and vital signs.
- Chest X-ray (only if last available chest X-ray, CT or MRI is older than 12 months).
- Drawing of blood samples for total IgG trough level (only for those patients who have their last IVIG infusion during the Screening Period).
- Drawing of blood samples for safety laboratory parameters including viral markers.
- Urine sampling including urine pregnancy test (in females of childbearing potential only).

6.1.2 Treatment Visits

A patient's eligibility must be confirmed (e.g., laboratory and viral testing results must be available) before dosing with *octanorm* is started. The first infusion of *octanorm* will be done around the time when the patient's next treatment with IVIG would have been due. Each patient who stays in the study for the whole period will receive 32 *octanorm* SC weekly infusions. After receiving training at the study site, the patient will infuse the first 4 infusions at the study site. After this the patient may continue with weekly *octanorm* SC infusions at home. However, every 4 weeks the infusion is to be given at the study site. In exceptional circumstances (e.g., vacation), and after discussion with the Sponsor, this interval may be extended by up to 2 weeks.

6.1.2.1 Treatment Visits 2, 5, 8 and 11 (Weeks 1, 4, 16, and 28)

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

- Determination of body weight.

- Physical examination including vital signs.
- Drawing of blood samples for total IgG trough level (before IMP administration).
- Drawing of blood samples for safety laboratory parameters. Urine sampling.
- At Visit 8 (Week 16): urine sampling for urine pregnancy test (in females of childbearing potential only).
- QoL assessment will take place before the first infusion at Visit 2.
- Drawing of blood for viral markers test and retention sample before the first infusion at Visit 2.
- IMP infusion.
- Assessment of local injection site reactions.
- Monitoring of AEs.
- Documentation of concomitant medication
- At Visits 8 and 11: collection and review of the **patient diary**. 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.

6.1.2.2 Treatment Visits 3, 4, 6, 7, 9, 10 and 12 (Weeks 2, 3, 8, 12, 20, 24 and 32)

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

- Determination of body weight.
- Drawing of blood samples for total IgG trough level (before IMP administration).
- IMP infusion.
- Assessment of local injection site reactions.
- Monitoring of AEs.
- Documentation of concomitant medication
- From Visit 6 onwards (i.e., those visits preceded by home treatment phase): Collection and review of the **patient diary**. 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.

6.1.3 Study Termination Visit (Visit 13, Week 33)

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.
- Urine sampling including urine pregnancy test (in females of childbearing potential only).

- QoL assessment.
- Collection and review of the **patient diary**.
- Changes in concomitant medications.
- AE monitoring.

6.1.4 Follow-up Phone Call (Week 36)

Four weeks after the last dose of IMP (and 3 weeks after the Termination Visit), a phone call will be made to the patient to check on any changes regarding AEs and concomitant medication. After the phone call, 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.

6.1.5 Time Windows Used in this Study, including Tolerances

There is a time window of ±2 days for all study visits (Visits 2 to 12) including the Termination Visit and the follow-up phone call (Table 3).

Table 3 Time Windows including Tolerances

Time point	Time stated	Tolerance
Screening	Up to 7 weeks before the first IMP administration	None
octanorm infusions	Weekly	±2 days
On-site Visits 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13	Weeks 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32	±2 days In exceptional circumstances (e.g., vacation) this may be extended by up to 2 weeks. Note: visit schedule should be calculated based on Visit 2 as the baseline, to avoid slippage.
Interval between Last Treatment Visit and (early) Termination Visit	1 week	±2 days
Blood and urine sampling	Before IMP administration	−1 day
octanorm infusion	Every week=every 7 days	±2 days

6.2 Duration of Study

6.2.1 Planned Duration for an Individual Patient

The duration of the entire study for each patient will be approximately 43 weeks.

6.2.2 Planned Duration for the Study as a Whole

The study will be considered completed when all patients have completed the planned observation period/Final Examination Visit.

The estimated start of the study (enrolment of first patient) is the second quarter of 2017, and the estimated end of the study (last visit of last patient) is the third quarter of 2018.

6.2.3 Premature Termination of the Study

Both the Investigator and the Sponsor reserve the right to terminate the study at any time. In this event, any necessary 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.

Regulatory authorities and independent ethics committees (IECs)/institutional review boards (IRBs) should be informed in accordance with national regulations.

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

6.2.3.1 Early Termination of the Entire Clinical Study

At any time, the study as a whole will be terminated prematurely if:

- New toxicological or pharmacological findings or safety reports invalidate the earlier positive benefit-risk-assessment.
- If more than 2 TEEs (i.e., ischaemic stroke, transient ischaemic attack, cerebral infarction, cerebrovascular accident, cerebral thrombosis, embolic infarctions, [acute] myocardial infarction, deep vein thrombosis, pulmonary embolism, venous thrombosis excluding thrombophlebitis) are observed and are assessed as probably or possibly related to *octanorm* treatment by Investigator and/or Sponsor.
- Any other reason rendering the continuation of the study impossible for the Sponsor.

6.2.3.2 Early Termination at an Individual Study Centre

At any time, the study can be terminated at an individual centre if:

- The centre cannot comply with the requirements of the protocol.
- The centre cannot comply with good clinical practice (GCP) standards.
- The centre's first patient is not recruited by 10 weeks after initiation of the centre.
- The required recruitment rate is not met.

Should the study be prematurely terminated, all study materials (patient diaries, IMPs, etc.) must be returned to the Sponsor.

7 ASSESSMENTS AND METHODS

7.1 Demographic and 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), and ethnic origin.

Medical history: All previous medical conditions and surgeries, the exact type of PI, all adverse conditions that have occurred during the last 30 days, with special emphasis on, but not restricted to, infections. Serious infections during the last 12 months should be recorded. Check for history or evidence of alcohol, drug, psychotropic agent or chemical abuse during the last 12 months. Obtained by interviewing the patient.

Previous and ongoing therapies: All previous drug and non-drug therapies (e.g., physiotherapy) during the last 30 days and IV antibiotics during the last 12 months. 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. Obtained only if last available chest imaging (X-ray, CT or MRI) 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.
- Number of episodes of any other infections (including acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, acute bronchitis, infectious diarrhoea etc), along with type and severity of infection, and time to resolution.
- Use and number of days of use 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 or study.
- Hospitalisations due to infections and number of days of hospitalisation, along with reason.
- Number of episodes of fever.
- QoL assessment.

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.

7.2.1 Serious Bacterial Infections

For the purpose of this study the following events will be considered as SBI:

- Bacterial pneumonia.
- Bacteraemia/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 4 Diagnostic Criteria for Serious Infection Types

Bacterial Pneumonia [a] • *Symptoms*: productive cough/change in character of sputum, dyspnoea or tachypnoea, 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 [b], 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)
Bacteraemia/sepsis [c] • *Symptoms:* chills, rigors. • *Physical findings:* fever, hypothermia, tachycardia, tachypnoea, 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** [d], leukocytosis (white blood cell (WBC) count >12,000/mm^3), differential WBC count demonstrating >10% immature (band) neutrophils, leukopenia, thrombocytopenia, coagulopathy, lactic acidosis.

Osteomyelitis/Septic Arthritis

- *Symptoms*: pain, decreased range of motion, tenderness, oedema, 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.**

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**

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 [e], CSF leukocytosis with neutrophil predominance, decrease in CSF glucose.

Note: Items in **bold** are considered essential diagnostic features.

[a] 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.

[b] 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.

[c] 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.

[d] 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 bacteraemia. Subjects meeting criteria for positive blood culture but without 2 or more of the sepsis criteria listed above will be classified as having bacteraemia.

[e] 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.

7.3 Safety Assessments

7.3.1 Assessments for Safety Endpoints

Any of the following drug safety information shall be collected:

- Adverse events (AEs) and serious adverse events (SAEs) temporally associated with the administration of IMP, comparator, or placebo (for definitions and reporting requirements, see Sections 7.3.2, 7.3.3, and 7.3.4)
- Pregnancies, drug overdose, interaction, medication error, lack of efficacy, and post-study SAEs (see Section 7.3.8)

7.3.2 Adverse Events (AEs)

7.3.2.1 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 unfavourable 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.
- **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.
- **Other significant AEs:** Any marked laboratory abnormalities or any AEs that lead to an intervention, including withdrawal of drug treatment, dose reduction, or significant additional concomitant therapy.
- **Withdrawal due to AE/ADR: AE/ADR** leading to **discontinuation of treatment** with IMP. 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.

7.3.2.2 Collection of AEs

The condition of the patient will be monitored throughout the study, i.e., up to 4 weeks after the last dose of IMP. At each visit, whether scheduled or unscheduled, AEs will be elicited using a standard nonleading question such as "How have you been since the last visit/during the previous study period?" In addition, the Investigator will check the patient diaries (if applicable) for any documented event.

Any AE or ADR which occurs during the study will be noted in detail on the appropriate pages of the CRF. If the patient reports several signs or symptoms representing a single syndrome or diagnosis, the diagnosis should be recorded in the CRF. The Investigator will grade the severity of all AEs or ADRs (mild, moderate, or severe), the seriousness (non-serious or serious), and the causality as defined in Sections 7.3.2.3, 7.3.3, and 7.3.2.4. The Sponsor is responsible for assessing the expectedness of each ADR (expected or unexpected) as defined in Section 7.3.2.5.

In the event of clinically significant abnormal laboratory findings, the tests will be confirmed and the patient followed up until the laboratory values have returned to normal and/or an adequate explanation for the abnormality has become available.

Diseases, signs and symptoms, and/or laboratory abnormalities already present before the first administration of IMP will not be considered AEs unless an exacerbation in intensity or frequency (worsening) occurs.

The Investigator will provide detailed information about any abnormalities and about the nature of and reasons for any action taken as well as any other observations or comments that may be useful for the interpretation and understanding of an AE or ADR.

7.3.2.3 Severity of AEs

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

The grading of an AE is up to the medical judgement of the Investigator and will be decided on a case-by-case basis.

7.3.2.4 Causality of AEs

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

- **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 aetiology 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).

7.3.2.5 Classification of ADRs by Expectedness

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 or other reference safety information.
- **Unexpected:** an ADR that is not listed in the current edition of the Investigator's Brochure or other reference safety information, or that differs because of greater severity or greater specificity.

7.3.2.6 Outcome of AEs

The outcome of all reported AEs has to be documented as follows:

1. Recovered, resolved
2. Recovering, resolving
3. Not recovered, not resolved
4. Recovered, resolved with sequelae
5. Fatal
6. Unknown

NOTE: A patient's **death** per se is not an event, but an outcome. The event which resulted in the patient's death must be fully documented and reported, even in case the death occurs within 4 weeks after IMP treatment end (i.e., up to the follow-up phone call) and regardless of whether or not it is considered treatment-related.

7.3.2.7 Action(s) taken

AEs requiring action or therapy must be treated with recognised 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 in an emergency situation.

The action taken by the Investigator must be documented:

a) General actions taken in the event of an AE

- None
- Medication (other than IMP) or other (e.g., physical) therapy started
- Test performed
- Other (to be specified)

b) IMP-related actions taken in the event of an AE

- None
- Product withdrawn
- Treatment interrupted
- Dose reduced
- Dose increased

The Investigator will follow up on each AE until it has resolved or until the medical condition of the patient has stabilised. Any relevant follow-up information will be reported to the Sponsor.

7.3.3 Serious Adverse Events (SAEs)

An **SAE** is any untoward medical occurrence that at any dose:

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

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 may hypothetically have caused death had it been more severe.

In deciding whether an AE/ADR is serious, medical judgment should be exercised. Thus, important AEs/ADRs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise 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.

Hospitalisation is NOT considered an SAE in case of:

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

7.3.4 SAE Reporting Timelines

All SAEs, whether or not they are suspected to be related to study treatment, are to be reported within 24 hours after recognition of the event by telephone, fax, or email:

To CRO:

- Telephone/Fax Number: +7 812 324 45 13
  Email: **safety@SMOOTHDD.com**

In addition, within 24 hours after recognition of the event by the site an Octapharma Serious Adverse Event Report must be submitted by the CRO to:

Octapharma's Corporate Drug Safety Unit
OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Strasse 235, 1100 Vienna, Austria
Fax: +43 1 61032-9949
E-mail: cdsu@octapharma.com

24 hours emergency telephone number: +43 1 40 80 500

The contact details will also be communicated at the study initiation visit.

7.3.5 Local 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 within approximately 1 day post-infusion using a 4-point rating scale: 0=none, 1=mild, 2=moderate, 3=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.

The following observations **must not be reported as local infusion site reactions** as all of them can be expected in all patients:

- Local mass (usually reported as "swelling") caused by the injected octanorm volume;
- Small blood drops at the injection site caused by the needle puncture(s);
- and short and immediate pain at the injection site caused by the puncture itself.

Any other local injection site reactions such as redness, pain (other than the pain caused by the puncture itself), pruritus, rash or other skin reactions, bleeding (other than small blood drops caused by the needle puncture), local thrombosis, induration or swellings (caused by other grounds than the injected volume) must be reported on the local injection site reaction page in the eCRF.

7.3.6 Laboratory Tests

The following laboratory parameters will be investigated during the study at the time points specified in Section 6 and shown in the flow chart of assessments in Table 1:

Table 5 Laboratory Tests and Time Points

Test	Timing	Laboratory
Total serum IgG trough levels	At Screening (if last IVIG infusion is given during Screening Period), before any infusion given at the study site and at (early) Termination Visit.	Local
Hematology (complete blood count, WBC differential, haematocrit, haemoglobin)	At Screening, and pre-infusion at Weeks 1, 4, 16 and 28, 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 and 28, and at (early) Termination Visit.	Local
Urinalysis: pH, glucose, ketones, leukocytes	At Screening, and pre-infusion at Weeks 1, 4, 16 and 28, and at (early) Termination Visit.	Local
Urine pregnancy test (women of childbearing potential)	At Screening, at Week 16, and at (early) Termination Visit; at other times if indicated.	Local
Virology: NAT: HAV, HBV, HCV, HIV, parvovirus B19	At Screening, at Week 1 and at (early) Termination Visit.	Local or central
Retention samples	At Week 1 and at (early) Termination Visit.	Central

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

7.3.6.1 Central Laboratory

Retention samples of all blood draws for virus safety will be kept at ≤–70°C at the central laboratory for possible future testing.

Samples must be frozen at ≤–70°C. At sites where a freezer of –70°C or below is not available, samples can be stored at or below –20°C. In such cases, shipment to the central laboratory should be performed shortly, but not later than 2 months, after the day of collection.

In case it is not possible to test at the local laboratory, the following laboratory tests will be done at a central laboratory:

- Virology: NAT (Technology of Nucleic Acid testing according to local procedures): hepatitis A virus (HAV), HBV, HCV, HIV, parvovirus B19.

At the Screening Visit, before the first *octanorm* infusion, samples will be taken for testing of viral markers at a local or central laboratory. A positive result on HIV, HCV or HBV viral markers is a non inclusion criterion and the results must be available before the start of IMP treatment. For patients positive in parvovirus B19 or HAV at baseline, follow-up samples may be omitted.

For details see the Central Laboratory Manual.

7.3.6.2 Local Laboratory

The laboratory tests to be done by the local laboratories of each study site are listed in Table 5.

The methods of determination and normal ranges for each parameter will be provided in the clinical study report.

7.3.7 Vital Signs and Physical Examination

The vital signs obtained at the time points specified in Section 6 are blood pressure, body temperature, pulse rate, and respiratory rate. Measurements will be carried out before and within 1 hour after the infusion of IMP, except for temperature which will only be measured before the infusion.

Physical examinations will be performed at the visits specified in Section 6. Both height and weight will be measured at baseline. In addition, weight will be measured at all visits prior to dosing.

After each on-site dose of *octanorm*, patients must be monitored at the study site for at least one hour.

7.3.8 Other Relevant Safety Information

a) Post-study related safety reports

Any SAE which occurs up to 4 weeks after the last IMP administration will be reported by the Investigator to the Sponsor. Proactive monitoring for post-study SAEs is not required.

In case a post-study SAE is identified, the Investigator should complete an SAE form and also state the relation to the clinical study in the report.

Deaths occurring within 4 weeks after the last IMP administration should also be reported, regardless of whether or not they are considered treatment-related.

b) Pregnancies

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

In case of pregnancy during the study, the Investigator should complete the Pregnancy Notification Form and send or fax it to the CRO (see Section 7.3.4 for the contact email and fax number).

Follow-up information on the outcome of both mother and foetus will be requested by a Sponsor representative.

c) Overdose, interaction, medication error and lack of efficacy

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

Drug overdose

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

Drug interaction

A drug interaction is a situation in which a substance or medicinal product affects the activity of an IMP, i.e., increases or decreases its effects, or produces an effect that none of the products would exhibit on its own. The reaction must be clearly identified as a drug interaction.

Medication error

A 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, or instructions for use/labelling. The reaction must be clearly identified as a medication error.

7.4 Other Assessments

7.4.1 Quality of Life Assessment

The QoL assessment will be made using the SF-36 Health Survey.

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 characterises 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 questionnaire is a standardised, validated instrument that has been widely used in clinical studies, including studies with PI patients.

8 DATA HANDLING AND RECORD KEEPING

8.1 Documentation of Data

8.1.1 Source Data and Records

Source data are defined as all information related to clinical findings, observations, or other activities in the study, written down in original records or certified copies of original records, allowing reconstruction and evaluation of the clinical study.

The Investigator will maintain adequate source records (e.g., case histories or patient files for each patient enrolled). Source records should be preserved for the maximum period of time required by local regulations.

For each patient enrolled, the Investigator will indicate in the source record(s) that the patient participates in this study.

All data entered in the CRF must be supported by source data in the patient records, with exceptions listed in Section 8.1.2.

The Investigator will permit study-related monitoring, audit(s), IEC/IRB review(s), and regulatory inspection(s), by providing direct access to the source data/records.

The Investigator may authorise site staff (e.g., sub-investigators, nurses) to enter study data into the CRF. This must be documented in the Delegation of Authority Log signed by the Investigator.

8.1.2 Case Report Forms

For each patient enrolled, an eCRF will be completed within the EDC system and approved by the Investigator or an authorised sub-investigator.

Study site staff (e.g., research nurse) will be responsible for entering patient data into the validated EDC system. All site personnel will be trained on the EDC system and study specific eCRFs prior to receiving access to the live database for data entry.

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 be listed in the Delegation of Authority Log.

8.1.3 Changes to Case Report Form (CRF) Data

Monitors will perform source data verification (SDV) as defined for the study.

If any errors or discrepancies in the eCRFs are found during data entry or review, discrepancies will be generated programmatically within the EDC system, and ‘manual’ queries will be generated by either a monitor or Data Management.

Discrepancies and queries can only be corrected by the Investigator(s) or other authorised site personnel. An audit trail documents all changes to the data over the entire study period. If the reason for a change is not obvious, a comment must be supplied in the query’s response,

stating the reason for the change, prior to closing. The study monitor should provide guidance to Investigator(s) and the Investigator(s)' designated representatives on making such corrections.

Once queries have been resolved by the site staff, the resolutions are assessed by Data Management. 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 and the database is ready for lock. All discrepancies will be resolved prior to database lock. There will be a final run of the programmed checks to ensure all discrepancies are closed out, SDV will be confirmed as complete by the monitor, and all eCRFs will be approved by the Investigator prior to database lock.

8.2 Information to Investigators

An Investigator's Brochure (IB) will be handed out to the Investigator before the start of the study. The IB 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 IB will be updated by the Sponsor at regular intervals and whenever relevant 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 Investigator will be kept informed of important data that relate to the safe use of the IMP as the study proceeds.

8.3 Responsibilities

The Investigator is accountable for the conduct of the clinical study. Responsibilities may be delegated to appropriately qualified persons.

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. 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.

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, site copies of all CRFs, 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 patient identification code list, which provides the unique link between named source records and CRF 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

An Independent Data Monitoring Committee will not be established for this study.

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

This uncontrolled study is designed to obtain data on IgG trough levels in PI patients in Russia, along with clinical safety and efficacy data. The sample size of approximately 20 to 25 evaluable patients will provide local data to supplement the PK data from the SCGAM-01 study that is compliant with the CHMP recommendations for this indication (CHMP Note for Guidance EMA/CHMP/BPWP/94033/2007 rev. 2). No formal sample size calculation is provided.

No attempts will be made for a balanced inclusion of male and female patients.

9.2 Statistical Analysis

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

In addition to the specific analyses detailed in the subsequent sections, all collected efficacy and safety assessments and derived endpoints will be presented by means of descriptive statistics.

If not detailed otherwise in the SAP, study parameters will be presented according to their data type. The number of subjects in the analysis population and the number of subjects contributing to each particular summary will be included in every presentation.

- Binary data (whether or not an event has occurred): counts and proportions
- Count data (the frequency of an event in a set time period): rate (count per unit time)
- Continuous data (measurements on a continuous scale, including quasi-continuous variables): arithmetic mean, standard deviation, median, lower and upper quartile, minimum, maximum

Scales data (ordinal and non-ordinal): absolute and relative frequencies. Where appropriate, results will be presented grouped by different subject characteristics (e.g., gender) as well as in total.

Additional descriptive and exploratory statistics, such as the geometric mean or confidence intervals, will be included as appropriate. If not mentioned otherwise, confidence intervals are to be understood as two-sided, 95% confidence intervals.

9.2.1 Populations for Analysis

The total set consists of all patients enrolled in the trial including drop-outs. For the statistical analyses the following 3 sets will be deployed:

The **safety set** consists of all patients who received at least one infusion of IMP; it is the set of patients exposed to treatment.

The **full analysis (FA) set** consists of all patients of the safety 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, according to the intention-to-treat (ITT) principle.

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

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

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

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

9.2.2 Efficacy Analysis Plan

The efficacy of *octanorm* in the prevention of infections will be evaluated by the following measurements:

- Number of episodes of SBI, per person-year on treatment, along with type and severity of infection, and time to resolution.
- Number of episodes of any other infections (including acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, acute bronchitis, infectious diarrhoea etc), along with type and severity of infection, and time to resolution.
- Use and number of days of use 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 or study.
- Hospitalisations due to infections and number of days of hospitalisation, along with reason.
- Number of episodes of fever.
- The QoL data will be presented descriptively by visit, along with the change from baseline (defined as the first infusion).

Trough levels of IgG will be summarised by infusion number and presented graphically as time profiles. In addition, the frequency of pre-next dose IgG trough levels below 5 g/L will be presented for each infusion.

9.2.3 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.

9.2.3.1 Adverse Events

All reported AEs will be coded according to Medical Dictionary for Regulatory Activities (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 ADRs are defined as any noxious and unintended response to an IMP related to any dose (i.e., a causal relationship between the IMP and an AE carries at least a reasonable possibility and a relationship cannot be ruled out).

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 ADRs.
- 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 ADRs divided by the total number of infusions.

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.

9.2.4 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 will the last available weight measurement be used for calculating the dose/kg bodyweight for the previous IVIG infusions (last observation carried forward, LOCF).

9.3 Randomisation, Stratification, and Code Release

Not applicable to this study.

10 ETHICAL/REGULATORY, LEGAL AND ADMINISTRATIVE ASPECTS

10.1 Ethical/Regulatory Framework

This study will be conducted in accordance with the ethical principles laid down in the Declaration of Helsinki. The study protocol and any subsequent amendment(s) will be submitted to an IEC/IRB and to the Regulatory Authority. The study will be conducted in compliance with the protocol, GCP guidelines, and applicable regulatory requirements.

The regulatory application or submission for regulatory approval will be made by the Sponsor or designated third party (e.g., CRO) 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, any other materials provided to the patients, and further requested information will be submitted by the Sponsor or the Investigator to the appropriate IEC/IRB and the Regulatory Authority. The study must be approved by the IEC/IRB and the Regulatory Authority before any IMP may be shipped to the study sites and 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.

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. The Investigator will complete the informed consent section of the CRF for each patient enrolled.

Each patient will be informed that his/her medical (source) records may be reviewed by study monitors, quality assurance auditors, or health authority inspectors, in accordance with applicable regulations, and that these persons are bound by confidentiality obligations.

10.4 Protocol Amendments

Any prospective change to the protocol will be agreed between the Investigator and the Sponsor prior to its implementation. Any such amendments will be submitted to the any

competent IEC/IRB and/or competent authority responsible as required by applicable regulations.

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

10.5 Confidentiality of Patient Data

The Investigator will ensure that the patient's confidentiality is preserved. On eCRFs or any other documents submitted to the Sponsor, the patients will not be identified by their names, but by a unique patient identifier. Documents not intended for submission to the Sponsor, i.e., the confidential subject identification code list, original consent forms, and source records, will be maintained by the Investigator in strict confidence.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Periodic Monitoring

The monitor will contact and visit the Investigator periodically to review all study-related source data/records, verify the adherence to the protocol and the completeness, correctness and accuracy of all CRF entries compared to source data. The Investigator will co-operate with the monitor to ensure that any discrepancies identified are resolved.

For this study, the first monitoring visit shall take place shortly after the inclusion of the first patient. Thereafter, monitoring frequency will depend on study progress, but is expected to be approximately every 4-6 weeks. A study Initiation Visit and Termination Visit must take place.

The monitor must be given direct access to source documents (original documents, data and records). Direct access includes permission to examine, analyse, verify, and reproduce any records and reports that are important to the evaluation of the clinical study. Source data will be available for all data in the CRFs, including all laboratory results.

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 inspectors, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and welfare of the patients have been adequately protected, and that all data relevant for the assessment of safety and efficacy of the IMP have been reported to the Sponsor.

12 REPORTING AND PUBLICATION

12.1 Clinical Study Report

A clinical study report (in accordance with relevant guidelines and the Sponsor's SOPs) will be prepared by the Sponsor after completion of the study. The Octapharma International Medical Director 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 multi-centre studies only in their entirety and not as individual centre data. Authorship will be determined by mutual agreement.

13 LIABILITIES AND INSURANCE

In order to cover any potential damage or injury occurring to a patient in association with the IMP or participation in the study, the Sponsor will contract insurance in accordance with local regulations.

The Investigator is responsible for dispensing the IMP according to this protocol and for its secure storage and safe handling throughout the study.

14 REFERENCES

1. Berger M: Choices in IgG replacement therapy for primary immune deficiency diseases: subcutaneous IgG vs. intravenous IgG and selecting an optimal dose. Current opinion in allergy and clinical immunology 2011;11:532-538.
2. Berger M, Jolles S, Orange JS, et al: Bioavailability of IgG Administered by the Subcutaneous Route. Journal of Clinical Immunology 2013;DOI 10.1007/s10875-013-9876-3-
3. Orange JS, Belohradsky BH, Berger M, et al: Evaluation of correlation between dose and clinical outcomes in subcutaneous immunoglobulin replacement therapy. Clin Exp.Immunol 2012;169:172-181.
4. Misbah S, Sturzenegger MH, Borte M, et al: Subcutaneous immunoglobulin: opportunities and outlook. Clin Exp Immunol 2009;158:51-59.
5. Hagan JB, Fasano MB, Spector S, et al: Efficacy and safety of a new 20% immunoglobulin preparation for subcutaneous administration, IgPro20, in patients with primary immunodeficiency. J Clin Immunol 2010;30:734-745.
6. Wasserman RL, Irani AM, Tracy J, et al: Pharmacokinetics and safety of subcutaneous immune globulin (human), 10% caprylate/chromatography purified in patients with primary immunodeficiency disease. Clin Exp Immunol 2010;161:518-526.
7. Wasserman RL, Melamed I, Kobrynski L, et al: Efficacy, Safety, and Pharmacokinetics of a 10% Liquid Immune Globulin Preparation (GAMMAGARD LIQUID, 10%) Administered Subcutaneously in Subjects with Primary Immunodeficiency Disease. J Clin Immunol 2011;DOI 10.1007/s10875-011-9512-z-
8. Berger M, Rojavin M, Kiessling P, et al: Pharmacokinetics of subcutaneous immunoglobulin and their use in dosing of replacement therapy in patients with primary immunodeficiencies. Clinical immunology (Orlando, Fla.) 2011;doi:10.1016/j.clim.2011.01.006-
9. Berger M: Subcutaneous Administration of IgG. Immunol.Allergy Clin.North Am. 2008;28:779-802.
10. Orange JS, Grossman WJ, Navickis RJ, et al: Impact of trough IgG on pneumonia incidence in primary immunodeficiency: A meta-analysis of clinical studies. Clin Immunol 2010;137:21-30.
11. Gardulf A, Hammarstrom L, Smith CI: Home treatment of hypogammaglobulinaemia with subcutaneous gammaglobulin by rapid infusion. Lancet 1991;338:162-166.
12. Borte M, Bernatowska E, Ochs HD, et al: Efficacy and safety of home-based subcutaneous immunoglobulin replacement therapy in paediatric patients with primary immunodeficiencies. Clin Exp Immunol 2011;
13. Borte M, Quinti I, Soresina A, et al: Efficacy and Safety of Subcutaneous Vivaglobin® Replacement Therapy in Previously Untreated Patients with Primary Immunodeficiency: A Prospective, Multicenter Study. Journal of Clinical Immunology 2011;DOI 10.1007/s10875-011-9588-5-
14. Gardulf A, Bjorvell H, Gustafson R, et al: Safety of rapid subcutaneous gammaglobulin infusions in patients with primary antibody deficiency. Immunodeficiency 1993;4:81-84.
15. Gardulf A, Bjorvell H, Andersen V, et al: Lifelong treatment with gammaglobulin for primary antibody deficiencies: the patients' experiences of subcutaneous self-infusions and home therapy. J.Adv.Nurs. 1995;21:917-927.
16. Gardulf A, Moller G, Jonsson E: A comparison of the patient-borne costs of therapy with gamma globulin given at the hospital or at home. Int.J.Technol.Assess.Health Care 1995;11:345-353.

17. Gardulf A, Hammarstrom L: Subcutaneous Administration of Immunoglobulins: What Are the Advantages? Clin Immunother 1996;6:108-116.
18. Hagan JB, Fasano MB, Spector S, et al: Efficacy and Safety of a New 20% Immunoglobulin Preparation for Subcutaneous Administration, IgPro20, in Patients With Primary Immunodeficiency. Journal of Clinical Immunology 2010;DOI 10.1007/s10875-010-9423-4-
19. Jolles S, Bernatowska E, de GJ, et al: Efficacy and safety of Hizentra((R)) in patients with primary immunodeficiency after a dose-equivalent switch from intravenous or subcutaneous replacement therapy. Clin Immunol 2011;doi:10.1016/j.clim.2011.06.002-
20. Wasserman RL, Melamed I, Nelson RP, et al: Pharmacokinetics of Subcutaneous IgPro20 in Patients with Primary Immunodeficiency. Clin Pharmacokinet. 2011;50:405-414.
21. Ochs HD, Gupta S, Kiessling P, et al: Safety and efficacy of self-administered subcutaneous immunoglobulin in patients with primary immunodeficiency diseases. J.Clin.Immunol. 2006;26:265-273.
22. Guidance for Industry - Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency. 2008.
23. Goldstein B, Giroir B, Randolph A: International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics
18. Pediatr.Crit Care Med. 2005;6:2-8.
24. Taylor E: Intravenous immune globulin (IVIG): hemolytic reactions. Can Adv Reaction Newsletter 2009;19:1-3.
25. Chapel HM, Spickett GP, Ericson D, et al: The comparison of the efficacy and safety of intravenous versus subcutaneous immunoglobulin replacement therapy. J.Clin.Immunol. 2000;20:94-100.
26. Brown BW, Brauner C, Chan A, et al: STPLAN Version 4.3, Calculations for Sample Sizes and Related Problems. n.a. 2006;1-184.

15 APPENDICES

Not applicable.