octapharma

CLINICAL STUDY PROTOCOL

CLINICAL PHASE III STUDY TO MONITOR THE SAFETY, TOLERABILITY AND EFFICACY OF SUBCUTANEOUS HUMAN IMMUNOGLOBULIN (OCTANORM) IN PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES WHO HAVE COMPLETED THE SCGAM-01 TRIAL

Investigational Product:	Octanorm
Indication:	Primary immunodeficiency diseases
Study Design:	Prospective, open-label, non-controlled, single-arm, multicenter phase III study
Sponsor:	OCTAPHARMA Pharmazeutika Prod.Ges.m.b.H., Oberlaaer Strasse 235, 1100 Vienna, Austria
Study Number:	SCGAM-03
BB-IND Number:	15617
ClinicalTrials.gov ID:	NCT02627300
Development Phase:	Phase III
Planned Clinical Start:	2nd quarter 2016
Planned Clinical End:	4th quarter 2020
Date of Protocol:	October 04, 2018
Version:	07

STUDY OUTLINE

<table>
<tr><td colspan="2">Name of Sponsor/Company:
OCTAPHARMA, Pharmazeutika Prod.Ges.m.b.H., Oberlaaer Strasse 235, 1100 Vienna, Austria</td></tr>
<tr><td>Name of Investigational Product:
Octanorm</td><td>Protocol Identification Code:
SCGAM-03</td></tr>
<tr><td>Name of Active Ingredient:
Human Normal Immunoglobulin</td><td>Edition / Date of Protocol:
October 04, 2018</td></tr>
<tr><td colspan="2">Title of Study:
Clinical phase III study to monitor the safety, tolerability and efficacy of subcutaneous human immunoglobulin (Octanorm) in patients with primary immunodeficiency diseases who have completed the SCGAM-01 trial.</td></tr>
<tr><td colspan="2">Indication:
Primary immunodeficiency (PI) diseases</td></tr>
<tr><td colspan="2">Number of Study Center(s):
4–6 selected study sites in the United States.</td></tr>
<tr><td>Study Duration: 2016 to 2020</td><td>Development Phase: III</td></tr>
<tr><td colspan="2">Objectives:
Primary:
To assess the medium-to-long-term safety and tolerability of Octanorm.

Secondary:
• To assess the effect of Octanorm on quality-of-life (QoL) measures.
• To obtain further data on the efficacy of Octanorm.</td></tr>
<tr><td colspan="2">Study Design:
The study is a prospective, open-label, non-controlled, single-arm, multicenter phase III study.</td></tr>
<tr><td colspan="2">Number of Patients:

Patients will be taken exclusively from the cohort of patients who completed the main study SCGAM-01 in the USA, with no restrictions as regards age or treatment regimen. Therefore, the theoretical maximum number of patients will be approximately 35 (the expected number in the main study). No statistical sample-size estimation was performed for this extension study.</td></tr>
</table>

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Name of Active Ingredient: Human Normal Immunoglobulin	**Edition / Date of Protocol:** October 04, 2018

Subject/Patient Selection Criteria:

Inclusion Criteria:

1. Completion of the main study SCGAM-01, with good tolerance of Octanorm (as determined by the investigator).
2. For adult patients: freely given written informed consent. For patients below the legal age of majority: freely given written informed consent from parents/legal guardians and written informed assent from the child/adolescent in accordance with local requirements.
3. For female patients of child-bearing potential, a negative result in a urine pregnancy test conducted at the Screening visit.
4. Willingness to comply with all aspects of the protocol, including blood sampling, for the duration of the study.

Exclusion Criteria:

1. Subject being without any IgG treatment for period greater than approximately 5 weeks between the last infusion of Octanorm in the SCGAM-01 study and the first infusion of Octanorm in the SCGAM-03 study.
2. Exposure to blood or any blood product or derivative, other than IgG used for regular PID treatment, within the 3 months before the first infusion in this study.
3. Planned pregnancy during the course of the study.

Test Product, Dose, Mode of Administration, and Batch Number(s):
Octanorm, human normal immunoglobulin for subcutaneous (SC) administration.

Octanorm will be administered subcutaneously every week (±2 days) or every second week (±2 days) at the doubled weekly dose.

If, during the study, the patient's body weight changes by > 5%, the dose is to be adjusted to keep the dose constant on a ‘milligram per kilogram body weight’ basis.

The patients will continue receiving the same Octanorm dose in milligram per kilogram body weight as was administered at the Week 64 infusion of the SCGAM-01-study.

The ‘corrected’ dosing conversion factor (DCF) will be calculated in the main study SCGAM-01 study, after recruitment of all planned patients for pharmacokinetic assessment. If the ‘corrected’ DCF is already known, then it will be used to calculate the dose in the extension study. Otherwise a value of 1.5 will be used. Later on the ‘corrected’ DCF may be used (for all patients).

The patients' Octanorm dose can be individualized, if considered necessary by the investigator, by titrating upward or downward. This individualization of dosing should take precedence over applying the corrected DCF.

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

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Duration of Treatment:

Patients may remain in the trial until Octanorm becomes commercially available in the USA, the Sponsor decides to terminate the trial, or December 2020 (whichever comes first). A patient may remain in the trial for up to approximately 4.5 years, i.e. receiving a total of approximately 234 Octanorm infusions (or less, if the infusions will be administered bi-weekly)

Reference Therapy, Dose, Mode of Administration:
Not applicable.

Study Outcome Parameters (Primary and Secondary Endpoints):
Safety (primary assessment):

- Occurrence of all treatment-emergent adverse events (TEAEs),
- Occurrence of temporally associated TEAEs,
- TEAEs by speed of infusion,
- Local injection-site reactions,
- Vital signs (blood pressure, pulse, body temperature, respiratory rate),
- Laboratory parameters (hematology, clinical chemistry, basic urinalysis, and tests for viral safety).

Efficacy:

- Measurement of trough total IgG levels; monitoring for infectious diseases.
- Occurrence of serious bacterial infections (SBIs).

Quality of Life:

For QoL assessments, each patient will continue using the same questionnaire as before. That is, the parent or guardian of patients who were below 14 years of age when they entered the main study SCGAM-01 will continue using the Child Health Questionnaire-Parent Form (CHQ-PF50), and patients who were ≥ 14 years of age when they entered the main study will continue using the SF-36 Health Survey.

Summary of Study Procedures and Statistical Analysis Plan
Study Procedures:
Patients will be enrolled only after written informed consent has been obtained by the patient or their legal guardian. For patients under the legal age of majority, written consent must be obtained from the parents or legal guardians. In addition, when required by the local regulatory authorities or Institutional Review Board (IRB), written assent must be obtained from children and adolescents based upon local requirements.

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The first study (Screening) visit of SCGAM-03 with the first Octanorm infusion will be the same visit as the visit in Week 65 (End-of-Study Visit) of the study SCGAM-01.

Eligible patients who have completed the SCGAM-01 study and were treated with any other commercially available SCIG before the start of the SCGAM-03 study (e.g. owing to a delay in local IRB approval for SCGAM-03) are permitted to enter the SCGAM-03 study.

The maximum allowed intermission of IgG treatment after completion of the SCGAM-01 study and before the start of treatment in the SCGAM-03 study is 5 weeks.

Patients for whom the Week 65 visit of the SCGAM-01 study is not identical to the First visit of the SCGAM-03 study will undergo a separate Screening visit with relevant screening procedures. Only after the patient's successful Screening and enrolment into SCGAM-03 study will the first infusion of Octanorm be permitted.

Screening visit assessments, to be performed before the First infusion, will include: physical examination (including weight); blood sampling for hematology, clinical chemistry, viral markers and trough total IgG, urine sample for urinalysis and urine pregnancy test (females of childbearing potential only), and completion of the same QoL questionnaire as used in the SCGAM-01 study. Note that these examinations will, for most patients, be performed within the framework of the main study SCGAM-01 (End-of-Study Visit in Week 65), in which case they need not be repeated at the same visit for SCGAM-03.

Patients will stay at the study site during the infusion, vital signs will be measured just before the start of each infusion given at the study site, then within 1 hour after the end of the infusion.

The patient's diary for the coming period of the home treatment will be issued to the patients. Ongoing adverse events and any relevant concomitant medications will be recorded.

At all subsequent study visits, the patients will undergo the following examinations at the site before the start of infusion: physical examination (including weight), blood sampling for hematology and trough total IgG, clinical chemistry, urine sample for urinalysis, with a urine pregnancy test if indicated. The patient's diary will be collected and reviewed. Other study assessments will be performed as indicated in the Flow Chart of Study Events.

One week after the last infusion, for both regular or premature termination, a termination visit will be performed at the site with the following assessments: physical examination (including vital signs and weight), blood sample for hematology, clinical chemistry, viral markers, and trough total IgG; urine sample for urinalysis and urine pregnancy test (females of childbearing potential only); completion of the QoL questionnaire; collection and review of the patient's diary.

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

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Up to 35 qualifying patients based on the inclusion and exclusion criteria will be enrolled into the SCGAM-03 study. An Independent Data Monitoring Committee will periodically review relevant data with emphasis on thromboembolic events (TEEs).

Statistical Analysis:

The following populations will be considered for the statistical analysis:

- The safety analysis set consisting of all patients who received at least part of one infusion of Octanorm.
- The full analysis set (FAS) is defined according to the intention-to-treat principle and consists of all patients of the safety analysis set who satisfy all major eligibility criteria and for whom any post- baseline data is available; it is the set of eligible patients with treatment effects measured.
- The per-protocol (PP) set consists of all patients of the FAS excluding those with major protocol deviations which may have an impact on the analysis of the primary endpoint. This is the set of patients who participated in the study as intended and for whom the primary endpoint can be evaluated as planned.

Only major protocol deviations with the potential to significantly affect the study results or to invalidate the interpretation of the data obtained will lead to exclusion of patients from the PP set. The membership of each patient in the respective analysis populations will be determined before statistical analysis in a data review meeting by a panel consisting of a medical expert from the Sponsor, the clinical study manager, the data manager and the study statistician

Safety Analysis Plan:

The safety analysis will comprise descriptive statistics, tabulations and listings of all TEAEs, safety laboratory results, vital signs and physical examination findings. All reported AEs will be coded according to MedDRA.

For this extension study, any AE is regarded as treatment-emergent if the patient migrated from the main to the extension study without being treated with another IgG product. If another product was used between the two studies, then an AE in the extension study is classified as treatment-emergent if onset or worsening is after start of the infusion of Octanorm at the screening visit. Only TEAEs are accounted for in the analysis.

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.

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.

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- Number of temporally associated TEAEs.
- Infusion rate at the onset of temporally associated TEAEs (frequencies and percentages).
- Narratives will be prepared describing each death, other SAEs, and other significant AEs that are judged to be of special interest because of clinical importance.

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

FLOW CHART OF STUDY EVENTS

ASSESSMENTS	Screening – First visit (Week 65 of SCGAM-01)	Octanorm Treatment Visits					Termination (ET)
SEQUENCE	---	---	Every 12 Wks[4] [every 24 wks]	---	Every 12 Wks[4] [every 24 wks]	---	---
WEEKS	1	12	24, 36, 48 [36]	60	72, 84, 94, 108, etc [84, 108, 132, etc]	Final Infusion Visit	One week after last infusion
Informed consent, In-/exclusion criteria[3]	x						
Body weight[3]	x	x	x	x	x	x	
Physical examination[3], vital signs[1]	x	x	x	x	x	x	x
IgG trough levels[3]	x	x	x	x	x	x	x
Hematology[3] (CBC, WBC differential, hematocrit, hemoglobin)	x	x	[Wk 36, only]	x	[every 24 wks]		x
Clinical Chemistry[3] (sodium, potassium, glucose, ALT, AST, LDH, total bilirubin, blood urea nitrogen, creatinine)	x	x	[Wk 36, only]	x	[every 24 wks]	x	x
Urine analysis[3]: pH, glucose, ketones, leukocytes, hemoglobin	x	x	[Wk 36, only]	x	[every 24 wks]	x	x
Viral markers[3]: HAV, HBV, HCV, HIV	x			x			x
Urine pregnancy test[2; 3]	x	x	[Wk 36, only]	x	[every 24 wks]	x	x
Infusion of IMP (on site)	x	x	x	x	x	x	
Check for local injection-site reaction	x	x	x	x	x	x	x
Patient diary hand-out and check	x	x	x	x	x	x	x
Quality-of-life questionnaire	x			x			x
Concomitant medication	x	x	x	x	x	x	x
Adverse events	x	x	x	x	x	x	x

[1] Measurements of the vital signs will be carried out before and after the infusion of IMP.

[2] For females of child-bearing potential.

[3] Procedures are to be conducted before the IMP administration (if applicable).

[4] Procedures marked with an "x" will be performed at every on-site visit which occur every 12-weeks. Procedures marked within brackets (eg, [Week 36] or [every 24 wks]) will only be performed at the study week within the brackets, which corresponds to every other on-site study visit.

PROTOCOL SIGNATURES

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

[redacted] [redacted] 17.10.2018

International Medical Director Signature Date
Octapharma Pharmazeutika Produktionsgesellschaft mbH
Oberlaaerstr. 235, A-1100 Vienna, Austria
Tel: [redacted]
[redacted]

[redacted] [redacted] 07 Oct 2018

Director, Clinical Operations Signature Date
Octapharma USA, Inc.
121 River Street, Suite 1201
Hoboken, NJ, USA
[redacted]

[redacted] [redacted] 11-OCT-2018

Manager Biometrics Signature Date
Octapharma Pharmazeutika Produktionsgesellschaft mbH
Oberlaaerstr. 235, A-1100 Vienna, Austria
Tel: [redacted]
[redacted]n

[redacted] [redacted] 17 OCT 2018

Head of Corporate Drug Safety Signature Date
Octapharma Pharmazeutika Produktionsgesellschaft mbH
Oberlaaerstr. 235, A-1100 Vienna, Austria
Tel: [redacted]
[redacted]

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LIST OF ABBREVIATIONS

Abbreviation	Description
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration–time curve
CHQ-PF50	Child Health Questionnaire-Parent Form
CI	Confidence interval
CRO	Contract research organization
CSF	Cerebrospinal fluid
DCF	Dosing conversion factor
eCRF	Electronic Case Report Form
EDC	Electronic data capture
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCG	Human chorionic gonadotrophin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IDMC	Independent Data Monitoring Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IMP	Investigational medicinal product
IRB	Institutional Review Board
IV	Intravenous
IVIG	Intravenously administered immunoglobulin
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
PI	Primary immunodeficiency
PK	Pharmacokinetic(s)
PP	Per protocol
QoL	Quality of life
SAE	Serious adverse event
SBI	Serious bacterial infection

Abbreviation	Description
SC	Subcutaneous
SCIG	Subcutaneously administered immunoglobulin
SF-36	Short Form Health Survey, 36 item
TEAE	Treatment-emergent adverse event
TEE	Thromboembolic event
Tmax	Time to maximum plasma concentration
WBC	White blood cell

1 INTRODUCTION

1.1 Background

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

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

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

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

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

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

Studies of the PK 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 single IVIG dose administered every 3 [or 4] weeks is split into 3 [or 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 (Tmax) was 62.6 h (2.6 days).[8]

With weekly SCIG administrations, only about 4.5 days elapse between the Tmax 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 40–50% 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 SCIG 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 (SBIs) was the most common primary efficacy endpoint in these studies. Secondary endpoints included overall infections (i.e. infections not meeting SBI criteria), missed days at work or school, days in hospital and days on antibiotics. Definitions of overall infections and SBI were not standardized across studies. In 6 studies, SBIs were defined by

FDA criteria and included bacterial pneumonia, meningitis, sepsis, osteomyelitis or visceral abscess. In 2 studies, a SBI was defined as an infection requiring hospitalization.[3]

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

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

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

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

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

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

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

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

1.2 Rationale for Conducting the Study

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

Self-administration at home with small portable pumps or syringes can easily be learned by the patients, which is another advantage of SC administered immunoglobulins (SCIG). It may remarkably improve the patient's quality of life and compliance as it reduces the frequency of hospitalizations and the need for home care. Administration of IgG via the SC

route provides more stable and well-balanced IgG plasma levels until the end of the treatment interval, in contrast with the peak IgG plasma concentrations attained with IVIG solutions which weaken at the end of dose. When effective IVIG therapy cannot be continued because of the lack of peripheral and central vein access, SCIG might also be an alternative treatment option. Experience has shown that replacement therapy with immunoglobulins is lifesaving. If replacement is started early, and if appropriate amounts are given with sufficient frequency, the cycle of recurrent infections and progressive lung damage can be arrested. Near to normal serum IgG levels can be easily maintained.

Post-dose peak levels of SCIG are reached usually 3–6 days after infusion. It has been shown that after infusion, exogenous IgG is distributed relatively rapidly between plasma and extravascular fluid until approximately half is partitioned in the extravascular space. Therefore, a rapid initial drop in serum IgG is to be expected. Several factors such as the endogenous production, the actual catabolism rate, the underlying disease or inter-patient variability help to explain the wide range observed for terminal half-lives. PK data are required for each new product to ensure that it will not behave differently from existing preparations, in terms of appropriate dose and timing of the infusions.

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

The principal purpose of the present (extension) study is to acquire additional safety and tolerability data for patients treated in the medium-to-long term with Octanorm. At the same time, efficacy and quality-of-life (QoL) data will also be acquired.

1.3 Benefit-Risk Statement

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

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

The safety profile of SCIG is well characterized. For Octanorm, 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 terms of efficacy, it can reasonably be assumed that Octanorm exhibits the same effectiveness as other SCIG brands.

Results from the main study (SCGAM-01) have been analyzed in Q1 2017 and none of the results or data acquired in that study affect the above benefit–risk assessment.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the study is to assess the medium-to-long-term safety and tolerability of Octanorm.

2.2 Secondary Objectives

The secondary objectives of the study are:

- To assess the effect of Octanorm on quality-of-life measures.
- To obtain further data on the efficacy of Octanorm.

3 INVESTIGATIONAL PLAN

3.1 Primary and Secondary Endpoints

3.1.1 Primary Endpoint

There is no single primary endpoint in this present extension study. The primary objective is to assess safety and tolerability in medium-to-long-term administration, and this will be assessed by means of the following variables:

- Occurrence of all treatment-emergent AEs (TEAEs) throughout the entire treatment period starting with the first infusion of IMP.
- Occurrence of temporally associated TEAEs.
- TEAEs by speed of infusion.
- Local injection-site reactions.
- Vital signs (blood pressure, pulse, body temperature, respiratory rate).
- Laboratory parameters (hematology, clinical chemistry and tests for viral safety).

3.1.2 Secondary Endpoints

Secondary assessment criteria will be for quality of life and efficacy:

- QoL assessments using the CHQ-PF50 from parent or guardian of patients <14 years of age and the SF-36 Health Survey in patients ≥14 years of age.
- Occurrence of serious bacterial infections (SBIs) as defined in Section 7.2.
- The annual rate of all infections of any kind or seriousness.
- Time to resolution of infections.
- Use of antibiotics (number of days and annual rate).

3.2 Overall Study Design and Plan

The study is a prospective, open-label, non-controlled, single-arm, multicenter phase III safety follow-up study with observation of patients receiving weekly (or bi-weekly at double the weekly dose) doses of Octanorm over a period of up to approximately 4.5 years

The study will be conducted at study sites in the United States that already participated in the SCGAM-01 trial.

Only patients who have completed the main study (SCGAM-01) may be enrolled.

Most patients will migrate directly from the main study into the present extension study. However, some patients are expected to complete the main study before the commencement of the extension study.

Eligible patients who have completed the SCGAM-01 study and were treated with any other commercially available SCIG before the start of the SCGAM-03 study (e.g. owing to a delay in local IRB approval for SCGAM-03) are permitted to enter the SCGAM-03 study.

In the intervening interval they must have received the commercially available SCIG at the approximately same dose which the patient had received in study SCGAM-01. For these patients, the screening visit will be regarded as a fresh start and all screening procedures are to be conducted.

The maximum allowed interval without any IgG treatment before the start of treatment in the SCGAM-03 study is approximately 5 weeks.

Each patient will be treated weekly (or bi-weekly at double the weekly dose) with Octanorm, either at the investigation site (on study visit days) or else at home. Thus the maximum number of study infusions of Octanorm may be up to 234 for each patient (or less if treated bi-weekly). A final examination will be performed 1 week after the last infusion, for both regular and premature termination of the patient's study participation.

The study will be ended when Octanorm becomes commercially available in the USA, the sponsor decides to terminate the trial, or December 2020 (whichever comes first). The maximum total duration of the study for an individual patient may be approximately 4.5 years. Study-related procedures will begin only after written informed consent has been obtained from the patient. For patients who are minors, written consent must be obtained from the parents or legal guardians. In addition, when required by the local regulatory authorities or Institutional Review Board (IRB), written assent must be obtained from children and adolescents based upon the age requirements established by those institutions.

The numbers of patients to be enrolled in each age group will follow the numbers emerging from the main study SCGAM-01 and willing and eligible to continue treatment. At the time of preparation of this protocol these numbers are at most:

- ≥2 years and <5 years of age: up to 5 patients
- ≥5 years and <12 years of age: up to 5 patients
- ≥12 years and <16 years of age: up to 10 patients
- ≥16 years and ≤75 years of age: up to 30 patients
- Total: approximately 35 patients.

An Independent Data Monitoring Committee will continue to periodically review relevant data with emphasis on thromboembolic events (TEEs).

The following interventions and procedures will be performed at predefined time points (see Section 6.1.2): Drawing of blood samples, determination of body weight, review of the patient's diary, physical examination including vital sign assessments, QoL assessments, assessments of local injection-site reactions, urine sampling, and urine pregnancy tests.

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

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

3.3.1 Study Design

The designs of the main study SCGAM-01 and of this extension study take into account the FDA's comments and requests included in the clinical hold letter (dated April 27, 2012) for IND 15019 for another SCIG of Octapharma (gammanorm 16.5%).

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

3.3.2 Dosing

The equivalent monthly dose of IgG is usually determined in one of two ways:

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

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

Compared with weekly administration, PK modelling and simulation (completed in May 2017) predicted that administration of Octanorm 16.5% on a biweekly basis at double the weekly dose results in comparable IgG exposure [slightly higher IgG peak (Cmax) and slightly lower trough (Cmin)].

Therefore, the proposed study design with respect to weekly or bi-weekly dosing is acceptable, having in mind that a corrected DCF will be applied once available. Appropriate dose levels will be maintained by regular monitoring of IgG trough levels.

If the exact DCF is not known, then a value of 1.5 will be used.

The patients will continue receiving the same Octanorm dose (in mg per kg body weight) as was administered at the Week 64 infusion of the SCGAM-01-study.

Dosing will take place on site at study visits, and otherwise at the patient's home, by self-administration or with assistance (relative, care giver etc.).

3.3.3 Control Group(s)

Does not apply in this extension study: all patients will continue the active treatment with Octanorm that they received in the main study SCGAM-01.

3.3.4 Target Parameters

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

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

3.3.5 Statistical Considerations

The FDA Guidance for Industry suggests that, based on historical data, a statistical demonstration of a serious infection rate per person-year less than 1.0 is adequate to provide substantial evidence of efficacy.[22] Therefore, the 99% CI for this rate will be calculated at a descriptive level, without formal statistical testing (statistical tests may be performed on an ad hoc basis if this is considered appropriate).

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

4 STUDY POPULATION

4.1 Population Base

Approximately 35 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. Completion of the main study SCGAM-01, with good tolerance of Octanorm (as determined by the investigator).
2. For adult patients: freely given written informed consent. For patients below the legal age of majority: freely given written informed consent from parents/legal guardians and written informed assent from the child/adolescent in accordance with local requirements.
3. For female patients of child-bearing potential, a negative result in a urine pregnancy test conducted at the Screening visit.
4. Willingness to comply with all aspects of the protocol, including blood sampling, for the duration of the study.

4.1.2 Exclusion Criteria

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

1. Subject being without **any** IgG treatment for period greater than 5 weeks between the last infusion of Octanorm in the SCGAM-01 study and the first infusion of Octanorm in the SCGAM-03 study.
2. Exposure to blood or any blood product or derivative, other than IgG used for regular PID treatment, within the 3 months before the first infusion in this study.
3. Planned pregnancy during the course of the study.

4.2 Prior and Concomitant Therapy

Details of any relevant concomitant medication (antibiotics, corticosteroids, premedication (if used), immunosuppressive or immunomodulatory drugs, blood or any blood product or derivative, IVIG other than Octanorm taken after the SCGAM-01 and before the SCGAM-03 study etc.) must be recorded in the electronic case report form (eCRF). Prior medication will be inferred from the study data of the main study SCGAM-01. For patients with an intermission between the studies SCGAM-01 and SCGAM-03 any additional medications taken in the intervening period are to be recorded.

4.2.1 Permitted Concomitant Therapy

Local anesthetics (EMLA or L-Max (lidocaine) cream, plaster, or similar product) to reduce pain associated with needle insertion are allowed. The use of such medication(s) must be recorded.

Routine premedication to alleviate potential tolerability problems is not allowed during the study. However, patients who experience (or experienced in the SCGAM-01 study) 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 should be avoided.

4.2.2 Forbidden Concomitant Therapy

Treatment with any IMP (other than IgG products) within 3 months before first infusion of Octanorm in SCGAM-03 study, or during the study, is forbidden.

Administration of any blood- or plasma-derived product is forbidden during the study and should only be given for emergency reasons. Patients will be withdrawn from the study if IgG preparations other than Octanorm are administered during the study.

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

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

Immunosuppressive and immunomodulatory drugs are also forbidden.

Octanorm must not be mixed with other medicinal products.

4.3 Withdrawal and Replacement of Patients

4.3.1 Premature Patient Withdrawal

Patients have the right to withdraw from the study at any time for any reason, without the need to justify. The responsible Investigator also has the right to withdraw patients from the study in case of AEs, poor compliance, or administrative reasons.

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 the patient's discontinuation.
- 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 this extension study. A pregnancy test is mandatory for all females of child bearing potential at the Screening Visit, Week 12 Visit, and then every 24-weeks at scheduled study visits following the

Week 12 Visit until the Termination Visit. All female patients of childbearing potential are responsible for using effective contraception during their study participation. If a pregnancy occurs, treatment with the IMP must be stopped immediately and Octapharma's Central Drug Safety Unit must be informed.

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

4.3.2 Patient Replacement Policy

Patients withdrawn from the study for any reason will not be replaced.

4.4 Assignment of Patients to Treatment Groups

In the main study SCGAM-01, patients were recruited into four age strata: ≥2 years and <5 years, ≥5 years and <12 years, ≥12 years and <16 years, and ≥16 and ≤75 years. In the present extension study, they will remain in the strata that they were in for analysis in the main study (irrespective of whether their age changed such as to imply a change of age stratum). Their maximum patient numbers will thus be the same as in the main study SCGAM-01. Each patient will be identified by this previously allocated number throughout the trial; no additional patient or randomization number will be used for this extension study.

All patients enrolled in this study will be treated with Octanorm.

Under no circumstances are patients who participate in this extension study and left it permitted to re-enroll.

4.5 Relevant Protocol Deviations

In the case of any major deviation from this study protocol, 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

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

5 INVESTIGATIONAL MEDICINAL PRODUCT(S)

5.1 Characterization of Investigational Product(s)

Name of Medicinal Product: Octanorm

Active ingredient of Octanorm: Human normal immunoglobulin

Table 1: Biochemical Characteristics of Octanorm

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

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

5.2 Packaging and Labeling

Octanorm is delivered in glass vials. Each Octanorm vial will be labeled in a booklet style as follows:

Master Label Canada

Investigational drug to be used only by a qualified investigator

Octanorm 16.5%
____mL
Protocol #: SCGAM-03
Patient #. |___|___|___|___|

Lot #.: _____
Exp. date: _____

Solution for subcutaneous injection.

1 mL contains: 165 mg protein of which ≥96% is human normal immunoglobulin G.

Store between 2-8°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. After first opening, use immediately.

Dosage: Please refer to the handling instruction provided.

Sponsor: OCTAPHARMA Pharmazeutika Prod.Ges.m.b.H.; Oberlaaerstr. 235, 1100 Vienna, Austria, Tel: [redacted]

Master Label US

Caution: New Drug - Limited by Federal (or United States) Law to Investigational Use Octanorm Study: **SCGAM-03** Unit size:____**mL**

1 mL contains: 165 mg protein of which ≥96% is human normal immunoglobulin G.

Solution for subcutaneous injection.

To be stored at 36 °F to 46 °F, protected from light. Must not be frozen. Keep out of the reach and sight of children.

Must be inspected visually for particulate matter and discoloration before administration. Solutions that are cloudy or have a deposit must not be used.

To be warmed up to room or body temperature before use. After first opening, use immediately. Patient No.: |__|_____|_____|_____|

Dosage: Please refer to the handling instruction provided. BB-IND number: 15617

Sponsor: OCTAPHARMA Pharmazeutika Prod.Ges.m.b.H.; Oberlaaerstr. 235, 1100 Vienna, Austria, Tel: [redacted]

5.3 Conditions for Storage and Use

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

Octanorm must not be used after its expiration date.

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

5.4 Dose and Dosing Schedule

Octanorm is to be administered subcutaneously every week (±2 days) or every second week (±2 days) at double the weekly dose.

A minimum interval of 4 days must be observed between two single subcutaneous infusions.

If, during the study, the body weight changes by >5%, the dose is to be adjusted to keep the dose constant on a 'mg per kg body weight' basis.

SCIG infusions will be administered at the study site or (self-administered) at home.

The infusion is to be given at the study site at Week 1, Week 12, and then every 12-weeks until the Final Infusion Visit.

Each of these study visit dates may deviate ± 2 weeks from the planned date. However, the deviations must not cumulate.

The patients' Octanorm dose can be individualized, if considered necessary by the investigator, by titrating upward or downward and should be based on the difference between each patient's measured serum total IgG trough levels while on Octanorm and each patient's *target* serum total IgG trough level as determined below. This individualization of dosing should take precedence over applying the corrected DCF.

5.5 Preparation and Method of Administration

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

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

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

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

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

Infusion sites:

The maximum number of infusion sites used simultaneously should not exceed 6.

Infusion sites should be at least 2 inches (approximately 5 cm) apart. The actual sites of infusion should be changed with each weekly (or bi-weekly) administration.

Infusion volume:

The volume can be up to 60 mL/per infusion site.

Infusion (flow) rate:

The maximum recommended flow rate is 60 mL/hr/site.

The maximum infusion rate for all sites combined is 240 mL/hr.

Increases in infusion rates and volumes may only be introduced if the previous 2 administrations were well tolerated by the patient.

The infusion volume and the flow rate should be increased gradually as tolerated to prevent infusion site reactions. See the parameters listed in Table 2.

Table 2: Infusion Volume and Flow Rate by Patient Weight

	Recommended Increase for Patients[2] <40 kg	**Recommended Increase for Patients[2] ≥40 kg**
Infusion volume mL/site per infusion cycle[1]	Approximately ≤5mL	Approximately ≤10 mL
Infusion flow rate mL/hour/site per infusion cycle[1]	Approximately ≤5mL	Approximately ≤10 mL

[1] weekly or biweekly depending on dosing regimen

[2] To account for non-precision flow rates of mechanical pumps, actual flow rate increases will be dependent on tubing size, number of infusion sites and needle gauge. Minor deviations in excess flow rates (<2 mL/site) would not be considered protocol deviations.

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

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

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

The inventory and drug dispensing log will be available to the monitor to verify drug accountability during the study. The study monitor will review all empty and partially used vials of IMP and will cross-check versus the patient source documentation (records), eCRF, and drug dispensing log.

After this check, and after the sponsor has granted written approval of destruction, empty or partially used vials should be destroyed at the study site following local policies. The destruction must be documented.

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

5.7.2 Assessment of Treatment Compliance

Patients will receive infusions at the study site and at home (administered at home by the patient or his/her relative or caregiver). 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/school/kindergarten/day care, inpatient hospital stays, and any changes in concomitant therapy between visits. The diary will be reviewed during the patient's infusion visit at the study site.

6 STUDY CONDUCT

6.1 Observations by Visit

6.1.1 Screening Visit

The Screening (First) Visit will in most cases be the same as the last study visit (Termination Visit scheduled in week 65, the End-of-study visit) of the main study SCGAM-01 (since most patients will migrate directly from the main study SCGAM-01 to the present extension study; Section 3.2). Screening procedures are to be conducted *before* the IMP administration for that visit.

If the treatment with Octanorm was interrupted between the SCGAM-01 and extension (SCGAM-03) studies (for details see Section 3.2), then all screening procedures (see study flow chart) are to be conducted at the new Screening visit.

Study-related procedures will begin only after written informed consent has been obtained by the patient or their legal guardian. At the Screening Visit the following activities will be performed (as stated above, these need NOT be duplicated at a single visit):

- Written informed consent.
- Check of inclusion and exclusion criteria.
- Documentation of medical history including all adverse conditions that have occurred after the end of the SCGAM-01 study.
- Recording of all previous drug and non-drug therapies administered after the end of the SCGAM-01 study.
- General physical examination, including body weight and 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).
- Infusion of Octanorm
- Check for injection-site reaction and assessment if necessary
- Issue of patient's diary
- Completion of QoL questionnaire.
- Recording of any concomitant medication and adverse events (only new ones, not previously recorded in the SCGAM-01).

6.1.2 Treatment and Assessment Visits

Each patient who stays in the study for the whole period may receive up to 234 weekly infusions of Octanorm (or less, if infused bi-weekly). On study visit days, administration will be performed on site; otherwise, at home (Section 3.3.2).

At the study visits, the following activities will be performed *before* IMP administration:

- General physical examination, including body weight and vital signs (every visit).
- Drawing of blood samples for total IgG trough level (every visit).
- Drawing of blood samples for safety laboratory parameters (Week 12 Visit, every 24-weeks at scheduled study visits following the Week 12 Visit, and the Final Infusion Visit).
- Drawing of blood samples for viral markers (Week 60 Visit and the Termination Visit).
- Urine sampling including urine pregnancy test (in females of childbearing potential only; Week 12 Visit, every 24-weeks at scheduled study visits following the Week 12 Visit, and the Final Infusion Visit).

During or after IMP administration:

- Completion of QoL questionnaire (Week 60 Visit).
- Collection of the patient diary. The Investigator will review the diary entries and will ask the patient about any AEs that may have occurred and any changes in concomitant therapies (medication and non-drug therapy). Any concomitant medication and adverse events will be recorded. Relevant diary data will be transferred to the eCRF. Discrepancies between patient diary entries and eCRF entries must be explained by the Investigator (every visit).
- Infusion of Octanorm (every visit).
- Check for injection-site reaction and assessment if any reaction is present (every visit).

For laboratory testing please refer to Section 7.3.4.

6.1.3 Termination Visit

One week after the Final Infusion Visit (after patient withdrawal or study termination by one of the events described in Section 6.2.3), a Termination Visit will be performed including the following assessments:

- General physical examination (including vital signs).
- Drawing of blood samples for safety laboratory parameters including viral markers.
- Drawing of blood samples for total IgG trough level.
- Urine sampling including urine pregnancy test (in females of childbearing potential only).

- Completion of QoL questionnaire.
- Collection and review of the patient diary as at the earlier visits (Section 6.1.2) with recording of any AEs and changes in concomitant medications.
- Assessment of any local infusion-site reactions.

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

6.1.4 Interpretation of Time Windows in This Study

For this study the following time windows apply (see Table 3):

Table 3: Time Windows Used in this Study

Time point	Time stated	Tolerance
On site Visits beginning with Week 12	Weeks 12, 24, 36, 48, 60, and each subsequent 12 week visit.	± 2 weeks
Interval between Last Treatment Visit and (early) Termination Visit	1 week	± 5 days
Blood and urine sampling	before IMP administration	-1 day
Octanorm infusions at patient's home	every week (= every 7 days) or bi-weekly (= every 14 days) at double the weekly dose	±2 days ±2 days

6.2 Duration of Study

6.2.1 Planned Duration for an Individual Patient

Patients will receive weekly (or bi-weekly) infusions until Octanorm becomes commercially available in the USA, or the Sponsor decides to terminate the study, or December 2020 (whichever comes first). The total number of infusions will vary for each patient based on the date the patient entered into Study SCGAM-03.

6.2.2 Planned Duration for the Study as a Whole

The study started enrolling in the second quarter of 2016. Completion of the study by the last patient is expected in December 2020, giving total study duration of approximately 4.5 years.

This duration may be shorter if the sponsor decides to end the trial earlier, or when Octanorm becomes commercially available in the USA (for details see Section 3.2).

6.2.3 Premature Termination of the Study

Both the responsible Investigators and the Sponsor reserve the right to terminate the study at any time. Should this be necessary, the procedures will be arranged on an individual study basis after review and consultation by both parties. In terminating the study, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the

patients' interests. Premature termination will be notified in accordance with applicable regulatory requirements.

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

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

Clinical Study:

- At any time the study as a whole will be terminated prematurely if e.g.:
  - New toxicological or pharmacological findings or safety reports invalidate the earlier positive benefit-risk-assessment.
  - If more than 2 TEEs (i.e. ischemic stroke, transient ischemic attack, cerebral infarction, cerebrovascular accident, cerebral thrombosis, embolic infarctions, [acute] myocardial infarction, deep vein thrombosis, pulmonary embolism, venous thrombosis excluding thrombophlebitis) are observed fulfilling the following criteria:
    - assessed as probably or possibly related to Octanorm treatment by Investigator and/or Sponsor;
    - confirmed by the Independent Data Monitoring Committee (IDMC).
  - Any other reason rendering the continuation of the study impossible for the Sponsor.

Study Center:

- At any time the study can be terminated at an individual center if e.g.:
  - The center cannot comply with the requirements of the protocol.
  - The center cannot comply with applicable standards.
  - The required recruitment rate is not met.

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

7 ASSESSMENTS AND METHODS

7.1 Background / Baseline Information

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

Demographic data: All demographic data (age, weight, height, calculated body mass index, ethnic origin, ABO Rhesus blood type) will be taken over from the main study SCGAM-01.

Medical history: All medical history (conditions and surgical treatment) will likewise be taken over from the main study SCGAM-01.

Previous and ongoing therapies: Similarly, previous drug and non-drug therapies (e.g. physiotherapy) will be taken over from the main study SCGAM-01.

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.

7.2 Efficacy Assessments

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

- Number of episodes of SBI, per person-year on treatment, along with type and severity of infection, and time to resolution (primary endpoint).
- Number of episodes of any other infections (including acute sinusitis, exacerbation of chronic sinusitis, acute otitis media, acute bronchitis, infectious diarrhea etc.), along with type and severity of infection, and time to resolution.
- Number of days of use and annual rate of antibiotics (oral, parenteral, oral plus parenteral, prophylactic and therapeutic), along with type and dosage of antibiotic.
- QoL assessments.

For the collection of data for the above measurements, each patient will be provided with an individual diary to be filled in by the patient during the home therapy time. The patient's diary will be checked for accuracy of the data by the Investigator and collected at each study visit. The data will be then transferred into the eCRF. A new diary will be handed out to the patient for the following period until the next infusion visit at the site.

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

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

- Bacterial meningitis.

The presence of any of these infections should be verified by the specific differentiated diagnostic examinations [22] given in Table 4:

Table 4: Diagnostic Criteria for Serious Infection Types

Infection: Bacteremia/sepsis [a] • *Symptoms:* chills, rigors. • *Physical findings:* fever, hypothermia, tachycardia, tachypnea, hypocarbia, hypotension (systolic blood pressure <90 mm Hg or a reduction of ≥40 mm Hg from baseline in the absence of other causes of hypotension), altered mental status, petechiae, purpura, oligouria, cutaneous vasodilation/vasoconstriction. • *Laboratory tests*: **positive blood culture [b]**, leukocytosis (white blood cell (WBC) count >12,000/mm^3), differential WBC count demonstrating >10% immature (band) neutrophils, leukopenia, thrombocytopenia, coagulopathy, lactic acidosis.
Infection: Bacterial Meningitis • *Symptoms*: headache, stiff neck, mental status changes, irritability, decreased feeding (infants), photophobia, nausea/vomiting, rigors, seizures. • *Physical findings*: Kernig's sign, Brudzinski's sign, meningococcal rash, fever of >38 °C oral or >39 °C rectal. • *Laboratory tests:* **positive cerebrospinal fluid (CSF) Gram stain and/or culture and/or positive CSF bacterial antigen assay,** positive blood culture [c], CSF leukocytosis with neutrophil predominance, decrease in CSF glucose.
Infection: Osteomyelitis/Septic Arthritis • *Symptoms*: pain, decreased range of motion, tenderness, edema, redness, warmth over the involved site (local inflammatory symptoms/signs may be lacking in adults). • *Physical findings*: evidence of soft tissue infection adjacent to the involved bone/joint, drainage from sinus tract from involved bone, fever of >38 °C oral or >39 °C rectal. • *Laboratory tests*: positive blood culture, positive probe to bone, positive bone aspirate culture, positive bone biopsy culture, positive bone histopathology, positive joint fluid Gram stain and culture. • *Imaging studies*: **positive X-ray, nuclear medicine bone scan, magnetic resonance imaging scan, or computed tomography scan showing bony destruction with radiolucent areas; for chronic osteomyelitis: sequestra, involucra.**
Infection: Bacterial Pneumonia [d] • *Symptoms*: productive cough/change in character of sputum, dyspnea or tachypnea, chills, chest pain, rigors, headache, fatigue, sweats, anorexia, myalgia. • *Physical findings*: rales; pulmonary consolidation as reflected by: dullness on percussion, bronchial breath sounds, egophony; fever >38 °C oral or >39 °C rectal, or <36 °C, hypothermia (temperature <36 °C oral or <37 °C rectal). • *Laboratory tests*: leukocytosis, differential WBC count of >10% band neutrophils, leukopenia, hypoxemia (PaO_2 <60 mm Hg on room air), positive blood culture, Gram stain and culture of deep expectorated sputum [e], positive culture with or without

positive Gram stain of transtracheal aspirate, pleural fluid culture, lung biopsy, bronchoscopy with bronchoalveolar lavage or protected brush sampling. • *Imaging studies*: **Pulmonary infiltrate with consolidation on chest X-ray** (new in comparison with baseline chest X-ray)
Infection: Visceral Abscess • *Symptoms:* abdominal pain, anorexia, weight loss, cough/pleuritic chest pain (hepatic abscess), rigors (seldom present). • *Physical findings:* intermittent fevers (temperature >38 °C oral or >39 °C rectal), abdominal tenderness, palpable mass, hepatomegaly, jaundice. • *Laboratory tests:* **positive Gram stain and/or culture from the infected site, with isolation of an appropriate pathogen,** positive blood culture, leukocytosis with accompanying left shift, differential WBC count of >10% immature (band) neutrophils, elevated serum amylase concentration (pancreatic abscess), elevated alkaline phosphatase concentration (hepatic abscess) pyuria in renal abscess. • *Imaging studies:* **typical findings on ultrasound, computed tomography scan, magnetic resonance imaging scan, or radionuclide scan**

Notes to Table 4:

Items in bold are considered essential diagnostic features.

a. Two of the following should be present to make the diagnosis of sepsis in adults: temperature >38 °C oral/>39 °C rectal or <36 °C oral or <37 °C rectal; heart rate >90 beats/min; respiratory rate >20 breaths/min, or PaCO2 <32 mm Hg; WBC count >12,000/mm3, <4,000/mm3, or >10% immature (band) forms. For pediatric patients, the definition of sepsis using age-specific criteria as recommended by the International Consensus Conference on Pediatric Sepsis should be employed.[23]

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

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

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

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

7.3 Safety Assessments

Any of the following drug safety information shall be collected: Adverse events (AEs) and serious adverse events (SAEs) temporally associated with administration of IMP.

7.3.1 Adverse Events

7.3.1.1 Definitions

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

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

- For patients who migrate into the extension study without interruption of Octanorm treatment (Section 3.2), all adverse events occurring in the extension study will be considered treatment-related. An adverse event recorded in the main study will not be recorded again in the present one.
- For patients who receive any other IgG brand between the main and the extension studies (Section 3.2), "treatment-emergent" will refer to events with onset after the start of the infusion with Octanorm at the screening visit of the extension study.

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

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

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.

7.3.1.2 Collection

The condition of the patient will be monitored throughout the study. At each visit, whether scheduled or unscheduled, AEs will be elicited using a standard non-leading question such as "How have you been since the last visit / during the previous study period?" For minor

patients not understanding the question, the answer must be obtained from parents or legal guardians. In addition, the patient diaries (if applicable) will be checked by the Investigator for any documented event.

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

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

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

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

7.3.1.3 Severity

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

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

7.3.1.4 Causality

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

- Probable: reports including good reasons and sufficient documentation to assume a causal relationship, in the sense of plausible, conceivable, likely, but not necessarily highly probable. A reaction that follows a reasonable temporal sequence from administration of the IMP; or that follows a known or expected response pattern to the suspected medicine; or that is confirmed by stopping or reducing the dosage of the medicine and that could not reasonably be explained by known characteristics of the patient's clinical state.
- Possible: reports containing sufficient information to accept the possibility of a causal relationship, in the sense of not impossible and not unlikely, although the connection

is uncertain or doubtful, for example because of missing data or insufficient evidence. A reaction that follows a reasonable temporal sequence from administration of the IMP; that follows a known or expected response pattern to the suspected medicine; but that could readily have been produced by a number of other factors.

- Unlikely: reports not following a reasonable temporal sequence from IMP administration. An event which may have been produced by the patient's clinical state or by environmental factors or other therapies administered.
- Not related (unrelated): events for which sufficient information exists to conclude that the etiology is unrelated to the IMP.
- Unclassified: reports which for one reason or another are not yet assessable, e.g. because of outstanding information (can only be a temporary assessment).

Classification of ADRs:

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

- Expected: an ADR that is listed in the current edition of the Investigator's Brochure (or other reference for 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.

7.3.1.5 Outcome

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

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

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

7.3.1.6 Action(s) taken

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

The action taken by the Investigator must be documented:

a. in general

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

b. on IMP

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

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

7.3.2 Local Reactions

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 after each infusion using a 4-point rating scale: 0=none, 1=mild, 2=moderate, 3=severe.

Investigators have to evaluate local reactions within approximately 1 hour after infusion at every study visit, 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 sticks; 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, bleedings (other than small blood drops caused by the needle stick), 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.

7.3.3 Serious Adverse Events

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

- results in death,
- is life-threatening,
- requires hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,

- is a congenital anomaly/birth defect,
- is another important medical event.

Hospitalization is NOT considered an SAE in case of:

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

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

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

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

SAE reporting timelines

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

Contact details will be communicated at the study initiation visit.

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

All SAEs should be reported via fax to the CRO responsible for the USA (Premier Research), fax number [redacted]

Octapharma's 24-hour emergency telephone number is [redacted].

7.3.4 Laboratory Safety Tests

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

The following laboratory tests will be performed during the course of the study to investigate the efficacy and safety and tolerability of Octanorm (Table 5). At each visit, laboratory tests are to be performed before infusion of Octanorm at the study site.

Table 5: Laboratory Tests and Time Points

Test	Timing	Laboratory
Total serum IgG trough levels	At screening and at all subsequent treatment visits.	Local
Hematology (complete blood count, WBC differential, hematocrit, hemoglobin)	At screening, at Week 12, continue every 24 weeks until the Final Infusion Visit, and at the Termination Visit.	Local
Clinical chemistry (sodium, potassium, glucose, ALT, AST, LDH, total bilirubin, blood urea nitrogen or blood urea, creatinine)	At screening, at Week 12, continue every 24 weeks until the Final Infusion Visit, and at the Termination Visit.	Local
Urinalysis: pH, glucose, ketones, leukocytes, hemoglobin.	At screening, at Week 12, continue every 24 weeks until the Final Infusion Visit, and at the Termination Visit.	Local
Urine pregnancy test (women of childbearing potential)	At screening, at Week 12, continue every 24 weeks until the Final Infusion Visit, and at the Termination Visit.	Local
Virology: HAV, HBV, HCV, HIV	At screening, at Week 60, and at the Termination Visit.	Local

WBC, white blood cells; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; HAV/HBV/HCV, hepatitis A/B/C virus; HIV, human immunodeficiency virus.

Local laboratory determinations will be done at the individual study sites according to local procedures.

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

7.3.5 Viral Safety Tests

At the Screening Visit, viral markers will be taken before the Octanorm infusion, and will be tested at the local laboratory according to the site's standard procedures. For patients positive in Hepatitis A virus at screening, follow-up samples may be omitted.

Further viral marker samples will be taken in Week 60 and at the (early) Termination Visit.

7.3.6 Vital Signs

To evaluate short-term tolerance, monitoring of vital signs including blood pressure, body temperature, pulse and respiratory rate will be performed at visits taking place at the clinic/study site; the Screening Visit, then at all subsequent study visits (at 12-weekly intervals), and finally at the Termination Visit (irrespective of whether termination is regular or premature).

Measurements will be carried out before the infusion and (approximately) within 1 hour after the infusion of IMP.

7.3.7 Physical Examination

A general physical examination will be performed at the Screening Visit according to routine procedures and will be as comprehensive as necessary to detect relevant abnormalities. If any findings are abnormal (only the findings newly occurred since end of the SCGAM-01 study),

the Investigator will document the start date and whether or not the abnormal finding is still present at the start of treatment. The physical examination will be repeated at all subsequent study visits (at 12-weekly intervals), and finally at the Termination Visit (irrespective of whether termination is regular or premature). Clinically relevant worsening from the status at screening will be documented as an AE.

7.3.8 Other Relevant Safety Information

a) Post study related safety reports

Any SAE which occurs up to four weeks after the completion of the study should be reported by the Investigator to the sponsor if the investigator becomes aware of it. Proactive monitoring for post-study SAEs is not required. If a post study SAE is identified, the investigator should complete a SAE form. Relation to the clinical study should be stated on the report.

If a patient dies within 4 weeks after the last IMP administration, this should be reported as well, irrespective of whether or not it is 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 (fetal exposure to the IMP) need to be reported.

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

c) Overdose, interaction and medication error

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

d) Drug overdose

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

e) Interaction

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

f) Medication error

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

7.4 Other Assessments

7.4.1 Drug Concentration Measurements

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

7.4.2 Quality of Life Assessment

QoL assessments will be made using the Child Health Questionnaire-Parent Form (CHQ-PF50) from parent or guardian of patients <14 years of age and the SF-36 Health Survey in patients ≥14 years of age. The QoL assessments will take place at the screening, at Week 60, and at the (early) Termination Visit.

7.5 Appropriateness of Measurements

Safety will be monitored by standard assessments.

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

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

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

8 DATA HANDLING AND RECORD KEEPING

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

8.1 Documentation of Data

8.1.1 Source Data and Records

Source data are defined as all of the information related to clinical findings, observations, or other activities in the study, written down in original records or certified copies of original records. The investigator will maintain adequate source records (e.g., case histories or subject/patient files for each subject/patient enrolled). Source records should be preserved for the maximum period of time required by local regulations.

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

All data entered in the CRF must be supported by source data in the subject/patient records with the 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 source data/records.

The investigator may authorize 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.

The following data must be verifiable from the source records: patient's inclusion in Study SCGAM-03, patient number, sex, weight, date of birth, written informed consent, medical history, main inclusion and exclusion criteria, local laboratory test results, PID relevant concomitant therapies (medication and non-drug therapy), any AE occurring in the course of the study, details of infusions (batch number, number of vials used, date, dose, rate and site(s)), date and reason for premature withdrawal (if applicable). As part of the source records, laboratory data will be reviewed by the Investigator, assessed as to their clinical significance, signed and dated.

8.1.2 Electronic Case Report Forms (eCRF)

For each patient enrolled, an eCRF will be completed within the electronic data capture (EDC) system and approved by the Investigator or an authorized sub-investigator.

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 eCRF before 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 appear on the delegation of authority log.

The following data may be entered directly into the EDC system, without prior record of source data, turning the eCRF into source: dates of blood sampling, vital signs.

If any errors in the eCRFs are found during the data review process discrepancies will be generated programmatically within the EDC system, and 'manual' queries will be generated by either a monitor or Data Management. The programmed checks fire automatically once an eCRF page is saved within the system. The outputs of the programmed checks are referred to as 'discrepancies'. Discrepancies are generated by the input of illogical eCRF data with the purpose to clarify the context or insertion of illogical or missing data with the site or designee.

All discrepancies (programmed and manual) will be submitted to the site personnel or monitor for the site within the EDC system. Once the site responds to a discrepancy, Data Management or the monitor will review the new or changed data to ensure an appropriate response and close the discrepancy within the system.

8.1.3 Changes to Case Report Form Data

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

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

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

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

8.1.4 Handling of Missing Data

In general, missing data will not be imputed: calculations pertaining to person-year computations will be based on observed values only. Only in case of missing body weight, the last available weight measurement will be used for calculating the dose per kg bodyweight (last observation carried forward).

If missing values occur in the confirmatory analysis of the primary endpoints, they will be imputed by worst observed values and thus be ranked at the end of the list for the Wilcoxon-Mann-Whitney test. Last-observation-carried-forward (LOCF) and observed-cases (OC) analyses will be applied as well as mixed models to explore the sensitivity of the results with regard to imputation techniques.

8.2 Information of Investigators

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

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

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

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

8.3 Responsibilities

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

A "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 tasks relating to the study.

The Investigator is responsible for coordinating the study locally.

8.4 Investigator's Site File

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

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

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

8.5 Provision of Additional Information

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

8.6 Independent Data Monitoring Committee

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

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

All the patients who complete the main study SCGAM-01 and who are willing and eligible to continue study treatment will be included in the present extension study. At the time of preparation of this protocol is it anticipated that approximately 35 patients will take part in the extension study (Section 3.2). No further sample-size considerations apply.

9.2 Statistical Analysis

No confirmatory statistical analysis will be performed; the results of this extension study will be presented at the descriptive level only.

9.2.1 Population for Analysis

The following populations will be considered for the statistical analysis:

The **safety analysis set** consists of all patients who received at least part of one infusion of Octanorm within this extension study.

The **full analysis set (FAS)** is defined according to the intention-to-treat principle and consists of all patients of the safety analysis set who satisfy all eligibility criteria and for whom any post screening data in this extension study are available. It is expected that the FAS will coincide with the safety set.

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

Only major protocol deviations with the potential to affect the study results significantly or to invalidate the interpretation of the data obtained will lead to exclusion of patients from the PP set; protocol deviations to be considered will include (but will not be limited to):

- Violations of the study entry criteria.
- Administration of any other blood or plasma-derived product or of any other immunoglobulin preparations during the SCGAM-03 study.
- Any prohibited concomitant medication (including long term corticosteroids, daily, ≥0.15 mg of prednisone or equivalent/kg/day, immunosuppressive and immunomodulatory drugs).
- Failure to attend two scheduled consecutive visits OR three or more scheduled visits during the study for reasons other than clinical reasons.

Efficacy endpoints will be analyzed on the basis of FAS. Analysis of the safety endpoints will be based on the safety set.

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

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

9.2.2 Efficacy Analysis Plan

No confirmatory efficacy analysis will be performed.

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

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

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

The FDA Guidance for Industry suggests that, based on historical data, a statistical demonstration of a serious infection rate per person-year less than 1.0 is adequate to provide substantial evidence of efficacy.[22] Therefore, this background information will be used for a descriptive evaluation of the serious infection rate in this extension study. Exploratory statistical testing may be performed if considered appropriate.

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

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.
- Infusion rate at the onset of temporally associated TEAEs
- Narratives will be prepared describing each death, other SAEs, and other significant AEs that are judged to be of special interest because of clinical importance.

9.3 Randomization / Stratification / Code Release

There is no randomization in this study. The patients will be recruited into 4 age strata (≥2 years and <5 years, ≥5 years and <12 years, ≥12 years and <16 years, and ≥16 years and ≤75 years).

9.4 Interim Analysis

No interim analysis is planned.

10 ETHICAL / REGULATORY, LEGAL AND ADMINISTRATIVE ASPECTS

10.1 Ethical / Regulatory Framework

This study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki. Before submission of the study protocol to the IRB and Competent Authority, the study will be registered in ClinicalTrials.gov. The study protocol and any subsequent substantial amendment(s), as well as a sample of the information sheet and informed consent form, any other materials provided to the patients, and further requested information will be submitted to the IRB and the Competent Authority. The study will be conducted in compliance with the protocol, GCP and the applicable regulatory requirements.

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

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

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

10.2 Approval of Study Documents

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

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

10.3 Patient Information and Informed Consent

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

For minor patients, freely given written consent must be obtained from parents or legal guardians. In addition, when required by the local regulatory authorities, IRBs, written assent

must be obtained from children and adolescents based upon the age requirements established by those institutions.

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

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

10.4 Protocol Amendments

Any prospective change to the protocol will be agreed between the Investigator (Coordinating Investigator in multicenter studies) and the Sponsor before its implementation. Any such amendments will be submitted to the IRB and/or Competent Authority responsible as required by applicable regulations. 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 Patients' Data

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

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Periodic Monitoring

The 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 subject/patient. Thereafter, monitoring frequency will depend on study progress but is expected to be approximately every 10-18 weeks.

The monitor must be given direct access to source documents (original documents, data and records). Direct access includes permission to examine, analyze, 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 IRB / Regulatory Authority inspectors, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and welfare of the patients have been adequately protected, and that all data relevant for the assessment of safety and effectiveness of the IMP have been reported to the Sponsor.

12 REPORTING AND PUBLICATION

12.1 Clinical Study Report

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

12.2 Publication Policy

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

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

13 LIABILITIES AND INSURANCE

To cover any damage or injury occurring to a patient in association with the investigational medicinal product or the participation in the study, the Sponsor will contract insurance in accordance with local regulations.

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

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