octapharma

Statistical Analysis Plan

Study ID	SCGAM-03
Study title	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.
Study phase	III

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Document History

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Final v2.0	17-Jul-2019	[redacted]	Ensure conformance with the latest protocol versions (v 7.0 for the US, v 5.0 for Canada) and decisions made with respect to the analysis of the predecessor study SCGAM.-01

Abbreviations

AE	Adverse Event
ALAT	Alanine Aminotransferase
ASAT	Aspartate Aminotransferase
BMI	Body Mass Index
CBC	Complete Blood Count
CHQ-PF50	Child Health Questionnaire - Parent Form
CI	Confidence Interval
CSR	Clinical Study Report
(e)CRF	(Electronic) Case Report Form
ELISA	Enzyme-Linked Immunosorbent Assay
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
IgG	Immunoglobulin G

IMP	Investigational Medicinal Product
ITT	Intention-To-Treat
IVIG	Intravenous Immunoglobulin
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
NAT	Nucleic Acid Test
PI	Primary Immunodeficiency
PP	Per Protocol
PT	Preferred Term
QoL	Quality of Life
TEAE	Treatment Emergent Adverse Event
TEE	Thromboembolic Event
WBC	White Blood Cell
SAF	Safety Set
SAP	Statistical Analysis Plan
SBI	Serious Bacterial Infections
SOC	System Organ Class

Table of Contents

1. Preface

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Octapharma Protocol SCGAM-03:

Study title for the USA: *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*

Study title for Canada: *Clinical phase III study to monitor the safety, tolerability and efficacy of subcutaneous human immunoglobulin (octanorm) in patients with primary immunodeficiency diseases, including (but not limited to) those who have completed the SCGAM-01 trial*

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

Study SCGAM-03 was initally designed as an extension of study SCGAM-01 in the sense that patients were to be taken exclusively from the cohort of patients who completed study SCGAM-01 in the USA; this was changed by allowing enrollment of Canadian patients who did not participate in the predecessor study. The primary focus of SCGAM-03 is to assess the medium-to-long-term safety and tolerability of *octanorm*.

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

The following documents were reviewed in preparation of this SAP:

- Clinical Study Protocol SCGAM-03, Final Version 07, dated October 4, 2018 (for the US), and Final Version 05, dated October 25, 2017 (for Canada) respectively.

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

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

2. Purpose

This SAP outlines all statistical analyses to be performed on data collected in study SCGAM-03, and the resulting output that will be compiled to support the completion of the Clinical Study Report (CSR).

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

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

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

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

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

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

3. Study Objectives and Endpoints

3.1. Study Objectives

3.1.1. Primary Objective

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

3.1.2. Secondary Objectives

The secondary objectives of the study are:

- To assess the effect of *octanorm* on quality-of-life (QoL) measures.
- To obtain further data on the efficacy of *octanorm*.

3.2. Study Endpoints (Target Variables)

3.2.1. Primary Target Variables

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 outcome variables:

- Occurrence of 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).
- Physical examination.
- Laboratory parameters (haematology, clinical chemistry and tests for viral safety).

3.2.2. Secondary Target Variables

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. Age here refers to the age at enrollment into study SCGAM-01, so that each patient will continue using the same questionnaire as before.
- Total IgG trough levels.
- Occurrence of serious bacterial infections (SBIs) as defined in Section 10.
- 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).
- Missed days from work/school/kindergarten/day care.

4. Study Methods

4.1. Overall Study Design and Plan

Study SCGAM-03 is designed as a prospective, open-label, non-controlled, single-arm, multicentre phase III safety follow-up study with observation of patients receiving weekly or bi-weekly doses of *octanorm* over a period of up to two years.

The study will be conducted at study sites in the United States that already participated in the SCGAM-01 trial, and at study sites in Canada enrolling 'de novo' patients who are under other SCIG treatment.

Most US patients will migrate directly from the main study to the present extension study. However, some patients are expected to complete the main study before the commencement of the extension study. Therefore, the following rules are instituted:

a) Patients who complete the main study after the start of the extension study will be required to migrate directly into the extension study, so that treatment with *octanorm* is not interrupted. (For these patients, the screening visit in the extension study will be the same as the final visit in the main study; extension-study screening tests that also constitute main-study tests for that visit do not need to be duplicated.) Use of an IgG product other than *octanorm* between the main and extension studies will disqualify a patient from entry to the extension study.

b) Patients who completed the main study before the start of this extension study will be allowed to continue IgG treatment with any commercially available SCIG until the time when they can be treated within the extension 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.)

Each patient will be treated weekly or bi-weekly with *octanorm*, either at the investigation site (on study visit days) or else at home. 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) A final examination will be performed 1 week after the last infusion, for both regular and premature termination of the patient's study participation.

4.2. Age groups

As of protocol version 9 of the predecessor study SCGAM-01, the age ranges for the four age strata were revised to: ≥2 years and <6 years, ≥6 years and <12 years, ≥12 years and <17 years, ≥17 years and ≤75 years. In the present extension study, patients 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). The maximum patient numbers in each age group will thus be the same as in the main study SCGAM-01. The analyses will reflect these age strata unless the number of patients per stratum is too low for reasonable statistical summaries; if this happens adjacent strata might be combined as indicated by the data.

In addition, and to align the analysis with the results of the SCGAM-01 study, a different definition of age groups (2 to < 12, 12 to < 17, 17 to 65, and > 65 years) will be evaluated, and also a comparison of male vs. female subjects will be performed for primary and secondary endpoints.

4.3. Selection of Study Population

The study population consists of patients of both sexes who completed study SCGAM-01. All patients therefore have a confirmed diagnosis of PI and require immunoglobulin replacement therapy due to hypogammaglobulinaemia or agammaglobulinaemia. All patients have been on stable treatment with *octanorm* during the SCGAM-01 study, possibly followed by a comparatively short period of compatible SCIG treatment with another (commercially available) SCIG product.

5. Sequence of Planned Analyses

5.1. Final Analyses and Reporting

As stated in section 4.1, each patient is treated with *octanorm* over a total periodof up to 4.5 years; one week after the last infusion a follow-up visit is performed, and the patient will be switched to a commercially available immunoglobulin product at the discretion of the investigator. Once the last patient has completed the study, data validation will be completed and the database will be locked according to the applicable standard operating procedures. This process includes a data review, the identification and classification of any protocol violations as detailed in section 7, and thus the patient disposition with respect to the analysis populations. All final, planned, analyses identified in the protocol and in this SAP will be performed only after the last patient has completed the study, the subject disposition has been agreed and documented, and the final SAP has been approved.

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

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

6. Sample Size Determination

Approximately 45 patients are planned in total:

- Patients will be taken from the cohort of patients who completed the main study SCGAM-01 in the USA and Canada. The theoretical maximum number of SCGAM-01 patients will be approximately 35 (the expected number in the main study).
- Approximately 10 de novo patients who are under other SCIG treatment, but did not participate in the main study SCGAM-01 are planned in Canada.

No further sample-size considerations apply.

6.1. Patient Replacement Policy

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

6.2. Premature Termination of the Study

Both, the responsible Investigators and the Sponsor, reserve the right to terminate the study as a whole or centre-wise 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. Please refer to the protocol for further details on premature termination.

7. Analysis Populations

The following populations will be considered for the statistical analysis:

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

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

Efficacy endpoints will be analysed on basis of the FAS.

Any analysis might be repeated on basis of the PP analysis set if indicated by the data or in case the PP population differs from the FAS by 3 patients or more, to allow for an assessment of the robustness of the results with respect to protocol violations.

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

8. General Issues for Statistical Analysis

Descriptive summaries will be presented for each of the primary and secondary variables. In general, summaries will be completed for all patients overall and by age group as described in section 4.2.

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

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

Whenever appropriate, the analyses will be stratified according to the predefined age groups taken from the SCGAM-01 study (2 to <6 | ≥6 to <12 | ≥12 to <17 | ≥17 to ≤75).

Additionally, for primary and secondary endpoints, the following subgroups will be investigated:

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

8.1. Analysis Software

Statistical analyses will be performed using SAS Software version 9.1 or higher.

8.2. Withdrawals

Patients who withdraw from the study prematurely will be considered in all data presentations for which they contribute data; in particular for the analysis of annual rates they will be considered with their actual observation periods.

8.3. Handling of Missing Data

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

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

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

For adverse events the following will be applied:

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

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

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

8.4. Derived and Computed Variables

The following derived and computed variables have been initially identified as important for the analysis of the primary and secondary target variables. It is expected that additional variables will be

required. The SAP will not be amended for additional variables that are not related to the primary target or key secondary target variables. Any additional derived or computed variables will be identified and documented in the SAS programs that create the analysis files. If the SAP is not amended, further derivations related to primary and secondary target variables will be described in the CSR.

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

Calculation of the confidence intervals of these rates will account for intra-patient correlation in incidents following a compound Poisson process model.[1]

With C_i infections for the i^{th} patient, and C total infections, the adjusted 2-sided 98% CI is calculated by:

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

- The **rate of infusions with one or more temporally associated AEs** will be calculated for each patient as r = (Number of infusions with one or more temporally associated AEs) / (Number of infusions started). An AE is defined as a temporally associated if, and only if, the onset (or worsening) is either during an infusion of study medication or within 72 hours of the end of the infusion. [Unit: N/A]
- The **rate of absence from work or school** will be based on the assumption of 200 working/school days per year, i.e. the rate is to be calculated as R = (1/200)*(Number of days absent from work or school) / (Patient years on *octanorm* treatment) [Unit: 1/years]

9. Study Subjects and Demographics

9.1. Disposition of Subjects and Withdrawals

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

- The frequency and percent of patients in each analysis population, age strata and enrollment group
- The disposition of patients (including number of patients enrolled, number of patients treated, number of completers)
- study withdrawals by reason of withdrawal

9.2. Protocol Violations

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

- All patients for the final analysis

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

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

9.3. Demographics and Other Baseline Characteristics

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

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

  (SAF, FAS, PP)

- Medical History (SAF)

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

- Prior and Concomitant Medications (SAF)

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

- Baseline Physical Examination, including vital signs (SAF)

General patient characteristics and background assessments already available in the SCGAM-01 database will be copied to the SCGAM-03 database for analysis; this includes demographics, medical history, previous and ongoing therapies.

9.4. Measurement of Treatment Compliance

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

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

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

10. Efficacy Analysis

No confirmatory efficacy analysis will be performed.

The rate of SBI per person-year (bacterial pneumonia, bacteraemia/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 two-sided 98% 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.

In case no serious bacterial infections are observed, it is not possible to calculate a confidence interval with the originally planned method using compound Poisson process model; if this happens, two additional analyses will be presented as sensitivity analyses:

1. The originally planned two sided 98% confidence interval will be calculated for the worse case that one bacterial infections would have been observed.
2. The confidence interval will be calculated using a standard Poisson distribution; this second model will also be used as a sensitivity analysis if a very small number of serious bacterial infections is observed, as within patient correlations are negligible for small number of serious bacterial infections.

The annual rate of all infections of any kind or seriousness will also be presented as point estimate, but along with the two-sided 90% CI. This CI will be calculated using a compound Poisson process model to account for intra-patient correlation in incidents as described above; in addition, and as a sensitivity analysis, the same CI will be calculated using the overdispersed Poisson regression model by means of the SAS procedure GENMOD.

The duration of infection will be summarised 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 QoL data will be presented descriptively by visit, along with the change from baseline (i.e. screening visit).

All absences from work or school will be listed with duration and reason for absence. The individual absence rates per person-year will calculated and summarized by descriptive statistics, including the two-sided 90% confidence interval, again calculated on basis of the compound Poisson process model.

All hospitalizations will be listed with duration and indication for the inpatient hospital stay. The individual hospitalizations days per person-year will calculated and summarized by descriptive statistics, including the two-sided 90% confidence interval, again calculated on basis of the compound Poisson process model.

11. Safety and Tolerability Analyses

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

11.1. Adverse Events

All reported AEs will be coded according to MedDRA.

An AE is defined as treatment-emergent, if first onset or worsening is during the *octanorm* treatment period. Only treatment-emergent AEs (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:

- 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.

11.2. Infusions with One or More Temporally Associated AEs

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

11.3. Infusion Site Reactions

Infusion Site Reactions are captured on a separate eCRF page; summaries will be prepared for

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

11.4. Clinical Laboratory Evaluations

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

- Standard hematology
    - Complete blood count [CBC]
    - WBC differential
    - Hematocrit
    - Hemoglobin
- Clinical chemistry
    - Sodium

  - Potassium
  - Glucose
  - Alanine aminotransferase [ALAT]
  - Aspartate aminotransferase [ASAT]
  - Lactate dehydrogenase [LDH]
  - Total bilirubin
  - Blood urea nitrogen
  - Creatinine
- Urinalysis
  - pH
  - Glucose
  - Ketones
  - Leukocytes
  - Hemoglobin
  - Urine pregnancy test (women of childbearing potential)

All laboratory assessments will be done at the local laboratories according to the site's standard procedures.

Total serum IgG trough levels will be determined by the local laboratories.

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

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

11.5. Viral Markers

Virology markers will be assessed at the screening visit, at visit 6 and at the (early) termination visit, and will include: HAV, HBV, HCV, HIV.

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

11.6. Vital Signs

To evaluate short-term tolerance, 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.

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

11.7. Further Safety Evaluations

11.7.1. Physical Examination

A general physical examination will be performed at the Screening Visit 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.

12. Reporting Conventions

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

12.1. General Reporting Conventions

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

12.2. Population Summary Conventions

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

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

13. References

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

14. Tables, Listings and Figures

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