Statistical Analysis Plan

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Study phase	III

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Approved by

Name *Function, affiliation*	*Date and signature*
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Document History

Version	Date	Author	Description
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V2.0	20-May-2021	[redacted]	Revision to definition of T_{eow} to include early termination subjects
v3.0	11-Feb-2022	[redacted]	Additional detail added to SAP to clarify intended table and listing output.

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

Contents

1. Preface

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Octapharma Protocol SCGAM-06: *Clinical phase 3 study to monitor the safety, tolerability, and efficacy of subcutaneous human immunoglobulin (CUTAQUIG) administered at modified dosing regimens in patients with primary immunodeficiency diseases*

This phase III study is conducted in the USA with the primary focus to monitor the safety, tolerability and efficacy properties of *CUTAQUIG* in patients when administered at a modified dosing regimens in patients with primary immunodeficiency diseases.

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-06, Version 02, dated August 28, 2019

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

[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 the SCGAM-06 study, 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 Objectives

The co-primary objectives of this study are to assess CUTAQUIG administered using the following infusion parameters:

- Compare total IgG trough levels from weekly infusions to every other week infusions
- Safety and tolerability when administered at increased infusion volumes at each infusion site
- Safety and tolerability when administered at increased infusion flow rates at each infusion site
- Safety and tolerability when administered on an every other week dosing regimen

3.1.2. Secondary Objective

The secondary objectives of this study are to:

- Assess the effect of CUTAQUIG on quality-of-life (QoL) measures
- Obtain further data on the safety and efficacy of CUTAQUIG

3.2. Study Endpoints (Target Variables)

3.2.1. Primary Target Variables

The co-primary objectives are to compare total IgG trough levels from weekly infusions to every other week infusions and to assess safety and tolerability of increased infusion volumes and increased infusion rates at each infusion site and every other week dosing. These will be assessed using the following variables:

- Change in individual total IgG trough levels from weekly infusions to every other week infusions (Cohort 3)
- Occurrence of treatment-emergent AEs (TEAEs) throughout the entire Stabilization and Treatment Periods starting with the first infusion of IMP
- Occurrence of TEAEs temporally associated with CUTAQUIG delivered during the Treatment Period
- Occurrence of TEAEs temporally associated with CUTAQUIG delivered during the Stabilization Period
- TEAEs by speed of infusion
- Local infusion-site reactions
- Laboratory parameters (hematology, clinical chemistry, urinalysis)

3.2.2. Secondary Target Variables

Secondary assessment criteria will evaluate quality of life, along with additional evaluations of CUTAQUIG safety and efficacy being administered according to 3 different infusion parameters. These will be assessed using the following variables:

- QoL assessments using the Short Form Health SurveySF-36 or SF-10
- Occurrence of serious bacterial infections (SBIs)
- Annual rate of all infections of any kind or seriousness
- Time to resolution of infections
- Use of antibiotics (number of days and annual rate)
- Individual profiles of IgG trough levels over time (all cohorts)

- Vital signs (blood pressure, pulse, body temperature, respiratory rate)

3.3. Overall Study Design and Plan

Study SCGAM-06 is designed as a prospective, open-label, non-controlled, 3-arm, multicenter, phase 3 study with observation of patients receiving weekly doses of CUTAQUIG at increasing infusion volumes or flow rates, receiving every other week doses of CUTAQUIG at double the weekly dose, over a period of up to approximately 6 months.

The study will be conducted at approximately 15 study sites in the United States of America.

Patients who participated in the SCGAM-03 trial may be provided the opportunity to participate along with new patients.

After completing the Screening Period and being assigned to 1 of 3 cohorts (as described below), patients will enter a 4-week Stabilization Period that will allow one to adjust and familiarize to CUTAQUIG. Patients completing the SCGAM-03 study at the same time of screening for the SCGAM-06 study will not be required to go into the Stabilization Period. Following the Stabilization Period, patients will enter a 24 week Treatment Period and begin their infusion parameters according to their Cohort assignments:

Cohort 1 (increased volume at each infusion site – patients will receive CUTAQUIG weekly and increase infusion volumes every 4 weeks): Patients will return to the clinic for the Treatment Period Baseline Visit, at which they will receive the same body-weight dependent (mg/kg) dose but the volume per site will be increased by up to 25 mL/site for patients ≥40 kg or 10 mL/site for patients <40 kg. Patients will receive this new volume per site for 4 weekly infusions (Treatment Period Baseline and Weeks 1, 2, and 3), and return to the clinic at Week 4 for their next infusion at an increased volume at each infusion site. This cycle will continue, with infusion volumes increasing up to 25 mL/site for patients ≥40 kg or 10 mL/site for patients <40 kg every 4th infusion until reaching a patient's maximum dose (in mL), maximum tolerated volume (maximum volume based on Investigator's decision of patient's tolerance), or 100 mL at 1 injection site – whichever is lower.

Cohort 2 (increased infusion rate - patients will receive CUTAQUIG weekly and increase infusion rates every 4 weeks): Patients will return to the clinic for the Treatment Period Baseline Visit, at which they will receive the same body-weight dependent (mg/kg) dose of CUTAQUIG but the infusion rate per site will be increased by up to 25 mL/hr/site for patients ≥40 kg or 10 mL/hr/site for patients <40 kg. Patients will receive this new flow rate for 4 weekly infusions (Treatment Period Baseline and Weeks 1, 2, and 3), and return to the clinic at Week 4 for their next infusion at an increased infusion rate. This cycle will continue, with flow rates increased up to 25 mL/hr/site for patients ≥40 kg or 10 mL/hr/site for patients <40 every 4th infusion until reaching either a maximum flow rate (100 mL/hr/site) or maximum tolerated flow rate (maximum flow rate based on Investigator's decision of patient's tolerance) is reached.

Cohort 3 (every other week dosing - patients will receive CUTAQUIG every other week at the equivalent of twice their weekly body-weight dependent [mg/kg] dose): Patients will return to the clinic for the Treatment Period Baseline visit to receive their first double mg/kg weekly dose and begin an every other week dosing schedule. Infusion volumes increases per site must not exceed 25 mL at the Treatment Period Baseline visit. If a patient's doubling of their weekly dose requires dosing with a volume of more than 25 mL per injection site, then they will be required to increase the number of infusion sites to remain below the maximum of 25 mL/site volume increase. If this occurs, after 2 infusions the patient may remove one of the newly introduced injection sites as long as the 25 mL/site increase limit is not exceeded.

Approximately 65 patients between the ages of ≥2 years and ≤75 years are planned for enrollment for the study into one of the following three cohorts:

- At least 15 patients in Cohort 1

- At least 15 patients in Cohort 2
- At least 35 patients in Cohort 3

3.4. Selection of Study Population

The study population consists of patients of both sexes who have a confirmed diagnosis of PI and require immunoglobulin replacement therapy due to hypogammaglobulinaemia or agammaglobulinaemia. All patients are established on a consistent or stable mg/kg dose of any SCIG treatment for a minimum of 3 months prior to Screening (Note: patients entering Cohort 3 must be on weekly SCIG infusions for a minimum of 12 weeks). IgG trough levels of 2 previous SCIG infusions are required within one year of Screening, with 1 trough level obtained within 3 months prior to enrollment. A trough serum IgG level $\geq$5.0 g/L in 2 previous infusions is required. Patients with no prior IgG trough level within 3 months prior to enrollment may use the Screening IgG trough level as their 2nd reading.

4. Sequence of Planned Analyses

4.1. Final Analyses and Reporting

As stated in section 3.3, each patient is treated with *CUTAQUIG* over a total period of approximately 28 weeks; one to two weeks 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 6, and thus the patient disposition with respect to the analysis populations.

As patients exit the trial, all data will be reviewed and source data verified. Once a patient's data is considered clean within the eCRF, the patient may be soft locked in order to facilitate database lock in the near future.

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.

5. Sample Size Determination

Approximately 65 patients who meet eligibility criteria will be enrolled in the study:

- At least 15 patients in Cohort 1
- At least 15 patients in Cohort 2
- At least 35 patients in Cohort 3

The co-primary endpoints will be analyzed descriptively, and no formal sample size calculation was done for the overall number of patients enrolled.

For Cohort 3 we plan for a confirmative analysis to evaluate whether the total IgG trough levels are maintained by an every other week dosing regimen; the following pair of hypotheses will be tested:

$$H_a: T_{eow} > T_w - 1 \quad \text{vs.} \quad H_0: T_{eow} \leq T_w - 1$$

where T_{eow} is the mean total IgG trough on steady-state dosing every other week, T_w is the same for weekly dosing, and a maximum decrease of 1 g/L for the mean total IgG trough level is considered acceptable.

T_w will be determined after completion of the Stabilization Period, T_{eow} at a given subject's final study visit where a valid IgG trough level is collected and reported within a suitable visit window. If a subject terminates from the study prior to the end of study visit (2 weeks following Week 24 infusion), or if a completed subject's end of study IgG trough is not valid or not collected, then the last study visit where a valid IgG trough level was collected will be considered T_{eow} .

This one-sided hypothesis will be tested by a paired t-test at the alpha=2.5% level of significance. Assuming 3.0 for the standard deviation common to both members of a pair, and 0.8 as the correlation between members of a pair, this results in a required minimum of 31 evaluable patients to achieve a power of 80%.

5.1. Patient Replacement Policy

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

5.2. Premature Termination of the Study

Both, the responsible Investigators and the Sponsor, reserve the right to terminate the study as a whole or center-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.

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

- New toxicological or pharmacological findings or safety reports invalidate the earlier positive benefit-risk assessment.
- If more than independent 2 TEEs (ie, 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 CUTAQUIG treatment by Investigator and/or Sponsor
    - Confirmed by the IDMC

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

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

- The site cannot comply with the requirements of the protocol
- The site cannot comply with applicable standards
- The site does not meet the required recruitment rate

Should the study be prematurely terminated, all study materials, including IMP, must be returned to the Sponsor.

6. 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 CUTAQUIG.

The full analysis set (FAS) is defined as all patients in the Safety Analysis Set who satisfy all major eligibility criteria and for whom any post-baseline data is available (per intention-to-treat principle). This set of eligible patients will be used for measurement of treatment effects. It is expected that the FAS will coincide with the safety set.

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

Only 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.

Efficacy endpoints will be analyzed using the FAS. Safety endpoints will be analyzed using the Safety Analysis Set. Selected analyses will be repeated for the PP population as detailed in the SAP and its appendices.

In the event that a patient is not treated according to the dosing regimen described for his assigned cohort, the original cohort assignment will still be used for safety and the ITT analyses (SAF and FAS populations). These patients will be removed from the PP population due to protocol violations.

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. Protocol deviations to be considered will include (but not 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-06 study.
- Any prohibited concomitant medication.
- Failure to attend two scheduled consecutive visits OR three or more scheduled visits during the study for reasons other than clinical reasons.

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.

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 substantial or non-substantial and with respect to its effect on the planned analysis. Only substantial 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.

7. 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 study cohort if applicable.

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.

7.1. Analysis Software

Statistical analyses will be performed using SAS Software version 9.3 or higher. Also, PRO CoRE 2.1 Smart Measurement® System software will be used to derive the component scores for the SF-36 and SF-10 questionnaires.

7.2. 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.

7.3. 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 *CUTAQUIG*.

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 considered prior if it starts before and ends before the day of first dose of study drug. A medication will be considered concomitant if it is taken on or after the day of first dose of study drug. A medication will be assumed to be concomitant if it cannot be definitely shown that the medication was not administered on or after the first dose of study drug. Missing dates will not be replaced.

7.4. 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 [Unit: years]
- **Body Mass Index**: BMI = (Body weight) / Height^2 [Unit: kg/m^2]
- The ***CUTAQUIG stabilization period*** is defined for patients that did not participate in the SCGAM-03 trial as the period between the day of first treatment with study drug to the end of the observation period. This will usually be the treatment period baseline visit.
- The ***CUTAQUIG* treatment period** is defined as the period between the day of first treatment with study drug in a modified dosing regimen to the end of the observation period. For patients that previously completed the SCGAM-03 trial, this is also the period of first treatment with the SCGAM-06 study drug. The end of the observation period will usually be the termination visit.
- The **rate of serious bacterial infections** per year during regularly repeated treatment with *CUTAQUIG* will be calculated as r = (Total number of serious bacterial infections occurring in the stabilization and treatment periods) / (Sum of stabilization and treatment periods)[Unit: 1/years]
- The **rate of other infections** will be derived using the same method

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

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

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

If there are 0 infections, an alternative method will be used to approximate the upper bound on the 98% confidence interval using a chi-square distribution and the following SAS code:

```
data poisson;
 events=0;
 sumyrs=xxx;
 ul=cinv(0.99,2*(events+1))/2;
 rate=events/sumyrs;
 ulinc=ul/sumyrs;
run;
where
sumyrs = duration of treatment in years
events = total number of events
```

rate = total number of events per person-year
ulinc = two-sided 98% CI - upper limit

- 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]

8. Study Subjects and Demographics

8.1. 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 study cohort; these will include

- The frequency and percent of patients in each analysis population, age strata (pediatric and adult) 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

8.2. Protocol Violations

Protocol violations will be checked on complete data for all patients prior to defining the analysis populations.

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 6.

Major protocol violations as well as all violations leading to exclusion from the PP population will be summarized by type of violation. Individual patients with these protocol violations will be listed.

8.3. 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 study cohort as applicable; these include:

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

  Prior medications will be presented by non-SCIG product and SCIG product. Concomitant medications will be presented by pre-medication and non-pre-medication. A medication will be considered a pre-medication if it is given prior to an infusion to prevent one or more previously experienced infusion-related symptoms.

  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) at Screening, Stabilization Period Baseline (Week 0), and Treatment Period Baseline

8.4. 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 *CUTAQUIG* 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)
- Injection sites
- Injection flow rates

Deviations from the planned treatment schedule will be examined by summarizing the number of patients with infusions, and 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. The number of patients with infusions, and the number of infusions with an incorrect dose administered will also be summarized.

Study drug exposure will be summarized by planned volume (mL), volume infused (mL), CUTAQUIG dose administered (mg), and CUTAQUIG dose administered by baseline body weight (mg/kg).

9. Efficacy Analysis

The rate of SBI per person-year (bacterial pneumonia, bacteremia/sepsis, osteomyelitis/septic arthritis, visceral abscess, bacterial meningitis) during treatment with CUTAQUIG will be summarized descriptively and a two-sided 98% CI will be presented. Calculation of this CI will account for intra-patient correlation in incidents following a compound Poisson process model. This analysis will also include summaries of the number of patients with any SBI, the number of SBIs, and the duration of treatment (annualized). Furthermore, all observed SBIs will be listed individually and in full detail.

Infections will be analyzed in the same manner as SBIs, except the analysis will be presented by Stabilization Group and Treatment Group separately. Further, the duration of infection will be summarized by severity. The individual characteristics of each infection, including the time to resolution will be listed.

The use of antibiotics will be summarized descriptively and 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. Similarly, systemic antibiotic usage will be presented where antibiotics with the following routes will be excluded: SC, SUBL, OCUL, OTIC, RECT, TOP, BUC, NASAL, TDERM, TOP OD, TOP OS, or TOP OU.

The QoL SF-10 and SF-36 data will be presented descriptively by summarizing derived component scores from PRO CoRE 2.1 Smart Measurement® System software. Observed andchange from baseline (defined as the Treatment Period Baseline Visit) data will be summarized by visit for the following derived component scores:

SF-10- Physical Summary Score and Psychosocial Summary Score;

SF-36- Physical Functioning 0-100 and Norm-based Score, Role Physical 0-100 and Norm-based Score, Bodily Pain 0-100 and Norm-based Score, General Health 0-100 and Norm-based Score, Vitality 0-100 and Norm-based Score, Social Functioning 0-100 and Norm-based Score, Role Emotional 0-100 and Norm-based Score, Mental Heath 0-100 and Norm-based Score, Physical Component Score, and Mental Component Score.

The derived scores and the responses from the SF-10 and SF-36 survey questions will be presented in the listings.

Total serum IgG trough levels will be summarized for observed and change from baseline during the Treatment Period for Cohort 1, 2, and 3.

For Cohort 3, the change in total IgG trough levels when switching from weekly to every other week infusions will be tested confirmatory by means of a one-sided, paired t-test at the α=0.025 level of significance. The following pair of hypotheses will be tested:

$$H_a: T_{eow} > T_w - 1 \quad \text{vs.} \quad H_0: T_{eow} \leq T_w - 1$$

where T_{eow} is the mean total IgG trough on steady-state dosing every other week, T_w is the same for weekly dosing, and a maximum decrease of 1 g/L for the mean total IgG trough level is considered acceptable.

T_w will be determined after completion of the Stabilization Period, T_{eow} at a given subject's final study visit where an IgG trough level is collected and reported within a suitable visit window. If a subject terminates from the study prior to the end of study visit (2 weeks following Week 24 infusion), then the last study visit where a valid IgG trough level was collected will be considered T_{eow} .

10. Safety and Tolerability Analyses

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

10.1. 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 *CUTAQUIG*. 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 statistics will be presented in a summary table:

- Total number of TEAEs reported.

Number of patients with

- Any TEAE
- Any drug related TEAE
- Any TEAE
- Any Drug Related TEAE
- Any Temporally Associated TEAE during Stabilization Period
- Any Temporally Associated TEAE during Treatment Period
- Any Local Site Reaction
- Any Severe TEAE
- Any Serious AE
- Product Withdrawn due to TEAE
- Study Discontinuation due to TEAE
- AE Outcome of Death

Also, the follow TEAE tabulations of patient incidence will be presented:

- Temporally associated treatment-emergent adverse events during stabilization period by system organ class and preferred term
- Temporally associated treatment-emergent adverse events during treatment period by system organ class and preferred term
- Local site reaction treatment-emergent adverse events by system organ class and preferred term
- Treatment-emergent adverse events excluding local site reactions by system organ class and preferred term
- Serious treatment-emergent adverse events by system organ class and preferred term
- Serious treatment-emergent adverse events leading to study discontinuation by system organ class and preferred term
- Non-serious treatment-emergent adverse events by system organ class and preferred term
- Treatment-emergent adverse events leading to product withdrawal by system organ class and preferred term

- Treatment-emergent adverse events leading to early study discontinuation by system organ class and preferred term
- Treatment-emergent adverse events by highest relationship to treatment by system organ class and preferred term
- Treatment-emergent adverse events by maximum severity by system organ class and preferred term
- Infusion total flow rate and temporally associated treatment-emergent adverse events
- Infusion total flow rate associated with temporally related treatment-emergent adverse events- non-local site reactions
- Infusion total flow rate associated with temporally related treatment-emergent adverse events- local site reactions only
- Infusion total flow rate/number of lines associated with temporally related treatment-emergent adverse events- local site reactions only
- Percentage of infusions with one or more temporally associated TEAE

The following table listings of interest will be presented:

- Table listing of serious treatment-emergent adverse events
- Table listing of related treatment-emergent adverse events
- Table listing of related serious treatment-emergent adverse events
- Table listing of treatment-emergent adverse events leading to death
- Table listing of treatment emergent adverse events leading to study drug discontinuation
- Table listing of treatment-emergent adverse events leading to study discontinuation
- Table listing of local site reactions
- Table listing of treatment-emergent incidences of fever safety

Further, all AE data collected, including the infusion rate at onset of TEAE will be presented in by-patient listings.

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

10.2. 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 *CUTAQUIG* 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.

10.3. Clinical Laboratory Evaluations

The following laboratory tests will be performed during the course of the study to investigate the safety and tolerability of *CUTAQUIG*; for the timing of these lab panels and tests please refer to section 7.3.4 (Laboratory Tests) of the protocol:

- Standard hematology
    - Complete blood count [CBC]

  - WBC differential
  - Hematocrit
  - Hemoglobin
- Clinical chemistry
  - Sodium
  - Potassium
  - Glucose
  - Alanine aminotransferase [ALAT]
  - Aspartate aminotransferase [AST]
  - Lactate dehydrogenase [LDH]
  - Total bilirubin
  - Blood urea nitrogen or blood urea 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 central 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.

10.4. 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 according to the flow chart of assessments provided in study outline.

Measurements will be carried out before 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.

10.5. Further Safety Evaluations

10.5.1. 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, 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 subsequent study

visits (at 12 week 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. Summary counts of patients with clinically significant abnormalities will be presented by visit.

11. 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.

11.1. 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.

11.2. 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 6 (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%).

12. 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

13. Tables, Listings and Figures

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