

Statistical Analysis Plan

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Study phase	III

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Document History

Version	Date	Author	Description
Final v1.0	07-Sep-2016	L. Trawniczek	New Document
Final v2.0	13-SEP-2016	L. Trawniczek	Reference to software SAS removed to allow also other statistical packages to be used.
Final v3.0	23-Mar-2018	L. Trawniczek	A calculation method for the confidence limit is added to address the case that no SBIs are observed. Correction of clerical error in the definition of the primary treatment period.

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

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1. Preface

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Octapharma Protocol SCGAM-04: *Clinical phase 3 study to evaluate the efficacy, tolerability and safety of subcutaneous human immunoglobulin (octanorm) in patients with primary immunodeficiency diseases.*

This phase III study is conducted to investigate efficacy and safety of *octanorm* in Russian patients with a confirmed diagnosis of primary immunodeficiency (PI) disease for submission to the national authorities and to support marketing authorization in the Russian Federation.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials¹.

The following documents were reviewed in preparation of this SAP:

- Clinical Study Protocol SCGAM-04, Version 01, dated August 9, 2016

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-04, 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 Reports²) 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 data files 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 evaluate the efficacy of *octanorm* in preventing serious bacterial infections (SBI) compared with historical control data.

3.1.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the tolerability and safety of *octanorm*.
- To assess the effect of *octanorm* on quality-of-life (QoL) measures.

3.2. Study Endpoints

3.2.1. Primary Endpoint

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

3.2.2. Secondary Endpoints

Secondary efficacy endpoints are:

- The annual rate of all infections of any kind or seriousness.
- Non-serious infections (total and by category).
- Time to resolution of infections.
- Use of antibiotics (number of days and annual rate).
- Hospitalisations due to infection (number of days and annual rate).
- Episodes of fever.
- Days missed from work/study due to infections and their treatment.
- QoL assessment using the SF-36 Health Survey.
- Trough levels of serum total IgG throughout the study.

Secondary safety endpoints are:

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

4. Study Methods

4.1. Overall Study Design and Plan

Study SCGAM-04 is designed as a prospective, open-label, non-controlled, single-arm, multicentre phase 3 study with an 8 weeks wash-in/wash-out period, followed by a 6-month efficacy period. Each patient who stays in the study for the whole period will receive 32 weekly subcutaneous (sc) infusions of *octanorm*.

Only patients suffering from PI who are on IVIG treatment may be enrolled. The study will be conducted at approximately 5 study sites in Russia.

Patients will be treated weekly with *octanorm*, either at the investigation site (for at least the first 4 infusions and every 4 weeks thereafter) or else at home.

Before starting home treatment, a diary will be provided to the patients for documenting the date, volume and speed of infusion, occurrence of infections, AEs and local tissue reactions at injection sites, missed days from work/study, inpatient hospital stays, and any changes in concomitant therapies between visits.

A final examination will be performed 1 week after the end of the last infusion, or 1 week after premature withdrawal of a patient from the study, with a telephone follow-up 3 weeks later.

4.2. Selection of Study Population

The study population consists of adult patients (≥ 18 years and ≤ 70 years) of both sexes with a confirmed diagnosis of PI who require immunoglobulin replacement therapy due to hypogammaglobulinaemia or agammaglobulinaemia. All patients must have at least 4 infusions on regular and stable treatment with an intravenous immunoglobulin (IVIG) prior to entering the study. Please refer to the protocol for a complete list of all inclusion and exclusion criteria.

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 period of approximately 32 weeks; one week after the last infusion a follow-up visit is performed. 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 deviations, and thus the patient disposition with respect to the analysis populations as detailed in section 7. 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.

No interim analysis is planned for this study.

6. Sample Size Determination

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

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

6.1. Patient Replacement Policy

Patients withdrawn from the study because of safety or efficacy reasons will not be replaced.

Patients withdrawn from the study for any other reason, e.g., major protocol violation, pregnancy or administrative reasons will also not be replaced. However, if the number of withdrawals exceeds the limit of 15%, the sponsor will assess the situation and decide on a possible replacement policy.

Patients who do not satisfy specific entry criteria during screening may be rescreened following discussion of the individual case with the sponsor.

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 set (SAF) consists of all patients who received at least part of one infusion of *octanorm*; it is the set of patients exposed to treatment.

The full analysis set (FAS) consists of all patients of the safety set who satisfy all major eligibility criteria and for whom any post-baseline data is available. It is the set of eligible patients with treatment effects measured, according to the intention-to-treat (ITT) principle.

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

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

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-04 study.
- Any forbidden concomitant medication (please refer to section 4.2.2 of the protocol).
- 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 SAF.

Efficacy endpoints will be analyzed 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.

8. General Issues for Statistical Analysis

Descriptive summaries will be presented for each of the primary and secondary endpoint variables.

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.

8.1. 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.

8.2. 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 (last observation carried forward, LOCF); 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 after start of the first infusion of *octanorm* (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.

8.3. 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 statistical 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 $(n+1)^{\text{th}}$ 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:** $BMI = (\text{Body weight}) / \text{Height}^2$ [Unit: kg/m²]
- 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.
- Because the octanorm treatment period also includes the wash-in/wash-out phase it is necessary to also define a **primary treatment period**, which starts on the date of the 9th infusion of octanorm (Visit 7/week9) and ends together with the octanorm treatment period defined above. This ensures that any occurring infection can be attributed to a steady-state treatment with octanorm unambiguously. [Unit: years]
- The **rate of serious bacterial infections** per year during regularly repeated treatment with *octanorm* will be calculated as $r = (\text{Total number of serious bacterial infections occurring in the primary treatment periods}) / (\text{Sum of primary treatment periods})$ [Unit: 1/years]
- The **rate of other infections** will be derived using the same method
- The **rate of infusions with one or more temporally associated AEs** will be calculated for each patient as $r = (\text{Number of infusions with one or more temporally associated AEs}) / (\text{Number of infusions started})$. 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 study** will be based on the assumption of 200 working/study days per year, i.e. the rate is to be calculated as $R = (1/200) * (\text{Number of days absent from work or study}) / (\text{Patient years on octanorm treatment})$ [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, and descriptive summaries of population data will be provided; these will include

- The number and percent of patients enrolled, treated, and who completed the study
- The number and percent of patients in each analysis set
- Study withdrawals by reason of withdrawal

9.2. Protocol Deviations

Protocol deviations will be checked on complete data for all treated patients prior to defining the analysis populations. The final decision regarding inclusion/exclusion of patients from the analysis sets will be taken on basis of the Protocol Adherence Report (PAR) and the Deviation Summary Report (DSR) during data review meeting(s) prior to database lock and final analysis, applying the definitions in section 7.

Relevant protocol deviations will be summarized by type of deviation, and individual patients with these protocol deviations 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, including:

- Demographics (Age, Gender, Race/Ethnicity, Height, Weight, BMI (calculated))
(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)

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)
- Injection sites
- Injection flow rates

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 3 days deviation individually.

10. Efficacy Analysis

No confirmatory efficacy analysis will be performed.

The rate of SBI per person-year (bacteraemia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, and visceral abscess) during the treatment period with octanorm will be presented as point estimates of the rate along with a two-sided 95% confidence interval (CI).

Calculation of this confidence interval 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 95% CI is calculated by:

$$\left[e^{\ln(r) - 1.96 \cdot \sqrt{\frac{\sum C_i^2}{C^2}}}; e^{\ln(r) + 1.96 \cdot \sqrt{\frac{\sum C_i^2}{C^2}}} \right]$$

If no serious bacterial events are reported, the upper 95% confidence limit will be calculated by use of the exact Poisson method.

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

All absences from work or study will be listed with duration and reason for absence. The individual absence rates per person-year will be calculated and summarized by descriptive statistics.

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.

An AE is defined as adverse drug reaction (ADR), if the causal relationship to the IMP is assessed as probable or possible.

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. 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 7.3.6 (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 [ASAT]
- Lactate dehydrogenase [LDH]
- Total bilirubin
- Blood urea nitrogen or urea
- Creatinine
- Urinalysis
 - pH
 - Glucose
 - Ketones
 - Leukocytes
 - Urine pregnancy test (women of childbearing potential)

All these laboratory assessments will be done at the local laboratories according to the site's standard procedures; in addition retention samples will be sent to a central laboratory at week 1 and at (early) termination visit.

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.

11.4. Viral Markers

Virology markers will be assessed at screening, and pre-infusion at weeks 1, 4, 16 and 28, and at the (early) termination visit, and will include: HAV, HBV, HCV, HIV, parvovirus B19.

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.

11.5. 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.

Measurements will be carried out before the infusion and within 1 hour after the infusion of IMP, except for temperature which will only be measured before the infusion.

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.

11.6. Further Safety Evaluations

11.6.1. 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 somatic or neurological diseases. The physical examination will be repeated at all subsequent site visits according to the study flow chart, and any changes in the assessment will be recorded. Clinically relevant worsening from the status at screening will be documented as an AE. All initial findings and changes will be listed.

11.6.2. Episodes of fever

The number and percentage of patients with fever, and the number of episodes of fever as totals and per person-year will be presented.

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 DDMMYYYY (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.