octapharma

Statistical Analysis Plan

Study ID	LAS-212
Study title	An open-label, multicenter, Post-Marketing Requirement (PMR) study to investigate the safety, tolerability and efficacy of Octaplas in the management of pediatric patients who require replacement of multiple coagulation factors.
Study phase	IV

Document author	Laurenz Trawnicek, Manager Biometrics, Octapharma
Document version	Final 7.0
Supersedes	6.0
Effective date	01-Dec-2017
Doc ID	2700

Protocol version this SAP is based upon	Final 10 (Doc ID: 2698, 29-Nov-2017)

Approved by

Franz-Josef Tarmann Clinical Project Manager, Octapharma	04-Dec-2017
Laurenz Trawnicek Manager Biometrics, Octapharma	01-Dec-2017
Wolfgang Frenzel International Medical Director, Octapharma	01. Dec. 2017

Document History

Version	Date	Author	Description
Final v1	19-Dec-2013	L. Trawnicek	New document
Final v2	24-Mar-2014	L. Trawnicek	Adjusted to match the revised protocol (v3); in particular the explicit monitoring of SAEs included in the primary endpoint definition.
Final v3	18-Mar-2015	L. Trawnicek	Minor adjustments to match the revised protocol (v5), including the IMP name (Octaplas instead of octaplasLG)
Final v4	10-Feb-2016	L. Trawnicek	Adjusted to match the revised protocol (v6); primarily improved wording and minor clarifications, but also some adjusted time windows.
Final v5	15-Jun-2016	L. Trawnicek	Adjusted to match the revised protocol (v7), in particular the removal of the pre-planned age-strata.
Final v6	08-Sep-2016	L. Trawnicek	The new protocol (v8) demand that at least ⅓ of the patients will be > 2 years is incorporated.
Final v7	01-Dec-2017	L. Trawnicek	Change of number of patients in the age groups (Neonates: max. 37 pts., Children: min. 13 pts.) Details on subgroups for analysis (Underlying diagnosis, surgery type, infusions) added

Abbreviations

ADR	Adverse Drug Reaction
BMI	Body Mass Index
CBC	Complete Blood Count
CI	Confidence Interval
CSR	Clinical Study Report
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intention-To-Treat
MedDRA	Medical Dictionary for Regulatory Activities

PMR	Post-Marketing Requirement
PP	Per Protocol
PT	Preferred Term
ROTEM	Thromboelastometry
SAE	Serious Adverse Event
SAF	Safety population
SAP	Statistical Analysis Plan
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
TE	Thrombotic Events
TEE	Thromboembolic Events
TEG	Thromboelastography
TFLs	Tables, Figures and Listings

Table of Contents

1. Preface

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Octapharma protocol LAS-212: An open-label, multicenter, Post-Marketing Requirement (PMR) study to investigate the safety, tolerability and efficacy of Octaplas in the management of pediatric patients who require replacement of multiple coagulation factors.

This phase IV study is conducted to assess the safety and tolerability of Octaplas in the pediatric population by monitoring serious adverse events (SAEs), adverse drug reactions (ADRs), thrombotic events (TEs), thromboembolic events (TEEs) and hyperfibrinolytic events, including laboratory parameters for metabolic derangements, renal function, and hematologic implications.

Due to the complex and highly variable and individual medical circumstances and interventions that are to be expected in this study, no single parameter or measurement of outcome is chosen as the primary endpoint. All data collected will be summarized and presented descriptively to facilitate the review of population homogeneity and general patterns within and between patients of similar baseline characteristics or disease patterns. No confirmatory hypothesis testing is planned. Any p-value or confidence interval presented is to be understood in the exploratory sense.

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 LAS-212, Version 10 (29-Nov-2017)

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). London: International Conference on Harmonization.

2. Purpose

This SAP outlines all statistical analyses to be performed on data collected in study LAS-212, 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 (TFLs) will be supplied in a separate document later when all feedback from authorities will be available.

[2] International Conference on Harmonization. (1996). Guideline for Industry. ICH Tpoic E3 (Structure and Content of Clinical Study Reports). London: International Conference on Harmonization.

3. Study Objectives and Endpoints

3.1. Study Objectives

3.1.1. Primary Objectives

The primary objective of the study is to assess the safety and tolerability of Octaplas in the pediatric population by monitoring serious adverse events (SAEs), adverse drug reactions (ADRs), thrombotic events (TEs), thromboembolic events (TEEs) and hyperfibrinolytic events, including laboratory parameters for metabolic derangements, renal function, and hematologic implications.

3.1.2. Secondary Objectives

The secondary objective is to assess the efficacy of Octaplas in the pediatric population by measuring hemostatic parameter improvements reflecting changes in hemostasis.

3.2. Study Endpoints (Target Variables)

3.2.1. Primary Endpoints

The primary (safety) endpoints are:

- Incidence of SAEs, ADRs (e.g., allergic reactions), TEs, TEEs and hyperfibrinolytic events, beginning after the start of the first infusion episode until the final examination (end of safety follow-up period).
- Clinically significant changes in laboratory parameters to assess for metabolic derangements, renal function, and hematologic implications as measured by the following: Chem 7 (metabolic panel), complete blood count (CBC), calcium and ionized calcium.

3.2.2. Secondary Endpoints

The secondary endpoints are:

- Clinically significant changes in hemostatic parameters as measured by the following: international normalized ratio (INR), prothrombin time (PT), activated partial thromboplastin time (aPTT), thromboelastography (TEG) or thromboelastometry (ROTEM).
- Volume (dose in mL/kg) of Octaplas used per infusion episode for each patient.
- Medically significant changes in vital signs
- Investigator's assessment of overall safety observed for each patient.

4. Study Methods

4.1. Overall Study Design and Plan

Study LAS-212 is designed as an open-label, multicenter, post-marketing requirement (PMR) phase IV study. Therefore no randomization or blinding procedures are performed.

This study will enroll a total of 50 pediatric patients from 0 to ≤16 years of age with acquired deficiencies due to liver disease and/or in pediatric patients requiring cardiac surgery or liver surgery who require replacement of multiple coagulation factors. The substitution of coagulation factors is also applicable for young children who require cardiac surgery and require priming of the cardiopulmonary by-pass circuit due to the dilution of the increased volume of the by-pass circuit relative to the circulating blood volume of the child.

The study infusion(s) of Octaplas will occur over a maximum 72-hour treatment period. The number of infusion episodes[3] and the actual total volume (dose in mL/kg) of Octaplas administered to a patient within the 72-hour treatment period will depend on the clinical setting and physician discretion. Each infusion dose will be at least 10mL/kg or one unit (unless a lesser dose is medically justified) and administered at a rate that should not exceed 0.020-0.025 mmol citrate per minute, which is equal to Octaplas per kg per minute. This limitation is not applicable for devices used for cardiopulmonary bypass or extracorporeal membrane oxygenation or similar. In case situations like e.g. a serious hemorrhage necessitates a rapid infusion ≥ 1mL/kg and the benefits outweigh the potential risks, the infusion speed can be ≥ 1mL/kg body weight.

After 72 hours (maximum duration) from the start of the first infusion of Octaplas, the study treatment period will end. Patients will be monitored for SAEs, ADRs, TEs, TEEs and hyperfibrinolytic events for 72 (±6) hours after the last Octaplas transfusion is completed (72-hour Safety Follow-up Period).

4.2. Selection of Study Population

The study population consists of pediatric patients of both sexes and ≤ 16 years of age, who require liver or cardiac surgery and/or with liver dysfunction associated with coagulopathy in whom replacement of multiple coagulation factors is required.

It is planned to enroll fifty patients from the following two age categories:

1. Neonates/Infants (0-2 years): a maximum of 37 patients
2. Children > 2 years and ≤ 16 years: a minimum of 13 patients. A full set of baseline characteristics will be collected to allow evaluation and comparison of study outcomes with respect to different patient characteristics as indicated by the data.

[3] An infusion episode is defined as any amount of Octaplas infusion given, with no more than 60 minutes break between 2 Octaplas infusions. If the time interval between the end of one Octaplas infusion and the beginning of the next Octaplas infusion is more than 60 minutes this will be counted as 2 different infusion episodes.

5. Sequence of Planned Analyses

5.1. Interim Analyses

No interim analysis is planned.

5.2. Final Analyses and Reporting

Due to the complex and highly variable and individual medical circumstances and interventions that are to be expected in this study, no single parameter or measurement of outcome is chosen as the primary endpoint. All data collected will be summarized and presented descriptively to facilitate the review of population homogeneity and general patterns within and between patients of similar baseline characteristics or disease patterns. No confirmatory hypothesis testing is planned. Any p-value or confidence interval presented is to be understood in the exploratory sense.

To allow a holistic review and interpretation of each course of treatment, all parameters relevant for the assessment of safety will be presented descriptively in full detail, by subgroups of interest as well as in total. The safety assessment will include the occurrence of SAEs, ADRs, TEs, TEEs and hyperfibrinolytic events. To facilitate the detection of any possible safety signal, all these events will be characterized and analyzed by age (≤ and > 2 years of age respectively), underlying diagnosis, seriousness, severity, relation to study drug and timely relationship to study drug administration. In addition to these pre-planned categories, the collected data will be examined to identify additional characteristics of interest such as particular types of surgeries or procedures, relevant concomitant medications, or Standardized MedDRA Queries (SMQs) covering a noticeable number of events. The occurrences of all specific safety events will be presented for all these categories and in total, together with the associated 95% confidence intervals.

The following subgroups/categories were identified during the ongoing medical review, and will be considered in the presentation of safety data as detailed above:

- Underlying Diagnosis
    - Congenital heart disease
    - Liver disease requiring transplant
    - Sepsis related coagulopathy
- Types of surgery
    - Cardiac
    - Orthotopic liver transplant
    - None
- No further characteristics were identified in medical history, concomitant medications or reported AE terms that called for further subgroup analyses.

To account for the abovementioned diversity in the study population, individual patient profiles will be generated, displaying the baseline characteristics as well as all interventions, treatment details and relevant measurements on a time scale. This will facilitate the review of each individual course of treatment by the trial medical monitor or expert to assess the efficacy of the treatment but also to detect any safety signal that might not be reflected in the ADR rates.

Hemostatic parameters will be presented descriptively per time point, including shift tables. Individual courses of hemostatic parameters will be presented graphically as Trellis plots.

Vital sign measurements will be summarized by descriptive statistics, including shift tables. All measurements outside the age-specific thresholds defined in the trial validation plan and/or the TFLs document will be listed and reviewed individually.

All safety laboratory data – absolute values as well as changes from baseline – will be presented descriptively per time point. All measurements outside the age-specific thresholds defined in the trial validation plan and/or the TFLs document will be listed and reviewed individually.

All data will be presented in total as well as in sub–groups reflecting age (≤ and > 2 years), gender, underlying diagnosis, surgical procedures performed as detailed above and to the extent appropriate.

6. Sample Size Determination

The chosen number of 50 pediatric patients is not derived from statistical considerations of power, but to gather enough clinical evidence to obtain a sound and meaningful medical assessment and sufficient safety information in a reasonable amount of time.

6.1. Patient Replacement Policy

There is no patient replacement policy defined for this protocol.

6.2. Premature Termination of the Study

If early termination of the study becomes necessary for whatever reason, the sponsor and the investigator will ensure that adequate consideration is given to the protection of the patients' interests. Such a premature termination will be communicated in accordance with applicable regulatory requirements. The Investigator will promptly inform the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) and provide a detailed written explanation. The pertinent regulatory authorities will be informed according to national regulations.

7. Analysis Populations

The following populations will be considered for the statistical analysis:

The safety population (SAF) will include all patients who received at least one infusion of Octaplas.

The full analysis set (FAS) is defined according to the intent-to-treat (ITT) principle and will include all patients of the SAF with any measurements on the primary endpoint variables (monitored for SAEs, ADRs, hemostatic parameters, safety laboratory parameters, vital signs, etc.).

The per-protocol (PP) population will include all patients who have completed the infusion episode(s) and the final examination without major protocol deviations, which may have an impact on the evaluation of the primary study outcome parameter(s).

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.

Examples of protocol deviations to be considered in this respect would be violations of the study entry criteria, dosing errors, the use of forbidden concomitant medications, or the occurrence of completely unrelated medical events that require an interruption of the study procedures. The final decision regarding inclusion/exclusion of patients from the analysis sets will be taken by a panel including the Clinical Project Manager, the study statistician and a medical expert during a data review meeting before database lock. The decisions taken will be based on a review of complete data listings, and documented before the database is locked and the analysis is 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 groups of particular interest as indicated by the data. Continuous, quantitative variable summaries will 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 the total number of patients in the analysis population unless otherwise specified.

8.1. Analysis Software

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

8.2. Withdrawals

Patients who withdraw from the study prematurely will be considered in all data presentations for which they contribute data.

A list of all withdrawals and the reasons of withdrawal will be included in appendix 16.2 of the CSR.

8.3. Handling of Missing Data

In general, missing data will not be imputed.

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

For medications the following will be applied: A medication will be assumed to be concomitant if it can be definitely shown that the medication was administered after start of the first Octaplas infusion and before the end of the observation period. 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. [Unit: years]
- **Body Mass Index**: BMI = (Body weight) / Height^2 [Unit: kg/m^2]

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 patient groups of particular interest as indicated by the data; these will include

- The frequency and percent of patients in each analysis population and subgroup considered in the data tabulations, including the age (≤ or > 2 years respectively).
- 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 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 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 groups of particular interest; these include:

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

  (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/or 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 Octaplas administered
- Total number of infusions administered
- Total number of bags and total volume of solution administered
- Infusion times and rates (mL/kg/min)
- Overall amount of product administered and batches used (only included in data listings)

During ongoing medical review it was noted that particular infusion patterns associated with cardiac surgeries due to the use of bypass circulation devices in clinical practice were not foreseen beforehand. To account for this the following categorization will be introduced for the analysis of infusion speed and dosing:

  - Normal infusion
  - Bypass priming
  - Bypass warming up

10. Efficacy Analysis

This study will examine the efficacy of Octaplas by measuring hemostatic parameter improvements reflecting changes in hemostasis.

The following hemostatic parameters will be assessed: INR, PT, aPTT and TEG with Kaolin activation or ROTEM EXTEM. Pre- and post-infusion episode samples for hemostatic and laboratory parameters will be tested. The pre-infusion episode laboratory samples should be drawn within 6 hours before the start of the first infusion episode and within 60 minutes prior to the start of the subsequent infusion episodes. Post-infusion episode samples should be drawn within 30 to 60 minutes after the end of each infusion episode.

Beside the complete descriptive and graphical presentations of all available parameters as described above (see sections 5.2 and 8), the actual data collected might suggest additional factors that potentially affect the hemostatic parameters after the results from the planned analysis are completed; in this case full details of additional analyses with respect to such covariates will be given in the CSR.

All efficacy endpoints will be presented on basis of both, the FAS and the PP analysis sets, to allow for an assessment of the robustness of the results with respect to protocol violations. The FAS analysis is considered to be the primary assessment of efficacy, and will be presented first in the report.

11. Safety and Tolerability Analyses

The primary objective of LAS-212 is to assess the safety and tolerability of Octaplas in the pediatric population by monitoring serious adverse events (SAEs), adverse drug reactions (ADRs), thrombotic events (TEs), thromboembolic events (TEEs) and hyperfibrinolytic events, including laboratory parameters for metabolic derangements, renal function, and hematologic implications.

This will be done by means of descriptive analyses of all safety related data available.

The analysis of the safety parameters will be performed for the SAF population.

The occurrence of SAEs, ADRs, TEs, TEEs and significant hyperfibrinolytic events will be reported. All these events will be characterized and analyzed by underlying diagnosis, seriousness, severity, relation to study drug and timely relationship to study drug administration. Subgroup analyses will be conducted for hyperfibrinolytic events in patients who undergo liver transplant.

All safety laboratory data – absolute values as well as changes from baseline – will be presented descriptively per time point. All measurements outside age-specific thresholds will be listed and reviewed individually.

All data will be presented in total as well as in sub–groups reflecting age (≤ and > 2 years), gender, underlying diagnosis, and surgical procedures performed as detailed in section 5.2.

11.1. SAEs, ADRs, TEs, TEEs and significant hyperfibrinolytic events

A Serious Adverse Event (SAE) is any untoward medical occurrence at any dose that

- results in death
- is life-threatening
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is another important medical event

An Adverse Drug Reaction (ADR) in the context of this study is any noxious and unintended response to Octaplas related to any dose; this means that a causal relationship between Octaplas and the reported reaction cannot be ruled out, i.e. the relationship must be determined to be at least possibly related to administration of Octaplas by the investigator or by Octapharma's medical expert or an adjudicator of the independent data monitoring committee (TEEs and TEs). Reactions with a missing or indeterminate causality assessment will also be classified as ADRs.

Serious adverse events (SAEs), thrombotic events (TEs), thromboembolic events (TEEs) and hyperfibrinolytic events will be handled in exactly the same fashion as ADRs in the context of the safety analysis. The only difference is that SAEs, TEs, TEEs and hyperfibrinolytic events will be included in the analysis regardless of the causality assessment; even if such an event is reported as not related to study drug, it will be included in all data listings and tabulations. For the remainder of this section the term 'event' will thus be used to refer to any SAE, ADR, TE, TEE or hyperfibrinolytic event. Only events that occur after the start of the first infusion episode will be collected and considered in the analysis.

All of the below will feature this classification (SAE, ADR, TE, TEE, hyperfibrinolytic event) as additional event characteristic if applicable.

All events for each patient, including multiple occurrences of the same reaction, will be listed in full detail, including reported term, MedDRA preferred term and system organ class, onset, duration, time to the event occurrence from last dose, causality, dosage, severity, seriousness and actions taken. The listing will include the number of the last infusion prior to each event and the relative time. An evaluation to identify any event with increased frequency over time will be performed.

The following will be given for the study as a whole and for patient groups of particular interest:

- Total number of events reported
- Number of events divided by the total number of infusions

On a per patient basis the incidence of events will be summarized by system organ class, preferred term and maximum severity. If a patient experiences an event more than once the event at the most severe occurrence will be considered. Patients will be included only once under each system organ class and only once in the overall totals under the most severe occurrence.

Events will be summarized by strongest relationship to study medication by system organ class and preferred term. If a patient experiences an event more than once the event most related to study medication will be considered. Patients will be included only once under each system organ class and only once in the overall totals under the most related to study medication occurrence.

Incidences of events (given as the number and percentage of patients) will be summarized overall and for patient groups of particular interest as follows:

- Events by system organ class, preferred term and maximum severity
- Events by system organ class, preferred term and strongest relationship
- Serious events by system organ class and preferred term
- Non-serious events[4] by system organ class and preferred term
- Events leading to withdrawal by system organ class and preferred term
- Events leading to death by system organ class and preferred term
- Other significant event by system organ class and preferred term*

* Other significant events will be assessed for relevance and inclusion in this tabulation by a medical expert on basis of listings of all non-serious events or marked laboratory abnormalities that lead to withdrawal of IMP treatment, and/or dose reduction and/or significant additional concomitant therapy (i.e. medications given intravenously).

Narratives will be prepared describing each death, each other serious event and those of the other significant events that are judged to be of special interest because of clinical importance. The narrative will address the following: nature and severity of reaction, clinical course leading up to event, indication of timing relevant to investigational medicinal product administration, relevant laboratory measurements, whether the drug was stopped, countermeasures or post-mortem findings, if any, and a causality assessment.

11.2. Clinical Laboratory Evaluations

The following laboratory tests will be performed during the course of the study to monitor metabolic derangements, renal function, and hematologic implications (section 7.3.5.3 of the protocol):

[4] Only TEs, TEEs, and hyperfibrinolytic events will be reported if non-serious; no other non-serious adverse events will be captured in this PMR study.

- Chem 7 panel: BUN, CO_2 (bicarbonate), serum chloride, serum creatinine, glucose, serum potassium, serum sodium
- CBC: WBC, RBC, hemoglobin, hematocrit, MCV, MCH, MCHC, RDW, platelets
- Ionized calcium

The following hemostatic parameters will be assessed before and after each infusion episode:

INR, PT, aPTT, TEG or ROTEM

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

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.

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 might 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 with cardiac surgery) 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. Tables, Listings and Figures

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