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Statistical Analysis Plan

Study ID	LAS-213
Study title	An open-label, multicenter, Post-Marketing Requirement study to investigate the safety and tolerability of octaplas™ in the management of pediatric patients who require therapeutic plasma exchange.
Study phase	IV

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Document History

Version	Date	Author	Description
Final v1	19-Dec-2013	L. Trawnicek	New document
Final v2	14-Mar-2014	L. Trawnicek	Adjusted to match the revised protocol (v2); in particular the explicit monitoring of SAEs included in the primary endpoint definition.
Final v3	03-Oct-2017	L. Trawnicek	Minor clerical corrections, Minimum age changed to 2 years, minor adjustments to ensure conformance with protocol version v6.
Final v4	07-Nov-2018	L. Trawnicek	Removal of specific age group requirements to match protocol v7.

Abbreviations

ADR	Adverse Drug Reaction
BMI	Body Mass Index
CBC	Complete Blood Count
CI	Confidence Interval
CSR	Clinical Study Report
DB	Database
(e)CRF	(Electronic) Case Report Form
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
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAF	Safety Population
SOC	System Organ Class
TE	Thrombotic Event
TEE	Thromboembolic Event
TFLs	Tables, Figures and Listings
TPE	Therapeutic Plasma Exchange

Table of Contents

1. Preface

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Octapharma protocol LAS-213: An open-label, multicenter, Post-Marketing Requirement study to investigate the safety and tolerability of octaplas in the management of pediatric patients who require therapeutic plasma exchange.

This phase IV study is conducted to assess 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 by measuring safety laboratory parameters.

The primary endpoint for this study is the monitoring of SAEs, ADRs, TEs and TEEs caused by the octaplas™ used for plasma exchange. All data collected will be summarized and presented descriptively to facilitate the review of population homogeneity and general patterns within and between age groups. The rates of occurrences of SAEs, ADRs, TE and TEEs events will be calculated, but 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-213, Version 07, dated October 19, 2018

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-213, 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 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 by measuring safety laboratory parameters.

3.1.2. Secondary Objectives

N/A, Remark: Efficacy will not be measured in this study.

3.2. Study Endpoints (Target Variables)

3.2.1. Primary Endpoint

The primary endpoint is the monitoring of SAEs, ADRs, TEs and TEEs caused by the octaplas™ used for therapeutic plasma exchange (TPE). All such events will be listed and the rate of such reactions per patient and per TPE procedure will be calculated, overall as well as for all relevant combinations of age groups and reaction characteristics.

3.2.2. Secondary Endpoints

The secondary endpoints are:

- Safety laboratory parameters (Complete Blood Count (CBC), the ‘Chem 7’ lab panel (Chem 7), and ionized calcium). Please refer to the protocol, section 7.3.5, for details on the laboratory tests performed.
- Investigator’s assessment of overall safety. This will be done by use of a scale of 3 categories (Poor/Moderate/Excellent); please refer to the protocol, section 7.3.1, for further details.

4. Study Methods

4.1. Overall Study Design and Plan

Study LAS-213 is designed as an open-label, multicenter, interventional, post-marketing requirement (PMR) phase IV study. Therefore no randomization or blinding procedures are performed.

- A minimum of 40 pediatric patients aged ≥ 2 years to ≤ 20 years will be enrolled into the study.

The total study treatment period will be a maximum of one week (i.e., 7 days). Within this period one or more TPE procedures will be conducted and documented, including start and stop time, total volume infused (mL), dose (mL/kg), and type of machine used.

Within 24 hours before each TPE procedure, vital signs will be assessed and blood will be drawn for safety labs (CBC and Chem 7) and for ionized calcium levels. If multiple vital signs, and/or laboratory assessments are made before and after the TPE, the assessment taken most proximal to the start (pre) and after the end of the TPE (post) should be recorded in the case report form (CRF). SAEs, ADRs, TEs, TEEs, and relevant changes in concomitant medications will also be recorded.

24 (+/- 2 hours) hours after each TPE the Investigator will provide an assessment of overall safety for the patient's treatment and blood will be drawn for ionized calcium levels to assess for citrate toxicity.

After the final follow-up after the last TPE in the 1-week (7-day) study treatment period, the clinical phase of the study is considered completed for the patient. No further study-related assessments will be performed, unless safety concerns (e.g. on-going SAEs) require follow-up.

4.2. Age groups

Age groups will be defined for the analysis on basis of the actual age distribution of the study population, ensuring reasonable group sizes as well as medically meaningful age ranges. These ranges will be decided during the data review process preceding the database (DB) lock. All data will be presented by these age groups as appropriate, as well as for all patients overall.

4.3. Selection of Study Population

The study population consists of pediatric patients of both sexes who need TPE. Please refer to the protocol, section 4.1 for a complete list of inclusion and exclusion criteria.

5. Sequence of Planned Analyses

5.1. Interim Analyses

No interim analysis is planned.

5.2. Final Analyses and Reporting

The purpose of this study is to assess safety and tolerability of octaplas™ in the pediatric population by monitoring SAEs, ADRs, TEs, TEEs, and by measuring safety laboratory parameters. No confirmatory testing is planned, but all data collected will be explored and presented descriptively in full detail, by age group as well as in total, to facilitate the review of population homogeneity and general patterns within and between the age groups. Any p-value or confidence interval presented is to be understood in the exploratory sense.

To facilitate the detection of any possible safety signal, all SAEs, ADRs, TEs, and TEEs will be characterized and analyzed by 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 indications for TPE, relevant concomitant medications, or SMQs covering a noticeable number of events. The rates of SAEs, ADRs, TEs, and TEEs will be presented for all these categories, together with the associated 95% confidence intervals, again per age group and in total.

Individual patient profiles or tabulations will be generated, displaying the baseline characteristics as well as all interventions, treatment details and measurements on a time scale. This will facilitate the review of each individual course of treatment by a medical expert to detect any safety signal that might not be reflected in the event rates.

6. Sample Size Determination

A minimum of forty (40) pediatric patients aged ≥ 2 years to ≤ 20 are planned to be enrolled into this study. The chosen number of 40 pediatric patients is not derived from statistical considerations of power, but to gather enough clinical evidence to obtain a sound and meaningful medical assessment.

6.1. Patient Replacement Policy

There is no patient replacement policy defined for this protocol. The number of withdrawals and the actual age distribution of the study participants will be monitored in order to define appropriate age groups for the data analysis prior to DB lock.

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 information available on the primary endpoint; these are all treated patients monitored for the above mentioned events (SAEs, ADRs etc.) after start of the TPE, and it is thus expected that this population will coincide with the SAF.

The per-protocol (PP) population will include all patients who have completed the infusion episode(s) and the final examination without major protocol deviations that would have an effect on the evaluation of the primary endpoint. Examples of protocol deviations to be considered in this respect would be violations of the study entry criteria, dosing errors, the use of prohibited 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 age group. 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; for calculations concerning the body weight, in particular the administered doses per kg, the latest available body weight measurement will be used.

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, and the definition of the age groups used for analysis.
  [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 age group; these will include:

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

9.2. Protocol Deviations

Protocol deviations 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 deviations will be summarized by type of deviation and by age group. 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, overall and by age group; 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
- Total volume (mL) of octaplas (blood group specific / blood group compatible) and FFP (if applicable) used per infusion episode and in total

- Actual dose (mL/kg) per infusion episode and in total (based on the latest available weight measurement for each TPE)
- Total number of infusions administered
- Total number of bags administered
- Infusion times and rates
- Overall amount of product administered and batches used (only included in data listings)

10. Efficacy Analysis

Efficacy will not be assessed.

11. Safety and Tolerability Analyses

To primary objective of LAS-213 is to assess safety and tolerability of octaplas in the pediatric population by monitoring SAEs, ADRs, TEs, TEEs, and by measuring safety laboratory parameters. This will be done by means of descriptive analyses of all safety related data available for the Safety Population.

11.1. SAEs, ADRs, TEs, and TEEs

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) and thromboembolic events (TEEs) will be handled in exactly the same fashion as ADRs in the context of the safety analysis. The only difference is that TEs and TEEs 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 ADR, TE, or TEE.

All of the below will feature this classification (SAE, ADR, TE, TEE) 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.

For each age group and for the study as a whole the following will be given:

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

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 each age group 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 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 events 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, please refer to section 7.3.5 of the protocol for further details.

Chem 7 panel	**CBC**	**Calcium**
Blood Urea Nitrogen	White Blood Cell	Ionized Calcium
CO_2 (bicarbonate)	Red Blood Cell	
Serum Chloride	Hemoglobin	
Serum Creatinine	Hematocrit	
Glucose	Mean Corpuscular Volume	
Serum Potassium	Mean Corpuscular Hemoglobin	

Serum Sodium	Mean Corpuscular Hemoglobin Concentration
	Red Cell Distribution Width

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 Hemolytic uremic syndrome) 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.