octapharma

CLINICAL STUDY PROTOCOL

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.

Investigational Product:	Octaplas
Indication:	Replacement of multiple coagulation factors in pediatric patients with acquired deficiencies due to liver disease and/or in pediatric patients requiring cardiac surgery or liver transplantation.
Study Design:	Open-label, multicenter, post-marketing requirement study
Sponsor:	Octapharma Pharmazeutika Produktionsges.m.b.H. Oberlaaerstrasse 235, 1100 Vienna, Austria
Study Number:	LAS-212
EudraCT and/or IND Number:	BL 125416/0: Required Pediatric Assessment
Development Phase:	Phase IV
Planned Clinical Start:	Q2 2014
Planned Clinical End:	Q4 2017
Date of Protocol:	19-Nov-2016
Version:	9.0
Coordinating Investigator:	Philip C. Spinella, M.D. 1 Children's Place/NWT 10th floor St Louis, MO, 63110, USA

STUDY OUTLINE

Name of Sponsor/Company: Octapharma Pharmazeutika Produktionsges.m.b.H.	
Name of Investigational Product: Octaplas	**Protocol Identification Code:** LAS-212
Name of Active Ingredient: Human Coagulation Active Plasma For Infusion, S/D treated	**Date of Final Protocol**: 19-Nov-2016
Title of Study: 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.	
Indication: Replacement of multiple coagulation factors in pediatric patients with acquired deficiencies due to liver disease and/or in pediatric patients requiring cardiac surgery or liver surgery (see package insert in **Appendix 1**).	
Number of Study Center(s): Up to 10 sites in North-America.	
Study Duration: 2nd quarter 2014 to 4th quarter 2017	**Development Phase:** IV
Objectives: Primary: 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. Secondary: To assess the efficacy of Octaplas in the pediatric population by measuring hemostatic parameter improvements reflecting changes in hemostasis.	
Study Design: Open-label, multicenter, post-marketing requirement Phase IV study.	
Number of Patients: Fifty (50) pediatric patients treated with Octaplas with targeted number of patients within the following two age categories: 1. Neonates/Infants (0-2 years): a maximum of 33 patients 2. Children > 2 years and ≤ 16 years: a minimum of 17 patients	
Patient Selection Criteria: Inclusion Criteria: 1. Patient requiring liver or cardiac surgery and/or patient with liver dysfunction associated with coagulopathy in whom replacement of multiple coagulation factors	

Name of Sponsor/Company: Octapharma Pharmazeutika Produktionsges.m.b.H.	
Name of Investigational Product: Octaplas	**Protocol Identification Code:** LAS-212
Name of Active Ingredient: Human Coagulation Active Plasma For Infusion, S/D treated	**Date of Final Protocol**: 19-Nov-2016

is required.

2. Voluntarily given, written and signed informed consent by the patient's legal representative(s) or guardian(s). Children deemed old enough by the Investigator/institution to understand the risks and benefits of the study should also be made aware of the risks/benefits of the study and provide written assent.
3. Male or female patient ≤ 16 years of age.

Exclusion Criteria:

1. Patient with known homozygous congenital deficiency of protein S.
2. Patient has a history of hypersensitivity reaction to blood or plasma-derived products or to any excipient of the investigational product.
3. Patient has an already known IgA deficiency with documented antibodies against IgA.
4. Patient has a congenital factor deficiency or platelet disorder requiring plasma treatment.
5. Patient is currently participating in another study investigating a new drug product or another interventional clinical study that may impact coagulation factors or has participated during the last three (3) months.
6. Patient received FFP, FP24 or any other plasma product other than Octaplas within the last 72 hours (cryoprecipitate and albumin are not exclusionary) prior to first Octaplas infusion.
7. Patient is on ECMO (Extracorporeal Membrane Oxygenation) when plasma is ordered by the treating physician for the first infusion episode.
8. Patient is pregnant.
9. Patient is predicted to require massive blood transfusion defined as more than 40 mL per kilogram of all blood products in a 24-hour period
10. Patient is receiving plasma exchange, therapeutic plasma exchange (TPE) or plasmapheresis.
11. Patient is a premature neonate defined as less than 37 weeks gestation.
12. Cardiac surgery patients who develop the need for plasma replacement greater than 72 hours after the end of the associated cardiac surgery and do not have coagulopathy due to hepatic dysfunction.

Test Product, Dose, Mode of Administration, and Batch Number(s):

Octaplas infusion solution for IV administration, ABO blood group compatible.

Name of Sponsor/Company: Octapharma Pharmazeutika Produktionsges.m.b.H.	
Name of Investigational Product: Octaplas	**Protocol Identification Code:** LAS-212
Name of Active Ingredient: Human Coagulation Active Plasma For Infusion, S/D treated	**Date of Final Protocol**: 19-Nov-2016
Duration of Treatment: The study infusion(s) of Octaplas will occur over a maximum 72-hour treatment period. After the final infusion episode there will be an additional 72-hour safety follow-up period for monitoring of adverse drug reactions.	
Reference Therapy, Dose, Mode of Administration, and Batch Number(s): None.	

Study Outcome Parameters (Primary and Secondary Endpoints):

Primary Endpoints:

- 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) and ionized calcium.

Secondary Endpoints:

- 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.

Summary of Study Procedures and Statistical Analysis Plan (SAP):

Study Periods:

Screening: At Screening, informed consent will be obtained from the legal representative(s) or guardian(s) of the patient. Children deemed old enough by the Investigator/institution to understand the risks and benefits of the study should provide written assent. Relevant medical history including relevant prior and on-going concomitant medications and demographic data will be recorded. The patient's eligibility will be checked based on the inclusion and exclusion criteria. A physical examination in accordance with the site's routine procedure will be performed. The patient's ABO blood group will be determined for compatibility. A pregnancy test for females at the age of ≥ 11 years or of childbearing potential (if younger than 11 years old) will be performed

Name of Sponsor/Company: Octapharma Pharmazeutika Produktionsges.m.b.H.	
Name of Investigational Product: Octaplas	**Protocol Identification Code:** LAS-212
Name of Active Ingredient: Human Coagulation Active Plasma For Infusion, S/D treated	**Date of Final Protocol**: 19-Nov-2016

prior to enrollment if it was not previously performed during the current hospital admission. Female patients of childbearing potential are excluded from the study if the pregnancy test is positive. Per physician discretion, he/she will decide if clinical indication for a plasma infusion is necessary and will place the plasma order accordingly. The type of surgical procedure indicated and important operative interventions will also be recorded. Patients determined to have a reasonable probability to receive intra-operative plasma transfusion according to the Investigator's clinical judgment may also be approached for consent to participate. If these patients are subsequently not prescribed plasma intra-operatively or postoperatively they will be determined to be a screening failure and not included in the analysis.

Pre-Infusion: Within 6 hours prior the start of the first infusion episode, vital signs and several laboratory tests will be assessed to measure metabolic derangements and renal function.

72-hour Study Treatment Period: The number of infusion episodes[1] and 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. The infusion rate of Octaplas 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. The first infusion dose will be at a minimum of 10 mL/kg or one unit unless a lesser dose is medically justified. If infusion episodes are performed and the dose administered is less than 10 mL/kg, the medical reason justifying this dosage will be recorded in the case report form (CRF), since at least 10 mL/kg are required to significantly increase the respective plasma protein levels.

Post-infusion episode samples should be drawn within 30 to 60 minutes after each infusion episode. If the patient requires priming of the cardiopulmonary bypass (CPB) circuit with plasma, the post-infusion episode samples should be drawn 30-60 minutes after reversal of heparin during the process of coming off CPB. For the first infusion episode it is mandatory that pre– and post–infusion episode samples for hemostatic and

[1] 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.

Name of Sponsor/Company: Octapharma Pharmazeutika Produktionsges.m.b.H.	
Name of Investigational Product: Octaplas	**Protocol Identification Code:** LAS-212
Name of Active Ingredient: Human Coagulation Active Plasma For Infusion, S/D treated	**Date of Final Protocol**: 19-Nov-2016

laboratory parameters be drawn for testing. If subsequent infusion episodes are performed (after the first infusion episode), laboratory testing and vital signs should be performed within a maximum of 60 minutes before the start and 60 minutes after the end of each infusion episode. If multiple vital sign assessments are taken within 60 minutes before and/or after the infusion, the vital signs that are assessed closest before the start and after the end of each infusion should be recorded. Pre- and post-infusion episode measurements to assess hemostatic and laboratory parameters should be recorded if available unless considered not medically necessary by the Investigator (e.g., the timing of the pre-infusion episode sample is close to or overlaps with the timing of the post-infusion episode sample and it is not necessary to perform, or testing is not medically appropriate for patient at that time, etc.). In the event that the pre- or post-infusion laboratory sample testing is not performed, the reason will be documented in the CRF. The study Treatment Period will end after 72 hours from the start of the first infusion of Octaplas, or after the end of the last infusion episode if the total duration of Octaplas treatment is <72 hours.

72-hour Safety Follow-up Period: Adverse drug reactions and relevant concomitant medications will be monitored for 72 (±6) hours after the last Octaplas transfusion is completed.

Final Examination: At the end of the 72-hour safety follow-up period, a final examination will be performed comprising of vital signs, Investigator assessment of safety (the safety assessment is to be carried out by the principal or sub-investigator) and laboratory testing (Chem 7, CBC and ionized calcium) for monitoring of metabolic derangements, renal function, and hematologic implications.

After the final examination, 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 ADRs) require follow-up.

Statistical Analysis Plan (SAP):

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

Name of Sponsor/Company: Octapharma Pharmazeutika Produktionsges.m.b.H.	
Name of Investigational Product: Octaplas	**Protocol Identification Code:** LAS-212
Name of Active Ingredient: Human Coagulation Active Plasma For Infusion, S/D treated	**Date of Final Protocol**: 19-Nov-2016

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, 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.

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 age-specific thresholds 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 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, surgical procedures performed and/or most relevant medical history and concomitant medications.

PROTOCOL SIGNATURES

This study is intended to be conducted in compliance with the protocol,
Good Clinical Practice and the applicable regulatory requirements.

Dr. Wolfgang Frenzel

25.11.2016

International Medical Director — Signature — Date
on behalf of the Sponsor
Octapharma Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Strasse 235
A-1100 Vienna, Austria

Philip C. Spinella, M.D.

Coordinating Investigator — Signature — Date
1 Children's Place/NWT 10th floor
St Louis, MO, 63110, USA

Laurenz Trawnicek

25-NOV-2016

Manager Biometrics — Signature — Date
Octapharma Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Strasse 235
A-1100 Vienna, Austria

Franz-Josef Tarmann

28-NOV-2016

Global Clinical Project Manager — Signature — Date
Octapharma USA, Inc.
121 River Street, Suite 1201
Hoboken, NJ, 07030, USA

TABLE OF CONTENTS

INDEX OF TABLES

LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE(s)	Adverse Event(s)
aPTT	Activated Partial Thromboplastin Time
BUN	Blood Urea Nitrogen
BW	Body Weight
CBC	Complete Blood Count
CDSU	Central Drug Safety Unit
CFT	Clot Formation Time
CPB	Cardiopulmonary bypass
CPM	Clinical Project Manager
CRF	Case Report Form
CRO	Contract Research Organization
CT	Clotting Time
ECMO	Extracorporeal Membrane Oxygenation
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EPL	Estimated percentage lysis
FAS	full analysis set
FDA	Food and Drug Administration
FFP	Fresh Frozen Plasma
FP24	Plasma frozen within 24 hours of collection
GCP	Good Clinical Practice
HAV	Hepatitis A Virus
HEENT	Head, Ears, Eyes, Nose and Throat
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous
ITT	Intent-to-Treat
K-time	time from the end of R until the clot reaches 20 mm
MA	Maximum Amplitude

MCF	Maximum Clot Firmness
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
ML	Maximum lysis
NIH	National Institute of Health
PMR	Post-Marketing Requirement
PP	Per-Protocol
PT	Prothrombin Time
RBC	Red Blood Cell
RDW	Red Cell Distribution Width
ROTEM	Thromboelastometry
R-time	Reaction time
SADR	Serious Adverse Drug Reaction
SAE(s)	Serious Adverse Event(s)
SAF	Safety Population
SAP	Statistical Analysis Plan
S/D	Solvent/Detergent
SDP	Solvent/Detergent (S/D) Treated and Pooled
SMQ	Standardized MedDRA Query
TE	Thrombotic Event
TEE	Thromboembolic Event
TEG	Thromboelastography
TNBP	Tri(n-butyl)phosphate
TPE	Therapeutic Plasma Exchange
WBC	White Blood Cell

1 INTRODUCTION

Octaplas is a solvent/detergent (S/D) treated and pooled (SDP) human plasma prepared from units of fresh frozen plasma (FFP) pooled according to their ABO blood group. It contains the normal constituents of plasma. Octaplas is a further development of octaplas® which is marketed in Europe since 1992. In January of 2013, Octaplas received regulatory approval by the Food and Drug Administration (FDA) for the US market. For Octaplas, a new prion affinity column was introduced in the manufacturing process of the product to eliminate potential prion proteins. Furthermore, the time of S/D treatment in the manufacturing process has been shortened from 4–4.5 hours to 1–1.5 hours. These measures increase the concentration of plasmin inhibitor and slightly increase the concentration of protein S compared with octaplas®. Octaplas has received marketing authorization in Australia, Germany, Portugal, the U.K., Ireland, Belgium, the Netherlands, Luxemburg, Sweden, Finland, Switzerland, Malta, and Canada. octaplas® is registered in 21 countries and Octaplas is registered in 13 countries including the United States.

Octaplas is labeled in the United States with the proprietary name octaplas™. In case the study will be conducted in countries outside of the United States where the product is licensed under the name Octaplas and the product octaplas is recognized as the predecessor product this could lead to mismatch or misunderstanding. Therefore the name Octaplas is used in the current protocol.

Octaplas does not contain red blood cells (RBCs), leukocytes and platelets. The RBCs and cell fragments are removed in several filtration steps during the production process. Therefore, adverse reactions caused by the presence of these cells (e.g., immunization against RBC antigens or febrile non-hemolytic reactions from cytokines liberated by leukocytes) are not expected to be associated with the infusion of this product.

Virus inactivation is performed using the S/D treatment method using the virus inactivating reagents 1% tri(n-butyl)phosphate (TNBP) and 1% Triton X-100 (Octoxynol). This virus inactivation procedure is effective against enveloped viruses such as human immunodeficiency virus, hepatitis B virus and hepatitis C virus. The efficacy of this virus inactivation procedure has been extensively validated according to current international guidelines. The S/D treatment has no effect on non-enveloped viruses such as hepatitis A virus (HAV) and parvovirus B19. However, the presence of neutralizing antibodies towards HAV and B19 in the starting plasma and the final product, result in immune neutralization and passive immunization which both serve to limit or prevent virus replication and thereby infection in recipients. **[1]**

The virus inactivating reagents (TNBP and Octoxynol) may remain in trace amounts in the final product. Toxicity studies performed in rats and dogs have shown that these levels are of no toxicological relevance to humans. Furthermore, no teratogenic, embryotoxic or mutagenic effects of TNBP and Octoxynol were observed in the toxicity studies performed.

In total, 15 prospective clinical studies and 9 retrospective studies with octaplas have been conducted. Of the 15 prospective studies, 2 were focused on safety aspects only, and of the 9 retrospective trials, 3 were mainly studying efficacy. In total, about 495 patients have been enrolled in the pro- and retrospective efficacy studies, including one observational study, and the patients were exposed to 2592 infusion episodes with octaplas/Octaplas or Uniplas (a plasma formulation compatible with all ABO blood groups).

Octaplas was developed as an alternative to plasma in order to prevent virus transmission. In addition, the product was developed to meet the request for a standardized, cell free plasma for infusion that contains high levels of pro- and anti-coagulants, in order to improve the therapeutic efficacy and reduce adverse reactions.

1.1 Rationale for Conducting the Study

This post-marketing requirement (PMR) study was requested by the FDA after Octaplas received marketing approval in the United States. This PMR study is planned to be conducted in 50 pediatric patients from 0 to ≤ 16 years of age with acquired deficiencies due to liver disease and/or who require cardiac surgery or liver transplantation in whom replacement of multiple coagulation factors is required.

The study is intended to obtain additional safety information on Octaplas in a routine clinical setting via the assessment of adverse drug reactions (ADRs), serious adverse events (SAEs) thrombotic events (TEs), thromboembolic events (TEEs) and hyperfibrinolytic events, and will be conducted in compliance with the protocol, ICH-GCP and other regulatory requirements.

1.2 Dose Rationale

Octaplas is for intravenous use only. Please refer to the package insert of Octaplas for further information regarding dose (**Appendix 1**).

1.3 Benefit-Risk Statement

There are several benefits associated with the administration of Octaplas. Octaplas has undergone additional steps for viral inactivation and removal. The combination of the S/D treatment and immune neutralization ensures a high degree of viral safety for this product. Antibodies against white blood cells are diluted and neutralized which abolishes the risk for immune Transfusion Related Acute Lung Injury (one of the most serious complications of transfusions today); this is a very favorable feature of Octaplas compared to plasma. Because cells and cellular debris are completely removed by multiple size exclusion filtration steps, adverse reactions attributable to residual blood cells, especially white blood cells, are not expected in conjunction with the use of Octaplas. The dilution effect on cytokines and allergens from the pooling of multiple units of single-donor FFP units diminishes the number and severity of adverse reactions that can occur due to the presence of allergens/soluble substances in plasma. Additionally, Octaplas has uniform and stable levels of both pro- and anti-coagulation factors. The combination of the uniformity of these factors in Octaplas and the consistent size of each unit could produce a more predictable hemostatic response following Octaplas transfusion compared to standard plasma. Comprehensive biochemical studies confirmed that Octaplas produced with the new column possesses a biochemical quality identical to its predecessor, octaplas®, with the advantage of offering an enhanced safety profile in terms of prion disease transmission such as Variant Creutzfeldt-Jakob Disease.

The adverse reactions that were observed in ≥ 1% of subjects who received octaplas were mild and included pruritus, urticaria, nausea, headache, and paresthesia. **[**2**]** Serious adverse

reactions that were associated with octaplas transfusion included anaphylactic shock, citrate toxicity and severe hypotension.

Other possible adverse reactions that may occur with the use of Octaplas are excessive bleeding caused by hyperfibrinolysis due to low levels of plasmin inhibitor in the product, thrombosis due to low levels of protein S, and citrate toxicity (hypocalcemia). The infusion rate should not exceed 1 mL/kg/min. Symptoms attributable to citrate toxicity can include fatigue, paresthesia and muscle spasms, especially in patients with liver function disorders. Because Octaplas is made from human plasma, it may carry a risk of transmitting certain infectious agents such as viruses and Variant Creutzfeldt-Jakob Disease. Other adverse reactions that have been reported in the post-marketing experience include hypersensitivity reactions including anaphylactoid and allergic type of reactions, alkalosis, cardiac arrest, circulatory overload, thromboembolism, tachycardia, respiratory arrest or failure, bronchospasm, pulmonary edema, dyspnea, tachypnea, abdominal pain, vomiting, rash, erythema, fever and/or chills, chest discomfort or pain, and seroconversions (passive transfer of antibodies).

High volumes or infusion rates may induce Transfusion Associated Volume Overload that is manifested dyspnea, hypoxia, and increasing oxygen demands. Pulmonary edema can often be seen on chest X-ray. High infusion rates may rarely cause cardiovascular effects as a result of citrate toxicity (fall in ionized calcium), especially in patients with liver function disorders. Octaplas should be used with caution in patients with risks for thrombotic complications because of the potential for increased risk of venous thromboembolism. In order to reduce the risk for venous thromboembolism, appropriate measures should be considered in all patients at risk for thrombotic complications subjected to coagulation factor support for an extended period of time (e.g., during long-term, large-volume therapeutic plasma exchange [TPE]) using Octaplas.

Administration of Octaplas must be based on ABO-blood group compatibility with the recipient. Hemolytic reactions can occur with ABO blood group mismatches. In emergency cases, blood group AB can be regarded as the universal plasma since it can be given to all patients.

Octaplas should not be used in patients with:

- Immunoglobulin A (IgA) deficiency
- Severe deficiency of protein S
- History of hypersensitivity to FFP or to plasma-derived products
- History of hypersensitivity reaction to Octaplas

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to assess the safety and tolerability of Octaplas in the pediatric population by monitoring SAEs, ADRs, TEs, TEEs and hyperfibrinolytic events, including laboratory parameters for metabolic derangements, renal function, and hematologic implications.

2.2 Secondary Objective(s)

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

3 INVESTIGATIONAL PLAN

3.1 Primary and Secondary Endpoints

Primary Endpoint(s)

- Incidence of SAEs, ADRs (e.g., allergic reactions; refer to **Section 7.3.2.1** for definition), 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) and ionized calcium (refer to **Section 7.3.5.3** for definition).

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.

Secondary Endpoint(s)

- 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.

3.2 Overall Study Timeline

The study started in the second quarter 2015 and is planned for completion by 4th quarter of 2017. The end of the study is defined as the last visit of the last patient participating in the study.

Study Flow Chart

Time-Points	**Screening/ Pre-Infusion** *(within 7 days prior to start of first infusion[1])*	**72-Hour Study Treatment Period (Infusion Episode(s)[2, 3]**	**72-Hour Safety Follow-up Period[3,4]**	**Final Examination** *72 hours after end of last study infusion episode[2]*
Inclusion/Exclusion criteria	X			
Informed consent/assent	X			
Physical examination[5]	X			
Medical history (incl. prior and current relevant concomitant medications[6])	X			
Vital signs[7]	X	X		X
Documentation of the type of surgical procedure indicated[8]	X			
Demographic data	X			
Blood group determination	X			
Hemostatic parameters[9]	X	X		
Laboratory parameters (Chem 7, CBC and ionized calcium)[9]	X	X		X
Pregnancy test[10]	X			
Ordering of plasma	X			
Administration of Octaplas		X		
Investigator Assessment of Safety[11]				X
Monitoring of SAEs and ADRs		←----------Continuously----------→		
Monitoring of TEs, TEEs, and hyperfibrinolytic events (regardless of causality)[12]				
Monitoring concomitant medication				

1. Screening time window of -7 days does not apply for informed consent/assent procedure.

2. An infusion episode is defined as any amount of Octaplas 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. For patients on CPB who are primed with plasma, a transfusion episode will begin with the initiation of the circuit with plasma and will end when the heparin is reversed during the process of coming off CPB. The study Treatment Period will end after 72 hours from the start of the first infusion of Octaplas, or after the end of the last infusion episode if the total duration of Octaplas treatment is <72 hours.

3. Single donor plasma (e.g. FFP, FP24, thawed plasma, etc.) should be avoided during the Treatment and Follow-up study periods. Patients receiving single donor plasma during the Treatment or Follow-up periods will be withdrawn from the trial. Plasma exchange, TPE or plasmapheresis is not permitted during the Treatment or Follow-up periods. Patients who develop the need for and undergo plasma exchange or plasmapheresis will be withdrawn from the trial.

4. The permitted visit window for the Safety Follow-up period and Final Examination is 72 hours (± 6 hours) after the end of the last Octaplas infusion. The Follow-up procedures (e.g., Investigator assessment of safety) may be performed sooner if it will not be practical to obtain at the 72-hour post final examination visit. If it is not medically feasible to obtain the final examination visit assessments at the 72 hours (± 6 hours) time point, the reason must be documented (e.g., patient discharged prior to 72 hours after the end of the last infusion, etc.).

5. A physical examination will be performed at the screening visit in accordance with the site's local standard procedures. This may include examination of dermatological and lymphatic system, head, eyes, ears, nose, throat [HEENT], respiratory tract, cardiovascular and gastrointestinal system, musculoskeletal system, neurological system, and endocrinological systems.

6. Details of any relevant prior (up to 7 days before the first administration of Octaplas) and concomitant medications administered during the trial period will be recorded on the case report form (CRF). All other transfusion products (e.g., albumin, cryoprecipitate, platelets) must be captured individually in the CRF. Routine medications that are considered standard and/or that have little or no impact on the study data results are not to be entered into the CRF (e.g., anesthesia medications, beta blockers, etc.). For details please see **Section 4.2**.

7. Vital signs will include heart rate, respiratory rate, temperature, arterial saturation and blood pressure assessment. Vitals should be assessed within a maximum of 6 hours before the start and 60 minutes after the end of the first infusion episode. All subsequent assessments should be accomplished within 60 minutes before and 60 minutes after each infusion episode. If multiple vital sign assessments are taken within 60 minutes before and/or after the infusion, the vital signs that are assessed closest before the start and after the end of each infusion should be recorded.

8. The type of surgical procedure indicated as well as start and stop dates and times of the procedure, estimated blood loss, use of ECMO and/or CPB will be recorded on the CRF.

9. Pre- and post-infusion episode samples for hemostatic and laboratory parameters will be tested. Pre-infusion samples for the first infusion episode should be drawn within 6 hours prior to the start of the first infusion episode (all the subsequent pre-infusion assessments are to be done within 60 minutes prior the infusion episode). Post-infusion episode samples should be drawn within 30 to 60 minutes after the end of each infusion. If the patient requires priming of the cardiopulmonary bypass (CPB) circuit with plasma, the post-infusion episode samples should be drawn 30-60 minutes after reversal of heparin during the process of coming off CPB. For the first infusion episode it is mandatory that, pre– and post–infusion episode samples for hemostatic and laboratory parameters be tested. If subsequent infusion episodes are performed, pre- and post-infusion episode laboratory tests should be performed unless considered not medically necessary by the Investigator (e.g., the timing of the pre-infusion episode sample is close to or overlaps with the timing of the post-infusion episode sample and it is not necessary to perform, etc.). In the event the pre- or post-infusion laboratory sample(s) are not drawn, the reason for not obtaining the sample(s) will be recorded on the CRF. If multiple hemostatic and laboratory parameters may be assessed before and/or after the infusion, the hemostatic and laboratory parameters that are assessed closest before the start and after the end of each infusion should be entered in the eCRF. TEG with Kaolin activation or ROTEM EXTEM testing should be performed as defined in **Section 7.3.5.3**.

10. Females ≥ 11 years old or females of childbearing potential (if younger than 11 years old) must have a negative pregnancy test prior to the first infusion episode to qualify for the study.
11. This Assessment of Safety should be performed by the principal investigator or sub-investigator.
12. For this trial a "clinically relevant hyperfibrinolytic event" is defined by one of the following test results in the presence of a bleed that requires intervention:
    - Kaolin TEG – estimated percentage lysis (EPL) > 7.5% at 30 min (after starting assay).
    - ROTEM EXTEM – maximum lysis (ML) > 7.5% at 30 min (after starting assay).

Laboratory Evaluations Flow Chart[1]

Time-Points	Pre-Infusion	Post-Infusion	Final Examination
	Before infusion episode	Between 30 and 60 minutes after each infusion episode	72 hours after end of last study infusion episode
Hemostatic parameters: INR, PT, aPTT, TEG or ROTEM	X	X	
Laboratory parameters: • Chem 7 panel: BUN, CO_2 (bicarbonate), serum chloride, serum creatinine, glucose, serum potassium, and serum sodium. • CBC: WBC, RBC, platelets, hemoglobin, hematocrit, MCV, MCH, MCHC, and RDW. • Ionized calcium	X	X	X

1. The following blood volume limits for sampling are recommended, if an Investigator decides to deviate from these, this should be justified. NIH Clinical Center Guidelines for Blood Drawn for Research Purposes in the Clinical Center (M95-9) rev 06/05/2009: For pediatric patients, no more than 5 mL/kg may be drawn for research purposes in a single day, and no more than 9.5 mL/kg may be drawn over any eight-week period.

3.3 Discussion of Study Design and Choice of Control Group(s)

Study Design

This is an open-label, multicenter, PMR study in 50 pediatric patients with acquired deficiencies due to liver disease and/or 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 will be conducted in up to 10 sites in North America. The following number of patients is planned to be enrolled:

1. Neonates/Infants (0-2 years): a maximum of 33 patients

2. Children > 2 years and ≤ 16 years: a minimum of 17 patients

Taking into consideration the small size of the target population of children with this disease condition and intervention indication, the proposed sample size of 50 children seems appropriate to obtain sufficient safety information in a reasonable amount of time.

Control Group(s)

This is an open-label study of Octaplas to investigate its safety, tolerability and efficacy in the management of pediatric patients who require replacement of multiple coagulation factors; there is no control group.

Since the sole aim of this PMR study is the gathering of information on the safety and efficacy of Octaplas in the indicated study population, it is reasonable to omit a concurrent control group.

Target Parameter(s)

The selection of the endpoints listed in **Section 3.1** is considered adequate to provide the most relevant information on the safety and efficacy aspects of Octaplas in this setting. Therefore, these target parameters are in congruence with the study rationale.

4 STUDY POPULATION

4.1 Population Base

In total, 50 pediatric patients who require replacement of multiple coagulation factors are expected to be enrolled according to the following inclusion and exclusion criteria.

Inclusion Criteria

Patients who meet all of the following criteria are eligible for the study:

1. Patient requiring liver or cardiac surgery and/or patient with liver dysfunction associated with coagulopathy in whom replacement of multiple coagulation factors is required.
2. Voluntarily given, written and signed informed consent by the patient's legal representative(s) or guardian(s). Children deemed old enough by the Investigator/institution to understand the risks and benefits of the study should also be made aware of the risks/benefits of the study and provide written assent.
3. Male or female patient ≤ 16 years of age.

Exclusion Criteria

Patients who meet any of the following criteria are not eligible for the study:

1. Patient with known homozygous congenital deficiency of protein S.
2. Patient has a history of hypersensitivity reaction to blood or plasma-derived products or to any excipient of the investigational product.
3. Patient has an already known IgA deficiency with documented antibodies against IgA.
4. Patient has a congenital factor deficiency or platelet disorder requiring plasma treatment.
5. Patient is currently participating in another study investigating a new drug product or another interventional clinical study that may impact coagulation factors or has participated during the last three (3) months.
6. Patient received FFP, FP24 or any other plasma product other than Octaplas within the last 72 hours (cryoprecipitate and albumin are not exclusionary) prior to first Octaplas infusion.
7. Patient is on ECMO (Extracorporeal Membrane Oxygenation) when plasma is ordered by the treating physician for the first infusion episode.
8. Patient is pregnant.
9. Patient is predicted to require massive blood transfusion defined as more than 40 mL per kilogram of all blood products in a 24-hour period
10. Patient is receiving plasma exchange, TPE or plasmapheresis.
11. Patient is a premature neonate defined as less than 37 weeks gestation.
12. Cardiac surgery patients who develop the need for plasma replacement greater than 72 hours after the end of the associated cardiac surgery and do not have coagulopathy due to hepatic dysfunction.

4.2 Prior and Concomitant Therapy

Details of relevant current and concomitant medications administered during the trial period will be recorded on the CRF. Relevant medications are defined as follows:

- Plasma products (e.g., octaplas™, regular plasma products, etc.) and all other blood products that are administered.
- Antifibrinolytics (**ε**-aminocaproic acid or tranexamic acid) and any other pharmaceutical pro- or anti-coagulants such as recombinant activated factor VII, any of the prothrombin complex concentrates, or fibrinogen concentrates.
- Vaso-active agents (epinephrine, norepinephrine, vasopressin, Milrninone, phenylepherine, Antidiuretics (desmopressin, DDAVP, DesmoMelt, Stimate, Minirin, etc.).
- Colloids (e.g., albumin, hydroxyethyl starches).
- Medications (including steroids) taken to treat or prevent ADRs (to Octaplas)
- Other medications that the Investigator considers relevant to report for this trial.

Routine medications that are considered standard and/or that have little or no impact on the study data results are not to be entered into the CRF (e.g., anesthesia medications, beta blockers, etc.). Any concomitant medications or changes thereof must be recorded. If the change influences the patients' eligibility to continue in the trial, the Sponsor must be informed.

Permitted Concomitant Therapy

The following concomitant medications are permitted:

- calcium-gluconate given IV in case of hypocalcemia (due to citrate toxicity),
- antihistamines and glucocorticoids given IV in case of anaphylactoid reactions, and
- red blood cells, platelet units if medically indicated.

It is permitted for patients to receive Octaplas or other plasma products (please see exceptions below) during the 72-hour follow-up period if medically indicated.

Although patient's requiring ECMO at study entry are excluded, ECMO is permitted therapy while on study if it is determined to be medically indicated after the start of the first infusion.

Forbidden Concomitant Therapy

Single donor plasma (e.g., FFP, FP24, thawed plasma, etc.) should be avoided during the Treatment and Follow-up study periods. Patients receiving single donor plasma during the Treatment or Follow-up periods should be withdrawn from the trial.

Plasma exchange, TPE or plasmapheresis is not permitted during the study. Patients who develop the need for and undergo plasma exchange or plasmapheresis during the Treatment or Follow-up periods will be withdrawn from the trial.

4.3 Withdrawal and Replacement of Patients

Premature Patient Withdrawal

Patients have the right to withdraw from the study at any time for any reason, without the need to justify their decision. The Investigator also has the right to withdraw patients in case of ADRs, protocol violations, or other reasons. Since an excessive rate of withdrawal can render the study non-interpretable, the unnecessary withdrawal of patients must be avoided.

For any discontinuation after study entry, the Investigator will obtain all the required details and document the reason(s) for discontinuation in the CRF. If the reason for withdrawal of a patient is an ADR, the main specific event or laboratory test will be recorded in the CRF, and the Investigator will make thorough efforts to clearly document the outcome.

Moreover a patient may be withdrawn from the study prior to completion for any of the following reasons:

- Whenever the patient/legal representative(s)/guardian(s) decides it is in the patient's best interest to withdraw
- Whenever the Investigator decides it is in the patient's best interest to be withdrawn
- Pregnancy

For any premature patient withdrawal after study entry, the Investigator will obtain all the required details and document the reason(s) for discontinuation in the CRF. Data of patients withdrawn prematurely will be included in the safety analysis.

Patients consented (enrolled) into the study pre-operatively for cardiac and liver surgery will be considered screening failures if they do not receive Octaplas intra-operatively or post-operatively. Patients who are consented but do not receive Octaplas intra-operatively will be eligible for study treatment while they remain in the intensive care unit. Patients who are discharged from the intensive care unit without being treated with Octaplas will be considered a screening failure.

Patient Replacement Policy

There is no patient replacement policy defined for this protocol. Fifty (50) pediatric patients will be treated in the study.

4.4 Assignment of Patients to Treatment Groups

All patients enrolled in this study will be treated with Octaplas. The Investigator will inform the Sponsor of new patients enrolled by the submission of patient entry information.

4.5 Relevant Protocol Deviations

If deviations from the protocol occur, the Investigator should promptly inform the monitor and the nature of the deviation must be reviewed and discussed. Any deviation must be documented, stating the reason and date, the action taken, and the impact for the patient and/or the trial. The documentation must be kept in the Investigator's Trial File and the Sponsor's Trial File. In case of any major protocol deviation the Investigator and the Sponsor will decide on whether the patient should be withdrawn from this study.

4.6 Subsequent Therapy

After the study treatment period has ended, subsequent therapy is at the treating physician's discretion.

5 INVESTIGATIONAL MEDICINAL PRODUCT(S)

5.1 Characterization of Investigational Product(s)

For Octaplas, a new prion affinity column was introduced in the manufacturing process of the product to eliminate potential prion proteins. Furthermore, the time of S/D treatment in the manufacturing process has been shortened from 4–4.5 hours to 1–1.5 hours. These measures increase the concentration of plasmin inhibitor and slightly increase the concentration of protein S compared with octaplas®.

The virus safety of Octaplas was maintained as shown by virus validation studies. With a total inactivation to below the detection limit, the shortened S/D procedure has a time-safety-margin of >98.3% versus >99.5% for the predecessor product.

5.2 Packaging and Labeling

Octaplas is delivered frozen in sterile, pyrogen free plastic bags containing 200 mL. The bags are vacuum sealed in a clear plastic wrap and delivered in cartons of 10 units.

Each octaplas™ bag will be labeled as shown below (for blood group A).

NDC 68209-952 – 01

Octaplas™
Pooled Plasma (Human), Solvent/Detergent Treated

For intravenous use only.

Rx only.

200 mL contain 9 - 14 g human plasma proteins, 0.88 - 1.48 g sodium citrate dihydrate, 0.06 - 0.24 g sodium dihydrogen phosphate dihydrate, 0.80 - 1.20 g glycine, ≤0.4 mg TNBP and ≤1.0 mg Octoxynol. This product contains no preservative.

Store at ≤–18°C (–0.4ºF) protected from light.

Thawed product should be used immediately and must not be refrozen.

Do not use product that is cloudy or has deposits.

Unused product must be discarded.

Caution: New Drug--Limited by Federal (or United States) law to investigational use

Exp. Date:

Lot No.:

U.S. License No. 1646

Manufactured by:
Octapharma AB
Elersvägen 40
SE-112 75, Sweden

Distributed by:

Octapharma USA Inc. Hoboken, NJ 07030 866-766-4860

Final labeling will comply with the national requirements of each country where the study is to be conducted.

Octaplas is labeled in the United States with the proprietary name octaplas^{TM}. In case the study will be conducted in countries outside of the United States where the product is licensed under the name Octaplas and the product octaplas is recognized as the predecessor product this could lead to mismatch or misunderstanding. Therefore the name Octaplas is used in the current protocol.

5.3 Conditions for Storage and Use

The shelf-life of Octaplas is 36 months when stored at ≤ -18°C (≤ -0.4°F) and protected from light. After thawing, the product must be used within 24 hours when stored at 1-6°C (33.8°F to 42.8°F) or within 8 hours when stored at room temperature 20 to 25°C (68°F to 77°F). See package insert in **Appendix 1**.

The Investigator/authorized personnel at the site will ensure that the product is stored in appropriate conditions with restricted access and in compliance with national regulations.

5.4 Dose and Dosing Schedule

The actual volume of Octaplas administered to a patient will depend on the clinical setting.

If the time interval between the end of one Octaplas infusion and the beginning of the next Octaplas infusion is no longer than 60 minutes, then this will be regarded as 1 infusion episode. If the time interval is more than 60 minutes, this will be counted as 2 different infusion episodes. For patients on CPB who are primed with plasma, a transfusion episode will begin with the initiation of the circuit with plasma and will end when the heparin is reversed during the process of coming off CPB.

The infusion rate of Octaplas should not exceed 0.020-0.025 mmol citrate per kilogram per minute, which is equal to <1 mL 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. The dose (mL) of Octaplas to be infused will depend on the age and BW of the patient. The first infusion dose will be at a minimum of 10 mL/kg or one unit unless a lesser dose is medically justified. If infusions are performed and the dose administered is less than 10 mL/kg the medical reason justifying this dosage will be recorded in the CRF, since at least 10 mL/kg are required to significantly increase the respective plasma protein levels

5.5 Preparation and Method of Administration

Octaplas will be used per the approved labeling for the product (see **Appendix 1**). Octaplas will be administered based on ABO-blood group compatibility. In urgent cases and in the circumstances that no same blood group is available (type A donor plasma for type A

recipient), patient can be administered plasma that is compatible to recipient's blood group (e.g., donor AB plasma can be administered to recipient with blood group A).

5.6 Blinding, Emergency Envelopes and Breaking the Study Blind

Not applicable. This is an open-label study.

5.7 Treatment Compliance

Drug Dispensing and Accountability

Octaplas will be supplied by the Sponsor. A drug dispensing and accountability log will be kept up-to-date at the Investigator's site, detailing the dates and quantities of the investigational medicinal product (IMP) received at the site and dispensed and administered to each patient. The inventory will be made available to the monitor to verify drug accountability during the study. Unused trial medication will be returned to the Sponsor designated clinical supplies depot or, if approved by the Sponsor in advance, may be destroyed at the Investigator site following local policies for destruction of biologic supplies. Empty bags will not have to be returned and will be destroyed at the study site following local policies after appropriate documentation.

Assessment of Treatment Compliance

Having in mind the setting and the fact that study drug administration will exclusively take place at the investigational site, full compliance is expected.

6 STUDY CONDUCT

6.1 Study Periods

Screening

The following assessments will be performed at Screening:

- Obtaining voluntarily given, written (signed and dated) informed consent by the patient's legal representative(s) or guardian(s). Children deemed old enough by the Investigator/institution to understand the risks and benefits of the study should also be made aware of the risks/benefits of the study and provide written assent. Patients determined to have a reasonable probability to receive intra-operative plasma transfusion according to the Investigator's clinical judgment may also be approached for consent to participate. If these patients are subsequently not prescribed plasma intra-operatively or postoperatively they will be determined to be a screening failure and not included in the analysis.
- Review of inclusion and exclusion criteria.
- Physical examination (see **Section 7.3.6**).
- Relevant medical history including prior medications (taken within 7 days prior to time 0 (study drug given) and on-going concomitant medication(s).
- Demographic data (height, BW, gender, date of birth, ethnicity).
- Determination of ABO blood group for compatibility.

- Pregnancy testing for females at the age of ≥ 11 or of childbearing potential (if younger than 11 years old). Results must be negative for the female patient to be in the study.
- Documentation of type of surgical procedure indicated for the patient and important operative interventions.
- Ordering of plasma if clinically indicated per physician discretion.

Pre-Infusion (Immediately Before First Infusion Episode)

The following assessments will be performed before the first infusion episode:

- Vital signs (see **Section 7.3.6**).
- Blood sample(s) for hemostatic parameters (see **Section 7.2.1**).
- Blood sample(s) for laboratory parameters (see **Section 7.3.5.3**).

Study Treatment Period

The number of infusion episodes and 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. After 72 hours from the start of the first infusion of Octaplas, the study treatment period will end. The following procedures will be performed during the study treatment period:

- Administration/infusion of Octaplas.
- Vital signs.
- Monitoring of ADRs (refer to **Section 7.3.2.1** for definition), TEs, TEEs, hyperfibrinolytic events and concomitant medications.
- 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 subsequent infusion episodes. Post-infusion episode samples should be drawn within 30 to 60 minutes after the end of each infusion episode. If the patient requires priming of the cardiopulmonary bypass (CPB) circuit with plasma, the post-infusion episode samples should be drawn 30-60 minutes after reversal of heparin during the process of coming off CPB. For the first infusion episode it is mandatory that pre- and -post-infusion episode laboratory testing is performed. If subsequent infusion episodes are performed, pre- and post-infusion episode laboratory tests should be performed unless considered not medically necessary by the Investigator (e.g., the timing of the pre-infusion episode sample is close to or overlaps with the timing of the post-infusion episode sample and it is not necessary to perform, etc.). In the event pre- or post-infusion laboratory sample(s) are not performed, the reason will be documented in the CRF. If multiple hemostatic and laboratory parameters may be assessed before and/or after the infusion, the hemostatic and laboratory parameters that are assessed closest before the start and after the end of each infusion should be entered in the eCRF.

Safety Follow-up Period

- ADRs, TEs, TEEs, hyperfibrinolytic events and concomitant medications will be monitored for 72 hours (± 6 hours) after the last Octaplas transfusion is completed.

Final Examination

Seventy-two hours (± 6 hours) after the end of the last study infusion episode, a Final Examination will be performed that consists of the following assessments:

- Vital signs (see **Section 7.3.6**).
- Physician Assessment of Safety (**Section 7.3.1**).
- Blood sample(s) for laboratory parameters (see **Section 7.3.5.3**).
- Monitoring of ADRs (refer to **Section7.3.2** for definition), TEs, TEEs, hyperfibrinolytic events and concomitant medications.

After the Final Examination, 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 ADRs) require follow-up.

6.2 Duration of Study

Planned Duration for an Individual Patient

There will be a maximum 72-hour study treatment period followed by a 72-hour follow-up period.

Planned Duration for the Study as a Whole

The study will be considered completed when all patients have completed the Final Examination.

The start of the study (enrollment of first patient) is 2nd quarter 2014 and the estimated end of the study is 4th quarter 2017.

Premature Termination of the Study

Both the Investigator and the Sponsor reserve the right to terminate the study 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.

Furthermore, the Investigator should promptly inform the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) and provide a detailed written explanation. The pertinent regulatory authorities should be informed according to national regulations.

Should the study be prematurely terminated, all study materials (completed, partially completed and blank CRFs, investigational product, etc.) must be returned to the Sponsor.

7 ASSESSMENTS AND METHODS

7.1 Background / Baseline Information

The following information will be captured upon enrollment:

- Physical examination with vital signs (see **Section 7.3.6**).
- Relevant Medical History including relevant prior medications (taken within 7 days prior to time 0 (study drug given)) and on-going relevant concomitant medications.

- Demographic data including height, BW, gender, date of birth, and ethnicity.
- Blood group determination.
- Blood samples for hemostatic and laboratory parameters (see **Sections 7.2.1** and **7.3.5.3**, respectively).
- Pregnancy testing for females ≥ 11 years old or of childbearing potential (if younger than 11 years old).
- Type of surgical procedure indicated and use of ECMO and/or CPB

7.2 Efficacy Assessments

7.2.1 Hemostatic Parameters

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

The following hemostatic parameters will be assessed: INR, PT, aPTT, TEG with Kaolin activation or ROTEM EXTEM testing.

7.3 Safety Assessments

7.3.1 Relevant Drug Safety Information

Any of the following drug safety information shall be collected after the start of the first infusion episode:

- SAEs
- ADRs temporally associated with administration of the investigational product (definitions and reporting requirements see **Sections 7.3.2** and **7.3.3**)
- AEs that fall into the category of TEs, TEEs and hyperfibrinolytic events
- Post-treatment related safety reports, pregnancies, drug overdose, interaction, abuse, misuse, medication error, lack of efficacy (see **Section 7.3.7**)

Non-serious AEs observed during the trial will not be captured in the CRF (except for TEs, TEEs, and hyperfibrinolytic events as explained above).

Post-treatment, the Investigator will provide an overall Assessment of Safety observed for each patient by indicating his or her opinion of one of the following 3 categories best describing the patient's experience with treatment while on study:

- Excellent: defined as the treatment was well tolerated by the patient
- Moderate: defined as adverse drug reaction(s) were observed, but easily resolved or not clinically significant
- Poor: Defined as adverse drug reaction(s) were observed requiring significant medical intervention

7.3.2 Adverse Events and Adverse Drug Reactions

7.3.2.1 Definitions

Adverse event (AE): An AE is any untoward medical occurrence in a study patient receiving an IMP and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not related to the IMP.

Adverse drug reaction (ADR): An ADR is any noxious and unintended response to an IMP related to any dose. The phrase "response to an IMP" means that a causal relationship between the IMP and an adverse event carries at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Withdrawal due to ADR/AE: Is a patient whose treatment with IMP is discontinued because of an ADR. Any such events will be followed up by the Investigator until the event is resolved or until the medical condition of the patient is stable. All follow-up information collected will be made available to the Sponsor.

7.3.2.2 Collection

The condition of the patient will be monitored throughout the study. ADRs/AEs will be elicited using a standard non-leading question such as "How have you been since the last evaluation?" If children or adolescent patients are unable to adequately understand and respond to this question, the information will be obtained from the patient's guardian and/or Investigator or study nurse.

Any ADR or above defined AE after the first administration of study drug which occurs during the study will be noted in detail on the appropriate pages of the CRF. If the patient reports several signs or symptoms, which represent a single syndrome or diagnosis, the latter should be recorded in the CRF. The Investigator responsible will grade the severity of all ADRs/AEs (mild, moderate or severe), the seriousness (non-serious or serious) and causality, as defined below (**Sections 7.3.2.3, 7.3.2.4,** and **7.3.3**). The Sponsor is responsible to assess the expectedness of each ADR/AE (expected or unexpected), as defined below (**Section 7.3.2.4**).

Diseases, signs and symptoms and/or laboratory abnormalities already existing before the first administration of IMP are not considered as ADRs/AEs when observed at a later stage unless they represent an exacerbation in intensity or frequency (worsening).

The Investigator responsible should always provide detailed information concerning any abnormalities and the nature of, and reasons for any necessary action(s), as well as any other observations or comments, which are useful for the interpretation and understanding of the patients' ADRs/AEs.

7.3.2.3 Severity

The intensity/severity of all ADRs/AEs will be graded as follows:

- mild: an ADR/AE, usually transient, which causes discomfort but does not interfere with the patient's routine activities;
- moderate: an ADR/AE which is sufficiently discomforting to interfere with the patient's routine activities;
- severe: an ADR/AE which is incapacitating and prevents the pursuit of the patient's routine activities.

Grading of an ADR/AE is up to the medical judgment of the Investigator and will be decided on a case by case basis.

7.3.2.4 Causality

The following causality definitions should be used for classification of each AE:

Probable: Reports or laboratory test abnormality, with reasonable time relationship to drug intake.
Unlikely to be attributed to disease or other drugs.
Response to withdrawal clinically reasonable.
Re-challenge not required.

Possible: Reports or laboratory test abnormality, with reasonable time relationship to drug intake.
Could also be explained by disease or other drugs.
Information on drug withdrawal may be lacking or unclear.

Unlikely: Reports not following a reasonable temporal sequence from IMP administration. An event which may have been produced by the patient's clinical state or by environmental factors or other therapies administered.

Not related: Reports for which sufficient information exists to conclude that the etiology is unrelated to the IMP.

Unclassified: Reports which for one reason or another are not yet assessable, e.g., because of outstanding information (can only be a temporary assessment).

The following causality definitions should be used for classification of each ADR:

Probable: Reports or laboratory test abnormality, with reasonable time relationship to drug intake.
Unlikely to be attributed to disease or other drugs.
Response to withdrawal clinically reasonable.
Re-challenge not required.

Possible: Reports or laboratory test abnormality, with reasonable time relationship to drug intake.
Could also be explained by disease or other drugs.
Information on drug withdrawal may be lacking or unclear.

Classification of ADRs:

ADRs will be classified by the Sponsor as either expected or unexpected:

- expected: an adverse event that is listed in the current edition of the Investigator's Brochure (IB).
- unexpected: an adverse event that is not listed in the current edition of the IB, or that differs because of greater severity or greater specificity.

7.3.2.5 Outcome

The outcome of all reported ADRs/AEs has to be documented as follows:

1. recovered, resolved
2. recovering, resolving
3. not recovered, not resolved
4. recovered, resolved with sequelae
5. fatal
6. unknown

NOTE: A patient's **death** per se is not an event, but an outcome. The event which resulted in patient's death must be fully documented and reported, even in case the death occurs within four (4) weeks after IMP treatment end, and without respect of being considered treatment-related or not.

7.3.2.6 Action(s) Taken

ADRs/AEs requiring action or therapy must be treated with recognized standards of medical care to protect the health and well-being of the patient. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment of an emergency situation.

The action taken by the Investigator must be documented:

a) in general
   - none
   - medication (other than IMP) or other (e.g., physical) therapy started
   - test performed
   - other (to be specified)

b) on IMP
   - none
   - product withdrawn
   - dose reduced
   - dose increased

The responsible Investigator will follow-up each ADR/AE until it is resolved or until the medical condition of the patient is stable and all relevant follow-up information will be reported to the Sponsor.

7.3.3 Serious Adverse Events (SAEs)

A **serious** AE is any untoward medical occurrence at any dose:

- results in death,
- is life-threatening (this implies that the patient was at an immediate risk of death at the time of the event, and not a hypothetical situation of what could or would have happened if, for example, no treatment had been administered),
- requires in-patient hospitalization or prolongation of existing in-patient hospitalization (hospitalization does not refer to the treatment of an ADR/AE on an out-patient status

or to hospitalization because of study-related procedures (e.g., infusion at two consecutive days) or because of an elective surgical procedure for which the date had been scheduled earlier),

- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- is another important medical event (e.g., suspected transmission of an infectious agent, or other reactions that should be reported in an expedited manner although they did not immediately result in one of the above seriousness criteria).

Medical judgment should be exercised in deciding whether an ADR/AE is serious in other situations. Important ADRs/AEs that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definitions above, should also be considered serious.

SAE reporting timelines

All SAEs occurring after the start of the first infusion episode are to be reported by telephone, fax or e-mail immediately to the Clinical Project Manager (CPM) or designee. Contact details will be communicated at the study initiation visit.

An Octapharma "Serious Adverse Event Report" must be completed and submitted within 24 hours after recognition of the event.

All SAEs, TEs, TEEs and hyperfibrinolytic events (**Section 7.3.4**)should be reported to:

Octapharma's Central Drug Safety Unit:
OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Strasse 235, 1100 Vienna, Austria
Fax: +43 1 61032-9949
E-mail: cdsu@octapharma.com

24 hours emergency telephone number: +1 (844) 338-7317 or +43 1 40 80 500

7.3.4 TEs, TEEs and Hyperfibrinolytic Events

To allow continuous monitoring of the product's safety, all hyperfibrinolytic events, TEs and TEEs and other safety information as defined below must be documented and reported to Octapharma. All the above mentioned events will be reported regardless of severity or relatedness to the product. For this trial a "clinically relevant hyperfibrinolytic event" is defined by one of the following test results in the presence of a bleed that requires intervention.

1. Kaolin TEG: estimated percentage lysis (EPL) > 7.5% at 30 min (after starting assay)

2. ROTEM EXTEM: maximum lysis (ML) > 7.5% at 30 min (after starting assay)

The following list includes diagnoses and symptoms of possible TEs and TEEs that could be expected to be reported:

Acute myocardial infarction

Increased heart enzymes*
Electrocardiogram signs of myocardial infarction*
Angina pectoris*
Acute coronary syndrome*

Chest pain or pressure*
Cardiac arrest**

(Ischemic) Stroke

Transient ischemic attack

Cerebrovascular accident

Vision or speech disorders*
Unilateral paresis/weakness
Movement disorders*
Dysphasia*
Sudden severe headache*

Deep vein thrombosis

Pain or tenderness in leg(s)*
Pain in calf/calves*
Swelling calf/calves/lower legs*

Pulmonary embolism

Unexplained shortness of breath*
Sudden chest pain getting worse with a deep breath, coughing, or chest movement*
Cyanosis*

Thrombophlebitis

Infusion site thrombosis

* Possible sign or symptom of TEE
** May be outcome of TEE

To determine/confirm a TE or TEE the following adjudicators will be involved:

Adjudicator 1 (Investigator)

On the corresponding safety reporting form of the CRF, the Investigator is specifically asked if the reported event is a TE or TEE in his/her opinion.

Adjudicator 2 (Octapharma Central Drug Safety Unit, CDSU)

Once a TEE/TE is recorded on the CRF, the event will be forwarded to Octapharma's Drug Safety Unit who will process the TEE/TE in routine manner (including assessments of expectedness, causality, seriousness, TEE/TE classification of event).

Adjudicator 3 (Independent Data Monitoring Committee, IDMC)

The IDMC will receive anonymized case reports and/or lists of all reported adverse reactions. Serious cases, probably or possibly related and suspected TEEs/TEs (as determined by Adjudicator 1 and/or Adjudicator 2) will be reviewed on an ad-hoc basis; other cases like ADRs and not related SAEs will be reviewed on a quarterly basis. The IDMC will then vote on all new cases (simple majority), record their judgment and return their decisions back to data management.

In case, the adjudicators disagree, the following scheme will be applied (**Table 1**):

Table 1: Scheme of Decision for Adjudicators

Determined as TEE/TE by Adjudicator 1?	Determined as TEE/TE by Adjudicator 2?	Determined as TEE/TE by Adjudicator 3?	Determined as TEE/TE in database?
Yes	no	no	yes
Yes	yes	no	yes

No	yes	no	yes
No	no	yes	yes
No	yes	yes	yes
Yes	no	yes	yes

Abbreviations: TE=thrombotic event; TEE=thromboembolic event

7.3.5 Laboratory Tests

7.3.5.1 Determination of Blood Group

The blood type will be clarified at Screening for determination of the patient's ABO blood group type compatibility.

7.3.5.2 Pregnancy Testing

Pregnancy testing will be done pre-infusion for females ≥ 11 years old or of childbearing potential (if younger than 11 years old). Females must have a negative pregnancy test in order to be in the study.

7.3.5.3 Laboratory Parameters[2]

The following laboratory parameters (**Table 2**) will be tested to assess renal, hematologic and metabolic function. These tests must be drawn within a maximum of 6 hours before the start of the first infusion episode and within 60 minutes before the start of subsequent infusion episodes, as well as within 30 to 60 minutes after each infusion episode and at the Final Examination. If the patient requires priming of the cardiopulmonary bypass (CPB) circuit with plasma, the post-infusion episode samples should be drawn 30-60 minutes after reversal of heparin during the process of coming off CPB.

Table 2: Laboratory Parameters

Chem 7 panel	**CBC**	**Ionized Calcium**
BUN	WBC	
CO_2 (bicarbonate)	RBC	
Serum Chloride	Hemoglobin	
Serum Creatinine	Hematocrit	
Glucose	MCV	
Serum Potassium	MCH	

[2] The following blood volume limits for sampling are recommended: If an Investigator decides to deviate from these, this should be justified. NIH Clinical Center Guidelines for Blood Drawn for Research Purposes in the Clinical Center (M95-9) rev 06/05/2009: For pediatric patients, no more than 5 mL/kg may be drawn for research purposes in a single day, and no more than 9.5 mL/kg may be drawn over any eight-week period.

Serum Sodium	MCHC
	RDW
	Platelets

Abbreviations: BUN=blood urea nitrogen; MCH=Mean Corpuscular Hemoglobin; MCHC=Mean Corpuscular Hemoglobin Concentration; MCV=Mean Corpuscular Volume; RDW=Red Cell Distribution Width; WBC=White Blood Cell

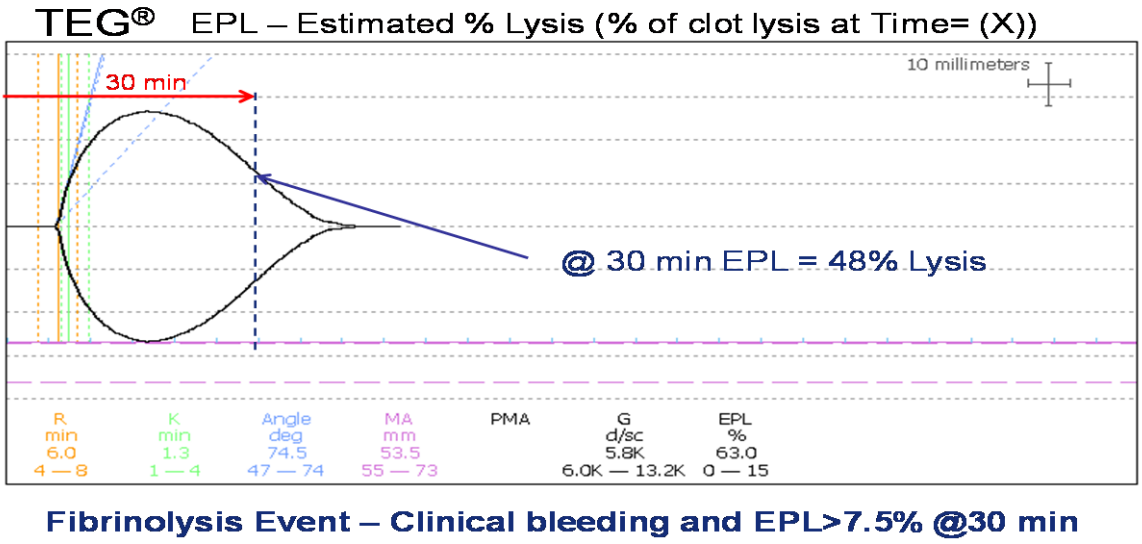
The following hemostatic parameters will be assessed (**Table 3**).

Table 3: Hemostatic Parameters

INR
PT
aPTT
TEG with Kaolin activation
ROTEM EXTEM*

Please be aware that either TEG **or** ROTEM assessment is to be carried out

Abbreviations: aPTT=Activated Partial Thromboplastin Time; INR=International Normalized Ratio; PT=Prothrombin Time; TEG=Thromboelastography; ROTEM=Thromboelastometry



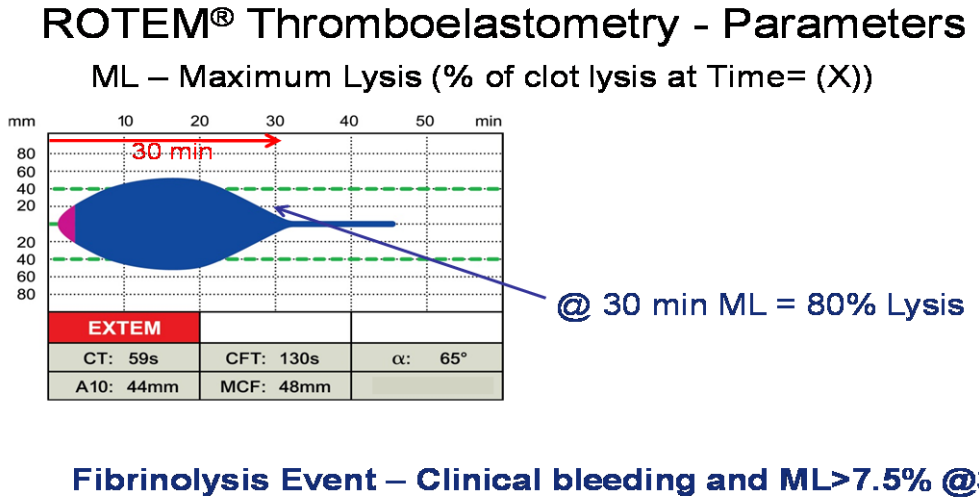
Fibrinolysis Event – Clinical bleeding and EPL>7.5% @30 min

For all infusion episodes, the TEG sample results should be recorded if testing is performed (e.g., when evaluating a potential hyperfibrinolytic event, or other clinical reason for testing). The parameters to be recorded are: reaction time (R-time), time from the end of R until the clot reaches 20 mm (K-time), slope between R and K (alpha angle), maximum amplitude of clot strength (MA), and EPL at 30 minutes in order to be able to assess the occurrence of a potential hyperfibrinolytic event. Heparin may be present in the blood of patients undergoing

anticoagulation. If anticoagulation by heparin is known or suspected, heparinase must be used to neutralize its effect. Failure to neutralize heparin may result in a lack of significant clot formation, and inability to diagnose fibrinolysis.

For all infusion episodes, the ROTEM with EXTEM assay test results should be recorded if testing is performed (e.g., when evaluating a potential hyperfibrinolytic event, or other clinical reason for testing). The following ROTEM test parameters (EXTEM) will be recorded: clotting time (CT), clot formation time (CFT), alpha angle, Maximum Clot Firmness (MCF), and ML at 30 minutes.

Please be aware that is sufficient to either assess kaolin TEG or ROTEM EXTEM samples.



Fibrinolysis Event – Clinical bleeding and ML>7.5% @30 min

In cases where the maximum blood volume drawn for lab testing becomes an issue, it is at the investigator's discretion to determine which laboratory assessments he/she sees most necessary to be done with this limited amount of blood volume based on the best interest of the patients care. If the laboratory testing is being drawn strictly for the study, and no other laboratory testing is needed to manage the patient clinically at the time of the sampling then this is the general order of importance for this trial: TEG/ROTEM, INR, PT, aPTT, Ionized Ca, Chem 7, CBC. In situations where lab tests are omitted due to maximum blood volume restrictions per protocol, an explanation should be added to the source notes and eCRF describing this.

The investigator classifies any result that is not within its respective normal result range as either clinically significant (CS) or not clinically significant (NCS). Medical judgement is required. For example, the investigator may not classify an abnormal result as CS unless it exceeds a certain level or appears in conjunction with other observations. An abnormal lab

value should be deemed clinically significant by the investigator if for instance either of the following conditions is met:

- The abnormality suggests a disease and/or organ toxicity that is new or has worsened from baseline
- The abnormality is of a degree that requires additional active management, e.g., change of dose, discontinuation of the drug, close observation, more frequent follow-up assessments, of further diagnostic investigation.

In the event of clinically significant abnormal laboratory findings, the tests will be repeated and followed-up until they have returned to normal and/or an adequate explanation is available.

7.3.6 Physical Examination and Vital Signs

At Screening, a physical examination will be performed.

A physical examination will be performed in accordance with the site's routine procedures. This may include examination of dermatological and lymphatic system, HEENT, respiratory tract, cardiovascular and gastrointestinal system, musculoskeletal system, and neurological system.

Vital signs will include heart rate, respiratory rate, temperature, arterial saturation, and blood pressure assessment. Vitals should be assessed within a maximum of 6 hours before the start of the first infusion episode and within 60 minutes before the start of subsequent infusion episodes, as well as within 30 to 60 minutes after each infusion episode and at the Final Examination. If multiple vital sign assessments are taken before and/or after the infusion, the vital signs that are assessed closest before the start and after the end of each infusion should be recorded.

7.3.7 Other Relevant Safety Information

Post study related safety reports: Any ADR which occurs after the completion of the study should be reported by the Investigator. The usual procedure for reporting post marketing safety information should be followed, but relation to the clinical study should be stated on the report.

If the Investigator becomes aware that a patient has died within four (4) weeks after the last IMP administration, this should be reported as well, without being considered treatment related or not.

Pregnancies: Every effort will be made to avoid a pregnancy during the use of an IMP.

Pregnancies occurring during the study (fetal exposure to the IMP) need to be reported.

In case of pregnancy during the study, the Investigator is asked to complete the pregnancy notification form and to send it (by fax) to the CPM / designee.

Follow-up information on the outcome of both mother and fetus will be requested by a Sponsor representative.

Overdose, interaction, abuse, misuse and medication error:

The following safety relevant information should be reported as an ADR or, if the reaction fulfils one of the criteria for seriousness, as a SADR.

Drug overdose: An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than that specified in the protocol, and higher than the known therapeutic dose and of clinical relevance. The reaction must be clearly identified as an overdose. Due to the study design, no overdose is expected.

Interaction: A drug interaction is a situation in which a substance/medicinal product affects the activity of an IMP, i.e., the effects are increased or decreased, or they produce an effect that none of the products exhibits on its own. The reaction must be clearly identified as drug interaction.

Abuse: An abuse is the deliberate use of a medicinal product that may lead to addiction accompanied by harmful physical or psychological effects. This is not relevant for the IMP but may be applicable for concomitant medications.

Misuse: Misuse is the deliberate administration or use of the medicinal product outside its described indication or outside the current state of the art medical practice (off-label-use). The reaction must be clearly identified as misuse.

Medication error: Medication error involves the inadvertent administration or unintended use of a medicinal product which may be caused by the naming, presentation of pharmaceutical form/packaging and instructions for use/labeling. The reaction must be clearly identified as a medication error.

7.4 Appropriateness of Measurements

Only standardized measurements that are widely used and generally recognized as reliable, accurate, and relevant will be used in this study.

8 DATA HANDLING AND RECORD KEEPING

8.1 Documentation of Data

Source Data and Records

Source data are defined as all the information related to clinical findings, observations, or other activities in the study, written down in original records or certified copies of original records allowing reconstruction and evaluation of the clinical study.

The Investigator will maintain adequate source records (e.g., case histories or patient files for each patient enrolled). Source records should be preserved for the maximum period of time required by local regulations.

For each patient enrolled, the Investigator will indicate in the source record(s) that the patient participates in this study.

The Investigator will permit study-related monitoring, audit(s), IEC/IRB review(s) and regulatory inspection(s), by providing direct access to source data/records.

Case Report Forms

The Sponsor will provide the CRFs in electronic format. They will be reviewed against source documentation at each monitoring visit. The Investigator should allocate sufficient time and space for the review and correction process.

For each patient enrolled, an electronic CRF (eCRF) will be completed within the Electronic Data Capture (EDC) system and approved by the Investigator or an authorized sub-investigator.

Study site staff (e.g., research nurse) will be responsible for entering all of the patient data into the validated EDC system. All site personnel will be trained on the EDC system and study specific eCRFs prior to receiving access to the live database for data entry, as defined in applicable SOPs. The site is also provided with the approved eCRF Completion Guidelines which will assist in data entry and data issues/questions. The site will be notified once the database is active to begin data entry. Additional site training may be provided as refreshers throughout the study, if needed. All persons allowed to enter or change eCRF data must appear on the delegation of authority log.

If any errors in the eCRFs are found during the data review process, discrepancies will be generated programmatically within the EDC system, and 'manual' queries will be generated by either a monitor or Data Management. The programmed checks fire automatically once an eCRF page is saved within the system. The output of the programmed checks is referred to as 'discrepancies'. Discrepancies are generated by the input of illogical eCRF data. The purpose of these objects is to clarify the use, context, or insertion of illogical or missing data with the site or designee.

All discrepancies (programmed and manual) will be submitted to the site personnel or monitor for the site within the EDC system. Once the site responds to a discrepancy, Data Management or the monitor will review the new or changed data to ensure an appropriate response and close the discrepancy within the system. The Investigator should ensure the accuracy, completeness and timeliness of the data reported to the Sponsor in the CRFs and in all required reports.

Changes to Case Report Form Data

Errors occurring in the EDC system can only be corrected by the Investigator(s) or other site personnel. An audit trail documents all changes to the data over the entire study period. If data is changed as a result of a query, a comment must be supplied within the query's text, stating the reason for the change, prior to closing. The study monitor should provide guidance to investigators and the investigators' designated representatives on making such corrections. In addition, any changes to a previously saved eCRF page that has not had a query generated will need to have a reason specified for the data change. This is handled within the EDC system and relevant prompts appear once any changes are made.

Once queries have been resolved by the site staff, the resolutions are assessed by Data Management for incomplete or ambiguous resolutions. If the query response provided confirms the data as correct, the discrepancy will be closed based on the query response. If the response does not adequately address the question raised, a new query will be issued for further clarification.

Manual checks are performed and programs are run throughout the study until the data is clean and the database is ready for lock. All discrepancies will be resolved prior to database lock. There will be a final run of the programmed checks to ensure all discrepancies are closed out, SDV will be confirmed as complete by the monitor, and all eCRFs will be approved by the Investigator prior to database lock.

All corrections on a CRF and on the source documents must be made in a way that does not obscure the original data. The correct data must be inserted, dated and initialed/authorized by trial site personnel. If reason for the change is not obvious, then a reason should be given. The Principal Investigator must, at a minimum, sign the final CRF page to attest to the accuracy and completeness of all the data. Once the data have been entered into the database, they will be checked and any discrepancies will be raised and returned to the Investigator for resolution. Data will be monitored and tabulated in accordance with the Data Management Plan.

8.2 Information of Investigators

An IB will be handed out to the Investigator before the start of the study. This IB contains all information in the Sponsor's possession necessary for the Investigator to be fully and accurately informed about the safety of the IMP under evaluation and the respective benefit-risk ratio.

The IB will be updated by the Sponsor at regular intervals and in case new information concerning the IMP becomes available.

The Investigator will be kept informed of important data that relate to the safe use of the IMP as the study proceeds.

8.3 Responsibilities

The Investigator is accountable for the conduct of the clinical study. If any responsibilities are delegated, the Investigator should maintain a list of appropriately qualified persons to whom he/she has delegated significant study-related duties.

The Investigator may authorize site staff (e.g., sub-investigators, nurses) to enter study data into the CRF. This must be documented in the "Delegation of Authority Log", filled in and signed by the Investigator responsible.

8.4 Investigator's Site File

At each study site, the Investigator is responsible for maintaining all records to enable the conduct of the study to be fully documented. Essential documents as required by GCP guidelines and regulations (e.g., copies of the protocol, study approval letters, all original informed consent forms, site copies of all CRFs, drug dispensing and accountability logs, correspondence pertaining to the study, etc.) should be filed accurately and kept by the Investigator for the maximum period of time required by local regulations.

The Investigator is responsible for maintaining a confidential patient identification code list, which provides the unique link between named source records and CRF data for the Sponsor. The Investigator must arrange for the retention of this confidential list for the maximum period of time required by local regulations.

No study document should be destroyed without prior written agreement between the Investigator and the Sponsor. Should the Investigator elect to assign the study documents to another party, or move them to another location, the Sponsor must be notified in writing.

8.5 Provision of Additional Information

On request, the Investigator will supply the Sponsor with additional data relating to the study, or copies of relevant source records, ensuring that the patient's confidentiality is maintained. This is particularly important when CRFs are illegible or when errors in data transcription are encountered. In case of particular issues or governmental queries, it is also necessary to have access to the complete study records, provided that the patient's confidentiality is protected in accordance with applicable regulations.

8.6 Independent Data Monitoring Committee (IDMC)

An IDMC will be established by the Sponsor. The IDMC will be composed of recognized experts in the field of hematology, transfusion medicine, immunology, pediatric surgery and/or pediatric critical care who are not actively recruiting patients.

The IDMC will review relevant quarterly safety line listings and SADR narratives periodically during the study and will give advice on the continuation, modification or termination of the study. A study specific Standard Operating Procedure will define in detail the composition, responsibilities and procedures of the IDMC.

9 STATISTICAL METHODS AND SAMPLE SIZE

The statistical analysis will be delegated under an agreement of transfer of responsibilities to an external Contract Research Organization (CRO). All Octapharma procedures and policies have to be met by this CRO. Discrepancies or exceptions are to be approved by the Sponsor's Manager of Biometrics.

9.1 Determination of Sample Size

A total of 50 pediatric patients are planned to be treated. The following number of patients is planned to be enrolled:

1. Neonates/Infants (0-2 years): a maximum of 33 patients

2. Children > 2 years and ≤ 16 years: a minimum of 17 patients

The primary purpose of this study is to assess safety and tolerability of Octaplas in the pediatric population by monitoring ADRs, TEs, TEEs and hyperfibrinolytic events, including relevant laboratory parameters. All data collected will be explored in full detail and no single parameter or measurement of outcome is chosen as the primary endpoint, and no statistical hypothesis is to be tested.

9.2 Statistical Analysis

A formal statistical analysis plan describing all details of the descriptive and explorative analyses to be performed will be prepared by the study statistician and approved by the Sponsor prior to the start of the statistical analysis.

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 all 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 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, 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.

To account for the abovementioned diversity in the study population, 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 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 age-specific thresholds 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 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 respectively), gender, underlying diagnosis, surgical procedures performed and/or most relevant medical history and concomitant medications.

Population for Analysis

The Safety (SAF) population 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 ADRs, hemostatic parameters, safety laboratory parameters, vital signs, etc.).

Patients who are consented (enrolled) to participate prior to an operative procedure and then did not get transfused will not be included in the ITT analysis.

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). Examples of protocol deviations to be considered in this respect would be 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 CPM, 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.

Efficacy Analysis Plan

The analysis of the efficacy parameters will be performed for the ITT and PP populations.

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

Adjustments for Covariates

Adjustments for covariates will be discussed in the SAP.

Data Presentation

In addition to the sampling statistics of the measurements, graphs showing the time profiles at the individual patient and group mean levels will be presented.

Safety Analysis Plan

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 > 2years), gender, underlying diagnosis, surgical procedures performed and/or most relevant medical history and concomitant medications.

9.3 Randomization / Stratification / Code Release

Not applicable.

9.4 Interim Analysis (if Applicable)

No interim analysis is planned.

10 ETHICAL / REGULATORY, LEGAL AND ADMINISTRATIVE ASPECTS

10.1 Ethical / Regulatory Framework

This study will be conducted in accordance with the ethical principles laid down in the Declaration of Helsinki. The study protocol and any subsequent amendment(s) will be

submitted to an IEC/IRB and to the Regulatory Authority. The study will be conducted in compliance with the protocol, GCP regulations and applicable regulatory requirements.

The submission for regulatory approval will be made by the Sponsor or designated third party (e.g., CRO) as required by national law.

10.2 Approval of Study Documents

The study protocol, a sample of the patient information and informed consent form, any other materials provided to the patients, and further requested information will be submitted by the Sponsor or the Investigator to the appropriate IEC/IRB and the Regulatory Authority. The study approval letter must be available before any patient is exposed to a study-related procedure.

The Sponsor, the Investigator and any third party (e.g., CRO) involved in obtaining approval, must inform each other in writing that all ethical and legal requirements have been met before the first patient is enrolled in the study.

10.3 Patient Information and Informed Consent/Assent

The Investigator will obtain freely given written consent from each patient's legal representatives or guardians after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards and any other aspect of the study which is relevant to the patient's decision to participate. The informed consent form must be signed, with name and date and time noted by the patient's legal representatives or guardians, before the patient is exposed to any study-related procedure, including screening tests for eligibility.

Children deemed old enough by the Investigator/institution to understand the risks and benefits of the study should also be made aware of the risks/benefits of the study and provide written assent.

The Investigator will explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, without any consequences for their further care and without the need to justify. The Investigator will complete the informed consent section of the CRF for each patient enrolled.

Each patient will be informed that his/her medical (source) records may be reviewed by the study monitor, a quality assurance auditor or a health authority inspector, in accordance with applicable regulations, and that these persons are bound by confidentiality obligations.

10.4 Protocol Amendments

Any prospective change to the protocol will be agreed between the Investigator (coordinating investigator in multi-center studies) and the Sponsor prior to its implementation. Any such amendments will be submitted to the IEC(s)/IRB(s) and/or competent authority responsible as required by applicable regulations. IEC/IRB approval will at a minimum be requested for any change to this protocol which could affect the safety of the patients, the objective/design of the study, any increase in dosage or duration of exposure to the IMP, an increase in the number of patients treated, the addition of a new test or procedure, or the dropping of a test intended to monitor safety.

10.5 Confidentiality of Patients' Data

The Investigator will ensure that the patient's confidentiality is preserved. On CRFs or any other documents submitted to the Sponsor, the patients will not be identified by their names, but by a unique patient number. Documents not for submission to the Sponsor, i.e., the confidential subject identification code list, original informed consent forms and source records will be maintained by the Investigator in strict confidence.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Periodic Monitoring

The monitor will contact and visit the Investigator periodically to review all study-related source data/records, verify the adherence to the protocol and the completeness, correctness and accuracy of all CRF entries compared to source data. The Investigator will cooperate with the monitor to ensure that any discrepancies identified are resolved.

For this study, the first monitoring visit shall take place shortly after the inclusion of the first patient. Thereafter, monitoring frequency will depend on study progress.

The monitor must be given direct access to source documents (original documents, data and records). Direct access includes permission to examine, analyze, verify and reproduce any records and reports that are important to the evaluation of the clinical study. Source data will be available for all data in the CRFs, including all laboratory results.

11.2 Audit and Inspection

The Investigator will make all study-related source data and records available to a qualified quality assurance auditor mandated by the Sponsor, or to IEC/IRB/regulatory inspectors, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and welfare of the patients have been adequately protected, and that all data relevant for the assessment of safety and effectiveness of the IMP have been reported to the Sponsor.

12 REPORTING AND PUBLICATION

12.1 Clinical Study Report

A clinical study report (in accordance with relevant guidelines and Sponsor's SOPs) will be prepared by the Sponsor after the completion of the study. The coordinating investigator will approve the final study report after review.

12.2 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is envisaged by an Investigator, the Investigator agrees to inform the Sponsor and to submit all manuscripts or abstracts to the Sponsor prior to submission to an editorial board or scientific review committee. This will allow the Sponsor to protect proprietary information and to provide comments based on information that may not yet be available to the Investigator.

In accordance with standard editorial and ethical practice, the Sponsor will support publication of multi-center studies only in their entirety and not as individual center data. Authorship will be determined by mutual agreement.

13 LIABILITIES AND INSURANCE

In order to cover any potential damage or injury occurring to a patient in association with the IMP or the participation in the study, Octapharma will contract insurance in accordance with local regulations.

The Investigator is responsible for dispensing the IMP according to this protocol, and for its secure storage and safe handling throughout the study.

14 REFERENCES

1. Rollag H, Solheim BG, Svennevig JL: Viral safety of blood derivatives by immune neutralization. Vox Sang 1998; 74 Suppl 1: 213-217.
2. Octaplas. Annotated prescribing information. Octapharma. Hoboken, New Jersey, USA.

15 APPENDICES

15.1 Appendix 1: Octaplas Package Insert

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Octaplas is a solvent / detergent (S/D) treated, pooled human plasma indicated for:

- Replacement of multiple coagulation factors in patients with acquired deficiencies
  - due to liver disease
  - undergoing cardiac surgery and liver transplant
- Plasma exchange in patients with thrombotic thrombocytopenic purpura (TTP)

2 DOSAGE AND ADMINISTRATION

For intravenous use only

Administer Octaplas based on AB0-blood group compatibility.

2.1 Dose

Replacement of coagulation factors in patients with acquired deficiencies due to liver disease or undergoing cardiac surgery or liver transplant

Initially infuse of 10 to 15 mL Octaplas per kilogram body weight. This should increase the patient's plasma coagulation factor levels by approximately 15-25%. If hemostasis is not achieved, use higher doses.

Adjust dose based on desired clinical response.

Monitor response, including measurement of activated partial thromboplastin time (aPTT), prothrombin time (PT), and/or specific coagulation factors.

Plasma exchange in patients with TTP.

Completely replace plasma volume removed during plasmapheresis with Octaplas. Generally, 1 to 1.5 plasma volumes corresponds to 40 to 60 milliliters per kg.[1,2]

2.2 Administration

Administer Octaplas after thawing using an infusion set with a filter.

Octaplas should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if turbid.

Avoid shaking.

Steps for Thawing:

- For water bath:
  - Thaw in the outer wrapper for up to 30 minutes in a circulating water bath at +30°C to +37°C (86°F to 98.6°F). An overwrap bag may be used to provide further protection of contents if appropriate.
  - Prevent water from contaminating the entry port.
  - The minimum thawing time is 30 minutes at 37°C (98.6°F). The thawing time depends on the number of bags in the water bath. If more than one plasma bag is thawed in the same water bath, then the thawing time can be prolonged, but should not exceed 60 minutes.

- For dry tempering system:
  - Place the Octaplas bags between the heating plates according to the manufacturer's instructions.
  - Thaw plasma following manufacturer directions between +30°C to +37°C (86°F to 98.6°F). Remove the product when the thawing process is completed. The thawing process may be monitored and recorded using the thawing device printer or barcode scanner recommended by the device manufacturer.
  - Monitor the thawing process and record using the thawing device printer or barcode scanner recommended by the device manufacturer.

Do not freeze Octaplas. Discard unused product.

3 DOSAGE FORMS AND STRENGTHS

Solution for infusion containing 45 to 70 mg human plasma proteins per mL in a 200 mL volume.

4 CONTRAINDICATIONS

Do not use Octaplas in patients with:

- IgA deficiency
- Severe deficiency of Protein S
- History of hypersensitivity to fresh frozen plasma (FFP) or to plasma-derived products including any plasma protein
- History of hypersensitivity reaction to Octaplas

5 WARNINGS AND PRECAUTIONS

5.1 Transfusion reactions

Transfusion reactions can occur with AB0 blood group mismatches. Administration of Octaplas must be based on ABO-blood group compatibility.

5.2 Hypervolemia

High infusion rates can induce hypervolemia with consequent pulmonary edema or cardiac failure. Monitor patients for signs and symptoms of pulmonary edema or cardiac failure and institute appropriate management.

5.3 Hyperfibrinolysis

Excessive bleeding due to hyperfibrinolysis can occur due to low levels of alpha2-antiplasmin (also named plasmin inhibitor). Monitor for signs of excessive bleeding in patients undergoing liver transplantation.

5.4 Thrombosis

Thrombosis can occur due to low levels of Protein S. Monitor for signs and symptoms of thrombosis in patients at risk.

5.5 Citrate Toxicity

Citrate toxicity can occur with volumes exceeding one milliliter of Octaplas per kg per minute. The infusion rate should not exceed 0.020-0.025 mmol citrate per kilogram per minute (i.e., less than one milliliter Octaplas per kg per minute). Symptoms attributable to citrate toxicity (hypocalcaemia) include e.g., fatigue, paresthesia and muscle spasms, especially in patients with liver function disorders. Administer calcium gluconate intravenously into another vein in order to minimize citrate toxicity.

5.6 Infection Risk from Human Plasma

Because Octaplas is made from human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. ALL infections suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Octapharma [1-866-766-4860] or FDA at 1-800-FDA-1088 or www.fea.gov/medwatch. *See Description (11)*

6 ADVERSE REACTIONS

Serious adverse reactions seen in clinical trials were anaphylactic shock, citrate toxicity and severe hypotension.

The most common adverse reactions observed in ≥ 1% of subjects included pruritis, urticaria, nausea, headache, and paresthesia.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adverse reactions observed in clinical trials derive from 9 clinical trials. The mean dose administered ranged from 6 to 15 milliliters/kg body weight; when used in plasma exchange the dose was between 15 to 75 milliliters/kg. Two of the studies were conducted in healthy volunteers (n=90).

In total, 359 subjects received about 600 transfusion episodes in these trials.

The following table shows the adverse reactions observed in ≥ 1% of subjects in order of severity:

Nervous system disorders
Headache, paresthesia
Gastrointestinal disorders
Nausea
Skin and subcutaneous tissue disorders
Pruritis, urticaria

6.2 Post-Marketing Experience

Because post-marketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.

Blood system disorders Hyperfibrinolysis
Immune system disorders Hypersensitivity reactions including anaphylactoid and allergic type of reactions
Metabolic and nutritional disorders Alkalosis
Cardiovascular disorders Cardiac arrest, circulatory overload, thromboembolism, tachycardia
Respiratory, thoracic and mediastinal disorders Respiratory arrest or failure, bronchospasm, pulmonary edema, dyspnea, tachypnoea
Gastrointestinal disorders Abdominal pain, vomiting
Skin and subcutaneous tissue disorders Rash, erythema
General disorders and administration site conditions Fever and/or chills, chest discomfort or pain
Investigations Seroconversions (passive transfer of antibodies)
Injury, poisoning and procedural complications Citrate toxicity

7 DRUG INTERACTIONS

Do not inject drugs containing calcium in the same intravenous line with Octaplas because precipitants may block the line.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy category C. Animal reproduction studies have not been conducted with Octaplas. It is not known whether Octaplas can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Octaplas should be given to a pregnant woman only if clearly needed.

8.2 Labor and Delivery

Efficacy and safety of Octaplas in labor or delivery is unknown.

8.3 Nursing Mothers

Efficacy and safety of Octaplas in lactating women is unknown.

8.4 Pediatric Use

Efficacy and safety of Octaplas have not been evaluated in pediatric patients.

8.5 Geriatric Use

Efficacy and safety of Octaplas have not been established in geriatric patients.

11 DESCRIPTION

Octaplas is a sterile, pyrogen free, frozen solution of solvent/detergent (S/D) treated pooled human plasma.

The active ingredient comprises plasma proteins such as albumin, immunoglobulins, other globulins, coagulation factors, complement proteins and protease inhibitors. The content and distribution of plasma proteins in Octaplas are comparable to reference ranges for healthy blood donors, except for Protein S and alpha2-antiplasmin. Within a mean total protein content of 57 mg/mL, albumin comprises ~50% and immunoglobulin classes G, A, and M comprise ~12%, ~3%, and ~1%, respectively. Protein S and alpha2-antiplasmin, which are labile to S/D treatment, are controlled to ensure levels in the final product of ≥ 0.4 International Units (IU) per mL. Plasma lipids and lipoproteins are reduced due to S/D treatment and subsequent oil and solid phase extraction.

Composition of Octaplas

Component	Quantity per 200 mL dose
Human plasma proteins	9.0 - 14.0 g
Sodium citrate dihydrate	0.88 - 1.48 g
Sodium dihydrogen-phosphate dihydrate	0.06 - 0.24 g
Glycine	0.80 - 1.20 g

Octaplas is manufactured from human plasma collected in US licensed plasma donation centers. All plasma donations are tested for viral markers in compliance with US regulation. In addition, the manufacturing plasma pool may not contain a titer of human Parvovirus B19 DNA exceeding 10.0 IU per microliter and must have a negative result in a test for human Hepatitis E Virus (HEV) RNA by NAT PCR with a sensitivity of ≤ 2.5 $\log_{10}$ IU/mL.

Each lot of Octaplas is manufactured from pooled plasma of a single AB0 blood group (A, B, AB, or 0). The manufacturing plasma pool is limited to 390 kg comprising 630-1,520 individual donors. Frozen plasma units are thawed and pooled. Sodium dihydrogen phosphate dihydrate is added as a buffer against increase in pH due to loss of CO_2. After filtration through a 1 µm pore size membrane, the plasma pool is treated with S/D reagents [1% tri(n-butyl) phosphate (TNBP) and 1% octoxynol for 1-1.5 hours at +30°C (86°F)] to inactivate enveloped viruses. The S/D reagents are removed by sequential oil and solid phase extraction procedures. Glycine is added to adjust the osmolality. Plasma with glycine is applied to a column filled with affinity ligand resin intended for selective binding of prion protein (PrP^{Sc}). The effectiveness of this step in removal of prion infectivity from the product has not been established. After sterile filtration, the product is filled into sterile polyvinyl chloride blood bags, labeled, deep-frozen and stored at a temperature of $\leq$ -18°C (-0.4°F). The finished product is tested for coagulation factors II, V, VII, VIII, IX, X and XI, Protein C, Protein S, alpha2-antiplasmin (also known as Plasmin Inhibitor), fibrinogen and ADAMTS13.

The S/D treatment step has been validated to effectively inactivate relevant pathogenic and model enveloped viruses as summarized in Table 1.

Table 1 Virus Reduction During Octaplas Manufacture

Production Step	Virus Reduction Factor [$\log_{10}$]			
	HIV-1	PRV	SBV	BVDV
S/D treatment [$\log_{10}$]	$\geq$ 5.05	6.56	$\geq$ 5.46	$\geq$ 4.04
Global Reduction Factor	**$\geq$ 5.05**	**6.56**	**$\geq$ 5.46**	**$\geq$ 4.04**

HIV-1: Human Immunodeficiency Virus – 1
PRV: Pseudorabies Virus
BVDV: Bovine Viral Diarrhea Virus
SBV: Sindbis Virus

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Octaplas replaces human plasma proteins.

12.2 Pharmacodynamics

Coagulation factor activities in the final product are controlled to obtain levels within the range of normal human plasma. Protein S and alpha2-antiplasmin, which are labile to S/D treatment, are controlled to ensure levels in the final product of $\geq$ 0.4 International Units (IU) per mL.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

TNBP and Octoxynol used in the manufacturing process for viral inactivation may be present in the final product at levels not exceeding 2.0 µg/mL for TNBP and 5.0 µg/mL for Octoxynol.

Toxicity

No evidence of toxicity was observed for TNBP + Octoxynol in sub-acute toxicity studies. [3]

Mutagenicity

No evidence of mutagenicity was observed in *in vitro* or *in vivo* mutagenicity studies performed for TNBP. [4-9]

14 CLINICAL STUDIES

The Octaplas predecessor product was studied in liver disease, liver transplantation, cardiac surgery and TTP.

An open-label parallel group study was performed in surgical patients who were allocated to receive either a single infusion of Octaplas (n=20) or no plasma treatment (n=26) during open-heart surgery.[10] A historical control group of patients having received standard single-donor FFP (n=20) was used to compare the efficacy and safety. The average dose of Octaplas was 700 mL (range 200 to 3400 mL), compared with 1012 mL (range 500 to 4000 mL) for standard FFP. The choice of plasma product (Octaplas or FFP) did not appear to influence the postoperative course with respect to volume of postoperative bleeding, the need for reoperation secondary to bleeding, or the length of the postoperative hospital stay. This study was not powered to detect any difference in efficacy.

A prospective, single-blind, randomized study was designed to investigate the safety and efficacy of Octaplas compared with standard FFP in adult patients with coagulopathies due to liver disease (LD) or liver transplantation (LTX), or for the management of newly diagnosed thrombotic thrombocytopenic purpura (TTP).[11-13] In total, 55 patients were included in the study. Three patients were suffering from TTP and all received Octaplas. Of the 24 patients with LD, 11 were treated with Octaplas, and out of the 28 LTX patients, 13 received Octaplas. Within the LD and the LTX groups, patients were comparable in all clinical aspects and in the dose of plasma given. There were no relevant changes in any of the coagulation factors, but protein C and fibrinogen improved considerably in both groups, accompanied by a corresponding improvement in partial thromboplastin time (PTT) levels 24 hours after infusion. Similar degrees of correction of prolonged international normalized ratio (INR) and PTT values were achieved with both Octaplas and FFP. All 3 patients with TTP attained platelet counts of $>50x10^9$/L by Day 10. This study was not powered to detect any difference in efficacy.

A prospective, non-randomized open-label study in intensive care patients was conducted in post-operative open heart surgery patients in the surgical intensive care unit who were in need of plasma transfusion for acute bleeding or for the risk of bleeding.[14] There were a total of 67 patients, 36 who received Octaplas (600 mL) and 31 who received FFP (600 mL). Parameters measured included PT, PTT, free Protein S and plasmin inhibitor. Parameters were measured before treatment and 60 minutes after termination of plasma infusion. The decrease in PT and PTT, and the rise in free Protein S were similar between the two study arms. Plasmin inhibitor declined after Octaplas and remained unaffected by FFP. Clinical hemostasis evaluations were also similar between the two treatment regimens. This study was not powered to detect any difference in efficacy.

In a randomized, open-label, controlled study, 60 healthy adult volunteers (mean age 32.6±9.1 years) received after a standard plasmapheresis (PPh) of 600 mL plasma, an administration of 1200 mL of Octaplas or the predecessor product in a cross-over design. Coagulation factors (FI, FII, FV, FVII, FVIII, FIX, FX, and FXI) and hemostatic parameters (aPTT, PT and protein C) were assessed post-infusion at 15 minutes, 2 hours and 24 hours. The primary analysis was to demonstrate equivalence for recoveries using a 10% margin. All coagulation and hemostatic parameters met the equivalence criterion. To verify the assumption of improvement of plasmin inhibitor (PI) concentrations, a test for superiority was conducted. Statistically significant differences between treatments were found at 15 minutes (P=0.0012) and 2 hours (P=0.0190) post-transfusion for the per protocol population. Increased levels of PI post-infusion of Octaplas, as compared to the predecessor product may be attributable to the increased concentrations of PI.

15 REFERENCES

1. Hellstern, P., et al. "Practical guidelines for the clinical use of plasma." Thromb Res. 107 Suppl 1 (2002): S53-S57.
2. Scully, M., et al. "Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies." British Journal of Haematology 158.3 (2012): 323-35.
3. Horowitz B: Potential accumulation of tri(n-butyl)phosphate in solvent-detergent virus-inactivated plasma products. Transfusion 1991;31:871
4. Hanna PJ, Dyer KF: Mutagenicity of organophosphorus compounds in bacteria and Drosophila. Mutat.Res. 1975;28:405-420
5. Batt KJ, Healy CE, Kneiss JJ, et al: Genotoxicity testing of tributyl phosphate. – 1992
6. Wangenheim J, Bolcsfoldi G: Mouse lymphoma L5178Y thymidine kinase locus assay of 50 compounds. Mutagenesis 1988;3:193-205
7. Assinder SJ, Upshall A: Paramorphogenic and genotoxic activity of Triton X-100 and sodium dodecyl sulphate in Aspergillus nidulans. Mutat.Res. 1985;142:179-181
8. Buttar HS, Swierenga SH, Matula TI: Evaluation of the cytotoxicity and genotoxicity of the spermicides nonoxynol-9 and octoxynol-9. Toxicol.Lett. 1986;31:65-73
9. Auletta CS, Kotkoskie LA, Saulog T, et al: A dietary oncogenicity study of tributyl phosphate in the CD-1 mouse. Toxicology 1998;128:135-14
10. Solheim, B. G. et al. "The Use of OCTAPLAS in Patients Undergoing Open Heart Surgery." DIC: Pathogenesis, Diagnosis and Therapy of Disseminated Intravascular Fibrin Formation. Ed. G. Müller-Berghaus and et al. Elsevier Science Publishers B.V., Netherlands, 1993. 253-62.
11. Evans, G., et al. "Solvent/detergent fresh frozen plasma as primary treatment of acute thrombotic thrombocytopenic purpura." Clin Lab Haematol 21.2 (1999): 119-23.
12. Freeman, J. W., et al. "A randomized trial of solvent/detergent and standard fresh frozen plasma in the treatment of the coagulopathy seen during Orthotopic Liver Transplantation." Vox Sang 74 Suppl 1 (1998): 225-29.
13. Williamson, L. M., et al. "A randomized trial of solvent/detergent-treated and standard fresh-frozen plasma in the coagulopathy of liver disease and liver transplantation." Transfusion 39.11-12 (1999): 1227-34.
14. Haubelt, H., et al. "Effects of solvent/detergent-treated plasma and fresh-frozen plasma on haemostasis and fibrinolysis in complex coagulopathy following open- heart surgery." Vox Sang 82.1 (2002): 9-14.

16 HOW SUPPLIED/STORAGE AND HANDLING

Octaplas is supplied in polyvinyl chloride blood bags containing 200 mL frozen solution and has a slightly yellow appearance.

NDC Number	Blood group
Octapharma Pharmazeutika Produktionsges.m.b.H	
68982-952 - 01	Blood group A
68982-953 - 01	Blood group B
68982-954 - 01	Blood group AB
68982-955 - 01	Blood group 0

Storage and Handling

- Store at ≤-18°C (-0.4°F) for 3 years from the date of manufacture.
- Store protected from light.
- Thaw product according to instructions in section 2.2.
- Use thawed product within 24 hr. if stored at 1 - 6°C (33.8°F to 42.8°F) or within 8 hr. if stored at 20 - 25°C (68°F to 77°F).
- Do not refreeze thawed product.
- Do not use product that is cloudy or has deposits.
- Discard product after the expiration date printed on the container label.

17 PATIENT COUNSELING INFORMATION

Inform patients to report:

- Early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, or anaphylaxis.
- Development of edema or volume overload including shortness of breath or breathing difficulties

Remind patients that Octaplas is made from human blood and may contain infectious agents that can cause disease. Report flu-like or other symptoms or viral infection.

Manufactured by:
Octapharma Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Strasse 235
A-1100 Vienna, Austria

Octapharma AB
Elersvägen 40
SE- 112 75, Sweden

U.S. License No. 1646

Distributed by:
Octapharma USA Inc.
121 River Street, Suite 1201
Hoboken, NJ 07030