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Reviewer Name(s)	Mitchell Frost, M.D.
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Supervisory Concurrence	
Applicant	Octapharma Pharmazeutika Produktionsges.m.b.H.
Established Name	Pooled Plasma (Human), Solvent/ Detergent Treated
(Proposed) Trade Name	Octaplas <sup>TM</sup> /Pooled Plasma (Human), Solvent Detergent Treated
Pharmacologic Class	Plasma Derivative
Formulation(s), including Adjuvants, etc	Solution for infusion containing 45 to 70 mg human plasma protein per mL in a 200 mL volume
Dosage Form(s) and Route(s) of Administration	Liquid frozen solution for intravenous administration containing 45 to 70 mg human plasma protein per mL in a 200 mL volume
Dosing Regimen	<ul style="list-style-type: none"> <li>• 10 to 15 milliliters per kg, Adjust the dose based on the desired clinical response</li> <li>• 1 to 1.5 plasma volumes (40 to 60 milliliters per kg)</li> </ul>
Indication(s) and Intended Population(s)	<ul style="list-style-type: none"> <li>• Replacement of multiple coagulation factors in patients with acquired deficiencies due to liver disease, and in patients undergoing cardiac surgery or liver transplantation.</li> <li>• For transfusion or plasma exchange in patients with thrombotic thrombocytopenic purpura (TTP)</li> </ul>

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Glossary

ABBREVIATION	DEFINITION
ACT	Activated Clotting Time
ADR	Adverse Drug Reaction
AE	Adverse Event
APLB	Advertising and Promotional Labeling Branch
aPTT	Activated Partial Thromboplastin Time
ASA	Aspirin
AT	Antithrombin
BLA	Biologics License Application
BIMO	Bioresearch Monitoring
BPAC	Blood Products Advisory Committee
CABG	Coronary Artery Bypass Grafting
CBER	Center for Biologics Evaluation and Review
CI	Confidence Interval
CRF	Case Report Form
CSP	Cryosupernatant
DAT	Direct Antiglobulin Test
DIC	Disseminated Intravascular Coagulation
DIS	Division of Inspections and Surveillance
FFP	Fresh Frozen Plasma
FPI	Full Prescribing Information
G-1	Generation 1
G-2a	Generation 2a
G-2b	Generation 2b
G-3a	Generation 3a
G-3b	Generation 3b
HAV	Hepatitis A Virus
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HEV	Hepatitis E Virus
HIV	Human Immunodeficiency Virus
HTR	Hemolytic Transfusion Reaction
IC	Informed Consent
IMP	Investigational Medicinal Product

IND	Investigational New Drug Application
INR	International Normalized Ratio
IQPP	International Quality Plasma Program
IV	Intravenous
LD	Liver Disease
LT	Liver Transplant
NAT	Nucleic Acid Amplification Testing
OBE	Office of Biostatistics and Epidemiology
Octaplas <sup>®</sup>	Octaplas Generation 1 and 2a
Octaplas <sup>™</sup>	Octaplas Generation 2b
OLT	Orthotopic Liver Transplantation
PeRC	Pediatric Review Committee
PEX	Plasma Exchange
PF24	Plasma Frozen Within 24 Hours After Phlebotomy
PI	Plasmin Inhibitor/ $\alpha$ -2 antiplasmin
PMR	Post Marketing Requirement
PPh	Plasmapheresis
PPTA	Plasma Protein Therapeutics Association
PREA	Pediatric Research Equity Act
PS	Protein S
PT	Prothrombin Time
SDP	Solvent/Detergent Plasma
TCC	Terminal Complement Complex
TE	Thromboembolic
TRALI	Transfusion Related Acute Lung Injury
TTP	Thrombotic Thrombocytopenic Purpura

## 1. Executive Summary

Octapharma has submitted an original biologics license application (BLA) for Octaplas<sup>™</sup>, a frozen, sterile, pyrogen-free, solvent/detergent treated, pooled human plasma product filled into 200 mL units. It is manufactured from 630 to 1,520 single donor units of either Source Plasma or recovered plasma of the same ABO blood group from US licensed blood establishments. Each unit of Source Plasma or recovered plasma is placed in a (b)(4) freezer within (b)(4) hours after blood draw so that a (b)(4) plasma core temperature will be reached by (b)(4) hours.

The original BLA refers to the product as OctaplasLG; however, the proprietary name of the US marketed product will be Octaplas<sup>™</sup>. From this point forward in this document,

Octaplas™ will be used when referring to OctaplasLG, except in the reporting of clinical trial data, in which case OctaplasLG is used.

Octaplas™ was developed for US market with the rationale to provide standardized, cell free human plasma for transfusion with improved viral safety compared to Fresh Frozen Plasma (FFP). Improved viral safety regarding enveloped viruses has been achieved through incorporation of a solvent/detergent (S/D) treatment step, validated to inactivate relevant enveloped viruses while preserving the activity of relevant plasma proteins, into the manufacturing process.

Octapharma has manufactured and studied five generations of S/D treated pooled human plasma products, all of which have similar manufacturing processes and comparable biochemical properties.

Below is a summary of the S/D plasma products produced by Octapharma and tested in clinical studies:

- Generation 1: Octaplas<sup>®</sup>, S/D treated, lyophilized, blood group specific (first approved in 1989, no longer marketed)
- Generation 2a: Octaplas<sup>®</sup>, S/D treated, liquid, frozen, blood group specific (marketed outside the U.S since 1992)
- Generation 2b: Octaplas™, S/D treated, prion removed, liquid, frozen, blood group specific (marketed outside the U.S since 2009)
- Generation 3a: Uniplas, S/D treated, liquid, frozen, blood group independent (---(b)(4)-----)
- Generation 3b: UniplasLG, S/D treated, prion removed, liquid, frozen, blood group independent (---(b)(4)-----)

Octaplas™ (Generation 2b) differs from previous generations of the product, Octaplas<sup>®</sup> lyophilized (Generation 1) or Octaplas<sup>®</sup> frozen (Generation 2a), in the following ways:

- The time of S/D treatment in the manufacture of Octaplas™ has been reduced from 4-4.5 hours to 1-1.5 hours to improve the concentration of S/D labile plasma proteins such as plasmin inhibitor (PI, also known as  $\alpha_2$ -antiplasmin) and Protein S (PS).
- The manufacturing process includes a chromatographic step for the selective binding of prions (PrP<sup>Sc</sup>) to a ligand in an attempt to reduce the risk of vCJD (however, the capacity for prion infectivity removal has not been established because clearance studies submitted to the BLA were considered to be insufficient)

Octaplas<sup>®</sup> (Generation 1) has been approved in 28 countries worldwide, totaling 7 million units sold and an estimated 2.3 million patients exposed. Octaplas™ (Generation 2b) was first approved in Germany in and subsequently has been approved in Australia, United Kingdom, Belgium, Finland, Ireland, Luxembourg, The Netherlands, Sweden, Portugal



and Switzerland, totaling (b)(4)--- units (200mL bags) sold and an estimated 41,500 patients exposed.

Octapharma has submitted data to support the following two of the six indications carried by FFP and PF24, which are listed in the current AABB Circular of Information and currently licensed in the US:

- Replacement of multiple coagulation factors in patients with acquired deficiencies due to liver disease, and in patients undergoing cardiac surgery or liver transplantation.
- For transfusion or plasma exchange in patients with thrombotic thrombocytopenic purpura (TTP).

Clinical data from each of the five product generations were considered in support of product approval because their manufacturing processes are similar and their biochemical properties are comparable. Nine evaluable studies submitted by Octapharma were considered in the review for safety and efficacy of Octaplas™. Limitations in the dataset related to study design were identified. In addition, many of the studies were small, uncontrolled, not hypothesis driven and were focused on comparison of one product generation to another, rather than on the indications for use.

Notwithstanding these limitations, most of the studies captured data from one or more of a number of predefined efficacy endpoints related to hemostasis, global measures of coagulation, and circulating levels of PS and plasmin inhibitor (PI) which provided substantial evidence to support the efficacy and safety for the proposed indications.

The nine clinical studies were categorized into three groups: three FFP comparator studies; four bridging studies; and two single arm studies. In total 528 subjects were studied in these nine studies. Efficacy conclusions drawn from these three groups of studies are as follows:

- The FFP comparator studies evaluated 188 subjects in three trials that compared safety and efficacy of Octaplas® to FFP in clinical conditions associated with coagulopathy (open heart surgery, liver disease, and liver transplantation) and three subjects with TTP.

The efficacy and safety outcomes were similar between Octaplas® and FFP in various clinical conditions where replacements of multiple coagulation factors were needed.

- The four bridging studies compared Octaplas™ to Octaplas® or UniplasLG. A total of 299 subjects were studied, including 90 healthy volunteers (all were exposed to Octaplas™), 84 heart surgery subjects and 125 subjects needing plasma for any condition.

Comparability in laboratory values was observed and supports comparability between product generations, resultant of their similar manufacturing and biochemical profiles. The exception was in Study LAS-203 which compared Octaplas<sup>®</sup> to Octaplas<sup>™</sup>. Higher PI levels were noted in Octaplas<sup>™</sup> than in Octaplas<sup>®</sup>; however, PI levels remained within the reference range with both products.

- Forty-one subjects were evaluated in the single arm studies which showed functional levels of coagulation factors were recovered in eight subjects with hereditary coagulation factor deficiencies. Hemostasis was achieved in 18/24 bleeding subjects (total for both studies) and prophylaxis for hemostasis was rated as effective by the investigator in 8/8 subjects undergoing an invasive procedure.

The overall safety profile of Octaplas<sup>™</sup> is acceptable. The majority of the reported adverse drug reactions were mild to moderate and seen in healthy volunteers. The most common ( $\geq 1\%$ ) adverse drug reactions reported were paraesthesia, headache, urticaria, nausea and pruritis. The healthy volunteers were not pre-medicated with either anti-allergic or antipyretic medications prior to plasma product infusion.

There were two serious adverse events reported. One was a case of severe hypotension and the other was anaphylactic shock. Both patients recovered with appropriate management. There were no deaths due to transfusion of any of the generations of Octapharma's solvent detergent plasma product reported in the clinical trials.

Pharmacovigilance data submitted by Octapharma was also reviewed. When taking into account all data sources (clinical trial data, literature reports and pharmacovigilance data) there have been no cases of transfusion related acute lung injury (TRALI) causally related to any generation of Octaplas nor has there been a reported transmission of HIV, HBV, HCV or HAV. Compared to the known safety profile from the clinical development program, no new safety signals have been identified after >2.3 million patients have been exposed to all Octaplas formulations.

Specific potential safety concerns with the product were identified during the review and were adequately addressed. The first is the use of Source Plasma in the manufacturing of the product. US Source Plasma has a higher viral marker rate when compared with recovered plasma from whole blood donations due to the different donor screening and qualification requirements used for each. This poses a theoretical increased risk for viral transmission. This potential risk is mitigated by adhering to the International Quality Plasma Program (IQPP) standards of the Plasma Protein Therapeutics Association (PPTA) with regard to plasma donation and viral marker monitoring, and testing of plasma for manufacture using FDA licensed kits including nucleic acid amplification testing for HAV, HBV, HCV, HIV and HEV. Further, (b)(4) lots manufactured from Source Plasma have been distributed since 2006 in Europe and Canada without report of seroconversion or transfusion transmitted disease. The risk of transmitting Creutzfeldt-

Jakob Disease (CJD) or variant Creutzfeldt-Jakob disease through US sourced plasma is, to date, only theoretical.

The low levels of PS in the product have a potential for increased risk for thromboembolism (TE) particularly in TTP patients. This was reported in the literature with the use of Octaplas<sup>®</sup>. Octaplas<sup>™</sup>, with its shortened time for undergoing S/D treatment, has higher PS when compared to Octaplas<sup>®</sup>. The PS levels in Octaplas<sup>™</sup> are within the lower limit of the reference range.

The low levels of PI in the product have the potential for risk of excessive bleeding secondary to hyperfibrinolysis. There were two literature reports citing an increased incidence of hyperfibrinolysis with the use of Octaplas<sup>®</sup> in patients undergoing liver transplantation. Since the introduction of Octaplas<sup>™</sup> with the improved manufacturing process resulting in increased levels of PI, there have been no literature and/or pharmacovigilance reports of an increased incidence of hyperfibrinolysis during liver transplantation.

The application triggered the Pediatric Research Equity Act (PREA). Octapharma requested a pediatric deferral for all age groups and the proposed pediatric plan was presented to the Pediatric Review Committee (PeRC). The PeRC agreed with the Division to grant a full deferral because the product is ready for approval in adults. Pediatric studies encompassing all age groups (< 16 years) will be completed in the post-marketing period for both indications for use.

The Octaplas<sup>™</sup> BLA was presented to the Blood Products Advisory Committee (BPAC) on September 20, 2012. The general consensus of the Committee was that the product was effective for the indications sought; however, the Committee discussed the limited safety data available with Octaplas<sup>™</sup>. The Committee recommended collection of additional safety data for the increased risk for hyperfibrinolysis and thromboembolism as the post-marketing studies.

In conclusion, the data support the efficacy of Octaplas<sup>™</sup> for the proposed indications.

The recommendation is for approval with the requirement for two postmarketing studies; one to further evaluate the risk for TE in TTP patients undergoing plasma exchange and the other to further evaluate the increased risk for hyperfibrinolysis in patients undergoing liver transplantation.

## 2. Clinical and Regulatory Background

### *Product Background*

Octapharma Pharmazeutika Produktionsges.m.b.H (Octapharma) has submitted an original biologics license application (BLA) for Pooled Plasma (Human), Solvent Detergent Treated for transfusion. The product is a frozen, sterile, pyrogen-free,

solvent/detergent treated (1% tri-n-butyl phosphate/ 1% octoxynol), pooled human plasma product filled in 200 mL doses into 300 mL polyvinyl chloride (PVC) plasma bags. It is manufactured from 630 units -----(b)(4)----- 1,520 ---(b)(4) --- (b)(4)----- plasma of the same ABO blood group from US licensed blood establishments. Each unit of Source Plasma or recovered plasma will be placed in a – (b)(4) freezer within (b)(4) hours after blood draw so that a (b)(4) plasma core temperature will be reached by (b)(4)hours.

The original BLA refers to the product as OctaplasLG; however, the proprietary name of the US marketed product will be Octaplas™. From this point forward in this document, Octaplas™ will be used when referring to OctaplasLG, except in the reporting of clinical trial data, in which case OctaplasLG will be used.

Octaplas™ was developed for US market under IND 13956. Octapharma's rationale for development was to provide standardized, cell free human plasma for transfusion with improved viral safety compared to Fresh Frozen Plasma (FFP). Improved viral safety regarding enveloped viruses has been achieved through incorporation into the manufacturing process of a solvent/detergent (S/D) treatment step validated to inactivate relevant enveloped viruses, while preserving the activity of relevant plasma proteins.

Octapharma has produced and studied five generations of S/D treated pooled human plasma products, all of which have similar manufacturing processes and comparable biochemical properties. Table 1 provides a summary of product development and marketing history.

**Table 1: Product Development and Marketing History**

Generation	Name	Presentation	ABO Specific	LG column	Commercial Status
1	Octaplas®	Lyophilized	Yes	No	No longer marketed
2a	Octaplas®	Liquid frozen	Yes	No	Marketed outside US since 1992
2b	Octaplas™	Liquid frozen	Yes	Yes	Marketed outside US since 2009
3a	Uniplas	Liquid frozen	No	No	---(b)(4)----- ---
3b	UniplasLG	Liquid frozen	No	Yes	---(b)(4)----- -

Octaplas™ (Generation 2b) differs from previous generations of the product, Octaplas® lyophilized (Generation 1) or Octaplas® frozen (Generation 2a), in the following ways:

- The time of S/D treatment at  $30 \pm 1^{\circ}\text{C}$  in the manufacture of Octaplas<sup>TM</sup> has been reduced from 4-4.5 hours to 1-1.5 hours to improve the concentration of S/D labile plasma proteins such as plasmin inhibitor (PI, also known as  $\alpha_2$ -antiplasmin) and Protein S (PS).
- The manufacturing process includes a chromatographic step for the selective binding of prions (PrP<sup>Sc</sup>) to a ligand in an attempt to reduce the risk of vCJD.

Octapharma has also developed Uniplas/UniplasLG, a non-blood group specific, solvent detergent plasma. The only difference in Uniplas/UniplasLG from Octaplas<sup>®</sup>/Octaplas<sup>TM</sup> is the removal of anti-A and anti-B antibodies; thereby, making it able to be universally transfused. Uniplas/UniplasLG is not licensed in the US or EU. All generations of the product are represented in the clinical trials submitted in support of the safety and efficacy of Octaplas<sup>TM</sup>.

Since the initial Octaplas<sup>®</sup> approval on October 27, 1989, Octaplas<sup>®</sup> has been approved in 28 countries worldwide, totaling 7 million units (200mL bags) sold and an estimated 2.3 million patients exposed. Octaplas<sup>TM</sup> was first approved in Germany in 2009 and subsequently has been approved in Australia, United Kingdom, Belgium, Finland, Ireland, Luxembourg, The Netherlands, Sweden, Portugal and Switzerland, totaling (b)(4)- units (200mL bags) sold and an estimated 41,500 patients exposed.

## 2.1 Disease or Health-Related Condition(s) Studied

Octapharma has submitted data to support the following two of the six indications carried by FFP and plasma frozen within 24 hours after phlebotomy (PF24), which are listed in the current AABB Circular of Information and currently licensed in the US:

- Replacement of multiple coagulation factors in patients with acquired deficiencies due to liver disease, and in patients undergoing cardiac surgery or liver transplantation.
- For transfusion or plasma exchange in patients with thrombotic thrombocytopenic purpura (TTP).

The other four indications for FFP and PF24 are:

- “Patients undergoing massive transfusion who have clinically significant coagulation deficiencies;
- Patients taking warfarin who are bleeding or need to undergo an invasive procedure before vitamin K could reverse the warfarin effect or who need only transient reversal of warfarin effect;
- Management of patients with selected coagulation factor deficiencies, congenital or acquired, for which no specific coagulation concentrates are available;
- Management of patients with rare specific plasma protein deficiencies, such as C1 inhibitor, when recombinant products are unavailable.”

## **2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)**

There are no pharmacologically unrelated treatments for the proposed indications.

## **2.3 Safety and Efficacy of Pharmacologically Related Products**

In 1998, FDA licensed PLAS+SD, a solvent/detergent treated, pooled human plasma, manufactured by V.I. Technologies Inc, Melville, NY. This product is no longer available on the US market. It was associated with thromboembolic (TE) events especially in liver transplantation and liver disease. The TE events were believed to be due to low levels of protein S (PS) in PLAS+SD.

Solheim et al.<sup>1</sup> have reported a mean PS level of 24 U/100 mL (range 14-37) in PLAS+SD, the normal reference range being 56-168 U/100 mL<sup>2</sup>. Octaplas™ has higher concentrations of PS than PLAS+SD had which may be attributable to manufacturing differences. Table 2 below summarizes the biochemical profile for Octaplas™, Octaplas® and FFP.

**Table 2: Biochemical profile of Octaplas™, Octaplas® and FFP expressed as mean and range of values**

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<sup>1</sup> Solheim BG, Hellstern P. Composition, efficacy, and safety of S/D-treated plasma. Transfusion 2003; 43:1176-1178.

<sup>2</sup> Hellstern P, Sachse H, Schwinn H, Oberfrank K. Manufacture and characterization of a solvent/detergent-treated human plasma. Vox Sang 1992; 63:178-185.

Parameter	Reference* (n=100)	Octaplas™ (n=12)	Octaplas® (n=24)	FFP (n=12)
aPTT (s)	28-41	29.5 (28.0-31.0)	33.4 (27.2-41.7)	35.2 (31.7-42.5)
FV (IU/ml)	0.54-1.45	0.85 (0.70-1.00)	0.95 (0.70-1.10)	0.90 (0.73-1.50)
FVII (IU/ml)	0.62-1.65	1.00 (0.70-1.20)	1.02 (0.89-1.40)	0.95 (0.67-1.38)
FVIII (IU/ml)	0.45-1.68	0.89 (0.70-1.30)	0.78 (0.50-1.00)	0.76 (0.52-1.13)
FX (IU/ml)	0.68-1.48	0.93 (0.85-1.03)	0.86 (0.76-0.92)	0.79 (0.62-0.99)
Protein C (IU/ml)	0.58-1.64	0.98 (0.90-1.10)	0.90 (0.75-1.06)	0.89 (0.79-1.05)
Protein S (IU/ml)	0.56-1.68	0.61 (0.50-0.70)	0.50 (0.41-0.55)	1.03 (0.71-1.39)
Plasmin Inhibitor (IU/ml)	0.72-1.32	0.48 (0.30-0.50)	0.32 (0.26-0.40)	1.04 (0.95-1.18)

*Adapted from Octapharma BLA submission, 3.2.S.3-Characterization, Table 2 page 3 and 4 of 6*

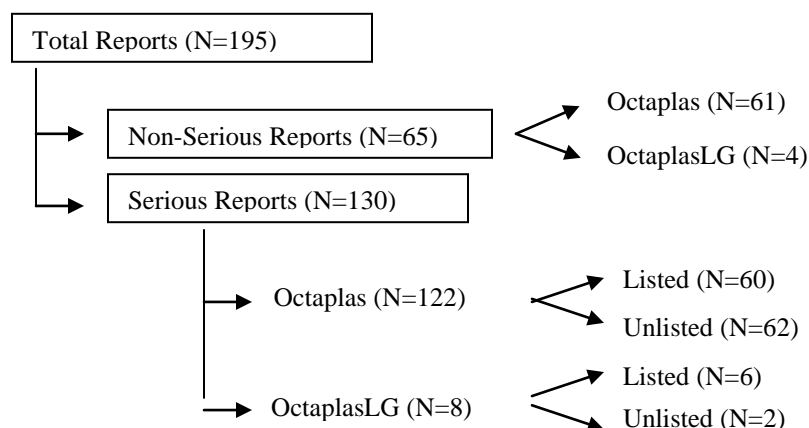
*\*Based on the testing of 100 healthy blood donors and defined by the 2.5 and 97.5 percentiles*

#### **2.4 Previous Human Experience with the Product (Including Foreign Experience)**

Octaplas® and Octaplas™ have combined sales outside the U.S. of approximately (b)(4) million units and an estimated 2.3 million patients exposed. The pharmacovigilance data has been reviewed by Dr. Michael Nguyen of the Office of Biostatistics and Epidemiology (OBE). The following is from his report:

FDA reviewed all submitted pharmacovigilance data from outside the United States for Octaplas® (Generation 1 and 2a) and Octaplas™. From 27 October 1989 to 31 August 2011, a total of 195 adverse event reports were received worldwide describing 407 types of events. Of these, 144 (74%) were spontaneous reports from healthcare providers, 36 (18%) from regulatory authorities, 13 (6%) from the medical literature, and 2 (1%) from clinical studies.

**Figure 1: Distribution of 195 Reports between Octaplas and OctaplasLG**



\* *Listed / unlisted* refers to whether the adverse event appears in the package label and was determined by Octapharma.

*Serious Reports*

Table 3 summarizes all serious reports on a patient basis. Each report was consolidated under the most serious and related condition, in terms of causality, to the administration of one of the generations of Octaplas products as determined by Octapharma pharmacovigilance reviewers. All adverse event reports were represented only once except one case that was listed twice as both a suspected transmission and hypersensitivity reaction.



**Table 3: Worldwide Summary of Serious Adverse Events for Octaplas® (Generation 1 and 2a) and Octaplas™ — October 1989 to August 2011 (N=130)†**

	Report Category	No. Unrelated Cases*		No. Related Cases**	
		Octaplas®	Octaplas™	Octaplas®	Octaplas™
1	Hypersensitivity reactions including anaphylactic and allergic reactions	2	0	42	5
2	Respiratory disorder (not elsewhere classified)	2	0	10	2
3	Circulatory overload	1	0	5	0
4	Seroconversions (passive transfer of antibodies)	0	0	5	0
5	Thromboembolism	0	0	4	0
6	Other (alkalosis, medication error, etc.)	2	0	2	1
7	Cardiac disorder (not elsewhere classified)	4	0	2	0
8	Isolated fever and chills	0	0	2	0
9	Citrate toxicity	0	0	1	0
10	Hyperfibrinolysis	0	0	1	0
11	TRALI	0	0	0	0
12	Hemolytic transfusion reaction	0	0	0	0
13	Suspected transmission of infectious agents	38	0	0	0
	TOTAL	49	0	74	8

\* Classified as not related, unlikely, unclassifiable

\*\* Classified as possible or probable

† All adverse event reports were represented only once except one case was listed twice as both a suspected transmission and hypersensitivity reaction.

The three most frequent serious adverse events reported after Octaplas® and Octaplas™ were hypersensitivity reactions, respiratory disorders, and circulatory overload. Reports of thromboembolism and hyperfibrinolysis, historically a source of concern with solvent/detergent-treated plasma products, were also detected.

**Table 4: Reviews of Health Outcomes of Interest**

Health Outcome	Summary Analysis
TRALI	<ul style="list-style-type: none"> <li>No cases reported that were causally related to Octaplas® or Octaplas™</li> <li>Many cases were “rule out TRALI” after patients experienced acute pulmonary edema</li> <li>High dosages and infusion rates can induce hypervolemia and pulmonary edema</li> </ul>
Viral transmission	<ul style="list-style-type: none"> <li>No transmission of HIV, HBV, HCV or HAV has been observed</li> </ul>
Acute hypersensitivity reactions	<ul style="list-style-type: none"> <li>Range from mild to serious</li> <li>Characterized by urticaria, fever, vomiting, hypotension, bronchospasm and dyspnea</li> </ul>
Thromboembolism	<ul style="list-style-type: none"> <li>Majority of cases derived from a single case series of TTP patients receiving plasma exchange</li> <li>Many had underlying risk factors (e.g. oral contraceptive use, pregnancy, obesity, family history)</li> </ul>
Hyperfibrinolysis	<ul style="list-style-type: none"> <li>Only 1 case reported in patient undergoing liver transplantation due to sporadic hepatitis C infection who received Octaplas® (Generation 2a)</li> <li>No cases have been reported after Octaplas™</li> </ul>

### *Deaths*

Reports of deaths occurring in association with the administration of the Octaplas products have been few and most have been judged by the sponsor to be unrelated to the product. Table 5 summarizes those death reports where the fatality was judged by the sponsor to be possibly related to the infusion of the Octaplas product.

**Table 5: Summary of Deaths Judged by Octapharma to be Possibly Related to Octaplas® and Octaplas™**

Manufacturer Report Number (Product)	Adverse Event (MedDRA preferred term)
LAS-011-02-IRL (Octaplas®)	fibrinolysis, hemorrhage, coagulopathy
LAS-015-02-IRL (Octaplas®)	therapeutic response decreased, cardiac arrest, fibrinolysis
LAS-006-07-DE (Octaplas®)	acute pulmonary edema
LAS-002-06-IRL (Octaplas®)	hypotension, cardiac arrest
LAS-024-10-LU (Octaplas®)	pulmonary edema, transfusion related circulatory overload

## **2.5 Summary of Presubmission Regulatory Activity Related to Submission**

A Type C meeting to discuss the clinical program was held in December 2008 (CRMTS #6901). As part of the meeting package, Octapharma queried as to an acceptable pathway for licensure of Octaplas<sup>TM</sup>. FDA responded by noting that Octaplas<sup>®</sup> has been studied and licensed in Europe for many years, and that submission of the following combination of clinical databases may constitute an acceptable path to U.S. licensure:

1. Final study reports for non-IND studies of Octaplas<sup>®</sup> (or Octaplas<sup>TM</sup>)
2. Final reports for bridging studies to permit the conclusion that Octaplas<sup>TM</sup> is comparable to Octaplas<sup>®</sup>
3. The submission of European post-marketing surveillance safety data
4. Agreement to a post-marketing requirement (PMR) to conduct a phase 4 clinical trial of the use of Octaplas<sup>TM</sup> in subjects undergoing orthotopic liver transplantation (OLT).

The bridging studies mentioned in item 2, above, would consist of preclinical studies (product characterization) and a phase 1 pharmacokinetics/safety study that compared Octaplas<sup>®</sup> and Octaplas<sup>TM</sup>.

An IND-Submission (IND 13956) for substitution of intentionally removed plasma was submitted to FDA on February 20, 2009. The clinical study was initiated on December 1, 2009 and completed on July 27, 2010.

## **3. Submission Quality and Good Clinical Practices**

### **3.1 Submission Quality and Integrity**

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty.

### **3.2 Compliance with Good Clinical Practices**

The data submitted by Octapharma in support of the Biologics License Application (BLA) were derived from studies conducted outside the US. Only one of the studies was conducted under Investigational New Drug Application (IND), IND 13956. Complete study reports submitted contained documentation that informed consent of subjects was obtained prior to initiation of the study (with the exception of Study LAS-201 in which informed consent was not required) and that an independent ethics committee was involved to approve of the protocol and continually review it.

The Division of Inspections and Surveillance (DIS) conducted Bioresearch Monitoring (BIMO) inspections of two sites:

- Study LAS-203 was conducted under US IND by a clinical investigator in Vienna, Austria. BIMO inspection concluded that the clinical site conducting

the study did not reveal problems that would impact the data submitted in the application.

- Study LAS-201 was an observational study and access to source documents was not permitted in accordance with European and German law (since obtaining informed consent was not required). During the inspection the FDA investigator was informed that study physicians reviewed the records and retrospectively selected subjects for enrollment into the study. Since the subjects' outcome was known prior to enrollment, this leads to a potential for selection bias.

Further, the study investigators did not enroll all subjects eligible for the study strictly by the study inclusion criteria. Some subjects were selected for enrollment based on the individual criteria of the study investigators in addition to the study required criteria.

Due to these findings the Division determined that the outcomes from this study were not interpretable.

### **3.3 Financial Disclosures**

The sponsor has attested to the absence of financial interests and arrangements with investigators through Form 3454.

## **4. Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### **4.1 Chemistry, Manufacturing, and Controls**

The product reviewer has determined that analytical characterization is comprehensive and complete. Comparability has been demonstrated throughout pharmaceutical development and the biochemical profile indicates acceptable product quality. The release specification is adequate to confirm product quality and manufacturing consistency.

All plasma donations are tested for viral markers in compliance with requirements of FDA. Only plasma pools that are negative by serological tests and/or nucleic acid amplification testing (NAT) assays for HIV, HBV, HCV and HAV, and that contain no more than 10.0 IU/μL Parvovirus B19 DNA are accepted for manufacture of Octaplas™.

Additional safety of Octaplas™ is based on S/D treatment, which is primarily effective in the inactivation of enveloped viruses. The safety of the product with respect to HAV and Parvovirus B19, two non-enveloped viruses, is enhanced by setting a minimum specification for the level of neutralizing HAV and Parvovirus B19 antibodies in the product.

Ligand chromatography was incorporated into the manufacturing process with the intent to remove prion protein (PrP<sup>Sc</sup>) infectivity. The clearance studies submitted to the BLA

were considered to be insufficient; therefore, prion infectivity removal capacity by the ligand chromatography step has not been established. The risk of transmitting Creutzfeldt-Jakob Disease (CJD) or variant Creutzfeldt-Jakob disease through US sourced plasma is, to date, only theoretical.

#### **4.2 Assay Validation**

Analytical methods have been validated to support quality control throughout manufacture and final product release and stability. The methods were well developed and are in use by Octapharma for control of other US- and/or EU-licensed plasma-derived products such as Factor VIII or Factor IX concentrates. Proper suitability controls were developed by Octapharma to ensure the validity of the methods. The S/D process used is validated to inactivate relevant pathogenic and model viruses.

#### **4.3 Nonclinical Pharmacology/Toxicology**

Based on results from nonclinical toxicology studies conducted with the inactivating detergents and extractables/leachables from the components used in the manufacture, Octaplas™ appear to be safe for use in the proposed clinical indications.

#### **4.4 Clinical Pharmacology**

No pharmacokinetic study was conducted.

#### **4.5 Statistical**

Clinical data from each of the five product generations were considered in support of product approval because their manufacturing processes are similar and their biochemical properties are comparable.

Limitations in the dataset included small, uncontrolled studies that lacked hypotheses and were focused on comparison of one product generation to another, rather than on the indications for use.

Nonetheless, most of the studies captured data from one or more of a number of predefined efficacy endpoints related to hemostasis, global measures of coagulation, and circulating levels of PS and plasmin inhibitor (PI) which provided substantial evidence to support the efficacy and safe use of Octaplas™ in the approved indications.

#### **4.6 Pharmacovigilance**

In addition to Octapharma's proposals for routine passive surveillance for all serious and unexpected adverse events, an enhanced safety monitoring plan has been implemented: two required studies to evaluate for the potential of excess risk of bleeding due to hyperfibrinolysis and thromboembolic events. OBE and OBRR agree with the enhanced safety monitoring plan as described below.

**Table 6: Pharmacovigilance Plan**

	Health Outcome	Octapharma Action Plan
<b>Important identified risks</b>	<ol style="list-style-type: none"> <li>1. Hypersensitivity and anaphylaxis</li> <li>2. Venous thromboembolism</li> </ol>	<ul style="list-style-type: none"> <li>▪ Routine (passive) surveillance</li> <li>▪ PMR Study LAS-214, “Non-interventional 2-arm study to evaluate the safety of Octaplas™ in patients treated for Thrombotic Thrombocytopenic Purpura (TTP) with special emphasis on monitoring the occurrence of thromboembolic events (TEEs)”</li> </ul>
<b>Important potential risks</b>	<ol style="list-style-type: none"> <li>3. General virus safety</li> <li>4. Hemolytic transfusion reaction</li> <li>5. TRALI</li> <li>6. Excessive bleeding due to hyperfibrinolysis</li> <li>7. ABO-incompatible OctaplasLG transfusion</li> </ol>	<ul style="list-style-type: none"> <li>▪ Routine (passive) surveillance</li> <li>▪ PMR Study LAS-215, “A non-interventional, open-label, multicenter, clinical study to investigate, safety, tolerability and efficacy of Octaplas™ in the management of pediatric patients who require therapeutic plasma exchange in ages &lt;16 years old”</li> </ul>
<b>Important missing information</b>	<ol style="list-style-type: none"> <li>8. Safety in pediatric, elderly and pregnant and nursing women</li> </ol>	Routine (passive) surveillance

#### 5. Sources of Clinical Data and Other Information Considered in the Review

Seventeen studies submitted by Octapharma were reviewed in support of the Octaplas™ approval for the proposed indications.

One of the studies was a retrospective study that evaluated tolerability. In this study ~ 5000 units of Octaplas® were transfused to 950 subjects and no adverse events (AEs) were reported. Since it is unlikely that there would be no AEs given the size of this study it was excluded from consideration of the safety and efficacy of the product.

Two of the studies (one evaluated anti-D immunization and one evaluated acquired, passive non-enveloped viral protection) were excluded from consideration of the safety and efficacy of the product because the studies were very small (N = 20 and 5 respectively).

Five of the remaining fourteen studies were literature reports without complete study reports and so were considered only for safety evaluation of the product.

The remaining nine clinical studies were considered in support of safety and efficacy of Octaplas™.

### 5.1 Review Strategy

The nine studies considered in support of safety and efficacy can be placed into one of three different groups. The groups and the studies they comprised of are as follows:

- Studies that include fresh frozen plasma (FFP) as the comparator product
  - LAS-1-02-D,
  - 19/PLAS/IV/91
  - LAS-1-03-UK

These studies were all prospective and unblinded, and only one was randomized. None of the studies were hypothesis driven and only one study had a non-laboratory based predefined clinical efficacy endpoint (subjective assessment of hemostasis).

- Bridging studies that compare one generation of the product with another
  - LAS-201
  - LAS-203
  - UNI-110
  - UNI-101

All four of these studies compared different generations of biochemically similar solvent/detergent plasma (SDP) products to one another. Two of the four studies were conducted in the patient population and the other two studies were conducted in healthy volunteers. One of the studies was an observational study from which efficacy conclusions could not be drawn due to the retrospective nature of the study and to potential selection bias (see Section 3.2, LAS-201).

- Single arm studies
  - 3PLASIV90
  - LAS-Study-1-D

These studies were conducted in 1990 and 1992, utilizing a formulation of the product that is no longer marketed.

The combined limitations of this nine study dataset are:

- There was no pivotal trial conducted to evaluate safety and efficacy
- Many of the studies were:
  - Small and uncontrolled
  - Underpowered to evaluate efficacy

- Not hypothesis driven
- Not focused on the indications for use
- Primarily designed to compare product generations to one another

Given these limitations, outcomes related to the primary objective for many of the studies were not always useful to evaluate product effectiveness. However, most of the studies had some predefined efficacy endpoints related to hemostasis, global measures of coagulation, and circulating levels of PS and PI ( $\alpha$ -2-antiplasmin). Review of the data with analysis of these specific predefined efficacy endpoints was performed to determine whether the data are supportive of product effectiveness. The review and analysis of the individual studies reported on below will focus on these predefined efficacy endpoints.

Octapharma has also submitted pharmacovigilance data on all generations of its pooled plasma products dating back to the first approval in 1992 of Octaplas<sup>®</sup> in the EU and these data have been reviewed as well (see Section 2.4 **Previous Human Experience with the Product**).

## **5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review**

- Module 1
  - 1.2 Cover Letters
  - 1.3.3 Debarment Certification
  - 1.3.4 Financial Disclosure
  - 1.6 Meetings
  - 1.9 Pediatric Administration Information
  - 1.12.1 Pre-IND Correspondence
  - 1.12.4 Request for Proprietary Name Review
  - 1.14 Labeling
  - 1.16 Risk Management Plans
- Module 2
  - 2.2 Introduction
  - 2.5 Clinical Overview
  - 2.7 Clinical Summary
- Module 5
  - 5.2 Tabular Listing of all Clinical Studies
  - 5.3.3.1 UNI-110
  - 5.3.3.1 LAS-203
  - 5.3.3.2 3PLASIV90
  - 5.3.5.1 UNI-101
  - 5.3.5.4 LAS-201
  - 5.3.5.1 19/PLAS/IV/91
  - 5.3.5.1 LAS-1-03-UK
  - 5.3.5.1 LAS-1-02-D
  - 5.3.5.2 LAS-Study 1-D
  - 5.3.6 Reports of Post-Marketing Experience
  - 5.4 Literature References



### 5.3 Table of Studies/Clinical Trials

**Table 7: Studies to Support Efficacy and/or Safety**

Study	Design	Product(s)	Disease	Total Subjects
<b>1. Studies using FFP as a comparator</b>				
LAS-1-02-D 1998	Prospective, controlled, open-label	Octaplas (G-2a*) and FFP	Open heart surgery	67
19/PLAS/IV/91 1992	Prospective, open-label, parallel group	Octaplas (G-1**), no plasma, and FFP	Open heart surgery	66
LAS-1-03-UK 1995	Prospective, randomized, multi-center, open-label	Octaplas (G-2a) and FFP	Liver disease, liver transplantation, TTP	55
<b>2. Bridging studies</b>				
UNI-101 1999	Phase II, prospective, randomized, controlled, blinded	Octaplas (G-2a) and Uniplas	Elective open heart surgery	84
LAS-201 2008	Observational, prospective, multi-center, sequential cohort, open-label	Octaplas (G-2a) and OctaplasLG	any clinical condition with a need for plasma	125
LAS-203 2009	Phase I, prospective, randomized, open-label, controlled, cross-over, single center	Octaplas (G-2a) and OctaplasLG	Healthy volunteers	60
UNI-110 2009	Phase I, prospective, randomized, double-blind, controlled, cross-over, single center	OctaplasLG and UniplasLG	Healthy volunteers	30
<b>3. Single arm studies</b>				
3PLASIV90 1990	Prospective, open-label	Octaplas (G-1)	Hereditary or acquired coagulation factor deficiency	11
LAS-Study 1-D 1992	Prospective, open-label, single center	Octaplas (G-1)	ICU patients w/ disseminated intravascular	30

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Study	Design	Product(s)	Disease	Total Subjects
<b>1. Studies using FFP as a comparator</b>				
			coagulation (DIC)	

\*Generation 2a

\*\*Generation 1

Please refer to [Appendix 1](#) for a more detailed tabulation of these studies.

## 5.4 Consultations

There was no contribution to the evaluation of the application that came from consultation outside the review team and the Division.

### 5.4.1 Advisory Committee Meeting

The Octaplas™ BLA was presented to the Blood Products Advisory Committee (BPAC) on September 20, 2012. The questions posed to the Committee were as follows:

1. Do the data show that Octaplas™ is effective:
  - a. For the management of preoperative or bleeding patients who require replacement of multiple coagulation factors?
  - b. As substitution of intentionally removed plasma (e.g. plasma exchange in patients with TTP)?
2. Do the data show that Octaplas™ has an acceptable safety profile for the indications stated in question 1?
3. If the answer to question 1 or question 2 is no, what additional studies should be performed premarketing for the proposed indications?
4. Please comment whether safety monitoring would be needed post approval specifically to monitor:
  - c. Thromboembolic events?
  - d. Excessive bleeding?
  - e. Transmission of HEV?

The general consensus of the Committee was that the product was effective for the indications sought; however, the Committee discussed the limited available safety data with Octaplas™. The Committee recommended collection of additional safety data for the increased risk for hyperfibrinolysis and thromboembolism as the post-marketing studies.

### 5.4.2 External Consults/Collaborations

There were no formal requests for input on the application from another Office within CBER (with the exception of the Office of Biostatistics and Epidemiology [OBE] which is discussed in Sections 2.4, 4.6 and 11.6), from another Center within the Agency or from outside the Agency.

## 5.5 Literature Reviewed

Below is a tabulation of literature reports submitted in support of Octaplas™.

**Table 8: Literature Reports**

Study	Design	Product(s)	Disease	Total Subjects
Chekrizova et al. 2006	Retrospective	Uniplas and Octaplas (G-2a)	Neonates with coagulopathy; Ob/Gyn patients; liver disease	111
Scully et al. 2007	Retrospective	Octaplas (G-2a) and cryosupernatant	Acute TTP	32
Edel et al. 2010	Retrospective	Octaplas (G-2a)	Acute TTP	8
Santagostino et al. 2006	Phase 4, prospective, open-label, multi-center	Octaplas (G-2a)	Inherited coagulation disorders	17
Demeyere et al. 2010	Prospective, randomized, single center	Octaplas (G-2a) and prothrombin complex concentrates	Cardio-pulmonary bypass surgery	40

Two of the studies evaluated the use of Octaplas® to treat a total of 40 patients with TTP. One study included 32 patients with a total volume of 1328 liters of Octaplas® used. Seven percent of patients experienced citrate reactions (tingling of the hands and feet or facial twitching and/or muscle cramps) despite pretreatment with calcium. Three percent experienced plasma-associated reactions from localized itching/hives to anaphylaxis. There were no deaths reported. There was one report of a superficial vein thrombosis that did not require anticoagulant therapy.

The second study evaluated eight patients with a total volume of 2201 liters of Octaplas® used. There were no adverse drug reactions reported. Both studies reported successful treatment of TTP with the use of Octaplas® during plasma exchange.

## 6. Discussion of Individual Studies/Clinical Trials

The nine clinical studies evaluated for safety and efficacy can be placed into one of three different groupings. Please refer to Section 5.1 for a listing of those groupings and the studies within them. Details of each of the nine studies are presented below.

### **6.1 Trial #1: LAS-1-02-D (Octaplas® G-2a in patients with coagulopathy, N=67)**

"Efficacy and tolerability of quarantine stored fresh frozen plasma and solvent/detergent treated plasma (Octaplas®) in patients of the surgical intensive care unit after open heart surgery"

#### **6.1.1 Objectives (Primary, Secondary, etc)**

The primary objective of this study was to investigate the difference in tolerability between Octaplas® (G-2a) and FFP, through evaluation of the level of activation of the coagulation/fibrinolysis system and vital signs after treatment.

Secondary objectives were to evaluate for potential differences in efficacy, measured by several pro-coagulant and inhibitory parameters of the coagulation system and a global assessment of hemostasis. Adverse drug reactions (ADR) were also assessed.

#### **6.1.2 Design Overview**

The design was as a prospective, single-center, non-randomized, open-label, study. The study consisted of 67 patients (36 Octaplas®, 31 FFP).

#### **6.1.3 Population**

The study population consisted of post-operative open heart surgery patients in the surgical intensive care unit that required plasma administration of plasma for acute hemorrhage or for the risk for hemorrhage. Patients included in the study met at least one of the criteria listed below:

- Antithrombin (AT) < 70 % and PT < 50 %
  - AT < 60 % and PT < 60 %
  - AT < 70 % and Fibrinogen < 120mg/dl
  - AT < 60 % and D-dimer > 1 µ/ml
  - AT < 50 % and D-dimer > 0.5 µ /ml.

Patients having received packed red cells, plasma or coagulation-promoting plasma preparations within the last 6 hours and patients that received massive transfusion within the last 24 hours were not included.

#### **6.1.4 Study Treatments or Agents Mandated by the Protocol**

A dose of 600 ml of Octaplas® or FFP was administered post-operatively. Both drugs were given by intravenous infusion at a speed of 30 ml per minute.

#### **6.1.5 Sites and Centers**

Klinikum der Stadt Ludwigshafen, Bremserstr. 79, Ludwigshafen, Germany

#### 6.1.6 Surveillance/Monitoring

Patients were monitored per ICU protocol. Laboratory values were measured before infusion, 30 minutes and 60 minutes after infusion.

#### 6.1.7 Endpoints and Criteria for Study Success

The difference between the following baseline and post-Octaplas<sup>®</sup>/FFP infusion coagulation laboratory parameters were evaluated:

- Prothrombin fragment 1+2
- Plasmin-antiplasmin complex
- D-dimers and Fibrin degradation products
- Platelets
- PT and aPTT
- Fibrinogen and Factor VIII
- AT, PS, free PS and PI

The general impression of hemostasis post-Octaplas<sup>®</sup>/FFP infusion was rated by the investigator as “good, satisfactory or not satisfactory”.

#### 6.1.8 Statistical Considerations & Statistical Analysis Plan

All analyses performed were exploratory and utilized descriptive statistics. There was no stated hypothesis and no sample size calculation was performed.

#### 6.1.9 Study Population and Disposition

The study population consists of 67 patients enrolled in the study from June 27, 1998 until September 18th, 1999.

##### 6.1.9.1 Populations Enrolled/Analyzed

The data of all 67 patients was included in the analysis. Thirty-six patients received Octaplas<sup>®</sup> and 31 received FFP.

##### 6.1.9.1.1 Demographics

**Table 9: Demographic Characteristics of Study Population (N = 67)**

	<b>Octaplas<sup>®</sup></b> <b>(N = 36)</b>	<b>FFP</b> <b>(N = 31)</b>
Age (years) mean $\pm$ SD (range)	66 $\pm$ 11 (34, 79)	72 $\pm$ 8 (55, 86)
Height (cm) mean $\pm$ SD (range)	168.1 $\pm$ 7.6 (143.0, 183.0)	166.7 $\pm$ 8.0 (143.0, 183.0)
Weight (kg) mean $\pm$ SD (range)	72.0 $\pm$ 14.6 (42.0, 109.0)	71.7 $\pm$ 13.5 (49.0, 108.0)

*Adapted from Octapharma Final Study Report LAS-1-02-D, page 17 of 32*

#### 6.1.9.1.2 Medical/Behavioral Characterization of the Enrolled Population

All but three patients had concomitant diseases, the most frequent being diabetes mellitus, hypertension and hyperlipidemia.

#### 6.1.9.1.3 Subject Disposition

All patients underwent open heart surgery with cardiopulmonary bypass.

#### 6.1.10 Efficacy Analyses

Global parameters of coagulation, PS, free PS and PI are reported below.

##### 6.1.10.1 Analyses of Primary Endpoint(s)

**Table 10: Absolute Mean Value Difference from Baseline at 30 and 60 minutes**

		<b>Octaplas<sup>®</sup></b> <b>(N = 36)</b>	<b>FFP</b> <b>(N = 31)</b>
<b>PT</b> <b>(%)*</b>	30 min. minus Baseline	6.0	5.2
	60 min. minus Baseline	6.9	5.1
<b>aPTT</b> <b>(sec)</b>	30 min. minus Baseline	-4.5	-7.8
	60 min. minus Baseline	-5.9	-8.7
<b>Total Protein S</b> <b>(U/dL)</b>	30 min. minus Baseline	-0.9	4.9
	60 min. minus Baseline	-1.2	5.4
<b>Free Protein S</b> <b>(U/dL)</b>	30 min. minus Baseline	5.2	3.9
	60 min minus Baseline	5.9	3.8
<b>Plasmin Inhibitor</b> <b>(U/dL)</b>	30 min. minus Baseline	-9.5	-3.6
	60 min. minus Baseline	-8.6	-1.7

*Adapted from Octapharma Final Study Report LAS-1-02-D, page 20 and 21 of 32*

*\*Expressed as percentage of normal from 50 healthy individuals*

The hemostasis assessment after treatment with Octaplas<sup>®</sup> was rated "good" for 40% of the patients (14), "satisfactory" for 33% (12) and "not satisfactory" for 28 % (10) of the patients. After treatment with FFP, hemostasis was evaluated as "good" for 42% (13), "satisfactory" for 35% (11) and "not satisfactory for 23% (7) of the patients.

#### 6.1.11 Safety Analyses

##### 6.1.11.1 Methods

All 67 patients received either 600 mL of Octaplas<sup>®</sup> or FFP and were included in the safety evaluation.

#### 6.1.11.2 Overview of Adverse Events

No ADRs were reported.

#### 6.1.11.3 Deaths

Fourteen deaths occurred, 4 patients who received Octaplas® and 10 who received FFP. The deaths occurred between 1 and 32 days after infusion of plasma product. Most of the deaths were due to cardiac failure and/or arrhythmia. None were related to plasma infusion.

### **6.2 Trial #2: 19-PLAS-IV-91 (Octaplas® G-1 in patients undergoing open heart surgery, N=66)**

“Evaluation of solvent/detergent treated fresh frozen plasma in patients undergoing open heart surgery”

#### 6.2.1 Objectives (Primary, Secondary, etc)

The objectives of the study were to compare the safety and efficacy of Octaplas® (G-1) with FFP during cardiac surgery.

#### 6.2.2 Design Overview

The design was as a prospective, single-center, non-randomized, open-label, study enrolling three different groups of subjects receiving either Octaplas® G-1 (n=20), FFP (n=20) or no plasma (n=26).

#### 6.2.3 Population

Inclusion criteria were: patients of both sexes; age above 18 years; elective open heart surgery; and given informed consent. Patients in the Octaplas® group and the FFP group also had acute indication for FFP.

Exclusion criteria were emergency surgery, allergy to plasma proteins, pregnancy, diabetes, uremia or hepatitis.

#### 6.2.4 Study Treatments or Agents Mandated by the Protocol

Patients who needed FFP during cardiac surgery and in the postoperative period were treated with Octaplas® (G-1). The product was given in 200 mL portions according to clinical indications. A group of patients not requiring plasma was followed as part of the study and an historical group of consecutive patients who received FFP during cardiac surgery was included in the study.

#### 6.2.5 Sites and Centers

Department of Surgery A, National Hospital Rikshospitalet, Norway

#### 6.2.6 Surveillance/Monitoring

Bleeding rate and blood consumption were monitored. Blood samples were analyzed for coagulation activity. Patients getting only Octaplas<sup>®</sup> as (not native) blood product were followed up for transmission of viral infection.

#### 6.2.7 Endpoints and Criteria for Study Success

There were no predefined efficacy endpoints. Criteria for evaluation of efficacy were:

- Blood loss
- Postoperative course
- Hematology parameters
- Coagulation parameters
- Plasma colloid osmotic pressure

#### 6.2.8 Statistical Considerations & Statistical Analysis Plan

Results were presented as mean values with standard deviation or range. A statistical comparison of the clinical and laboratory data was done for the Octaplas<sup>®</sup> group and the no plasma group. The Mann-Whitney U test was used for continuous data while Chi-square or Fischer test was used for categorical data. There was no stated hypothesis and no calculation of sample size.

#### 6.2.9 Study Population and Disposition

In total 66 patients were included in the study.

##### 6.2.9.1 Populations Enrolled/Analyzed

Twenty who received Octaplas<sup>®</sup>, 26 who received no plasma and 20 who were in the historical FFP group.

##### 6.2.9.1.1 Demographics

**Table 11: Demographic Characteristics of Study Population (N = 66)**

	Octaplas <sup>®</sup>	FFP	No Plasma
Number (male/female)	20 (15/5)	20 (10/10)	26 (17/9)
Age (years) mean $\pm$ SD	66.2 $\pm$ 10.7	66.5 $\pm$ 9.6	61.4 $\pm$ 9.8
Weight (kg) mean $\pm$ SD	73.7 $\pm$ 9.0	67.8 $\pm$ 12.0	69.8 $\pm$ 12.8

*Adapted from Octapharma Final Study Report 19/PLAS/IV/91, page 19 of 26*



#### 6.2.9.1.2 Medical/Behavioral Characterization of the Enrolled Population

**Table 12: Medical Characterization of Study Population (N = 66)**

	<b>Octaplas<sup>®</sup></b> <b>(N = 20)</b>	<b>FFP</b> <b>(N = 20)</b>	<b>No Plasma</b> <b>(N = 26)</b>
Cardiac Ejection Fraction (%) mean $\pm$ SD	58 $\pm$ 17	63 $\pm$ 13	63 $\pm$ 19
New York Heart Assoc. Heart Failure Stage 2 (n)	5	3	11
New York Heart Assoc. Heart Failure Stage 3-4 (n)	15	17	15
Diabetes (n)	3	0	1
Uremia (n)	4	5	0
Previous Myocardial Infarction (n)	10	11	7
ASA treatment (n)	4	5	4
Anticoagulation (n)	9	11	7

*Adapted from Octapharma Final Study Report 19/PLAS/IV/91, page 19 of 26*

#### 6.2.9.1.3 Subject Disposition

All patients underwent cardiac surgery and were followed postoperatively. There were no dropouts or discontinuations.

#### 6.2.10 Efficacy Analyses

##### 6.2.10.1 Analyses of Primary Endpoint(s)

**Table 13: Post-operative Course and Complications**

<b>Parameter</b>	<b>Octaplas<sup>®</sup></b> <b>(N = 20)</b>	<b>FFP</b> <b>(N = 20)</b>	<b>No plasma</b> <b>(N = 26)</b>
Reoperation for bleeding (n)	4	4	2
Respirator time (h)	38	57	6
Post-operative bleeding (mL) mean $\pm$ SD	1139 $\pm$ 716	993 $\pm$ 571	684 $\pm$ 316
Need for circulatory support (n)	1	1	0

Parameter	Octaplas <sup>®</sup> (N = 20)	FFP (N = 20)	No plasma (N = 26)
Post-operative hospital stay (days)	6	6	5

*Adapted from Octapharma Final Study Report 19-PLAS-IV-91, page 20 of 26*

Coagulation parameters and plasma colloid osmotic pressure are not reported for the FFP group; therefore, without that context the values for the Octaplas<sup>®</sup> group are unable to be interpreted.

#### 6.2.11 Safety Analyses

##### 6.2.11.1 Methods

All 66 patients were included in the safety evaluation.

##### 6.2.11.2 Overview of Adverse Events

There was one ADR reported, a transient fever reaction in the Octaplas<sup>®</sup> group.

##### 6.2.11.3 Deaths

There were no deaths reported.

##### 6.2.11.4 Nonfatal Serious Adverse Events

**Table 14: Postoperative Complications**

	Octaplas <sup>®</sup> (N = 20)	FFP (N = 20)	No plasma (N = 26)
Myocardial Infarction (n)	0	2	0
Arrhythmia (n)	7	7	15
Organ failure (n)	6	3	3
Pneumonia (n)	1	0	1
Thrombosis (n)	1	4	1

*Adapted from Octapharma Final Study Report 19-PLAS-IV-91, page 20 of 26*

### 6.3 Trial #3: LAS-1-03-UK (Octaplas<sup>®</sup> G-2a in patients with liver disease, liver transplantation, and TTP, N=52)

“Clinical Evaluation of Solvent/Detergent Treated Fresh Frozen Plasma ('Octaplas') in the Management of Thrombotic Thrombocytopenic Purpura, and in Correction of Coagulopathy due to Liver Disease or Liver Transplantation”

### 6.3.1 Objectives (Primary, Secondary, etc)

The primary objective of the study was to evaluate, in a clinical setting, the efficacy and viral safety of Octaplas® in:

- The management of the coagulopathy of liver disease
- Liver transplantation
- The management of newly diagnosed TTP requiring either plasma infusion or plasma exchange

The secondary objective was to examine the efficacy of Octaplas® in reversing the following preexisting laboratory abnormalities:

- In liver disease patients, prolonged prothrombin time and low factors II, VII and protein C.
- In liver transplant patients, low fibrinogen and factors II, V, VII, VIII and protein C.
- In newly diagnosed TTP, low platelet count, red cell fragmentation on blood film, elevated lactate dehydrogenase, creatinine and abnormalities of von Willebrand factor multimers.

### 6.3.2 Design Overview

The study was a phase 2, prospective, randomized, single-blind (patients were unaware of the product they received) study to evaluate the tolerability, efficacy and viral safety of Octaplas® in liver disease (LD), liver transplant (LT) and TTP patients. Of the 52 subjects who completed the study, 24 liver disease (LD) subjects (11 FFP, 13 Octaplas®), 25 liver transplant (LT) subjects (13 FFP, 12 Octaplas®) and 3 TTP subjects were fully evaluable. All TTP subjects received Octaplas®.

### 6.3.3 Population

#### *Inclusion Criteria*

Patients included in the study were required to fulfill the following criteria:

- Presentation with either:
  - LD, with a prothrombin time prolonged > 4 seconds from control, in whom replacement with FFP was considered necessary and who were hemodynamically stable

OR

- Orthotopic liver transplantation with a prothrombin time prolonged > 4 seconds from control, in whom replacement with FFP was considered necessary and who were hemodynamically stable

OR

- Newly diagnosed TTP requiring treatment with plasma infusion or plasma exchange
- ≥ 18 years of age.
- Blood group A or O

### *Exclusion Criteria*

The following patients were excluded from participation:

- Patients under 18
- Pregnant women
- Patients of B or AB blood groups
- Patients who had previously reacted to FFP
- Patients in the LD group who had received blood products within the previous 6 months, because of the possibility that viral sera-conversion might relate to these products and not to the FFP
- Rh negative patients if anti-D was present
- Patients with known IgA antibodies
- Current intravenous drug users
- Hemodynamically unstable patients

LT and TTP patients who had received blood products within the last 6 months were allowed to enter the study, provided that all relevant information was fully documented.

#### 6.3.4 Study Treatments or Agents Mandated by the Protocol

In the LD group an initial Octaplas or FFP dose of 400 mL over 1 - 2 hours was repeated as clinically required. For the LT patients an initial dose was also 400 mL, infused, with further infusions given during surgery as indicated. For both LD and LT groups randomized treatment (Octaplas<sup>®</sup> or FFP) had to be continued up to 24 hours after the initiation of treatment, after this FFP could be used if more was required. For TTP patients, Octaplas<sup>®</sup> was given as a plasma infusion or as part of a plasma exchange procedure as required up to 3 L/day for 14 days. If more FFP was required after 14 days, FFP could be used.

#### 6.3.5 Sites and Centers

Queen Elizabeth Hospital, Birmingham, UK  
Addenbrooke's Hospital, Cambridge, UK  
St James' Hospital, Leeds, UK

#### 6.3.6 Surveillance/Monitoring

Body temperature, heart rate and blood pressure were measured prior to and at 15 minutes (LT and TTP patients only), 30 minutes, 60 minutes, 120 minutes and 4 hours after the start of plasma infusion. Observations of skin changes were at the above times and at 24 hours after the start of plasma infusion.

Viral serology (anti-HIV 1 and 2, anti-hepatitis B core antigen, anti HCV, anti parvovirus B19 and anti-HAV were measured pre-infusion and at 6 months post-infusion.

Coagulation variables (prothrombin time, partial thromboplastin time, factors II, VII and protein C for LD patients and prothrombin time, partial thromboplastin time, fibrinogen,

factors II, V, VII, VIII and protein C for LT patients) were measured prior to, post initial 400 mL plasma infusion and 24 hours after completion of the initial infusion. In TTP patients hematological and coagulation variables (Hemoglobin, white blood cell count, platelet count and blood film for red blood cell fragmentation, prothrombin time, partial thromboplastin time, multimeric analysis of von Willebrand factor to look for high molecular weight forms) were measured from samples taken daily prior to plasma infusion/exchange until the completion of treatment.

#### 6.3.7 Endpoints and Criteria for Study Success

Predefined efficacy endpoints in the LD/LT groups were global measures of coagulation, and correction of specific coagulation factors as well as Protein C. In the TTP group predefined efficacy endpoints were platelet count and laboratory values.

#### 6.3.8 Statistical Considerations & Statistical Analysis Plan

Comparisons of variables between patients receiving FFP or Octaplas i.e., differences in baseline values and in improvement from baseline values post-treatment, were made using the Mann-Whitney 2-tailed non-parametric test at the 5% level of significance. Data for TTP patients were considered descriptively only. There was no stated hypothesis and no calculation of sample size.

#### 6.3.9 Study Population and Disposition

##### 6.3.9.1 Populations Enrolled/Analyzed

Twenty four LD patients, 28 LT patients and 3 TTP patients were recruited to the study. Three LT (1 FFP, 2 Octaplas<sup>®</sup>) patients were excluded from the analysis because of protocol violations, leaving a total of 24 LD patients, 25 LT and 3 TTP patients.

### 6.3.9.1.1 Demographics

**Table 15: Demographic Data and Medical Characterization**

<b>Liver Disease Group</b>		
	<b>Octaplas®</b>	<b>FFP</b>
Number of patients	13 (3F, 10M)	11 (3F, 8M)
Median patient age in years (range)	50 (30 – 69)	52 (26 – 66)
Median plasma dose mL/kg (range)	12 (11 – 15)	13 (11 – 17)
Diagnosis:		
Alcoholic LD	8	4
Cryptogenic cirrhosis	2	3
Hepatitis	3	2
Primary sclerosing cholangitis	---	2
<b>Liver Transplant Group</b>		
Number of patients	12 (7F, 5M)	13 (6F, 7M)
Median patient age in years (range)	47 (20 – 66)	51 (23 – 67)
Median plasma dose mL/kg (range)	44 (25 – 104)	44 (7 – 98)
Diagnosis: (some patients have multiple diagnoses)		
Alcoholic LD	4	3
Autoimmune hepatitis	1	1
Cystic fibrosis	---	1
Decompensated LD	---	1
Full fulminant LD	1	---
Hemangiothelioma	1	---
Hepatoma	---	---
Hepatitis	2	1
Polycystic LD	1	3
Primary biliary cirrhosis	2	1
Primary sclerosing cholangitis	---	1
Rejection previous LT	1	3
<b>TTP Group</b>		
Number of patients	3 (1F, 2M)	---
Median patient age in years (range)	36 (26 – 64)	---

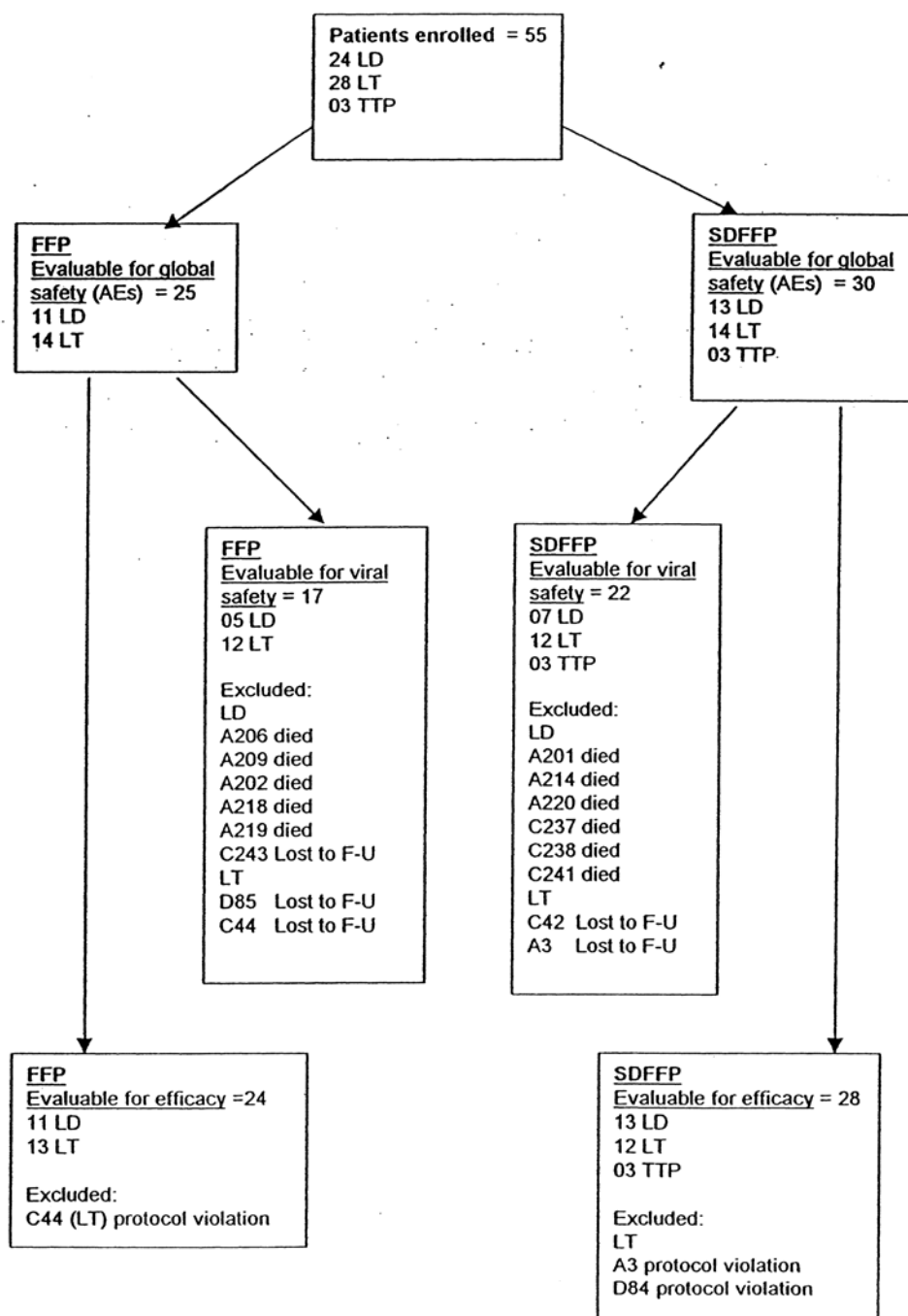
*Adapted from Octapharma Final Study Report LAS-1-03-UK, page 50 and 51 of 57*

### 6.3.9.1.2 Medical/Behavioral Characterization of the Enrolled Population

See Table 15

#### 6.3.9.1.3 Subject Disposition

### **Figure 2: Disposition of Patients**



Source: Octapharma Final Study Report LAS-1-03-UK, page 30 of 57

Three LT (2 Octaplas<sup>®</sup>, 1 FFP) patients were excluded from the analysis because of protocol violations. The two patients randomized to receive Octaplas<sup>®</sup> each received infusions of FFP subsequent to Octaplas<sup>®</sup> infusions but still within the initial 24 hour period, which was against protocol. The patient randomized to receive FFP was transfused with FFP units that were not prepared specifically as a control for the study.



### 6.3.10 Efficacy Analyses

#### 6.3.10.1 Analyses of Primary Endpoint(s)

The table below shows global measures of coagulation following 400 mL of plasma in the LD/LT groups. The degree of correction of the global measures of coagulation was similar for both products within each clinical setting (i.e., LD or LT).

**Table 16: Effects of FFP and Octaplas® on INR/aPTT after 400 mL of Plasma**

		<b>FFP Baseline</b>	<b>Octaplas® Baseline</b>	<b>FFP After 400 mL Plasma</b>	<b>Octaplas® After 400 mL Plasma</b>
INR median (range)	LD	2.0 (1.4-3.1)	3.0 (1.5-5.8)	1.8 (1.4-2.4)	2.3 (1.5-3.3)
	LT	1.5 (0.9-3.9)	1.5 (1.0-3.9)	1.6 (1.0-3.5)	1.6 (1.0-3.2)
aPTT prolongation* (sec) median (range)	LD	23 (10-69)	27 (7- >100)	20 (9-49)	27 (7-60)
	LT	13 (-12-90)	15 (-3-63)	14 (-3-74)	22 (-2-57)

Source: Williamson et al. 1999

\*aPTT values are expressed as the difference between the clotting times (in sec) of the test plasma and the laboratory control

The degree of correction of coagulation factors measured, including Protein C was also similar for the two products within each clinical setting.

Three TTP patients were reported to have attained platelet counts  $> 50 \times 10^9/L$  by day 10.

### 6.3.11 Safety Analyses

#### 6.3.11.1 Methods

All 55 patients enrolled in the study were included in the safety population.

#### 6.3.11.2 Overview of Adverse Events

There were two acute drug reactions in one LD patient (nausea, pruritis) who received Octaplas®. There were two reports of hemorrhage, both in LT patients, one

who received Octaplas<sup>®</sup> and one who received FFP. No thrombotic events were reported. The table below shows all the reported adverse events.

**Table 17: Adverse Events**

Event	Octaplas <sup>®</sup> (N = 30)	FFP (N = 25)
Pruritis	1 LD (3%)	---
Confusion	1 TTP (3%)	---
Convulsion Grand Mal	1 TTP (3%)	---
Cortical Blindness	1 TTP (3%)	---
Nausea	1 LD (3%)	---
Hepatitis	1 LD (3%)	1 LD (4%)
Hemorrhage	1 LT (4%)	1 LT (3%)
Anuria	---	2 LT (8%)
Total	5 (17%)*	4 (16%)

*Adapted from Octapharma Final Study Report LAS-I-03-UK, page 42 of 57*

#### 6.3.11.3 Deaths

Two deaths were recorded in the immediate post-study period (study period was 24 hours). Both patients were from the LD group and both died as a result of worsening of their underlying liver disease. Nine further deaths in LD group patients occurred at later dates outside of the formal study period and are reported to have died from liver failure due to their underlying liver disease.

#### *Narratives of Deaths*

- A male patient aged 49 years, with acute hepatitis and treated with ranitidine 150 mg twice daily (for 1 month) and lactulose 20 mL three times per day (for 2 weeks) was randomized to receive Octaplas<sup>®</sup>. On May 3, 1995 the patient was infused with 5 units. No remarkable changes in pulse, body temperature or blood pressure were noted during the infusion. The patient died on --(b)(6)-----. The investigators recorded the relationship of the AE to investigational treatment as "not assessable". The case report form (CRF) states that "Patient died dearly as a result of underlying severe liver disease".
- A male patient, aged 60 years, with a diagnosis of alcoholic hepatitis was treated pre-study with ceftazidime 1 g three times per day (for 7 days); augmentin 1.2g three times per day (for 7 days); fluconazole 100mg daily (for 7 days) and ranitidine 150mg twice daily (for 10 days). He was randomized to receive FFP and was infused with 5 units on May 10, 1995. There were no remarkable changes in pulse, blood pressure or body temperature during the infusion. The patient died on --- (b)(6) ----. The investigators recorded the

relationship of the AE to investigational treatment as "not assessable". The CRF states that "Patient died dearly as a result of underlying severe liver disease".

#### 6.3.11.4 Nonfatal Serious Adverse Events

No other serious AEs were recorded.

### **6.4 Trial #4: UNI-101 (Uniplas, Octaplas® G-2a or no plasma in cardiopulmonary bypass surgery patients, N=84)**

A prospective, parallel group, randomized, controlled, observer-blind, single-center, phase 2 study investigating the tolerability and safety of Uniplas in patients undergoing open heart surgery

#### 6.4.1 Objectives (Primary, Secondary, etc)

Uniplas is designed as a non-ABO specific product. UNI-101 was designed to evaluate the compatibility of Uniplas across all ABO blood groups through monitoring complement activation (occurs with ABO incompatibility) and the direct antiglobulin test (DAT) when compared with Octaplas®, an ABO blood group specific product.

Complement activation was identified by measuring levels of C3bc (the activation product of C3 indicating activation of the first part of the complement cascade) and terminal complement complex (TCC). TCC is an aggregation of C5, C6, C7, C8 and C9 and indicates activation of the terminal pathway of the complement cascade.

#### *Primary Objective*

The primary objectives of the study were to show that:

1. After administration of Uniplas no additional activation of the complement system (by measuring C3bc and TCC) occurs when compared to normal activation during open heart surgery
2. There are no incompatibility reactions (sensitized red blood cells [RBC], i.e., DAT positive) due to low titers of anti-A or anti-B antibodies in Uniplas

#### *Secondary Objectives*

The secondary objective of the study was to show that the treatment with Uniplas is safe, by monitoring the vital signs, recording adverse events (AEs) in all groups and to investigate the viral safety in the active treatment groups.

The secondary objective of the study in terms of efficacy was to measure global coagulation parameters.

#### 6.4.2 Design Overview

UNI-101 was a randomized, controlled, observer blinded study with 3 treatment groups receiving either Uniplas or Octaplas<sup>®</sup> and 1 group who received no plasma. All subjects underwent cardiac surgery, including:

- Coronary artery bypass grafting (CABG), single or multiple grafts
- Valvular surgery
- Combined CABG and Valvular surgery

The cohort groups were as follows:

- Group 1 = subjects with blood groups A, B or AB received Uniplas (N=25)
- Group 2 = subjects with blood group O received Uniplas (N=11)
- Group 3 = subjects with any blood group received Octaplas<sup>®</sup> (N = 19)
- Group 4 = eligible subjects who had given informed consent (IC) but who did not require any peri-operative plasma transfusion (no-plasma group) (N=29)

Subjects who received Uniplas were stratified by blood group into one of three groups: A or B (stratum 1); AB (stratum 2); or O (stratum 3).

#### 6.4.3 Population

##### *Inclusion Criteria*

Subjects who met the following criteria were to be included into the study:

1. Male or female, undergoing elective designated surgical procedures
2.  $\geq 18$  years of age
3. Given written IC

##### *Exclusion Criteria*

Subjects who met the following criteria were not to be included into the study:

1. Undergoing emergency CABG
2. Suffering from unstable angina pectoris (i.e., rapidly worsening angina; severe angina at rest or prolonged and severe ischemic chest pain without ECG or enzyme evidence of significant myocardial infarction)
3. History of exposure to viral hepatitis during the last 6 months
4. History of hypersensitivity to blood products
5. Having IgA deficiency with documented antibodies against IgA
6. History of, or suspected drug abuse
7. Pregnant women
8. Participating in another clinical study currently or during the past 3 months

#### 6.4.4 Study Treatments or Agents Mandated by the Protocol

Uniplas or Octaplas<sup>®</sup> were administered in units of 200 mL bags in an amount dependent upon the clinical situation (coagulopathy due to blood loss and/or dilution, and for

warfarin reversal). Generally, 2 to 3 units were administered as a starting regimen for subjects requiring plasma transfusion. For both products only 1 batch was used.

The number of subjects per blood group (stratum) was based on the expected frequency of the different blood groups in the target population (A: 49%, B: 8%, AB: 4%, O: 39%) and is given in Table 18.

**Table 18: Allocation of Subjects to Treatment Groups**

		Stratum			
Treatment Groups		1 (A or B)	2 (AB)	3 (O)	Goal
Group 1	Uniplas	$\geq 16$	2	---	18
Group 2	Uniplas	---	---	18	18
Group 3	Octaplas <sup>®</sup>	$\geq 8$	1	9	18
Group 4	no plasma	n.a.	n.a.	n.a.	$\geq 18$

*Source: Uniplas-Study Report UNI-101; June 2001, Amended Oct 2009, Page 25 of 75*

#### 6.4.5 Sites and Centers

Rikshospitalet, National Hospital University of Oslo Institute of Immunology, N-0027  
Oslo, Norway

#### 6.4.6 Surveillance/Monitoring

**Table 19: Schedule of Events**

Parameter	Screening	Baseline	During Surgery	During Infusion	After Infusion	After Surgery	Day 1 Post-op	Day 2 Post-op	6 Months Post-op
<b>Vital signs</b>									
heart rate		X			A	X	X		
blood pressure		X			A	X	X		
<b>Adverse Events</b>									
any		X	X	A	A	X	X	X	
<b>Hematology</b>									
hematocrit		X			A	X	X	X	
hemoglobin		X			A	X	X	X	
hemoglobin, free		X			A	X	X	X	
visible hemolysis in plasma		X			A	X	X	X	
Bilirubin		X			A	X	X	X	
Haptoglobin		X			A	X	X	X	
<b>Immune hematology</b>									
blood group	X	X			A	X	X	X	
anti-A titer, IgM <sup>†</sup>		X			A	X	X	X	
anti-B titer, IgM <sup>‡</sup>		X			A	X	X	X	
anti-A titer, IgG <sup>†</sup>		X			A	X	X	X	
anti-B titer, IgG <sup>‡</sup>		X			A	X	X	X	
Direct antiglobulin test (DAT)		X			A	X	X	X	
<b>Coagulation</b>									
ACT		X				X	X	X	
aPTT		X				X	X	X	
<b>Urine</b>									
Hemoglobinuria		X			A	X	X	X	
<b>Complement</b>									
C3bc		X			A	X	X	X	
TCC		X			A	X	X	X	
<b>Viral markers</b>									
anti-HIV-1/2		X							X
HBsAG		X							X
anti-HBc		X							X
anti-HCV		X							X
anti-CMV		X							X
anti-HTLV I+II		X							X
anti-HAV		X							X
anti-parvovirus B19		X							X
<b>Other</b>									
Creatinine		X				X			
LDH, ASAT, ALAT		X				X	X	X	
<b>Medical history</b>	X								
<b>Medical examination</b>	X								
<b>6 months questionnaire</b>									X

Source: Uniplas-Study Report UNI-101; June 2001, Amended Oct 2009, Page 21 of 75

<sup>†</sup>Blood group A or AB; <sup>‡</sup>Blood group B or AB

Key: X = to be done in any group; A = to be done in subjects receiving active treatment

#### 6.4.7 Endpoints and Criteria for Study Success

Efficacy was determined through an evaluation of complement activation and incompatibilities due to anti-A and anti-B antibodies. The primary efficacy endpoints were:

- An increase in C3bc compared to baseline (a difference in increase between Uniplas and Octaplas<sup>®</sup> of at least 20 units was defined as clinically relevant)
- A positive DAT graded as +, ++, +++, or ++++ compared to baseline

The following additional efficacy measurements were assessed at baseline, after each transfusion episode, after surgery, and on days 1 and 2 post-operatively:

- Activated partial thromboplastin time (aPTT)
- Activated clotting time (ACT)

#### 6.4.8 Statistical Considerations & Statistical Analysis Plan

For the statistical analysis the subjects were divided into 3 treatment groups depending on their blood group and the treatment received:

- The first treatment group included all patients with blood group A, B or AB who received Uniplas
- The second treatment group included subjects with blood group O who received Uniplas
- The third treatment group included subjects with any blood group who received Octaplas<sup>®</sup>

The non-randomized no plasma group included all subjects who gave informed consent and who did not require any plasma transfusion.

For the primary safety parameter of the maximum increase in C3bc compared to baseline, for each subject, the increase from baseline to all post-operative measurements was calculated, and the maximum among these increases was compared on the basis of following hypothesis ( $H_0$ ):

$H_0$ : The maximum increase in C3bc is the same for all 3 treatment groups

vs. the alternative hypothesis ( $H_A$ ):

$H_A$ : The maximum increase in C3bc is different between the 3 treatment groups.

The Analysis of Variance (ANOVA) model with treatment as factor in the model was used to test  $H_0$  versus  $H_A$ . If  $H_0$  was rejected, Scheffe's method of multiple comparisons was used. The 95% confidence interval for the difference between treatment groups was then calculated using the mean square error from the ANOVA model as the estimated standard deviation.

For the primary safety parameter of any change in the DAT, any positive reaction (graded as +, ++, +++, +++) was summarized per treatment group using counts and percentages of subjects.

#### *Determination of Sample Size*

The maximum increase in C3bc post-operatively was used as the basis for justification of sample size. From Solheim et al., it was estimated the increase in C3bc post-operatively would be approximately 75 units (ranging from 5 to 80) both for Octaplas<sup>®</sup> and "no plasma". From the same publication it was estimated the standard deviation would be approximately 23 units. A clinically relevant difference in increase was set to 20 units. Assuming a power of 80% and a significance level fixed at 5%, 18 subjects were required per treatment group.

#### 6.4.9 Study Population and Disposition

##### 6.4.9.1 Populations Enrolled/Analyzed

All 84 patients enrolled into the study were included in the analysis. Complete data sets (baseline/after surgery/ 1 day post-op/2 days post-op) to evaluate the changes in response to either treatment were available for 73 subjects in the evaluation of the aPTT and for 67 subjects in the evaluation of ACT.

##### 6.4.9.1.1 Demographics

**Table 20: Subject Demographics**

		All subjects N=84	Treatment group			
			Uniplas, arm 1 N=25	Uniplas, arm 2 N=11	Octaplas <sup>®</sup> , N=19	No plasma, N=29
		N (%)	N (%)	N (%)	N (%)	N (%)
<b>Sex</b>	<b>Male</b>	49 (58)	13 (52)	5 (45)	11 (58)	20 (69)
	<b>Female</b>	35 (42)	12 (48)	6 (54)	8 (42)	9 (31)
<b>Blood group</b>	<b>A</b>	45 (54)	20 (80)	-	11 (58)	14   48
	<b>B</b>	7 (8)	4 (16)	-	2 (10)	1 (3)
	<b>AB</b>	1 (1)	1 (4)	-	-	-
	<b>O</b>	31 (37)	-	11 (100)	6 (32)	14 (48)
<b>Age</b>	<b>Mean (range)</b>	68 (31 – 88)	71 (52 – 88)	70 (52 – 78)	67 (42 – 79)	66 (31 – 84)

*Adapted from: Octapharma/UNI-101, February 2002; Section 14.1 Table 6.2.2*



6.4.9.1.2 Medical/Behavioral Characterization of the Enrolled Population

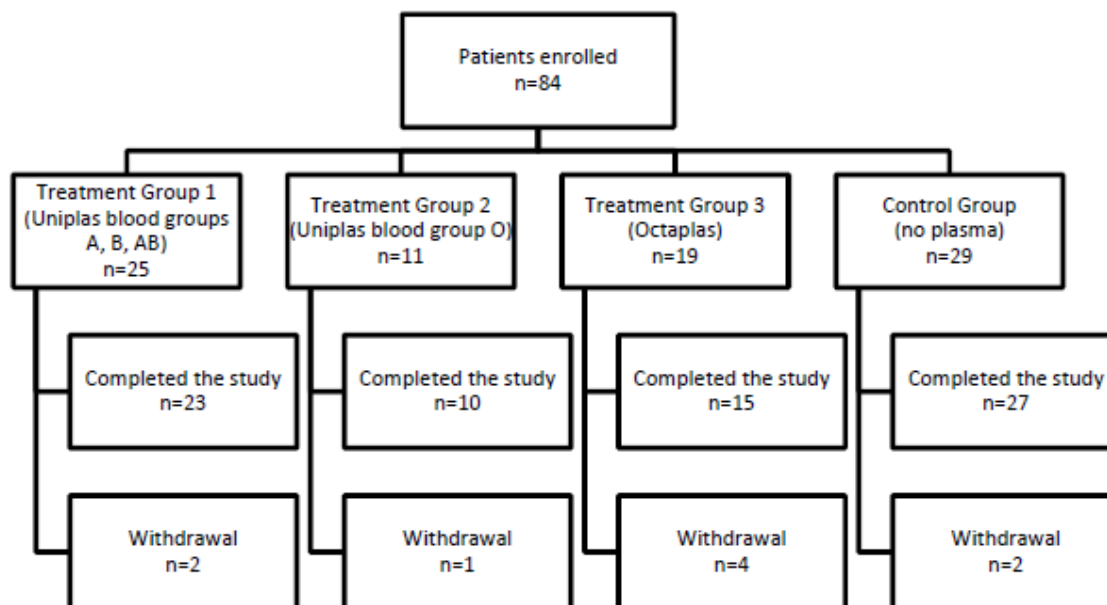
**Table 21: Subjects Risk Factors**

		All subjects N=84	Treatment group			
			Uniplas, arm 1 N=25	Uniplas, arm 2 N=11	Octaplas <sup>®</sup> , N=19	No plasma, N=29
			N (%)	N (%)	N (%)	N (%)
Risk Factors	Patients with risk factors	65 (77)	19 (76)	9 (82)	17 (90)	20 (69)
	Redo-surgery	17 (20)	7 (28)	3 (27)	5 (26)	2 (7)
	Previous angioplasty	2 (2)	---	---	---	2 (7)
	Endocarditis	6 (7)	3 (12)	---	1 (5)	2 (7)
	Pulmonary hypertension	5 (6)	1 (4)	3 (27)	1 (5)	---
	Chronic obstructive pulmonary disease	3 (4)	1 (4)	1 (9)	1 (5)	---
	Emergency operation	3 (4)	2 (8)	---	---	1 (3)
	Left main stem stenosis	6 (7)	2 (8)	2 (18)	---	2 (7)
	Ventricular fibrillation/tachycardia	2 (2)	1 (4)	---	---	1 (3)
	Hypercholesterolemia	25 (30)	9 (36)	3 (27)	6 (32)	7 (24)
	Previous stroke	5 (6)	1 (4)	---	2 (10)	2 (7)
	Arteriosclerosis	8 (10)	2 (8)	1 (9)	2 (10)	3 (10)
	Previous MI	21 (25)	7 (28)	2 (18)	4 (21)	8 (28)
	Anticoagulation	23 (27)	9 (36)	3 (27)	8 (42)	3 (10)
	Diabetes	13 (16)	2 (8)	2 (18)	4 (21)	5 (17)
	Uremia	6 (7)	3 (12)	---	1 (5)	2 (7)
	Hypertension	22 (26)	3 (12)	3 (27)	6 (32)	10 (34)

*Adapted from: Octapharma/UNI-101, February 2002; Section 14.1 Table 8.1*

#### 6.4.9.1.3 Subject Disposition

**Figure 3: Disposition of Study Subjects**



*Source: Octapharma Response to Information Request Dated July 23, 2012, page 2.*

There were two protocol deviations. A subject allocated to treatment arm 3 (Octaplas<sup>®</sup>), received in addition to Octaplas<sup>®</sup> also 2 units of Uniplas. Another subject allocated to receive Uniplas, was treated with Octaplas<sup>®</sup>.

#### 6.4.10 Efficacy Analyses

##### 6.4.10.1 Analyses of Primary Endpoint(s)

There were no reported differences in complement activation or incompatibility reactions between patients who received Octaplas<sup>®</sup> or Uniplas; however, these data did not impact the indications sought in this BLA.

##### 6.4.10.2 Analyses of Secondary Endpoints

**Table 22: Changes in the aPTT over time, n=73**

Treatment Group	After Surgery vs. Baseline	Post-op Day 1 vs. Baseline	Post-op Day 2 vs. Baseline
	Mean $\pm$ s.d. [sec]		
Group 1 Uniplas n=22	14.82 $\pm$ 18.39	3.32 $\pm$ 8.16	2.91 $\pm$ 5.69
Group 2 Uniplas n=9	9.00 $\pm$ 9.53	0.00 $\pm$ 4.36	0.11 $\pm$ 4.51
Group 3 Octaplas <sup>®</sup> n=16	8.50 $\pm$ 7.98	1.50 $\pm$ 6.74	4.06 $\pm$ 6.94
Group 4 no plasma n=26	0.50 $\pm$ 29.28	-6.31 $\pm$ 29.90	-3.92 $\pm$ 31.09

Source: Uniplas-Study Report UNI-101; June 2001, Amended Oct 2009, Page 63 of 75

**Table 23: Changes of ACT Over Time, n=67**

Treatment Group	After Surgery vs. Baseline	Post-op Day 1 vs. Baseline	Post-op Day 2 vs. Baseline
	Mean $\pm$ s.d. [sec]		
Group 1 Uniplas n=20	-14.60 $\pm$ 12.93	-7.30 $\pm$ 19.85	-15.25 $\pm$ 22.69
Group 2 Uniplas n=6	-22.17 $\pm$ 12.95	-20.83 $\pm$ 11.18	-24.00 $\pm$ 10.10
Group 3 Octaplas <sup>®</sup> n=15	-23.73 $\pm$ 15.67	-10.53 $\pm$ 24.22	-13.27 $\pm$ 24.36
Group 4 no plasma n=26	-16.62 $\pm$ 17.67	-10.77 $\pm$ 17.89	1.96 $\pm$ 21.64

Source: Uniplas-Study Report UNI-101; June 2001, Amended Oct 2009, Page 64 of 75

#### 6.4.10.3 Subpopulation Analyses

There were no subpopulation analyses.

#### 6.4.10.4 Dropouts and/or Discontinuations

All data available were included into the statistical evaluation. Missing data were not replaced.

#### 6.4.11 Safety Analyses

##### *Exposure to Investigational Medical Product*

The dose of the investigational product was adjusted to the individual requirements of each subject. The minimum dose given in the active treatment groups was one transfusion with one bag for either Uniplas (n=10) or Octaplas<sup>®</sup> (n=1). The maximum dose given during one transfusion episode was seven bags of Uniplas. The maximum total dose given to one individual patient during the study was 23 bags of Uniplas. The

mean dose, inclusive of both Uniplas and Octaplas<sup>®</sup>, was approximately 4 bags. In total, 68 transfusions with Uniplas were recorded in Groups 1 and 2. In the Octaplas<sup>®</sup> group (Group 3), 30 transfusions were recorded.

#### 6.4.11.1 Methods

Adverse events were actively collected from all enrolled subjects.

#### 6.4.11.2 Overview of Adverse Events

In total 55 AEs were observed in 26 subjects during the study. Eleven of 36 subjects who received Uniplas, 8 of 19 subjects who received Octaplas<sup>®</sup> and 7 of 29 subjects from the no plasma group experienced AEs. No skin reactions or jaundice were observed.

**Table 24: Number of AEs, Sorted According to MedDRA Terminology**

Adverse Event	Frequency of AE			
	Uniplas, arm 1 N=25	Uniplas, arm 2 N=11	Octaplas <sup>®</sup> , N=19	No plasma, N=29
Aortic injury			1	
Arterial rupture NOS			1	
Atrial fibrillation	1		1	
Atrial flutter	1	1		6
Blood pressure decreased				1
Cardiac output decreased				1
Cardiac pacemaker insertion	1	1	1	
Cardiac tamponade			1	
Cerebrovascular accident NOS		1		
Death NOS			1	
Dialysis NOS	1		1	
Hemorrhage NOS	1	1		
Heart rate decreased			1	
Heart valve replacement NOS		1		
Hemiplegia		1		
Intubation NOS	1			
Infection at the site of the pacemaker				1
Left ventricular failure	1			1
Mechanical complication of implant		1	1	
Mitral valve repair NOS	1			
Myocardial infarction			1	
Post-operative hemorrhage			2	

Adverse Event	Frequency of AE			
	Uniplas, arm 1 N=25	Uniplas, arm 2 N=11	Octaplas <sup>®</sup> , N=19	No plasma, N=29
Respiratory failure (excluding neonatal)	2			1
Slow sinus activity	1	1	1	
Ventilator				1
Extra-corporeal circulation (2 periods) during operation	1	1		
Intra-aortic balloon				1
Intra-operative death (massive surgical bleeding)			1	
Para-valvular leak	1			
Re-operation	1	1	3	
Surgical problem		1		
<b>TOTAL</b>	<b>14</b>	<b>11</b>	<b>17</b>	<b>13</b>

Source: Uniplas-Study Report UNI-101; June 2001, Amended Oct 2009, Page 37 of 75

#### 6.4.11.3 Deaths

Two subjects died on the day of surgery:

- A subject who received Octaplas<sup>®</sup> experienced two serious AEs (aortic injury and massive surgical bleeding) resulting in intra-operative death. The subject was a 75 year old female patient with aortic and mitral valve stenosis caused by endocarditis following rheumatic fever and required reoperation of the mitral valve. For both AEs the investigator did not assess any causal relationship to the investigational product. The patient is reported to have had a large fissure in the posterior aorta and this reviewer agrees that the AEs and death were not related to the investigational product.
- A subject who received Octaplas<sup>®</sup> experienced three serious AEs (arterial rupture, mechanical complication of implant and death) leading to the death on the day of operation. The subject was a 74 year old male requiring surgery due to stenosis of the aortic valve and mitral valve incompetence. At the conclusion of surgery it was not possible to wean from extra-corporal circulation due to myocardial failure, complicated by rupture of the pulmonary artery. For both AEs the investigator did not assess any causal relationship to the investigational product. This reviewer agrees that the two AEs and death were not related to the investigational product.

Seven subjects died after discharge from the hospital:

- A subject from the group receiving Uniplas died after a cardiac infarction during a hospital stay starting approximately 10 weeks after discharge from the hospital where the heart surgery was performed.
- A subject from the group receiving Uniplas died from multi-organ failure approximately three weeks after discharge from the hospital where the heart surgery was performed.
- A subject from the group receiving Uniplas died of sudden death approximately ten days after discharge from the hospital where the heart surgery was performed.
- A subject from the group receiving Octaplas<sup>®</sup> died of sudden death at home approximately two months after receiving the investigational product.
- A subject from the group receiving Octaplas<sup>®</sup>, suffered from a cerebrovascular accident, approximately three weeks after the heart surgery, during a hospital stay starting immediately after discharge from the hospital where the heart surgery was performed.
- A subject who received no plasma died (reason unspecified). It is not recorded how long after discharge the death occurred.
- A subject who received no plasma died from a brain neoplasm. It is not recorded how long after discharge the death occurred.

#### 6.4.11.4 Nonfatal Serious Adverse Events

Eleven AEs that occurred in 5 subjects (1 received Uniplas [Group 2], 4 received Octaplas<sup>®</sup> [Group 3]) were graded as "serious". These included: hemiplegia, cerebrovascular accident, aortic injury, arterial rupture, post-operative hemorrhage, mechanical complication of implant and cardiac tamponade.

#### 6.4.11.5 Adverse Events of Special Interest (AESI)

The test results for 75 subjects were available for viral safety analysis at 6 months (9 subjects died prior to the 6-month time point). All subjects tested negative at baseline and at the 6-month follow-up for anti-HIV, anti-HCV and anti-HTLV-I/II. All subjects tested negative at baseline and at the 6-month follow-up or were positive at baseline for HBsAG, anti-HBc, anti-CMV-IgG, and anti-Parvovirus-B19 IgG.

The 6-months samples yielded positive results for anti-HAV-IgG in 31 subjects. Eleven received Uniplas, 9 received Octaplas and 11 no plasma. Twenty-nine of these subjects were tested positive for anti- HAV-IgG in the baseline samples. Two of these subjects (1 Uniplas and 1 Octaplas<sup>®</sup>) were tested negative in the baseline samples and seroconversions in these 2 subjects were confirmed by HAV –(b)(4)- analyses.

Both, the Uniplas and the Octaplas<sup>®</sup> batch were also HAV---(b)(4) tested, and showed negative results. Both subjects received red blood cells during the operation or during the post operative phase.

#### 6.4.11.6 Clinical Test Results

There were no acute drug reactions reported.

#### **6.5 Trial #5: LAS-201 (Octaplas<sup>®</sup> G-2a or OctaplasLG in patients needing plasma for any clinical condition, N=125)**

A sequential cohort study to compare tolerability and efficacy in patients receiving Octaplas<sup>®</sup> or OctaplasLG

##### 6.5.1 Objectives (Primary, Secondary, etc)

The objective of the study was to assess the effectiveness and tolerability of Octaplas<sup>®</sup> and OctaplasLG and to compare the outcomes in patients treated with Octaplas<sup>®</sup> with those treated with OctaplasLG.

##### 6.5.2 Design Overview

This study was designed as a non-interventional, sequential cohort, observational, open, prospective, multi-center study. The observation period per patient depended on the indication to be treated, but generally was expected to be a period of 1 to 2 days. Any follow-up observations beyond the immediate observation period relating to safety were documented wherever possible. Initially, all patients enrolled in the study received Octaplas<sup>®</sup> with the intent for 60 patients to be documented in this cohort. Once OctaplasLG was marketed, an additional 60 patients were enrolled.

In total, 65 patients were enrolled into the Octaplas<sup>®</sup> cohort and 60 patients were enrolled into the OctaplasLG cohort.

##### 6.5.3 Population

###### *Inclusion Criteria*

Patients of any age who required a transfusion with Octaplas<sup>®</sup> or OctaplasLG were eligible for study enrolment. Possible indications included:

1. Emergency substitution of coagulation factors and proteinase inhibitors in case of a clinically relevant bleeding tendency
2. Actual bleeds accompanied by complex hemostatic disorders, especially in cases of liver disorders or disseminated intravascular coagulation (DIC)
3. Dilution or consumption coagulopathy
4. Coagulation factor V and XI deficiencies
5. Thrombotic thrombocytopenic purpura (TTP)
6. Plasma exchange procedures (PEX)

Reference was made to the package insert approved at the time of this study. If the responsible physician decided that treatment with Octaplas<sup>®</sup> or OctaplasLG was

indicated, the patient could then be enrolled into the study, taking into account the labeled contraindications, warnings, and precautions.

#### *Exclusion Criteria*

Patients with known relative contraindications (i.e., latent or apparent cardiac decompensation, hypovolemia, hypervolemia, lung edema and selective serum IgA deficiency), as well as patients with known absolute contraindications (i.e., hypersensitivity to plasma proteins and antibodies against IgA), were not to be treated with Octaplas® or OctaplasLG.

#### 6.5.4 Study Treatments or Agents Mandated by the Protocol

The treatment regimen did not follow a defined protocol. Usual clinical practice was followed; patients were treated with Octaplas® and OctaplasLG according to the physician's prescription and the patient's needs.

#### 6.5.5 Sites and Centers

Institute for Transfusion Medicine, University Hospital, Jena, Germany

Department for Transfusion and Blood Donation, Südharz Krankenhaus, Nordhausen, Germany

Department for Internal Medicine and Intensive Care, University Hospital, Dresden, Germany

Clinic for Internal Medicine with focus on nephrology and internistic intensive care, Charité University, Berlin, Germany

Clinic for General, Visceral and Transplantation Surgery, Charité University, Berlin, Germany

#### 6.5.6 Surveillance/Monitoring

Before the first treatment with Octaplas® or OctaplasLG, the physician recorded the patient's available baseline characteristics (sex, date of birth, weight, blood group, diagnosis, and indication for use) and details of any plasma-derived or blood products given 24 hours before, during or within 48 hours after the treatment with Octaplas® or OctaplasLG were also documented.

One treatment episode was defined as the time period when Octaplas® or OctaplasLG were administered. Within one treatment episode, one or more bags could be transfused. If the time difference between two Octaplas® or OctaplasLG transfusions was more than



four hours, then the subsequent Octaplas<sup>®</sup> or OctaplasLG administrations were documented as a new treatment episode.

Whether the use of Octaplas<sup>®</sup> or OctaplasLG was considered by the physician to be successful (yes/no question) was recorded, and the reason for the positive or negative assessment was documented. If any laboratory tests were done to assess the therapeutic effect of Octaplas<sup>®</sup> or OctaplasLG, including but not limited to Quick test (PT) or the International Normalized Ratio (INR), these also were recorded. No investigations were allowed to be initiated for the purpose of this non-interventional trial.

Details of any adverse drug reactions (ADRs) were recorded.

#### 6.5.7 Endpoints and Criteria for Study Success

The effectiveness of Octaplas<sup>®</sup> and OctaplasLG was an objective assessment by the physician based on clinical or laboratory parameters relevant for the indication of whether the use of the product was successful or not.

#### 6.5.8 Statistical Considerations & Statistical Analysis Plan

There was no stated hypothesis testing.

All patients included in the study who received at least one dose of Octaplas<sup>®</sup> or OctaplasLG were included in the statistical evaluation.

The statistical analysis of all parameters was descriptive. Particularly for the comparison of the effectiveness and safety of Octaplas<sup>®</sup> or OctaplasLG, descriptive statistics were used.

#### *Determination of Sample Size*

The statistical sample size calculation was based on the 95% confidence interval for the probability of observing a rare event. For a sample size of 59 in which no events had been observed, the upper bound of the 95% confidence interval for the probability of an event was 0.05. The event of interest was defined to be a patient with at least one ADR. Thus, with a sample size of 59, ADRs with an incidence of at least 5% could be detected with sufficient confidence (95%). Therefore, the planned sample size was  $2 \times 60 = 120$  patients, with 60 patients per cohort (Octaplas<sup>®</sup> or OctaplasLG).

#### 6.5.9 Study Population and Disposition

##### 6.5.9.1 Populations Enrolled/Analyzed

In total, 65 patients were enrolled into the Octaplas<sup>®</sup> cohort and 60 patients were enrolled into the OctaplasLG cohort.

#### 6.5.9.1.1 Demographics

**Table 25: Subject Demographics**

	All patients n=125	Octaplas <sup>®</sup> n=65	OctaplasLG n=60
<b>Sex</b>			
Male	74 (59%)	33 (51%)	41 (68%)
Female	51 (41%)	32 (49%)	19 (32%)
<b>Age [years]</b>			
Mean $\pm$ s.d. [min, max]	58 $\pm$ 18 [17, 88]	59 $\pm$ 16 [21, 83]	57 $\pm$ 20 [17, 88]
<b>Weight [kg]</b>			
Mean $\pm$ s.d. [min, max]	77 $\pm$ 17 [36, 130]	77 $\pm$ 17 [36, 125]	77 $\pm$ 17 [40, 130]

*Adapted from: Octapharma/LAS-201; October 2010, Section 14.1*

#### 6.5.9.1.2 Medical/Behavioral Characterization of the Enrolled Population

The following lists the numbers of patients in the study per specific indications of usage of Octaplas<sup>®</sup> or Octaplas LG:

- PEX = 27
- Cardiothoracic surgery = 7
- Peri/intra-op = 18
- DIC = 33
- Multiple coagulation factor deficiency = 27
- TTP = 5
- Non-surgical bleeding = 4
- Liver transplant = 2
- Other = 2

#### 6.5.9.1.3 Subject Disposition

All patients were treated with Octaplas<sup>®</sup> or Octaplas LG and were therefore included in the statistical analysis.

#### 6.5.10 Efficacy Analyses

##### 6.5.10.1 Analyses of Primary Endpoint(s)

The efficacy of the treatment with Octaplas<sup>®</sup> or OctaplasLG was judged by the investigator based on clinical and laboratory parameters relevant for the indication.

For some patients, more than one treatment episode with Octaplas<sup>®</sup> or OctaplasLG was administered. For the statistical evaluation, the judgment about success was decided from the individual's last treatment episode.

Overall treatment success was reported as 98.5% (64/65) in the Octaplas<sup>®</sup> group and 95.0% (57/60) in the OctaplasLG group. Treatment success was reported as 100% in both groups when PEX is excluded. Treatment success in the PEX group with Octaplas<sup>®</sup> was 92.3% (12/13) and 89.5% (17/19) in the OctaplasLG group.

#### 6.5.10.2 Analyses of Secondary Endpoints

There were no secondary endpoints in the study.

#### 6.5.11 Safety Analyses

The Octaplas<sup>®</sup> cohort (N=65) was exposed to a total of 101 liters of Octaplas<sup>®</sup> while the OctaplasLG cohort (N=60) was exposed to a total of 145.2 liters of OctaplasLG.

##### 6.5.11.1 Methods

Adverse events were actively collected from all enrolled subjects.

##### 6.5.11.2 Overview of Adverse Events

In the Octaplas<sup>®</sup> cohort, no ADR was reported. In the OctaplasLG cohort, one single ADR was reported. This event was reported as severe and serious.

##### 6.5.11.3 Deaths

The causes of death in the five patients whose clinical course led to their death were as follows and are not considered related to the products.

- Occlusion of mesenteric blood vessel following septic course with renal failure and circulatory collapse (patient died 1 day following Octaplas<sup>®</sup> infusion)
- Prolonged hemorrhagic shock in patient with DIC (patient received a total of 16 bags of OctaplasLG)
- Heart failure and kidney failure (patient received a total of 2 bags of OctaplasLG)
- Cardiogenic shock, uncontrollable hemorrhage, and thrombocytopenia (patient received a total of 3 bags of OctaplasLG)
- Craniocerebral trauma (patient received a total of 4 bags of OctaplasLG)

##### 6.5.11.4 Nonfatal Serious Adverse Events

The single reported ADR involved a 60-year-old woman in the OctaplasLG cohort. One treatment episode was recorded for this patient. Her underlying illness was chronic obstructive pulmonary disease. She was awaiting lung transplantation and had specific human leukocyte antigen (HLA) antibodies. The indication for OctaplasLG was documented as exchange transfusion, “tissue plasminogen activator for sensitization prior to transplantation”. The patient received a total volume of 2200 mL (= 11 bags) of OctaplasLG over 160 minutes. The resulting volume per body weight was 36.7 mL/kg body weight. No plasma/blood products or coagulation-promoting agents other than OctaplasLG were administered.

During the transfusion of OctaplasLG, the patient developed severe hypotension which lasted over 20 minutes and which was assessed as severe and life-threatening. The administration of OctaplasLG was interrupted or reduced and 1 mL of Akrinor (cafedrine hydrochloride / theodrenaline hydrochloride), diluted 1:4, given intravenously. The event resolved.

The treatment episode with OctaplasLG was not completed in this patient. The reasons for stopping the treatment episode were specified by the investigator as:

1. Severe hypotensive circulatory regulation
2. Transplantation cancelled because of the poor quality of the donor organ.

After the occurrence of this ADR, samples of the two OctaplasLG batches used in this patient were tested for human neutrophil antigen (HNA)-antibodies and HLA I+II. All analyses revealed negative results.

#### **6.6 Trial #6: LAS-203 (Octaplas<sup>®</sup> G-2a and OctaplasLG in healthy volunteers, IND study, N=60)**

A comparative, open-label, randomized, cross-over phase 1 trial in healthy volunteers to investigate the relative efficacy, safety and tolerability of OctaplasLG vs. Octaplas<sup>®</sup>

##### **6.6.1 Objectives (Primary, Secondary, etc)**

The objectives of the study were the assessment of the relative efficacy, safety and tolerability of OctaplasLG and Octaplas<sup>®</sup>.

##### *Primary Objective*

The primary objective was to compare the efficacy of OctaplasLG with that of Octaplas<sup>®</sup>, in terms of the relative recovery of coagulation factors and other hemostatic parameters.

##### *Secondary Objectives*

The secondary objective was to compare the safety and tolerability of OctaplasLG with Octaplas<sup>®</sup> in terms of hematological and clinical chemistry parameters and AE monitoring.

### 6.6.2 Design Overview

The study was performed as an open-label, block-randomized, cross-over study, consisting of two groups of 30 healthy male and female individuals.

### 6.6.3 Population

#### *Inclusion Criteria*

1. Subject had to provide signed informed consent
2. Subject had to be capable of understanding and complying with all aspects of the study protocol
3. Subject had to be capable of understanding and signing the information sheet for plasmapheresis (PPh), including standard procedures and side effects
4. Healthy male or female volunteers,  $\geq 18$  years of age
5. Female subjects had to have a negative pregnancy test (HCG-based assay)
6. Female subjects had to use adequate methods of contraception
7. Subjects were not to have any clinically relevant abnormalities in medical history and general physical examination
8. A standard health insurance had to be in place for the subject

#### *Exclusion Criteria*

1. Pregnancy or lactation
2. Subject had received tattoos within the last 3 months
3. Subject had been treated therapeutically with fresh frozen plasma, blood or plasma derived products in the previous 6 months
4. History of severe hypersensitivity to blood products or plasma protein
5. History of angioedema
6. History of coagulation disorder or bleeding disorder and any known abnormality affecting coagulation, fibrinolysis or platelet function
7. Subject had clinically significant abnormal laboratory values
8. Subject had IgA deficiency
9. Seropositivity for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), human immunodeficiency virus (HIV)-1/2 antibodies
10. Symptoms of a clinically relevant illness within 3 weeks before the first study day
11. History of or a suspected drug or alcohol abuse
12. Subject was already participating in another clinical study
13. Any investigational medicinal product (IMP) administration within the last 4 weeks

#### 6.6.4 Study Treatments or Agents Mandated by the Protocol

Each subject in this cross-over study underwent two PPh sessions (at least 4 weeks apart) immediately followed by infusions with either Octaplas<sup>®</sup> or OctaplasLG and was randomly assigned to 1 out of 2 treatment sequences (A or B). Subjects in treatment Sequence A received Octaplas<sup>®</sup> after the first PPh then OctaplasLG after the second, while subjects in treatment Sequence B received OctaplasLG after the first PPh then Octaplas<sup>®</sup> after the second.

During each PPh approximately 600 mL plasma was removed. A total amount of 1200 mL of Octaplas<sup>®</sup> or OctaplasLG was administered after the end of PPh in units of 200 mL bags. The transfusion rate did exceed 0.020 – 0.025 millimole citrate/kg body weight /minute, which is equal to  $\leq 1$  mL/kg body weight/minute.

The duration of the study for an individual subject was between 7 and a maximum of 10 weeks. The duration of each individual plasma infusion was dependent from the individually calculated transfusion rate, which was not to exceed 0.020 to 0.025 millimole citrate /kg body weight/minute, but was finished within about 1 hour.

#### 6.6.5 Sites and Centers

Dept of Clinical Pharmacology, Medical University of Vienna Austria

#### 6.6.6 Surveillance/Monitoring

**Table 26: Schedule of Assessments**

Parameter	Visit 1 Screening	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Time-points		≤4 weeks after Visit 1	24 ±3 h post- PPH Period 1	7 days post start of PPh Period 1	≥4 weeks after Visit 2	24 ±3 h post- PPH Period 2	7 days post start of PPh Period 2
In/Exclusion criteria	X						
Physical exam	X						X
Medical history	X						
Demographic data	X						
Randomization		X					
Eligibility check		X			X		
ECG	X						X
Vital Signs	X	X	X	X	X	X	X
---(b)(4)-----		X			X		
Blood sampling	X	X	X	X	X	X	X
Pregnancy test	X	X			X		X
Drug screening	X						
Blood group bedside test		X			X		
Study drug administration		X			X		
Assessment of tolerability		X			X		
AE and concomitant medication monitoring	X	X	X	X	X	X	X

Source: Report Clinical Study LAS-203; December 2011, Page 15

\*---(b)(4)----- (continuously: ECG, heart rate, oxygen saturation; periodically:  
blood pressure)

**Table 27: Laboratory Parameters and Blood Sampling Time-Points**

	Visit 1	Visit 2 and Visit 5				Visit 3 & 6	Visit 4 & 7
Time-points		≤30 min before PPh	<5 min post-PPh	15 min (±2 min) post-infusion	2 h (±15 min) post-infusion	24 h (±3 h) post start of PPh	7 days post start of PPh
Blood group testing	X						
Pregnancy test	X	X					X
IgA	X						
Viral testing	X						
Drug screen	X						
Coagulation factors	X	X	X	X	X	X	
Hematology	X	X	X	X	X	X	X
Hemostatic parameters	X	X	X	X	X	X	
Clinical chemistry	X	X	X	X	X	X	X

*Source: Report Clinical Study LAS-203; December 2011, Page 16*

#### 6.6.7 Endpoints and Criteria for Study Success

##### *Primary Endpoint*

The primary endpoint comprised of coagulation factors (FI, FII, FV, FVII, FVIII, FIX, FX, and FXI) and hemostatic parameters (aPTT, PT and protein C).

##### *Secondary Endpoint*

As a secondary efficacy endpoint, the concentration of plasmin inhibitor was measured to verify the assumption of its improvement. The sponsor stated that values of plasmin inhibitor were measured by validated assays from blood samples obtained within 30 minutes before PPh, 5 minutes after the end of PPh and 15 minutes and 2 hours after the end of IMP infusion and 24 hours and 7 days after initiation of PPh.



#### 6.6.8 Statistical Considerations & Statistical Analysis Plan

For the computation of CI the coverage probability was set to 90%. For the secondary efficacy parameter plasmin inhibitor, exploratory two-sided 95% CIs were presented.

All measurements were analyzed descriptively by presenting relative frequency for qualitative data and characteristics of the sampling distributions for metrically scaled data (arithmetic means, standard deviation, median, minimum and maximum). For data that were assumed to be log-normally distributed the following characteristics were provided in addition: geometric mean, geometric standard deviation and coefficient of variation.

##### *Primary Efficacy Analysis*

The analysis of the efficacy parameters was performed for the intent-to treat (ITT) population and the per protocol (PP) population. The analysis based on the PP population was the primary analysis.

The PP population included less than the planned 60 subjects; therefore, a post-hoc power analysis was performed. The post-hoc power analysis was done for individual primary endpoints (without adjustment for multiple testing) and used to support interpretation of efficacy analysis results in case of lower number of subjects included than expected.

Thus, the sponsor analyzed efficacy parameters for the extended per protocol (EPP) population, based on experience from a previous trial, which suggested to them that subjects receiving at least 75% of the IMP can achieve changes in coagulation factors that are still in the confidence limits for equivalence.

For the analysis of the primary efficacy endpoints the time profiles for the factor levels and hemostatic parameters as well as their differences to baseline (post-PPh) were analyzed descriptively.

To assess the efficacy of the two treatments in restoring coagulation factor levels and hemostatic parameters an individual relative recovery was computed. For each efficacy parameter, treatment and subject, this recovery was defined as the maximum of the difference within 2 hours after infusion to the 5 minutes post-PPh value divided by the value 5 minutes post-PPh and multiplied by 100 to yield an interpretation as a percentage. For aPTT the recovery was defined as the minimum of the relative difference.

For each coagulation/hemostatic parameter, the relative recoveries were further analyzed by performing two one-sided paired t-tests for the hypothesis testing problem:

$H_0: \text{mean}(|\text{REC}(\text{OctaplasLG}) - \text{REC}(\text{Octaplas}^{\text{®}})|) > 10.0\%$

vs.

$H_1: \text{mean}(|\text{REC}(\text{OctaplasLG}) - \text{REC}(\text{Octaplas}^{\text{®}})|) \leq 10.0\%$

A type I error of 0.05 was chosen for the t-tests. These were supplemented by the presentation of the associated 90% CI for the mean treatment differences of the relative recoveries.

The limit of 10.0% chosen in the formulation of the hypothesis was considered by the sponsor to reflect a clinically relevant difference in the treatment efficacy.

### *Safety Analysis*

The analysis of all safety parameters was based on the safety population.

Overall AEs were described in terms of rate of occurrence. All reported AEs were displayed with the original terms used by the investigator, preferred terms and system organ class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA; Version 13.0).

For the assessment of overall product tolerability, a 2-point rating scale of either 'well tolerated' or 'not well tolerated' was used. This was a subjective judgment by the investigator and the subject, based on the severity of any side effect of the treatment.

### *Determination of Sample Size*

To assess the efficacy of the two treatments in restoring coagulation factor levels and hemostatic parameters, an individual relative recovery was computed. For each efficacy parameter, treatment and subject, this recovery was defined as the maximum (minimum for aPTT) of the relative difference within 2 hours after infusion to the 5-minute post-PPH value.

The confirmatory statistical analysis attempted to demonstrate that the mean treatment differences of recovery for all of the parameters mentioned was contained inside the interval [-10.0%; 10.0%] which the sponsor considered to be a clinically irrelevant difference.

This was done by performing the two one-sided t-tests approach on the paired treatment differences. For these tests, a type I error of 0.05 was chosen to test the pair of hypotheses.

To estimate the sample size needed for this hypothesis testing, problem blinded results from an ongoing cross-over plasma study conducted by the sponsor were used to obtain estimates of the expected effect size and dispersion.

In the above mentioned study the average period differences for the relative recovery of all efficacy parameters were smaller than 5.5 and showed a maximum standard deviation of about 14.5.

Considering the estimates of mean recovery difference and standard deviation separately for each factor level and hemostatic parameter it was found that a sample size of 60 subjects was sufficient to reject the null hypothesis given the significance level of 0.05 and power of 0.8.

#### 6.6.9 Study Population and Disposition

##### 6.6.9.1 Populations Enrolled/Analyzed

Safety population:

The safety population consisted of all subjects who received at least one of the study treatments in any study period.

Three analysis populations were defined for the efficacy analysis:

- **Intent-to-Treat population:** The intent-to-treat (ITT) population consisted of all subjects in the safety population (all subjects receiving at least one of the study treatments in any study period) with any measurements on the primary endpoint variables (coagulation/haemostatic parameters) in either treatment period. Comparison of the two tested plasma products was performed only on subjects with relevant data available in both treatment periods.
- **Per Protocol population:** The Per Protocol (PP) population consisted of all subjects in the ITT analysis population who completed the study without significantly violating the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the efficacy assessments. Subjects with evaluable efficacy measurements in only one of the study periods were not considered to have completed the study as per protocol. Only subjects who received the full planned dose of tested plasma products in both treatment periods were included in the PP population.
- **Extended Per Protocol population:** The Extended Per Protocol (EPP) population was defined during the data review meeting and consisted of all subjects included in the PP population plus those subjects, who received  $\geq 75\%$  of the planned dose of tested plasma products in both treatment periods, and for whom this dose reduction was the only reason for exclusion from PP population. The results of efficacy analyses in the EPP population were to be used to support results of analyses in PP population in case of lack of power of statistical tests due to the limited number of subjects in the PP population.

##### 6.6.9.1.1 Demographics

**Table 28: Subject Demographics**

	All treated subjects N=60
<b>Sex</b>	
Male	35 (58%)
Female	25 (42%)
<b>Age (years)</b>	
Mean $\pm$ s.d.	32.6 $\pm$ 9.11
Min, Max	20, 53
<b>Height (cm)</b>	
Mean $\pm$ s.d.	176.6 $\pm$ 10.46
Min, Max	157.0, 197.0
<b>Weight (kg)</b>	
Mean $\pm$ s.d.	76.7 $\pm$ 14.33
Min, Max	50.0, 108.0

*Adapted from: LAS-203 Clinical Study Report; January 2011, Section 14.1, page 7 of 206*

#### 6.6.9.1.2 Medical/Behavioral Characterization of the Enrolled Population

The study enrolled healthy volunteers.

#### 6.6.9.1.3 Subject Disposition

A total of 68 subjects were screened for possible participation in the study. From these, 5 subjects were not randomized to treatment: 1 subject was a screening failure because she had an IgA deficiency and 4 subjects withdrew consent before randomization.

From the resulting 63 randomized subjects, 3 subjects did not receive IMP for the following reasons:

- Withdrawal by the investigator because the subject donated blood, the day before the visit
- PPh not possible due to venous problems
- Withdrawal due to a non-treatment emergent AE that occurred during the PPh (hypotension during PPh)

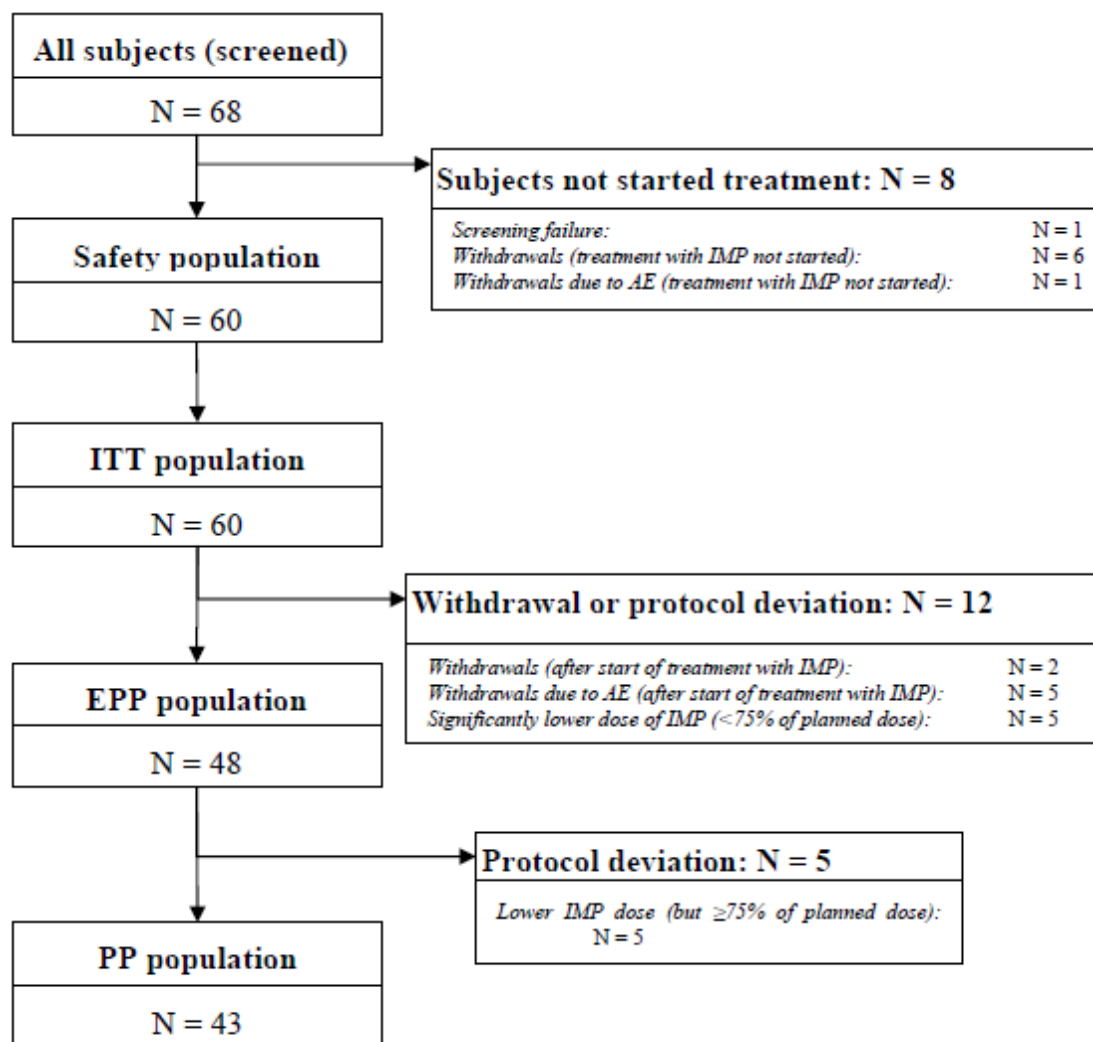
The resulting 60 subjects received at least one treatment with IMP and represented the Safety as well as the ITT population.

A total of 7/60 subjects in the Safety/ITT population did not complete the study as planned, either due to a treatment-emergent AE (N=5; [anaphylactic shock, circulatory collapse, dyspnea, laryngeal edema and tachycardia]), at the subject's request (N=1), or for other reasons (N=1).

From the 53 subjects who completed the study as planned, 5 subjects were not included in the EPP population (N=48) because they received a significantly lower IMP dose (i.e., <75% of the planned dose) in at least one treatment period.

Furthermore, 5 of 48 subjects from the EPP population were not included in the PP population (N=43) because they did not receive the complete dose of IMP (i.e., at least 75% of the planned dose in both treatment periods).

**Figure 4: Disposition of Study Subjects**



Source: Report Clinical Study LAS-203; December 2011, Page 34

## 6.6.10 Efficacy Analyses

### 6.6.10.1 Analyses of Primary Endpoint(s)

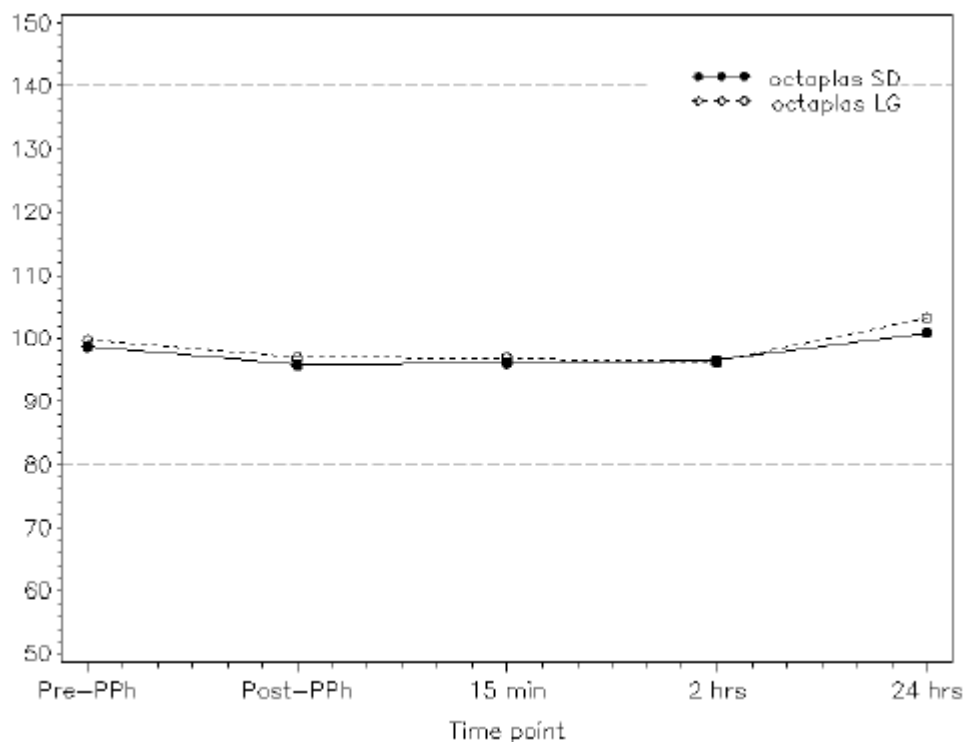
As less than 60 subjects were finally included in the efficacy analysis, the post-hoc power analysis was performed with n=43 subjects. In all cases the power calculated was >90% (0.908) for all parameters of the primary endpoint.

For Octaplas<sup>®</sup> group, the coagulation and hemostatic parameter were evaluated at 15 minutes post-transfusion only for 42 subjects (PP population), because no values are available for one of the subjects at this time point.

Dashed lines in the figures below, showing time courses of efficacy parameters, depict reference ranges for the selected parameter.

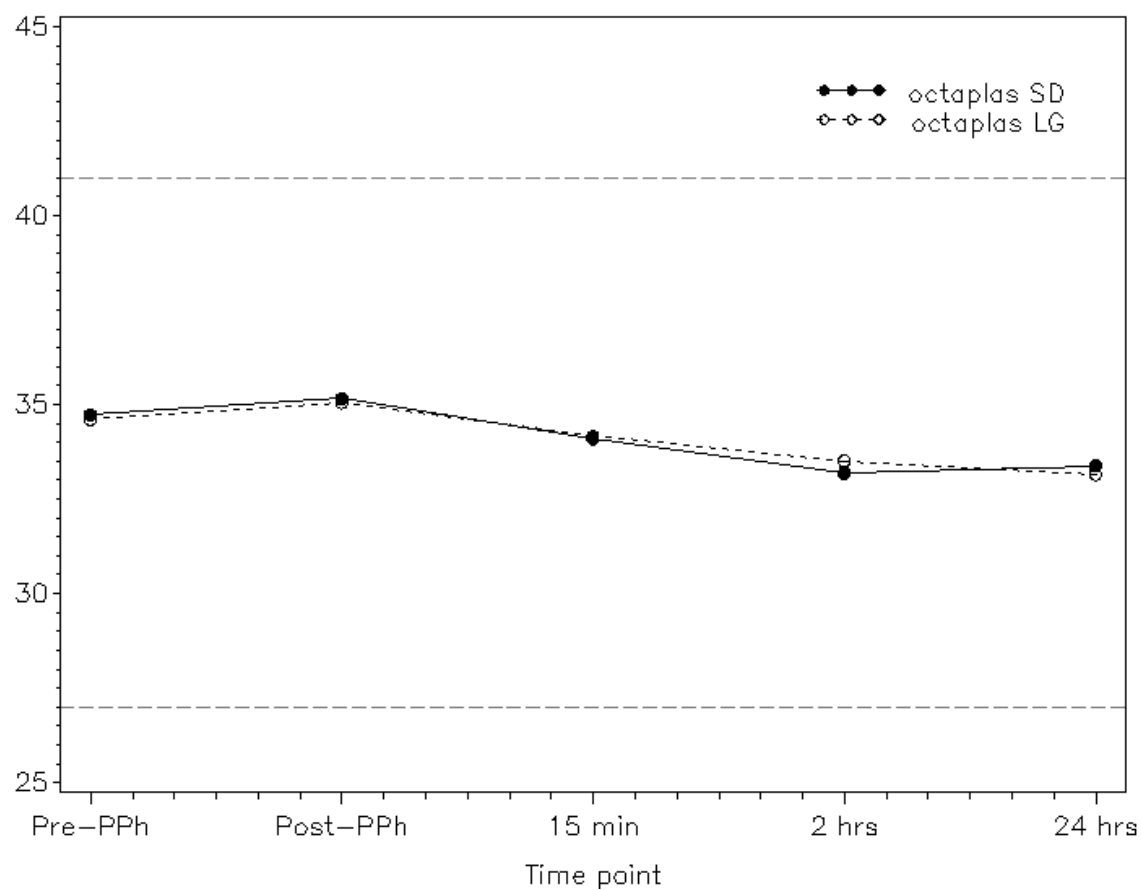
#### *Hemostatic Factors*

**Figure 5: Mean PT Values (%) - PP population**



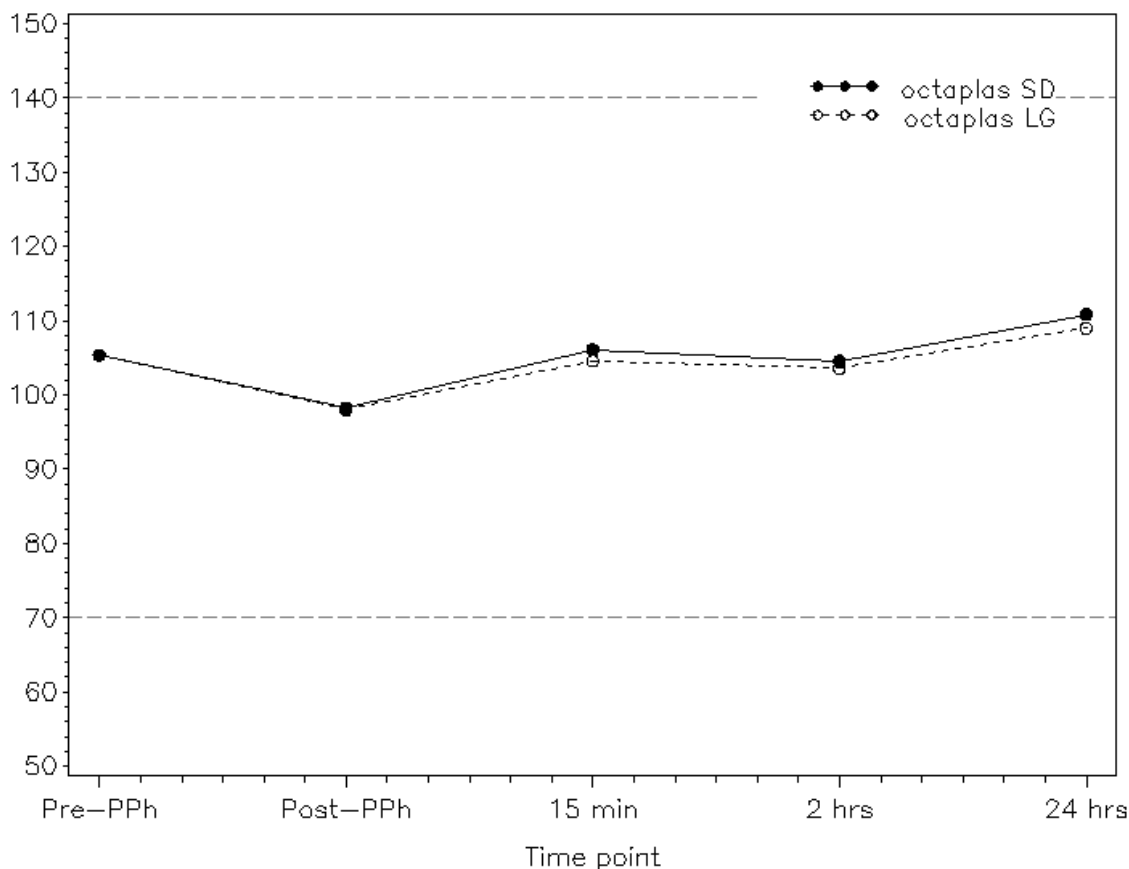
Source: Report Clinical Study LAS-203; December 2011, Page 41

**Figure 6: Time Courses of aPTT**



Source: Report Clinical Study LAS-203; December 2011, Page 43

**Figure 7: Time Courses of Protein C**



Source: Report Clinical Study LAS-203; December 2011, Page 44

### Hemostatic Parameters – Recovery Results

**Table 29: Hemostatic Parameters – Evaluation of Recovery Paired Differences Between Treatments – PP (N=43)**

Parameter	Mean	Std Dev	Std Error	Min	Median	Max	Lower 90% CL	Upper 90% CL
PT (%)	1.49	7.12	1.09	-11.4	0.1	23.0	-0.34	3.31
aPTT (%)	-1.13	5.00	0.76	-14.0	-0.6	9.3	-2.42	0.15
Protein C (%)	0.26	8.18	1.25	-34.3	0.7	16.3	-1.84	2.35

Source: Report Clinical Study LAS-203; December 2011, Page 46

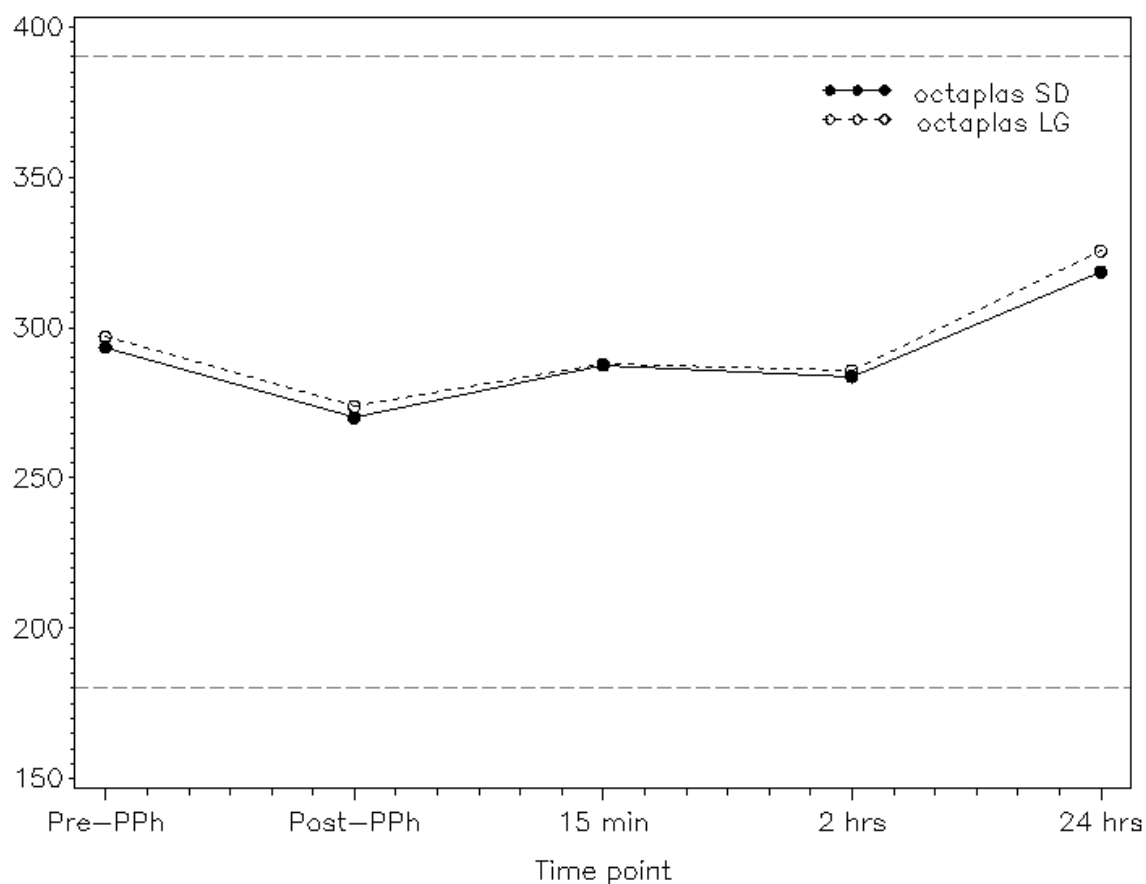
All 90% CIs were within the tested interval  $[-10\%; 10\%]$  and the null hypothesis ( $H_0$ :  $(\text{mean}(|\text{REC}(\text{OctaplasLG}) - \text{REC}(\text{Octaplas}^{\text{®}})|) > 10.0\%)$ ) can be rejected for each of the



hemostatic parameters. Also, paired t-test calculations were performed and returned p-values <0.0001.

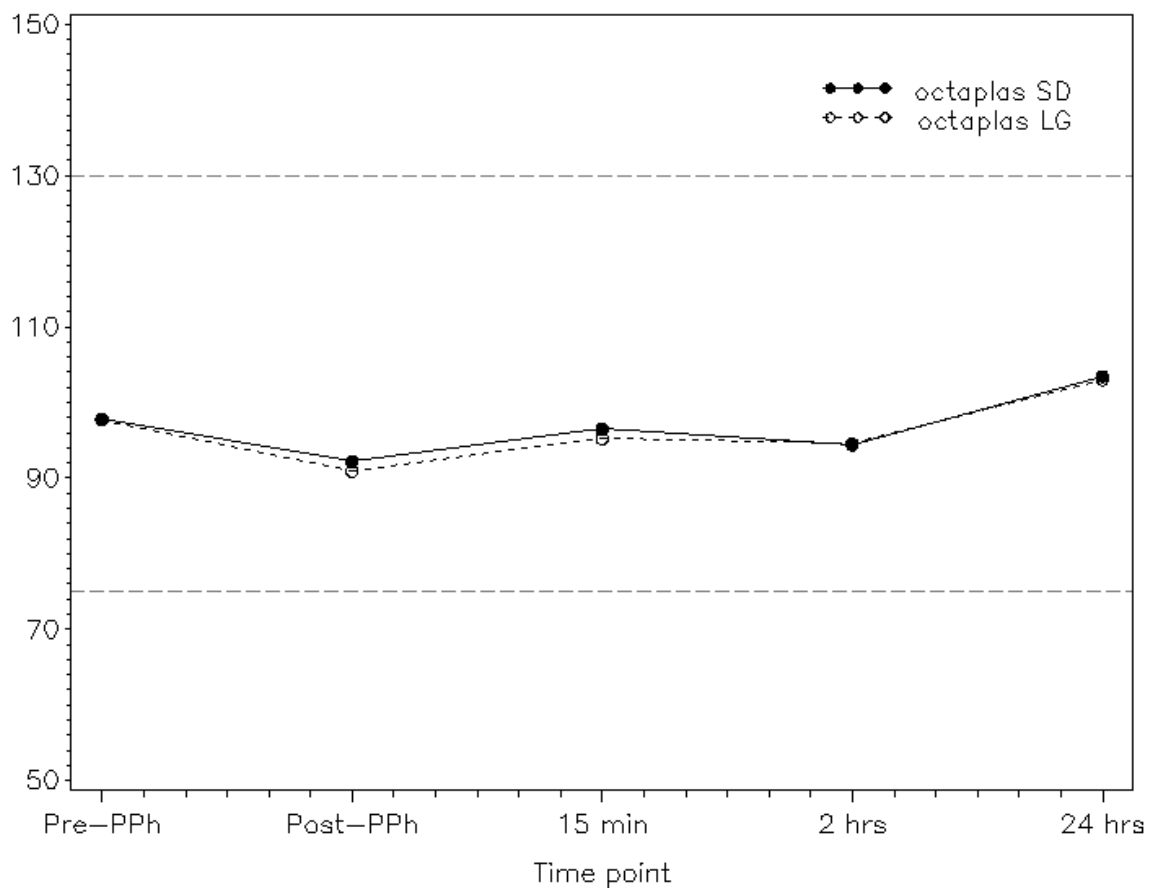
### *Coagulation Factors*

**Figure 8: Time Courses of Factor I Levels – PP Population**



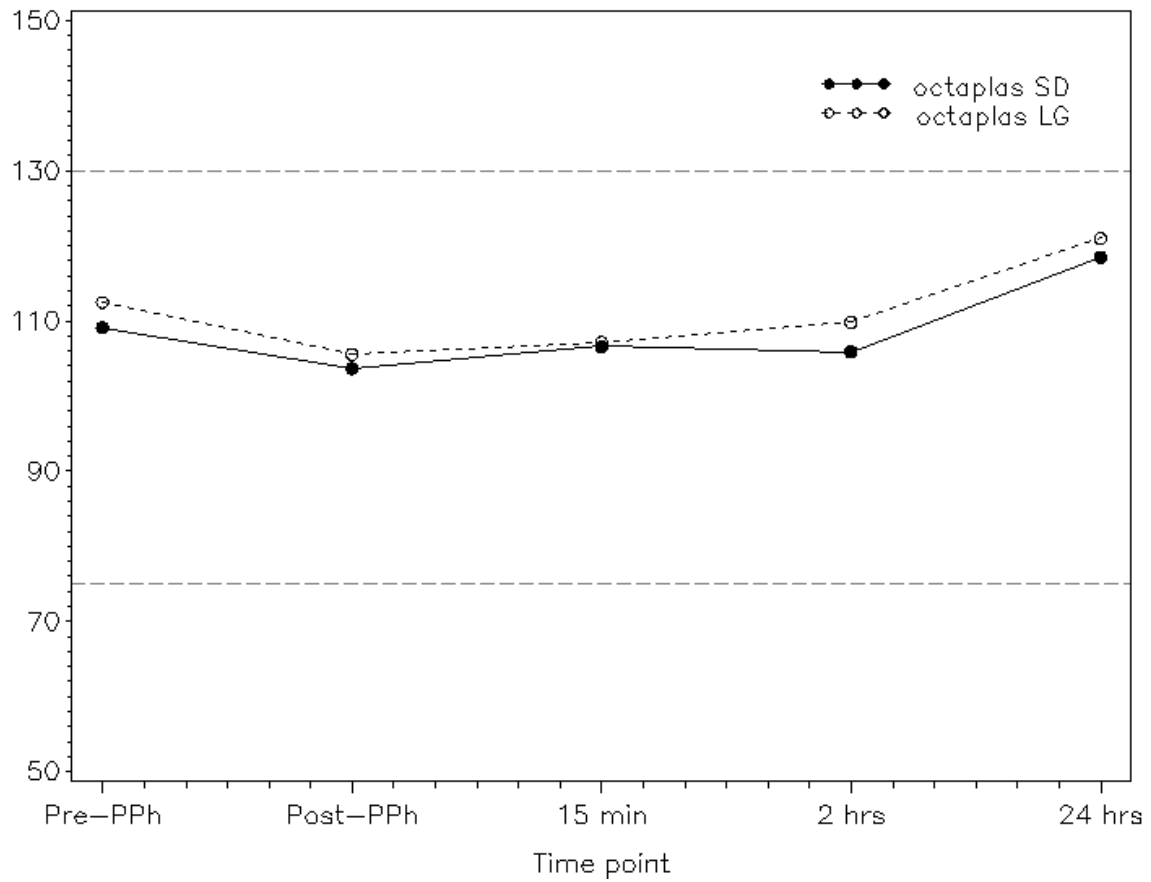
*Source: Report Clinical Study LAS-203; December 2011, Page 48*

**Figure 9: Time Courses of Factor II Levels – PP Population**



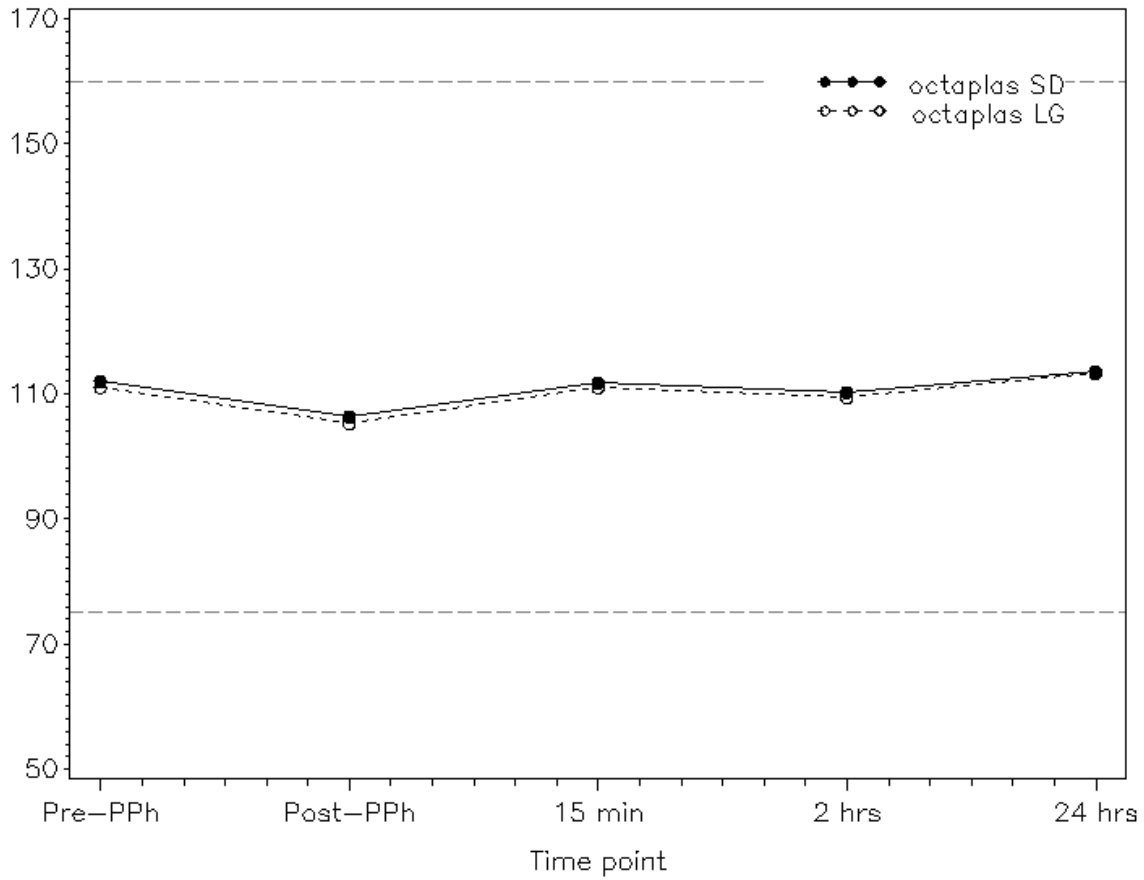
*Source: Report Clinical Study LAS-203; December 2011, Page 49*

**Figure 10: Time Courses of Factor V Levels – PP Population**



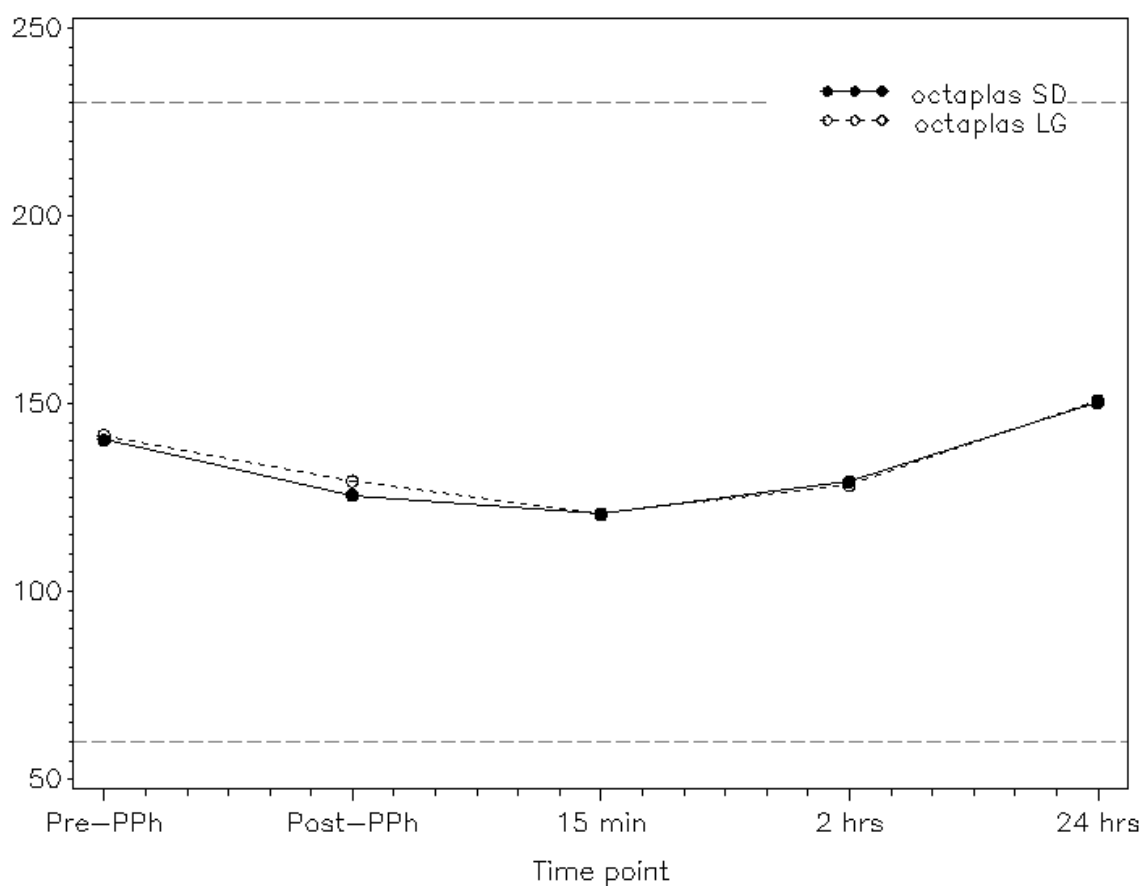
*Source: Report Clinical Study LAS-203; December 2011, Page 50*

**Figure 11: Time Courses of Factor VII Levels – PP Population**



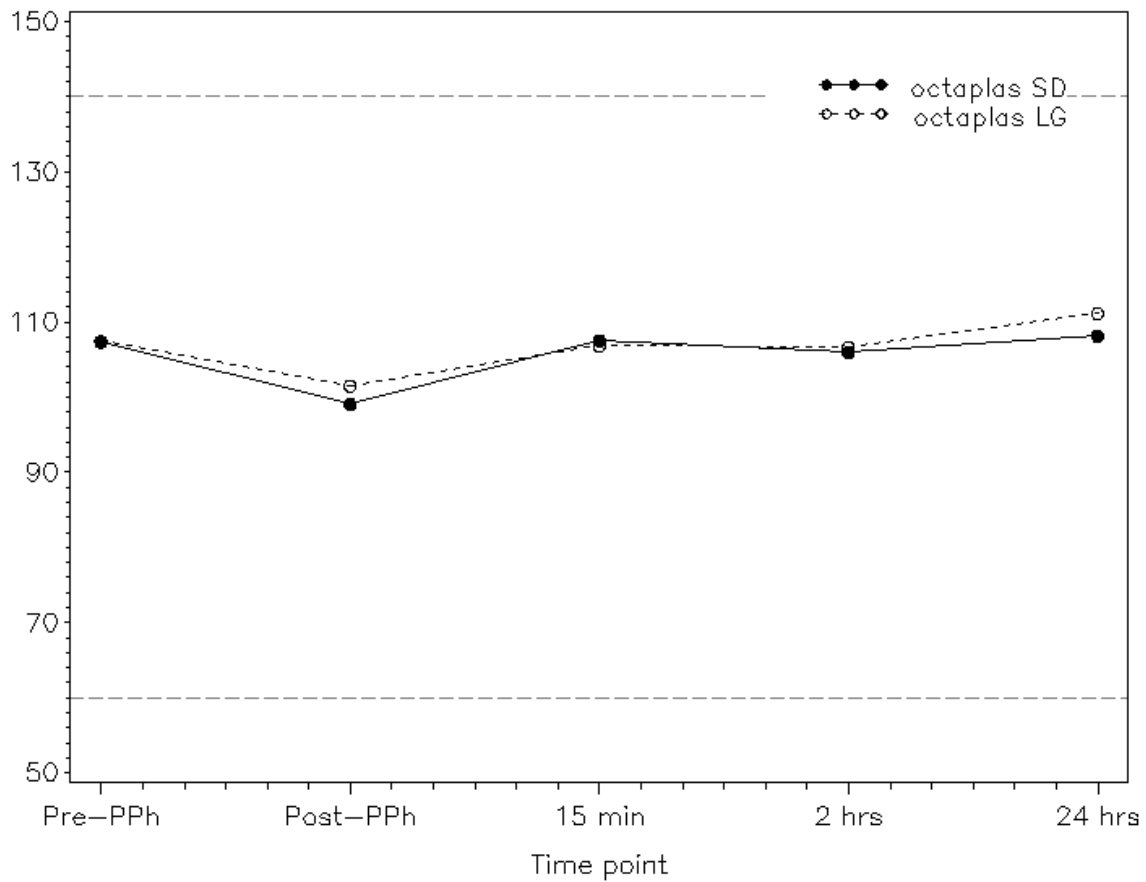
*Source: Report Clinical Study LAS-203; December 2011, Page 52*

**Figure 12: Time Courses of Factor VIII Levels – PP Population**



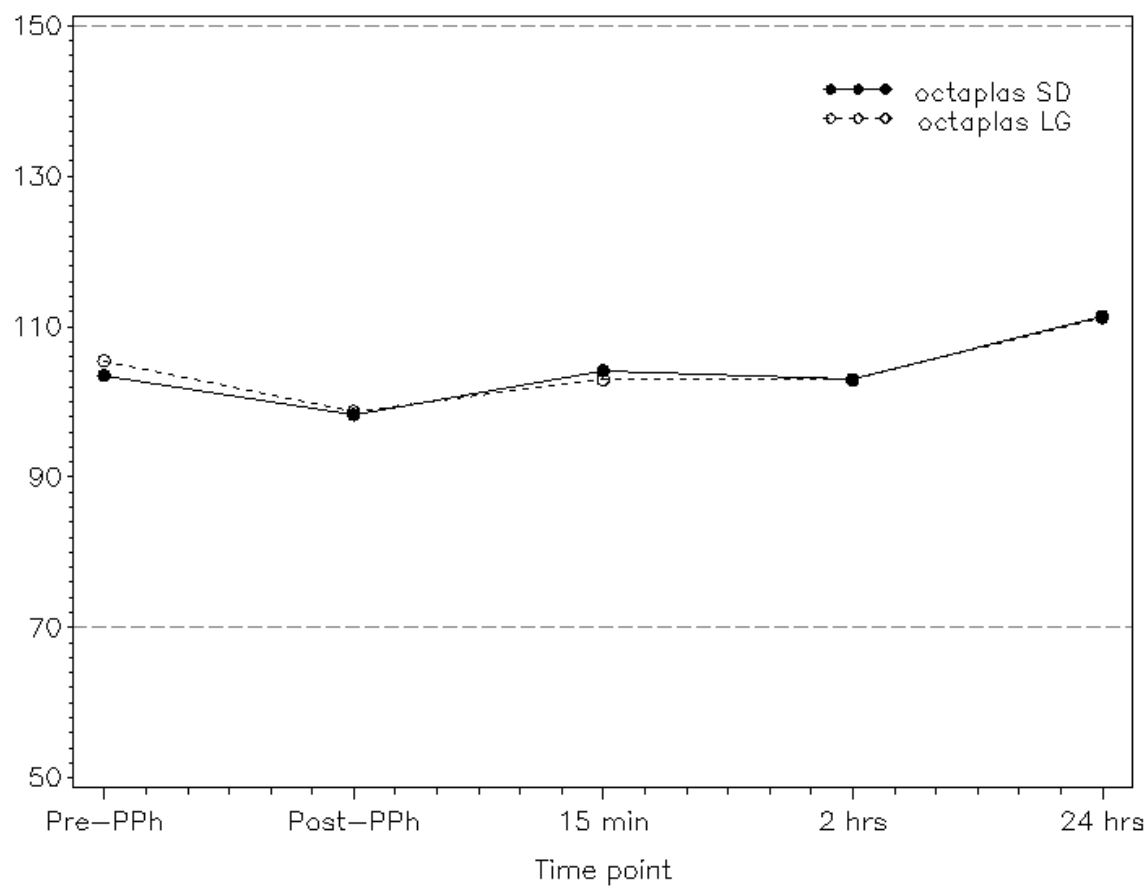
*Source: Report Clinical Study LAS-203; December 2011, Page 53*

**Figure 13: Time Courses of Factor IX Levels – PP Population**



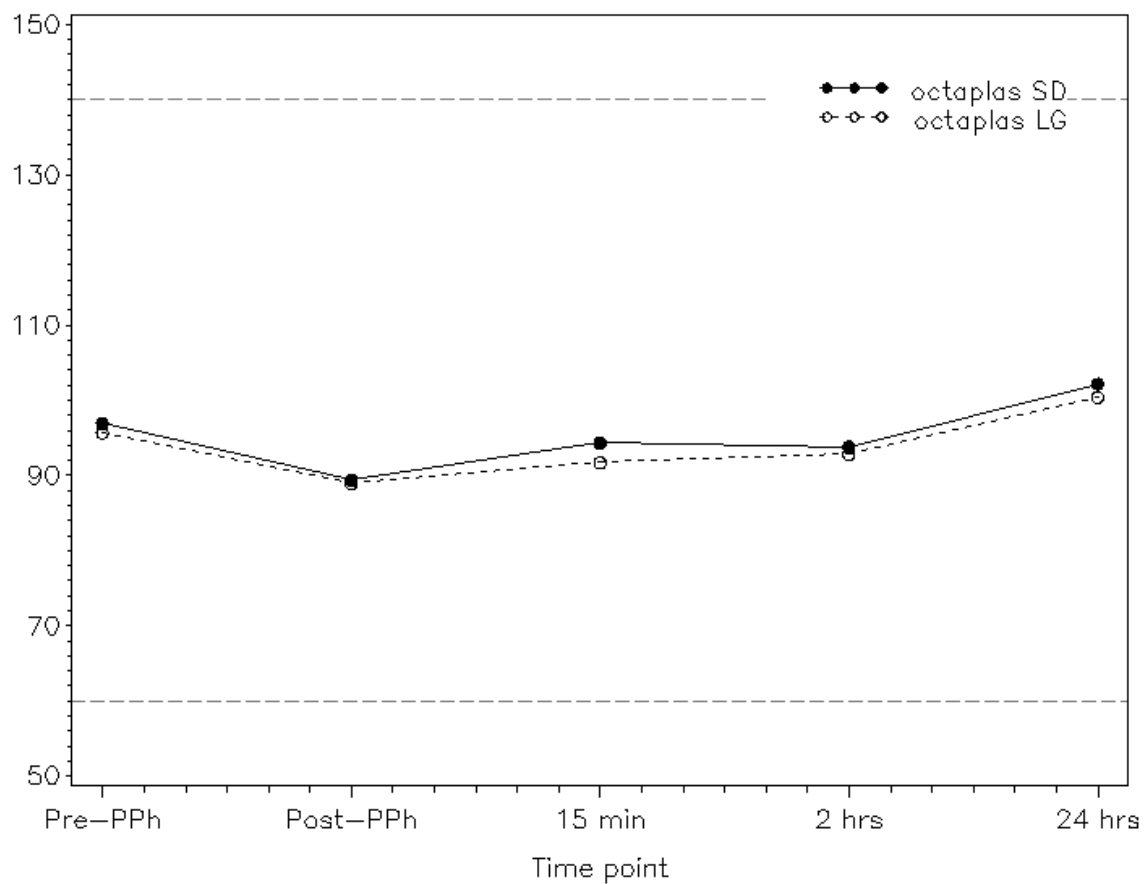
*Source: Report Clinical Study LAS-203; December 2011, Page 54*

**Figure 14: Time Courses of Factor X Levels – PP Population**



*Source: Report Clinical Study LAS-203; December 2011, Page 55*

**Figure 15: Time Course of Factor XI Levels – PP Population**



*Source: Report Clinical Study LAS-203; December 2011, Page 56*



*Coagulation Factors – Recovery Results*

**Table 30: Coagulation Factors – Evaluation of Recovery Paired Differences  
Between Treatments – PP Population (N=43)**

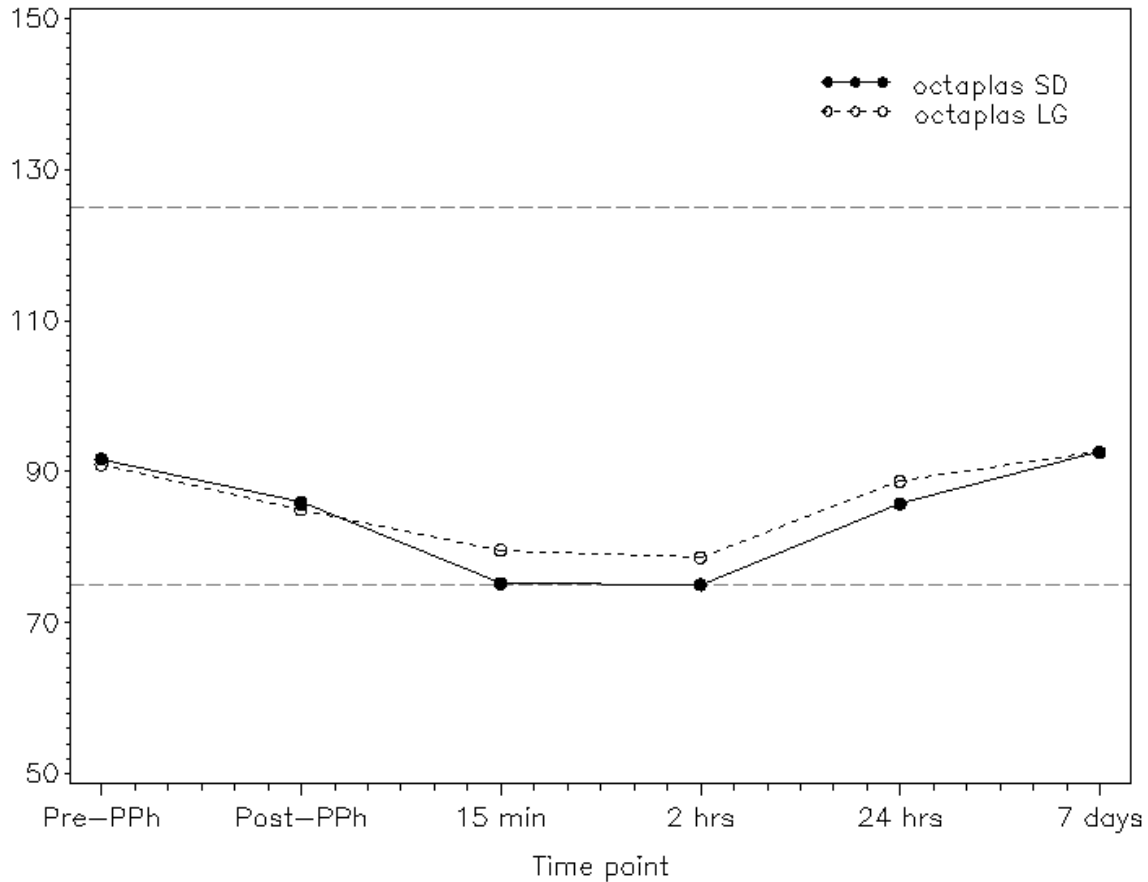
Parameter	Mean	Std Dev	Std Error	Min	Median	Max	Lower 90% CL	Upper 90% CL
FI [%]	1.01	9.01	1.37	-17.9	-0.6	27.0	-1.30	3.32
FII [%]	-0.41	6.76	1.03	-14.8	-1.3	16.8	-2.14	1.33
FV [%]	0.61	10.53	1.61	-23.9	2.4	19.3	-2.09	3.31
FVII [%]	0.80	11.98	1.83	-25.1	0.8	37.7	-2.27	3.87
FVIII [%]	3.71	11.36	1.73	-38.3	2.4	28.4	0.79	6.62
FIX [%]	2.22	10.03	1.53	-24.6	1.8	18.0	-0.36	4.79
FX [%]	2.07	10.72	1.64	-19.7	1.2	48.3	-0.68	4.82
FXI [%]	1.70	8.50	1.30	-17.1	3.1	21.8	-0.48	3.88

*Source: Report Clinical Study LAS-203; December 2011, Page 59*

All 90% CIs were within the tested interval  $[-10\%; 10\%]$  and the null hypothesis ( $H_0$ :  $(\text{mean}(|\text{REC}(\text{OctaplasLG}) - \text{REC}(\text{Octaplas}^{\text{®}})|) > 10.0\%)$ ) can be rejected for each of the coagulation factors. Also, paired t-test calculations were performed and returned p-values  $\leq 0.0005$ .

#### 6.6.10.2 Analyses of Secondary Endpoints

**Figure 16: Time Courses of Plasmin Inhibitor Concentration**



*Source: Report Clinical Study LAS-203; December 2011, Page 62*

For the PP population, differences between treatments at 15 minutes (mean = -5.51) and 2 hours post-transfusion (mean = -4.50) were statistically different with p-values of 0.0012 and 0.0190 respectively.

#### 6.6.10.3 Subpopulation Analyses

There were no subpopulation analyses.

#### 6.6.11 Safety Analyses

Of the 60 subjects who received IMP at least once, 43 subjects received 1200 mL OctaplasLG and 1200 mL Octaplas® as planned. The table below shows the total volume administered and the mean dose per kilogram given for each IMP.

**Table 31: Subject Exposure to Study Drug**

	IMP	Total Dose (mL)	Dose (mL/kg/body weight)
Mean dose given (all subjects were included in calculation)	OctaplasLG	1149.5	15.26
	Octaplas®	1098.1	14.92

*Source: Report Clinical Study LAS-203; December 2011, Page 66*

#### 6.6.11.1 Methods

Adverse events were actively collected from all enrolled subjects.

#### 6.6.11.2 Overview of Adverse Events

In total, 158 treatment-emergent AEs were observed in 52/60 subjects (86.7%) in the Safety/ITT population. Seventy-seven occurred during the OctaplasLG study period and 81 occurred during the Octaplas® study period.

The frequency of AEs by System Organ Class (SOC) was similar between treatment groups. Nervous system disorders were the most frequent AE (i.e., paraesthesia and headache), occurring in 34% and 31% in OctaplasLG and Octaplas® treatment periods respectively. Paraesthesia occurred in 18% of subjects in the OctaplasLG treatment period and in 10% of subjects in the Octaplas® treatment period. Headache occurred in 16% of subjects in OctaplasLG treatment period and in 14% of subjects in the Octaplas® treatment period. Urticaria occurred in 14% of subjects in OctaplasLG treatment period and in 11% of subjects in Octaplas® treatment period.

Eight non-treatment-emergent AEs were reported from 7 subjects, including 1 subject who was randomized but was withdrawn due to the AE before he received IMP. There was 1 serious AE (anaphylactic shock) while receiving OctaplasLG.

The most frequently reported and treatment-related AEs were urticaria (25 AEs), dyspnea (5 AEs), chest discomfort (4 AEs) and paraesthesia (including oral paraesthesia) (4 AE).

The transfusion of plasma was terminated due to an AE, before the full volume was administered, in 10 subjects who received OctaplasLG and in 5 subjects who received Octaplas®. In 1 subject, both treatment periods were affected.

#### 6.6.11.3 Deaths

There were no deaths in the study.

#### 6.6.11.4 Nonfatal Serious Adverse Events

There was 1 serious AE (anaphylactic shock) while receiving OctaplasLG.

A 25-year-old healthy male volunteer (blood group O) received OctaplasLG (20 mL/minute). Five minutes into the IV infusion (100 mL administered), the volunteer experienced an anaphylactic reaction (bronchospasm with decreased breath sounds, flush, hypotension, and tachycardia) of severe intensity. He received IV therapy including diphenhydramine, prednisone, theophylline, suprarenin (epinephrine, 1:100 1 mL, IV), Voluven (hydroxyethyl starch 130/0.4; sodium chloride) and Berodual (ipratropium and fenoterol) and recovered the same day.

The investigator assessed the life-threatening event as probably related to OctaplasLG. Octapharma assessed the case as serious, listed and probably related to the IMP administration.

### **6.7 Trial #7: UNI-110 (OctaplasLG and UniplasLG in healthy volunteers, N=30)**

A comparison of safety, tolerability and efficacy of universal plasma (UniplasLG) vs. standard S/D plasma (OctaplasLG) in healthy volunteers. A randomized, double-blind, cross-over trial

#### 6.7.1 Objectives (Primary, Secondary, etc)

The objective of the study was to assess the safety, tolerability and efficacy of UniplasLG in comparison to a blood group specific, routinely used S/D plasma (OctaplasLG).

##### *Primary Objective*

The primary objective was to compare the safety and tolerability of UniplasLG, assessed by clinical and laboratory parameters, with a standard S/D plasma (OctaplasLG).

##### *Secondary Objectives*

The secondary objective was to compare the efficacy of UniplasLG, measured by coagulation factors, with a standard S/D plasma (OctaplasLG).

#### 6.7.2 Design Overview

The study was performed as a double-blind, block-randomized, cross-over trial, consisting of 2 groups of 15 healthy volunteers each. The study was designed to compare the equivalence of UniplasLG to OctaplasLG focusing primarily on the occurrence of hemolytic transfusion reaction (HTR). After an initial examination, volunteers were randomly assigned to 1 of 2 treatment sequences. Subjects in treatment sequence A

received UniplasLG first and OctaplasLG second, while subjects in treatment sequence B received OctaplasLG at first and UniplasLG second.

Subjects with blood group O would be less likely to develop signs of incompatibility after UniplasLG administration since they carry both anti-A and anti-B antibodies and have no A or B antigens on the red blood cells (RBCs). Therefore, blood group O subjects were excluded from participation in UNI-110.

### 6.7.3 Population

#### *Inclusion Criteria*

Healthy volunteers, at least 18 years of age and of blood group A, B or AB, and who fulfilled the following inclusion/exclusion criteria, were eligible to participate in the study:

1. Subjects capable of understanding and complying with all aspects of the protocol
2. Signed informed consent
3. Fulfils criteria of plasma donors according to the standard questionnaire for blood components donors of the Dept. of Blood Group Serology and Transfusion Medicine
4. Women had to have a negative pregnancy test (human chorionic gonadotropin [HCG]-based assay)
5. Women had to use sufficient methods of contraception (e.g., intrauterine device, oral contraception)
6. Normal findings in medical history and physical examination unless the investigator considered an abnormality to be clinically irrelevant
7. Standard health insurance

#### *Exclusion Criteria*

1. Pregnancy or lactation
2. Refusal to accept blood products
3. Tattoos within the last 3 months
4. Treatment with FFP or blood products in the previous 6 months
5. Subjects with a history of severe hypersensitivity reaction in general and hypersensitivity to blood products or plasma protein in particular
6. History of angioedema
7. History of coagulation or bleeding disorder and any known abnormality affecting coagulation, fibrinolysis or platelet function
8. Any other clinically relevant history of disease
9. Any clinically significant abnormal laboratory values incl. immunoglobulin A (IgA) deficiency
10. Seropositivity for hepatitis B surface antigen (HBsAg), HCV, HIV-1/2 antibodies
11. Symptoms of a clinically relevant illness within 3 weeks before the first trial day
12. Subjects with a history of, or suspected, drug or alcohol abuse

13. Subjects currently participating in another clinical study or who had participated during the past month

#### 6.7.4 Study Treatments or Agents Mandated by the Protocol

Each subject in this cross-over study underwent two PPh sessions (at least 4 weeks apart) immediately followed by infusions with either UniplasLG or OctaplasLG and was randomly assigned to 1 out of 2 treatment sequences (A or B). Subjects in treatment Sequence A received UniplasLG after the first PPh then OctaplasLG after the second, while subjects in treatment Sequence B received OctaplasLG after the first PPh then UniplasLG after the second.

During each PPh approximately 600 mL plasma was removed. A total amount of 1200 mL of UniplasLG or OctaplasLG was administered after the end of PPh in units of 200 mL bags. The transfusion rate did exceed 0.020 – 0.025 millimole citrate/kg body weight/minute, which is equal to  $\leq 1$  mL/kg body weight/minute.

#### 6.7.5 Sites and Centers

Dept. of Clinical Pharmacology, Medical University of Vienna Austria

#### 6.7.6 Surveillance/Monitoring

**Table 32: Overall Study Events**

	Visit 1 Screening	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Time Points		≤ 4 weeks after Visit 1	24 h post- PPh No. 1 (± 2 h)	7 days post-PPh No. 1	≥ 4 weeks after Visit 2	24 h post- PPh No. 2 (± 2 h)	7 days post-PPh No. 2	12 weeks After Visit 5 (± 7 days)
In/Exclusion criteria	X	X						
Physical exam	X							X
Questionnaire for blood components donors	X							
Medical history	X							
Demographic data	X							
Vital Signs	X	X	X	X	X	X	X	X
ECG/Oxygen saturation monitoring		X			X			
Blood sampling	X	X	X	X	X	X	X	X
Urinalysis	X							X
Pregnancy test	X	X			X			X
Drug screening	X							
Randomization		X						
Study drug administration		X			X			
12-lead ECG	X							X
AE monitoring		X	X	X	X	X	X	X

Source: Report Clinical Study UNI-110; February 2011, Page 21 of 86

**Table 33: Laboratory Parameters and Time-Points**

	Visit 1	Visit 2 and Visit 5				Visits 3 & 6	Visits 4 & 7	Visit 8
Time Points		≤ 30min before PPh	< 5min post-PPh	15min (± 2min) post-transfusion	2h (± 5min) post-transfusion	24h (±2h) post-PPh	7days post-PPh	12weeks (± 7days) after Visit 5
Hb, Hct	X	X	X	X	X	X	X	X
RBC, WBC, platelets	X	X						X
Free Hb, haptoglobin, indirect bilirubin	X	X	X	X	X	X	X	X
DAT	X	X	X		X	X	X	X
Complement (CH50, C3c, C4)		X	X	X	X	X	X	
Calcium	X	X	X	X	X			X
Sodium, potassium	X	X						X
Creatinine	X	X						X
ALAT, GGT	X	X						X
Total protein	X	X						X
aPTT, PT, Fbg	X	X	X	X	X	X		X
FII, FV, FVII, FVIII, FIX, FX, protein S, plasmin inhibitor		X	X	X	X	X		
IgA	X							
Viral markers	X							X
Determination of blood group	X							

Source: Report Clinical Study UNI-110; February 2011, Page 28 of 86

#### 6.7.7 Endpoints and Criteria for Study Success

Efficacy was assessed by evaluation of the following coagulation parameters:

- aPTT, PT
- Fbg, FII, FV, FVII, FVIII, FIX, FX , FXI
- Protein S
- plasmin inhibitor



The primary safety variable of the study was the change in hemoglobin (Hb) plasma concentration between the sample taken prior to PPh and 15 minutes after the end of plasma transfusion.

Also recorded as a safety parameter, was the change in Hb plasma concentration between the time immediately after PPh (before the start of transfusion) and after the end of transfusion, which may be less affected by the hemoconcentration effect of PPh.

#### 6.7.8 Statistical Considerations & Statistical Analysis Plan

All measurements were analyzed descriptively by presenting relative frequency for qualitative data and characteristics of the sampling distributions for metrically scaled data (arithmetic means, standard deviation, median, minimum and maximum). Individual treatment differences were calculated for metrically scaled parameters and mean treatment differences were estimated along with 95% confidence intervals.

For all statistical tests the significance level  $\alpha$  was fixed at 0.05.

All collected efficacy and safety assessments were presented by means of descriptive statistics in statistical summary tables and individual subjects' listings. Continuous data (measurements on a continuous scale, including quasi-continuous variables) were summarized using arithmetic mean, standard deviation, median, lower and upper quartile, minimum, maximum, geometric mean and geometric standard deviation (for data that were considered to be log-normally distributed). Categorical data (ordinal and non-ordinal) were described using absolute and relative frequencies.

The analysis plans were as follows:

##### *Primary Safety Analysis*

The equivalence of Hb change between treatment groups was analyzed using a standard analysis of variance (ANOVA) model with treatment, period, sequence effects and subject effect nested within sequence. Using the square root of residual mean squares as an estimate of the variance, a two-sided 90% confidence interval for the treatment difference of the Hb change was computed and compared with the predefined equivalence range of [-0.5 g/dL ; +0.5 g/dL].

The following null hypothesis was tested:

H<sub>0</sub>: The Hb change after UniplasLG treatment was not within the equivalence range [-0.5 g/dL ; +0.5 g/dL] of OctaplasLG treatment.

vs.

H<sub>1</sub>: The Hb change after UniplasLG treatment was within the equivalence range [-0.5 g/dL ; +0.5 g/dL] of OctaplasLG treatment.

The hypothesis was tested by the 2 one-sided approach. The level of significance was set at  $\alpha = 0.05$ .

#### *Secondary Safety Analysis Plan*

Secondary safety endpoints were analyzed descriptively between the 2 treatments with mean treatment differences estimated along with 95% CI for continuous parameters (median treatment differences with distribution-free 95% CI if normality assumptions were remarkably violated) and shift tables for categorical variables.

All AEs occurring after initiation of study treatments were displayed in summary tables, listings and figures. Incidences of AEs were given as numbers and percentages of subjects within each treatment group.

#### *Efficacy Analysis Plan*

Efficacy was assessed by coagulation parameters measured on the study day before any intervention, after the end of PPh and at different time-points following transfusion of study drug.

The changes from the pre-treatment value to maximum (or minimum where appropriate) were calculated for both treatment periods and the Wilcoxon Signed Rank Test was applied for differences  $D_t - D_c$ , where  $D_t$  was the difference in test period, and  $D_c$  was the difference in the control (comparator) period.

#### *Determination of Sample Size*

The study was conducted as a single-centre trial with a total of 30 subjects, i.e. 15 subjects per treatment sequence. The chosen sample size of 15 subjects per treatment arm was based on the following considerations:

- To detect HTR, the change in Hb plasma concentration between the sample taken prior to PPh and 15 min after the end of plasma transfusion (Hb change) was chosen as a primary safety endpoint among other markers of hemolysis. In order to conclude that the mean Hb change is equivalent between UniplasLG and OctaplasLG, a 90% confidence interval for the difference between the treatment means was derived.
- For such 2 one-sided tests procedure for additive equivalence of paired means with bounds -0.5 and 0.5 for the mean difference and a significance level of 0.05 assuming a mean difference of 0.2, a common standard deviation of 0.57 and correlation 0.5, a sample size of 24 subjects is sufficient to obtain a power of at least 0.8. Therefore, to account for a possible drop-out rate of up to 20% of the

subjects, it was planned to enroll 30 subjects (15 per treatment arm) into the study.

## 6.7.9 Study Population and Disposition

### 6.7.9.1 Populations Enrolled/Analyzed

Two analysis populations were defined:

#### *Safety population*

The safety population consisted of all subjects who received at least one of the 2 study treatments (UniplasLG or OctaplasLG) in any study period.

#### *Per-protocol population (PP)*

The PP population consisted of all subjects who completed the trial without significant violations considered to potentially affect the efficacy assessments. Subjects with evaluable safety and/or efficacy measurements in only one of the study periods were not considered to have completed the trial as per protocol.

#### 6.7.9.1.1 Demographics

**Table 34: Subject Demographics**

	Treatment Sequence		Total N=30
	Group A N=15	Group B N=15	
Male	8 (53%)	9 (60%)	17 (57%)
Female	7 (47%)	6 (40%)	13 (43%)
Age (years) Mean $\pm$ s.d. [min, max]	30.6 $\pm$ 5.97 [24, 41]	40.6 $\pm$ 9.73 [23, 55]	35.6 $\pm$ 9.42 [23, 55]
BMI (kg/m <sup>2</sup> ) Mean $\pm$ s.d. [min, max]	23.26 $\pm$ 4.01 [18, 31]	24.27 $\pm$ 4.01 [17, 31]	23.77 $\pm$ 3.98 [17, 31]

*Adapted from: Report Clinical Study UNI-110; February 2011, Page 39 of 86*

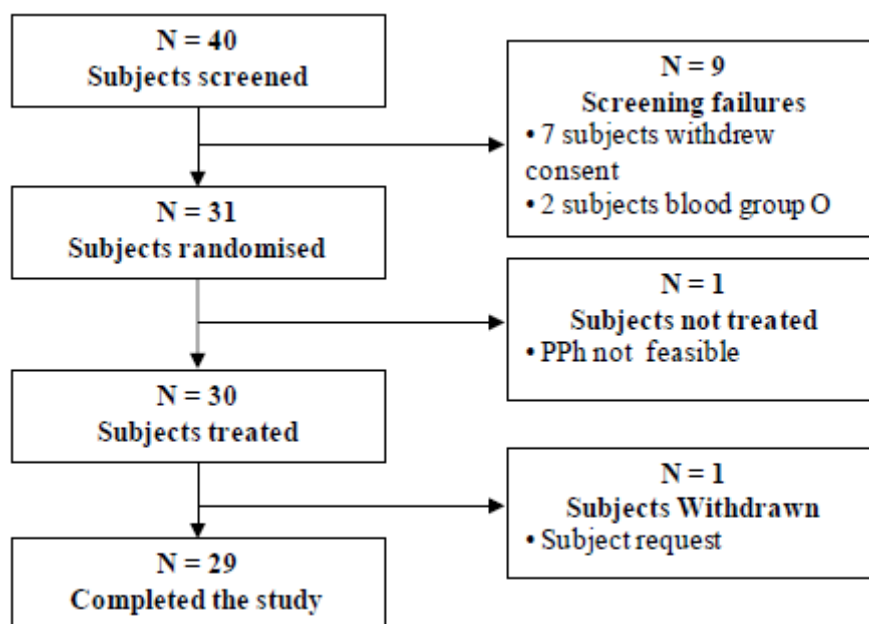
#### 6.7.9.1.2 Medical/Behavioral Characterization of the Enrolled Population

The study enrolled healthy volunteers.

#### 6.7.9.1.3 Subject Disposition

In total, 40 subjects were screened for the study. Of these, 9 subjects were not randomized (7 withdrew their consent, 2 had a blood Group O) and one was randomized but never received the treatment drug due to PPh not feasible (venous access problem). Hence, 30 subjects received at least one study treatment. Of these, one subject randomized to Group A (UniplasLG → OctaplasLG) withdrew from the study early, at her own request after study period 1, during which she experienced dyspnea. Subsequently, 29 subjects completed the study.

**Figure 17: Disposition of Subjects**



Source: Report Clinical Study UNI-110; February 2011, Page 36 of 86

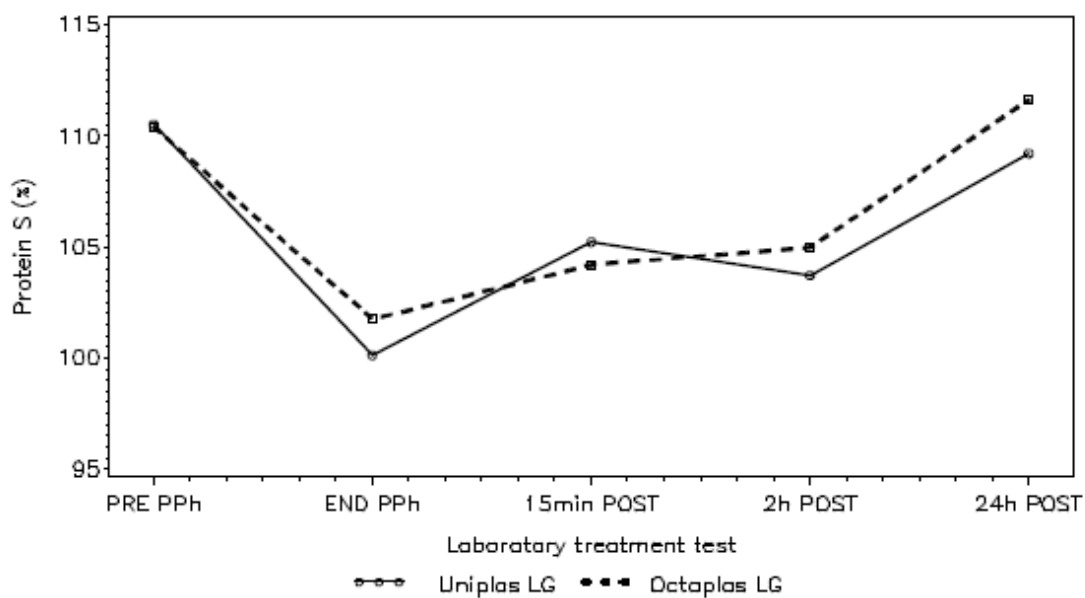
## 6.7.10 Efficacy Analyses

### 6.7.10.1 Analyses of Primary Endpoint(s)

Efficacy was assessed by evaluation of coagulation parameters. The following coagulation parameters were assessed: aPTT, PT, Fbg, Factor II, FV, FVII, FVIII, FIX, FX and FXI, PS and PI. These parameters were evaluated before PPh, immediately after PPh, 15 min and 2 h after plasma transfusion and 24 h post-transfusion. The two products were similar when mean values for the stated coagulation parameters were compared over time.

The following figures plot the mean values at each time-point for PS and PI, for both OctaplasLG and UniplasLG. The range for normal values is at the bottom of each figure. The mean values over time are similar for the two products and remained within the normal range.

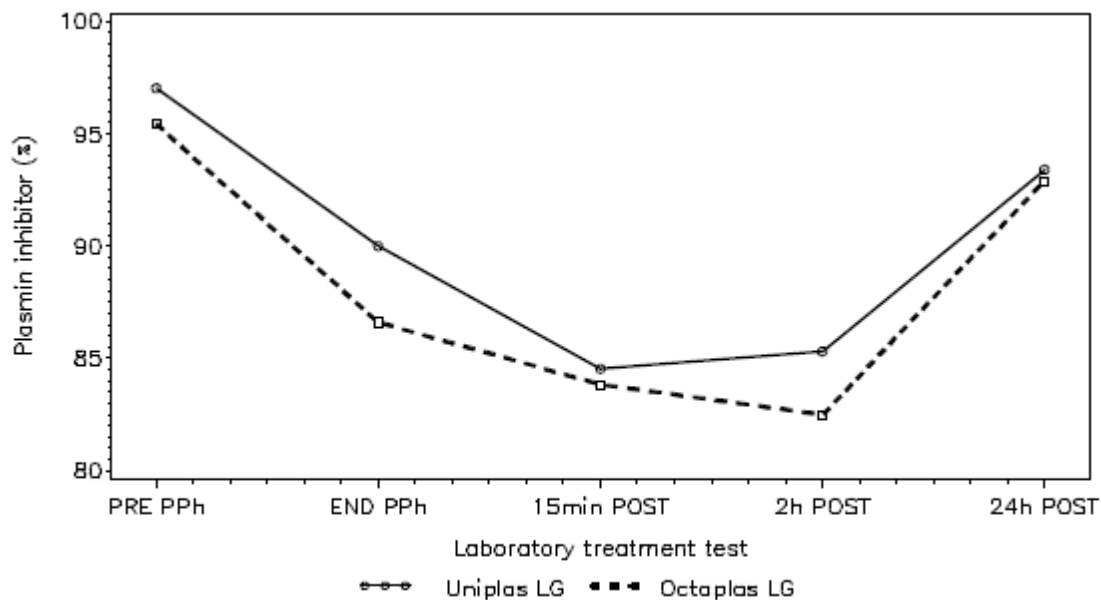
**Figure 18: Time Courses of Protein S– Safety Population**



Normal range: 60-140%

Source: Report Clinical Study UNI-110; February 2011, Page 81 of 86

**Figure 19: Time Courses of Plasmin Inhibitor – Safety Population**



Normal range: 75-125%

Source: Report Clinical Study UNI-110; February 2011, Page 82 of 86

#### 6.7.10.2 Analyses of Secondary Endpoints

The primary safety variable of the study was the change in Hb plasma concentration between the sample taken prior to PPh and 15 min after the end of plasma transfusion. The change in Hb plasma concentration between the time immediately after PPh (before start of transfusion) and after the end of transfusion was also recorded, theoretically avoiding the hemoconcentration effect of PPh. The two products were similar with regard to the change in Hb plasma concentration.

The secondary safety variables of the study included other markers of HTR. They comprised laboratory markers (i.e. DAT, complement activation, free Hb, haptoglobin, indirect bilirubin) and clinical symptoms of hemolysis.

Both in the PP and safety populations, mean haptoglobin levels were within normal range (30 to 200 mg/dL) for both treatments throughout the study period. They varied from a minimum of 91 mg/dL to a maximum of 118 mg/dL. None of the individual haptoglobin levels were found to be below or above the normal range, apart from one single measurement 7 days post-transfusion 2 (209 mg/dL).

Free Hb concentrations were noted to rise following PPh, then decrease and remain within normal range from 15 minutes post-transfusion through 7 days post-transfusion.

Indirect bilirubin values remained within the normal range, as did levels of indicators for complement activation. There were no positive DAT results reported at any time during the study period.

### 6.7.10.3 Subpopulation Analyses

There were no subpopulation analyses.

### 6.7.11 Safety Analyses

#### 6.7.11.1 Methods

Adverse events were actively collected from all enrolled subjects.

#### 6.7.11.2 Overview of Adverse Events

AEs were recorded throughout the study and analyzed in the safety population. No premedication was used prior to plasma infusion. In total, 92 AEs were observed in 27 subjects, of which 48 AEs occurred during the UniplasLG study period and 44 during the OctaplasLG study period. No SAEs were reported during the study.

The frequency of AEs by System Organ Class (SOC) was similar between treatment groups. Nervous system disorders were the most frequent AE (e.g., paraesthesia and headache), occurring in 67% and 50% in UniplasLG and OctaplasLG treatment periods respectively. Paraesthesia occurred in 16.7% of subjects in both treatment study periods and headache occurred in 16.5% of subjects in UniplasLG treatment period and in 20% of subjects in OctaplasLG treatment period. Urticaria occurred in 20% of subjects in UniplasLG treatment period and in 16.5% of subjects in OctaplasLG treatment period.

AEs of urticaria (3 subjects), dyspnea (2 subjects) and sensation of foreign body (1 subject) led to the early termination of plasma transfusions in 4 subjects in the UniplasLG treatment period and 3 subjects in the OctaplasLG treatment period, but did not lead to permanent withdrawal from the study (2 of the subjects were recorded with AEs leading to early termination of plasma transfusions in both treatment periods, developing urticaria during both UniplasLG and OctaplasLG infusions).

#### 6.7.11.3 Deaths

There were no deaths during the study.

#### 6.7.11.4 Nonfatal Serious Adverse Events

No SAEs were reported during the study.

#### 6.7.11.5 Adverse Events of Special Interest (AESI)

Viral status (HBs antigen, anti-HBc, anti-HAV, anti-HCV, anti-HIV-1/2, anti-CMV, and anti-parvovirus B19 antibodies) was assessed at screening and at Visit 8. Subjects with observed changes in viral status from negative to positive between screening and Visit 8

were asked to have additional blood draws (not mandatory) in order to confirm the expected clearance of the passively transmitted antibodies.

Seventeen subjects presented changes in antibody status from negative to positive between screening and Visit 8 (anti-HAV, only: n=16; anti-parvovirus B19 and anti-HAV: n=1). In none of them clinical symptoms were recorded. They were all asked to undergo follow-up blood draws every 4 weeks until antibody clearance.

Of the 17 volunteers with HAV seroconversion:

- One received a vaccination against hepatitis A at 6 months after the last plasma transfusion and remained positive for anti-HAV antibodies until the end of follow-up (February 02, 2010)
- Two did not respond to the written invitation to participate in the virus follow-up investigations and could not be reached
- Fourteen had become seronegative for anti-HAV antibodies within 3 to 7 months after the last plasma transfusion, suggestive of a passive transmission of antibodies during plasma transfusion

The subject who seroconverted for parvovirus B19 (IgG) (as well as HAV) remained positive until the end of the follow-up period (February 02, 2010). This subject has not reported any matching symptoms (e.g., erythema infectiosum, aplastic anemia or acute symmetric polyarthropathy).

Passive immunization could theoretically be expected after transfusion of plasma containing antibodies against parvovirus B19. However, the persistence of passively transfused anti-parvovirus B19 antibodies for more than 8 months is unlikely. No other subject treated with products from the same batch seroconverted or developed any signs of infection.

### **6.8 Trial #8: 3PLASIV90 (Octaplas® G-1 in patients with hereditary or acquired coagulation factor deficiency, N=11)**

Evaluation of solvent/detergent treated fresh frozen plasma in the management of patients with hereditary and acquired coagulation disorders

#### **6.8.1 Objectives (Primary, Secondary, etc)**

- To assess the effects of Octaplas® on coagulation parameters in patients with a hereditary or acquired coagulation factor deficiency, and its clinical effects on the stopping or prevention of bleeding
- To assess the tolerability of Octaplas® in these patients



### 6.8.2 Design Overview

The trial was an open-label, non-controlled, prospective study, whereby all patients with a hereditary or acquired coagulation factor deficiency seen at the study center were to be enrolled.

### 6.8.3 Population

#### *Inclusion Criteria*

Patients meeting the following criteria were to be included in the study:

- Patients of both sexes between 18 and 80 years of age, belonging to one of the following 3 groups:
  - *Patients with a hereditary clotting factor deficiency*  
Among the factor deficiency patients followed by the Hematology Department of the Beilinson Medical Center there were 9 families with factor XI deficiency, 4 families with factor VII deficiency, 1 family with mild factor IX deficiency, and 2 families with factor X deficiency. Those patients have an indication for the administration of plasma in case of bleeding or before elective surgical procedures.
  - *Patients undergoing a therapeutic plasmapheresis*  
These patients suffer from an acquired coagulation disorders due to either TTP (thrombocytic thrombopenic purpura) or dysproteinemia (e.g. mixed cryoglobulinemia, or Waldenström's maeroglobulinemia).
  - *Patients with an acquired coagulopathy requiring surgery*  
These patients suffer from a chronic liver disease which results into a deficiency in certain vitamin K dependent coagulation factors (e.g. FII, FVII, FIX, FX). Severe cases such as patients requiring liver transplantation may present with a deficiency in a number of coagulation factors.
- Informed consent obtained.

#### *Exclusion Criteria*

The following conditions excluded patients from participation in the study:

- Presence of a florid viral infection
- Need for additional blood derivatives beside Octaplas<sup>®</sup>
- Presence of anti-IgA antibodies
- Existence of an IgA-deficiency
- Allergy to plasma proteins
- Cardiac decompensation

### 6.8.4 Study Treatments or Agents Mandated by the Protocol

According to their primary disease, patients were transfused with Octaplas<sup>®</sup> either for therapy or prophylaxis of bleeding, with the quantity of Octaplas<sup>®</sup> required by the clinical situation. During the procedures, the patients were evaluated for tolerability and adequacy of procedures.

#### 6.8.5 Sites and Centers

Department of Hematology, Beilinson Medical Center, Petah Tiqva, Israel

#### 6.8.6 Surveillance/Monitoring

Prior to entry into the study patients' medical history and baseline medical condition was assessed along with viral testing (anti-HIV 1/2, HTLV1-Ab, HBsAg, HBs-Ab, CMV-Ab and EBV-Ab) and baseline coagulation parameters (FII, FV, FVII, FVIII, FIX, FX, FXI and FXII).

During the study post-treatment coagulation parameters were measured at baseline and at 30 minutes, 1, 2, 12, 24, 48 and 72 hours after the infusion of Octaplas®. An overall subjective rating of effectiveness and tolerability by the investigator, and adverse events were also recorded.

#### 6.8.7 Endpoints and Criteria for Study Success

Predefined efficacy endpoints were recovery of coagulation factors in hereditary coagulation factor deficiency and the investigators clinical impression of overall effectiveness for stopping or preventing bleeding.

#### 6.8.8 Statistical Considerations & Statistical Analysis Plan

This was an exploratory study with no sample size calculation or hypothesis testing.

#### 6.8.9 Study Population and Disposition

##### 6.8.9.1 Populations Enrolled/Analyzed

A total of 11 patients were enrolled in the study. Each patient received one course of Octaplas treatment either for therapy or prophylaxis of bleeding.

##### 6.8.9.1.1 Demographics

A total of 6 female (mean age 43 years [20 – 75 years]) and 5 male (mean age 52 years [35 – 71 years]) patients were enrolled in the study.

##### 6.8.9.1.2 Medical/Behavioral Characterization of the Enrolled Population

Two patients were admitted for an ongoing bleeding episode. This was a moderate hemarthrosis of the left knee in a patient with congenital FX deficiency, and extensive menorrhagia lasting for 3 days in a patient with congenital FXI deficiency.

In eight patients, Octaplas® was given before an invasive procedure to prevent bleeding, and one patient received Octaplas® during a plasmapheresis.

Eight patients enrolled in the study had a congenital coagulation factor deficiency. This deficiency was isolated in 7 cases, and one patient had a deficiency in both FV and FX.

Three patients had an acquired combined coagulopathy associated with a severe liver disease.

#### 6.8.9.1.3 Subject Disposition

A total of 11 patients were enrolled in the study. No patient was prematurely withdrawn from the study.

#### 6.8.10 Efficacy Analyses

##### 6.8.10.1 Analyses of Primary Endpoint(s)

The results demonstrated:

- Effective replacement of deficient coagulation factors as shown by expected recovery levels in eight patients with hereditary coagulation factor deficiency
- Hemostasis was achieved in two patients with bleeding (hemarthrosis and menorrhagia)
- Prophylaxis was rated as “good” in eight patients undergoing invasive procedures

#### 6.8.11 Safety Analyses

The 11 patients were exposed to one single course of Octaplas<sup>®</sup> treatment at an average dose of 2.9 units, range 2 to 8 units, corresponding to a mean volume of 580 mL Octaplas<sup>®</sup>, range 400 to 1600 mL.

##### 6.8.11.1 Methods

All patients exposed to Octaplas<sup>®</sup> were included in the safety analysis population.

##### 6.8.11.2 Overview of Adverse Events

Two patients experienced a total of three adverse reactions, consisting of an anaphylactoid reaction, and urticaria with pruritis. These adverse reactions resolved with anti-histamine therapy and both patients recovered.

##### 6.8.11.3 Deaths

There were no deaths.

#### 6.8.11.4 Nonfatal Serious Adverse Events

No serious adverse events occurred in this study.

### **6.9 Trial #9: LAS-Study 1-D (Octaplas® G-1 in patients in the ICU with coagulopathy, N=30)**

Prospective Study on Efficacy and Tolerability of Solvent/Detergent-Treated Plasma in Intensive Unit Care Patients

#### 6.9.1 Objectives (Primary, Secondary, etc)

The primary objective was to assess the effects of Octaplas® on coagulation and circulation parameters as well as on manifest bleedings.

The secondary objective was to assess the acute tolerability of Octaplas® when given as therapy in patients suffering from disseminated intravascular coagulation and/or dilution or loss coagulopathy.

#### 6.9.2 Design Overview

The trial was an open-label non-controlled prospective study, whereby all patients during the postoperative period in the intensive care unit requiring plasma therapy were to be enrolled.

#### 6.9.3 Population

##### *Inclusion Criteria*

Although not formalized in a study protocol, the principal investigator and co-investigators agreed that patients meeting the following criteria were to be included in the study:

- Patients of either sex and age
- Patients with disseminated intravascular coagulation and/or dilution or loss coagulopathy requiring treatment with human plasma
- Verbal informed consent obtained.

##### *Exclusion Criteria*

Although not formalized in a study protocol, the investigators agreed that the following conditions excluded patients from participation in the study:

- Unconscious patients
- No administration of blood products, including plasma or plasma derivatives within 6 hours before start of administration of Octaplas®
- Participation in another clinical trial.

#### 6.9.4 Study Treatments or Agents Mandated by the Protocol

All patients received Octaplas® in this open non-controlled study.

#### 6.9.5 Sites and Centers

Klinikum Ludwigshafen, "Transfusionsmedizin und Immun-hamatologie" and "Anaesthesiologie und operative Intensivmedizin", Germany

#### 6.9.6 Surveillance/Monitoring

Prior to entry into the study patients' medical history and baseline medical condition was assessed along with coagulation parameters (PT, aPTT, Fibrinogen, Thrombin Time, Antithrombin III activity, d-Dimers and platelet count). Within 10 to 60 minutes after the infusion of Octaplas® the same coagulation parameters were measured.

#### 6.9.7 Endpoints and Criteria for Study Success

Predefined efficacy endpoints were improvement in coagulation parameters.

#### 6.9.8 Statistical Considerations & Statistical Analysis Plan

This was an exploratory study with no sample size calculation or hypothesis testing.

#### 6.9.9 Study Population and Disposition

A total of 30 patients were enrolled in the study.

##### 6.9.9.1 Populations Enrolled/Analyzed

###### 6.9.9.1.1 Demographics

A total of 9 female (mean age 61 years [41 – 84 years]) and 21 male (mean age 61 years [37 – 68 years]) patients were enrolled in the study.

###### 6.9.9.1.2 Medical/Behavioral Characterization of the Enrolled Population

Only patients suffering from disseminated intravascular coagulation and/or dilution or loss coagulopathy and requiring treatment with human plasma were included in the study.

###### 6.9.9.1.3 Subject Disposition

No patient was prematurely withdrawn from the study.

#### 6.9.10 Efficacy Analyses

##### 6.9.10.1 Analyses of Primary Endpoint(s)

Improvement in PT, aPTT Fibrinogen and Antithrombin III were seen. Additionally, a

hemostatic effect was reported by the investigators in 16 of 22 patients who had manifest bleeding prior to infusion.

#### 6.9.11 Safety Analyses

##### 6.9.11.1 Methods

All patients exposed to Octaplas<sup>®</sup> were included in the safety analysis population.

##### 6.9.11.2 Overview of Adverse Events

There were no adverse drug reactions reported.

##### 6.9.11.3 Deaths

There were no deaths.

##### 6.9.11.4 Nonfatal Serious Adverse Events

There were no serious adverse events reported.

#### 7. Integrated Overview of Efficacy

An integrated efficacy analysis is not possible because of the heterogeneity in efficacy endpoints, studied populations and indications for treatment in the clinical studies. As noted previously, many of the studies were small and uncontrolled, underpowered to evaluate efficacy, not hypothesis driven and were not focused on the indications for use. Also, many of the studies were primarily designed to compare product generations to one another.

Given these limitations, outcomes related to the primary objective for many of the studies were not always useful to evaluate product efficacy. Nonetheless, most of the studies captured data from one or more of a number of predefined efficacy endpoints related to hemostasis, global measures of coagulation, and circulating levels of PS and PI which provided evidence to support the efficacy and safety of Octaplas<sup>™</sup> in the approved indications.

The nine clinical studies reviewed were divided into three groups and efficacy conclusions drawn from these three groups are as follows:

- The FFP comparator studies evaluated 188 patients in three trials that compared safety and efficacy of Octaplas<sup>®</sup> to FFP in clinical conditions associated with coagulopathy. The efficacy and safety outcomes were similar between prior generations of Octaplas<sup>®</sup> products and FFP in various clinical conditions where replacements of multiple coagulation factors were needed.
- The four bridging studies compared Octaplas<sup>™</sup> to Octaplas<sup>®</sup> or UniplasLG.

A total of 299 subjects were studied, including 90 healthy volunteers (all exposed to Octaplas™), 84 heart surgery patients and 125 patients needing plasma for any condition. Comparability in laboratory values was observed and supports comparability between product generations, resultant of their similar manufacturing and biochemical profiles. The exception was for PI values in Study LAS-203 (PI levels were noted to be higher in Octaplas™ vs. Octaplas®).

- The single arm studies showed functional levels of coagulation factors were recovered in eight patients with hereditary coagulation factor deficiency. Hemostasis was achieved in 18/24 bleeding patients (total for both studies) and prophylaxis for hemostasis was rated as effective by the investigator in 8/8 patients undergoing an invasive procedure.

## 8. Integrated Overview of Safety

The overall safety profile of Octaplas™ is acceptable. The majority of the reported adverse drug reactions were mild to moderate and seen in healthy volunteers. The most common ( $\geq 1\%$ ) adverse drug reactions reported were paraesthesia, headache, urticaria, nausea and pruritis. The healthy volunteers were not pre-medicated with either anti-allergic or antipyretic medications prior to plasma product infusion. The table below shows the pooled safety database for Octaplas® (Generation 1 and 2a) and Octaplas™.

**Table 35: Pooled Safety Database for Octaplas™ and Octaplas® from Nine Clinical Studies Considered in Support of Safety and Efficacy**

Adverse Event	Octaplas™ (N = 120) # (%)	Octaplas® (N = 239) # (%)
Anaphylactoid reaction	0	1 (0.4%)
Pruritis	2 (1%)	3 (1%)
Urticaria	19 (15%)	13 (5%)
Fever	0	1 (0.4%)
Nausea	4 (3%)	2 (0.8%)
Headache	19 (15%)	11 (4%)
Paraesthesia	21 (17%)	8 (3%)
Hyperfibrinolysis	0	0
TRALI	0	0

There were two serious adverse reactions reported. One was a case of severe

hypotension and the other was anaphylactic shock. Both patients recovered with appropriate management. There were no deaths due to transfusion of any of the generations of Octapharma's solvent detergent plasma product reported in the clinical trials.

One of the major risks of treatment with blood components, including plasma, is transmission of infectious disease agents. This risk has been largely reduced by donor screening questionnaires, and screening of donors by serology and NAT.

Octaplas™ is a product pooled from up to 1520 plasma donations. Risk of patient exposure to a large number of donors is offset by solvent/detergent treatment to remove enveloped viruses. Risk from non-enveloped viruses in Octaplas™ is reduced by limiting viral load using NAT, and by minimal titer specifications for HAV and B19 neutralizing antibodies. To date, there have been no documented cases of infection with HBV, HCV or HIV associated with the use of Octaplas® or Octaplas™.

One case of B19 transmission (NAT positive after 9 months) has been reported with the use of Octaplas manufactured prior to the implementation of Parvovirus B19 DNA limits (i.e., B19 not to exceed more than 10.0 IU/μL in the manufacturing plasma pool). No clinical symptoms were observed or reported in this patient. There have been no cases of HAV transmission reported.

Despite the very low presumptive prevalence of vCJD infection in US donors, the pooling of plasma for the manufacture of Octaplas™ may increase the risk of vCJD due to the absence of significant prion clearance in manufacturing (i.e. estimated clearance of vCJD agent by the ligand gel column of only 0.83 log<sub>10</sub>). Nevertheless, the potential for showing reduction in risk of transfusion related acute lung injury (TRALI) (see below) indicates that the potential benefit of TRALI reduction would exceed the potential added vCJD risk.

Three specific safety concerns with plasma in general and with solvent/detergent treated plasma are discussed below:

#### *Low Protein S levels and risk of Thromboembolism*

In 1998, FDA licensed PLAS+SD, a solvent/detergent treated, pooled human plasma, manufactured by V.I. Technologies Inc, Melville, NY. This product is no longer available on the US market. It was associated with thromboembolic events (TE) events especially in liver transplantation and liver disease. The TE events were believed to be due to low levels of PS in PLAS+SD. Solheim et al.<sup>3</sup> have reported a mean PS level of 64 U/100 mL (range 55-71) in Octaplas® (Generation 2a) vs. 24 U/100 mL (range 14-37) in PLAS+SD, the normal reference range being 56-168 U/100 mL<sup>4</sup>. Differences in PS

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<sup>3</sup> Solheim BG, Hellstern P. Composition, efficacy, and safety of S/D-treated plasma. Transfusion 2003; 43:1176-1178.

<sup>4</sup> Hellstern P, Sachse H, Schwinn H, Oberfrank K. Manufacture and characterization of a solvent/



between products may be attributable to manufacturing differences. The level of PS in Octaplas™ is higher than the levels detected in Octaplas® (Generation 2a) (see Table 2).

In 2003, Yarranton et al.<sup>5</sup> published a retrospective review of the occurrence of venous thromboembolism (VTE) in 68 consecutive patients with TTP (25 male, 43 female) undergoing plasma exchange (PEX). Eight documented VTE events were noted in seven patients (5 deep venous thromboses (DVTs), 1 pulmonary embolus (PE), 1 PE + pulmonary arterial thrombosis and 1 PE + DVT). VTE occurred at a mean of 53 days following the first PEX. Octaplas® (Generation 2a) was the last plasma to be used in PEX prior to the VTE in 7/8 events. Other replacement fluids used were FFP and cryosupernatant (CSP). All the DVTs were associated with central venous catheters. The one pulmonary artery thrombosis was related to a Swan–Ganz catheter in the pulmonary artery. Other acquired precipitating factors for VTE for the eight events included pregnancy (n=1), immobility (n=8), and obesity (n=3).

PS levels were not routinely measured during PEX prior to the VTE event; however, archived plasma samples were available for one patient. Mean PS levels were lower in this patient following Octaplas® compared with CSP; however, for both treatments the mean levels remained within the normal reference range.

Yarranton et al. reported a background rate of 3% for VTE in this patient population<sup>6</sup>. The rate in their study was 12%. There have been no further reports of VTE associated with Octaplas® or Octaplas™ in the clinical studies, literature references or post-marketing reports.

The risk of TE remains a concern especially where large volumes are needed but this may be mitigated in Octaplas™ which has higher levels of PS (within the lower limit of the reference range, see Table 2)

*Low PI ( $\alpha_2$  antiplasmin) levels and risk of bleeding (hyperfibrinolysis)*

Hyperfibrinolysis may occur during orthotopic liver transplantation (OLT) and has been associated with excessive bleeding during the procedure. Low levels of PI in Octaplas® (Generation 2a) have been implicated in an increased incidence of hyperfibrinolysis seen in patients undergoing OLT, as reported by de Jonge et al.<sup>7</sup> De Jonge and his colleagues reported the experience of 41 patients treated with FFP or Octaplas® (N= 21 FFP, N=20

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detergent-treated human plasma. Vox Sang 1992; 63:178-185.

<sup>5</sup> Yarranton H, Cohen H, Pavord SR, Benjamin S, Hagger D, Machin SJ. Venous thromboembolism associated with the management of acute thrombotic thrombocytopenic purpura. Br J Haematology 2003; 121:778-785.

<sup>6</sup> Rizvi, MA, Vesely, SK, George, JN, Chandler, L, Duvall, D, Smith, Gilcher, RO. Complications of plasma exchange in 71 consecutive patients treated for clinically suspected thrombotic thrombocytopenic purpura–hemolytic–uremic syndrome. Transfusion 2000; 40:896–901.

<sup>7</sup> de Jonge J., Groenland THN, Metselaar HJ, et al. Fibrinolysis during liver transplantation is enhanced by using solvent/detergent virus-inactivated plasma (ESDEP®). Anesth Analg 2002; 94:1127-31.

Octaplas<sup>®</sup>). Hyperfibrinolysis was seen in 6/21 (29%) of the patients who received FFP and 15/20 (75%) of the patients who received Octaplas<sup>®</sup>.

Intra-operative plasma samples from both patient groups were analyzed and markers of fibrinolysis (D-dimer and fibrin degradation products [FDP]) were higher in the Octaplas<sup>®</sup> group than in the FFP group. This is in contrast to levels at the time of anesthesia onset, when no difference in PI levels was detected between the two groups. PI levels in the FFP treated group decreased from 0.76 IU/mL to a low of 0.58 IU/mL by procedure end. The PI level in the Octaplas<sup>®</sup> treated group began at 0.64 IU/mL, dropped to a low of 0.27 IU/mL by the time of reperfusion, and was at a level of 0.40 IU/mL by procedure end. Analysis of the Octaplas<sup>®</sup> lots used in these patients showed levels of PI to be  $0.28 \pm 0.02$  IU/mL (normal, 0.95 – 1.20 IU/mL)<sup>8</sup>. The PI levels in these lots appear to be lower than those measured in Octaplas<sup>™</sup> (see Table 2).

Two cases of hyperfibrinolysis were reported from Ireland.<sup>9</sup> The authors reported that shortly after the change from FFP to Octaplas<sup>®</sup> (derived from US donor plasma), 2 of 22 patients died intraoperatively during liver transplantation with severe coagulopathy and excessive bleeding. Both patients were noted to have hyperfibrinolytic activity, indicated by increasing D-dimer and decreasing fibrinogen. PI levels were not reported.

Solheim et al<sup>10</sup> reported that the Norwegian experience with Octaplas<sup>®</sup> did not reveal any issues with fibrinolysis during the period of 1993 – 2001, during which 208 liver transplants were performed using Octaplas<sup>®</sup>.

Since the introduction of Octaplas<sup>™</sup>, which has an improved manufacturing process resulting in increased levels of PI, there have been no literature and/or pharmacovigilance reports of an increased incidence of hyperfibrinolysis during liver transplantation.

## 9. Additional Clinical Issues

### 9.1 Special Populations

#### 9.1.1 Human Reproduction and Pregnancy Data

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

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<sup>8</sup> Hellstern P, Sachse H, Schwinn H, Oberfrank K. Manufacture and characterization of a solvent/detergent-treated human plasma. Vox Sang 1992; 63:178-185.

<sup>9</sup> Magner JJ, Crowley KJ, Boylan JF. Fatal fibrinolysis during orthotopic liver transplantation in patients receiving solvent/detergent-treated plasma (Octaplas). J Cardiothorac Vasc Anesth 2007; 21(3):410-3.

<sup>10</sup> Solheim B, Bergan A, Brosstad F, Innes R, Svennevig JL. Fibrinolysis during liver transplantation is enhanced by using solvent/detergent virus-inactivated plasma (ESDEP<sup>®</sup>). Anesth Analg 2003; 96:1230-1231.

#### 9.1.2 Use During Lactation

Efficacy and safety of Octaplas in lactating women is unknown.

#### 9.1.3 Pediatric Use and PREA Considerations

The application triggered PREA as a new indication. Octapharma requested a pediatric deferral for all age groups. The pediatric assessment was presented to the Pediatric Review Committee (PeRC) on September 12, 2012. The PeRC agreed with the Division to grant a full deferral because the product is ready for approval in adults; however, pediatric studies encompassing all age groups (< 16 years) will need to be completed in the post-marketing period for both indications for use.

Octapharma has agreed to conduct the following postmarketing required pediatric studies in ages < 16 years old:

- An open-label, multicenter, clinical study to investigate, safety, tolerability and efficacy of Octaplas™ in the management of pediatric patients who require multiple plasma coagulation factors to be completed by February 2016
- An non-interventional, open-label, multicenter, clinical study to investigate, safety, tolerability and efficacy of Octaplas™ in the management of pediatric patients who require therapeutic plasma exchange to be completed by March 2017

#### 9.1.5 Geriatric Use

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

### 10. Conclusions

In conclusion, the data support the effectiveness of Octaplas™ in the proposed indications.

### 11. Risk-Benefit Considerations and Recommendations

#### 11.1 Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
<b>Analysis of Condition</b>	<ul style="list-style-type: none"> <li>Acquired multiple coagulation factor deficiencies due to liver disease can predispose to bleeding that may become uncontrollable.</li> <li>Acquired multiple coagulation factor deficiencies during the course of cardiac surgery or liver transplantation can predispose to bleeding that may become uncontrollable.</li> <li>TTP can lead to thrombocytopenia, microangiopathic hemolytic anemia, neurologic abnormalities, renal abnormalities and thrombotic microangiopathies.</li> </ul>	<ul style="list-style-type: none"> <li>Uncontrolled bleeding is a progressive, life-threatening condition.</li> <li>TTP is a life-threatening condition with a mortality rate of approximately 90% without plasma exchange therapy.</li> </ul>
<b>Unmet Medical Need</b>	<ul style="list-style-type: none"> <li>FFP and PF24 are available for the above conditions.</li> <li>The clinical data from randomized, controlled trials to support the effectiveness of FFP and PF24 in the above conditions is lacking.</li> <li>FFP and PF24 are dispensed with volume variability (~200 to 250 mL) and a wide range of variability in the levels of coagulation proteins and inhibitors, and carry a risk for viral transmission and TRALI.</li> </ul>	<ul style="list-style-type: none"> <li>There unmet medical need for a plasma product with improved viral safety, less risk for development of TRALI and standardized with less variability in coagulation proteins and inhibitors.</li> </ul>
<b>Clinical Benefit</b>	<ul style="list-style-type: none"> <li>Many of the nine studies reviewed to support efficacy and safety were small and uncontrolled, underpowered to evaluate efficacy, were not hypothesis driven, were not focused on the indications for use and were primarily designed to compare product generations to one another; however, most of the studies captured data from one or more of a number of predefined efficacy endpoints related to hemostasis, global measures of coagulation and circulating levels of PS and PI which provided substantial evidence to support effectiveness and safe use of the product.</li> <li>The product is dispensed in a standardized volume (200 mL) and must meet a release specification which provides less variability in the levels of coagulation proteins and inhibitors.</li> <li>The product has been marketed outside the U.S. since 2009 and the predecessor product since 1989 with a total patient exposure of approximately 2.3 million without a documented transmission of HIV, HBV, HCV or HAV and on cases of TRALI that were causally related to the product or its predecessor.</li> </ul>	<ul style="list-style-type: none"> <li>The evidence for clinical benefit with regard to viral safety and potential for decreased risk for the development of TRALI exists</li> </ul>
<b>Risk</b>	<ul style="list-style-type: none"> <li>The use of source plasma in the manufacturing process with an increased risk for non-enveloped viral transmission is a safety concern identified during the review of the product.</li> </ul>	<ul style="list-style-type: none"> <li>The risk for increased non-enveloped viral transmission due to source plasma is theoretical.</li> </ul>
<b>Risk Management</b>	<ul style="list-style-type: none"> <li>The risk for hyperfibrinolysis due to low PI levels in the product and the risk for thromboembolism due to low PS levels have been reported in the literature with use of the predecessor product.</li> </ul>	<ul style="list-style-type: none"> <li>PS levels are higher in Octaplas<sup>TM</sup> than in the predecessor product and are at the low end of the reference range.</li> <li>Octapharma will conduct two PMR studies, one to further assess the risk for thromboembolism with use of the product in the treatment of TTP and a second to further assess the risk for hyperfibrinolysis with use of the product in liver transplantation.</li> </ul>

## 11.2 Risk-Benefit Summary and Assessment

### *Use of Source Plasma*

Octaplas™ will be manufactured from 630 – 1,520 units of Source Plasma or recovered plasma, supplied by US licensed blood establishments and placed in the freezer within (b)(4) hr of blood draw. US Source Plasma has a higher viral marker rate when compared with recovered plasma from whole blood donations due to the different donor screening and qualification requirements used for each. This poses a theoretical increased risk for viral transmission when Source Plasma is used; however, this potential risk is mitigated by:

- Source Plasma blood establishment quality management in accordance with the International Quality Plasma Program (IQPP) standard of the Plasma Protein Therapeutics Association (PPTA) that governs donor qualification, quality assurance, donor deferral, education and training of personnel and viral marker monitoring; and
- Adventitious agents testing of individual units or mini-pools or manufacturing plasma pools, as appropriate, using FDA licensed kits including nucleic acid amplification testing for HAV, HBV, HCV, HIV and HEV.

Further, (b)(4) lots manufactured from Source Plasma have been distributed since 2006 in Europe and Canada without report of seroconversion or transfusion transmitted disease.

### *Viral Safety*

Unlike plasma derivatives, Octaplas™ manufacture incorporates one viral inactivation step rather than two orthogonal, targeted steps in order to avoid potential damage to any of the multiple proteins in the product that are required for its safety and efficacy. The solvent/detergent treatment process results in adequate reduction factors for enveloped viruses such as HIV, HCV and HBV. The current risks for transmission of HIV and HCV infection with FFP are 1:1.4 million units and 1:1.1 million units respectively.<sup>11</sup> The risk for transmission of HBV infection with FFP is 1:280,000 to 1:357,000 units.<sup>12</sup> However, this calculated estimate for HBV transmission was prior to widespread nucleic acid amplification testing (NAT) for HBV; therefore, the current risk is presumably lower.

Viral transmission of non-enveloped viruses is mitigated by:

- Control of viral load by NAT; only plasma pools negative for HAV and that contain a maximum of 10.0 IU/  $\mu$ L of parvovirus B19 are accepted and

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<sup>11</sup> Zou S, Dorsey KA, Notari EP, et al. Prevalence, incidence, and residual risk of human immunodeficiency virus and hepatitis C virus infections among United States blood donors since the introduction of nucleic acid testing. *Transfusion* 2010; 50:1495-1504.

<sup>12</sup> Zou S, Stramer SL, Notari EP, et al. Current incidence and residual risk of hepatitis B infection among blood donors in the United States. *Transfusion* 2009; 49:1609-1620.

- Immune neutralization based on specified minimum antibody levels against HAV, parvovirus B19 and HEV in the final product

With regard to the risk for transmission of Hepatitis E Virus (HEV), the data on the burden in the plasma pool and the prevalence of antibodies in plasma donations and/or plasma pools is unavailable. However, mitigation of HEV transmission will be addressed similarly to HAV and parvovirus B19. A validated HEV NAT to control virus level in the manufacturing plasma pool has been implemented and a specified level of antibody against HEV in the final product will not be less than 0.2 IU/mL.

#### *Transmission of CJD or vCJD*

The risk of transmitting Creutzfeldt-Jakob Disease (CJD) or variant Creutzfeldt-Jakob disease through US sourced plasma is, to date, only theoretical.

#### *Thromboembolism and Hyperfibrinolysis*

The following has been reported in patients who received Octaplas®:

- Thromboembolism (presumably due to low Protein S concentrations in Octaplas®) in patients undergoing plasma exchange for TTP: and
- An increased incidence of hyperfibrinolysis (presumably due to low plasmin inhibitor concentrations in Octaplas®) in patients undergoing liver transplantation.

These are isolated reports involving small numbers of patients and all patients received the predecessor product to the current version of Octaplas™. The current version has an improved manufacturing process resulting in increased levels of PS that are within the lower limit of the reference range and increased levels of plasmin inhibitor which mitigate these risks. Further, Octapharma has agreed to postmarketing studies for each of these risks in the respective clinical settings.

#### *Conclusion*

Each of the identified potential risks above is associated with a proposed mitigation strategy. Further, there is experience showing the potential reduction in risk of TRALI. These data indicate that the potential benefit of TRALI reduction may outweigh the potential risks with the product and exceeds the theoretical risk for transmission of CJD/vCJD.

Octaplas also benefits from uniformity of volume per unit (i.e., standardized dose) of 200 mL vs. 200 – 250 mL for FFP, as well as the requirement for product to meet final release specifications which provides less variability of levels of coagulation proteins and inhibitors when compared to FFP (see Table 2).

### **11.3 Discussion of Regulatory Options**

The regulatory option to approve the product with the requirement for two PMR studies to study the potential for excessive bleeding due to hyperfibrinolysis and TE that may be possible due to the levels of PS and PI being lower than FFP in the product. However, Octaplas™ has higher levels of PS and PI than the predecessor product due to the improvement in the manufacturing process.

### **11.4 Recommendations on Regulatory Actions**

It is recommended that Octaplas™ be approved for the proposed indications.

### **11.5 Labeling Recommendations**

Proprietary Name: The sponsor's proprietary name, Octaplas™, was reviewed by the Advertising and Promotional Labeling Branch (APLB) and was found to be acceptable.

Physician labeling: The final Octaplas™ labeling is Physicians Labeling Rule compliant.

Full Prescribing Information (FPI): APLB reviewed the original FPI submitted by the sponsor. Comments from a promotional and comprehension perspective were provided to OBRR on August 1, 2012.

Comments regarding the FPI were conveyed to the sponsor on August 15, 2012. The sponsor subsequently submitted a revised FPI in September, 2012. APLB reviewed the revised FPI and provided additional comments to OBRR for discussion with the sponsor. FDA's comments were conveyed to the sponsor on October 11, 2012. Additional comments were submitted to the sponsor on October 12, 2012. Negotiations continued through several more exchanges and the sponsor accepted all of FDA's remaining comments and recommendations. All FPI issues have been adequately resolved in preparation of final approved labeling.

### **11.6 Recommendations on Postmarketing Actions**

## **PEDIATRIC REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

The submission of pediatric studies is deferred until September 30, 2016 for study #1 below and until October 31, 2017 for study #2 below because.

1. This product is ready for approval for use in adults and the pediatric studies have not been completed.

The deferred pediatric studies required under 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported according to 21 CFR 601.70 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below:

1. An open-label, multicenter, clinical study to investigate, safety, tolerability and efficacy of Octaplas™ in the management of pediatric patients who require multiple plasma coagulation factors in ages < 16 years old

Final Protocol Submission: July 2013

Study Completion Date: February 2016

Final Report Submission: September 2016

2. A non-interventional, open-label, multicenter, clinical study to investigate, safety, tolerability and efficacy of Octaplas™ in the management of pediatric patients who require therapeutic plasma exchange in ages < 16 years old

Final Protocol Submission: August 2013

Study Completion Date: March 2017

Final Report Submission: October 2017

## **POSTMARKETING REQUIREMENTS UNDER 505(o)**

The sponsor has committed to the following:

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)).

An analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of thromboembolism in the thrombotic thrombocytopenia purpura (TTP) patient population and risk of hyperfibrinolysis in the liver transplantation patient population.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Clinical studies to further assess these potential risks are needed because Octaplas™ contains lower PS and PI levels than found in FFP. The completed clinical studies are considered too small to reliably assess the potential for adverse events.



Therefore, based on appropriate scientific data, it was determined that the sponsor be required to conduct the following studies:

1. Non-interventional 2-arm study to evaluate the safety of Octaplas™ in patients treated for Thrombotic Thrombocytopenic Purpura (TTP) with special emphasis on monitoring the occurrence of thromboembolic events (TEEs)

Final Protocol Submission: August 2013

Study Completion Date: December 2017

Final Report Submission: July 2018

2. Non-Interventional 2-arm study to evaluate the safety of Octaplas™ versus FFP in patients undergoing orthotopic liver transplantation (LTX) with a special emphasis on hyperfibrinolysis

Final Protocol Submission: October 2013

Study Completion Date: April 2017

Final Report Submission: November 2017

## Appendix 1: Tabulation of Studies Evaluated for Efficacy and/or Safety

Study Number Investigator; Site; Study Period; Publication	Design	Number of Subjects	Diagnosis/Indication	Product Treatment Regimen	Evaluation Criteria	Results (Efficacy)	Results (Safety)
LAS-1-02-D Haubelt et al; Germany; 1998-1999; <i>Vox Sanguinis</i> 2002	Prospective; Drug surveillance study (cohorts of 5 received FFP or Octaplas® sequentially) Open label	Total n =67; Octaplas® n=36; FFP n=31	Post-op open heart ICU with impaired hemostasis (dilution, blood loss, DIC, or a combination)  No formal Inclusion/Exclusion criteria were specified	Octaplas® Generation 2a, dose 600 mL FFP or Octaplas®	Parameters measured before treatment and 60 min after termination of plasma infusion: PT, aPTT, fibrinogen, FVIII, ATIII, free PS and PS activity, prothrombin fragments F1+2, D-dimers, fibrinogen degradation products, plasmin– antiplasmin complexes, plasminogen, PI and trypsin inhibitor	PS activity did not increase after Octaplas® infusion but did show an increase after infusion with FFP. PI declined after Octaplas® and remained uninfluenced by FFP. With the exception of PS and PI, Octaplas® and FFP improved hemostasis and fibrinolysis to a similar degree. Free PS did show improvement with Octaplas® and FFP.	No ADRs reported

Study Number Investigator; Site; Study Period; Publication	Design	Number of Subjects	Diagnosis/Indication	Product Treatment Regimen	Evaluation Criteria	Results (Efficacy)	Results (Safety)
19/PLAS/IV/91 Solheim et al; Norway; 1992; <i>DIC; Pathogenesis, Diagnosis and Therapy of Disseminated Intravascular Fibrin Formation 1993</i>	Prospective; Open label (Octaplas® FFP and no plasma groups)	Total n = 66 Octaplas® n=20; no plasma n=26; FFP n=20	Elective open heart surgery	Octaplas® Generation 1, mean dose 700 mL	Blood loss, hematologic and global coagulation parameters	No significant difference in post-op blood loss (Octaplas® vs. FFP), revision for bleeding respirator time, circulatory support and hospital stay (all 3 groups) Octaplas® Group avg 3.5 units (range 1-17), FFP avg 4.05 units (range 2- 16)	1 ADR (transient fever reaction in Octaplas® Group)
LAS-1-03-UK Williamson et al; Multi-center UK; 1995-1997; <i>Transfusion 1999</i>	Prospective; Randomized; Open label; Single-blind	Total n = 55 FFP n=25; Octaplas® n=30	LD (PT>4sec) n=24 (FFP n=11, Octaplas® n=13) 23 prior to invasive procedure  LT n=28 (FFP n=14, Octaplas® n=14)  TTP n=3 (all Octaplas®)	Octaplas® Generation 2a, mean dose 12-13 mL/kg LD, 44 mL/kg LT	Coagulation factors, PTT, INR	Octaplas® and FFP showed similar degrees of correction of prolonged INR and PTT	2 ADRs (nausea, pruritis) reported in 1 subject with LD who received Octaplas®

<b>Study Number Investigator; Site; Study Period; Publication</b>	<b>Design</b>	<b>Number of Subjects</b>	<b>Diagnosis/Indication</b>	<b>Product Treatment Regimen</b>	<b>Evaluation Criteria</b>	<b>Results (Efficacy)</b>	<b>Results (Safety)</b>
LAS-203; Jilma; IND 13956 Austria; 2009-2010; <i>Publication N/A</i>	Prospective; Open label; Cross over	60 healthy individuals; PEX after PPh  PP n=43	Healthy volunteers	Octaplas® Generation 2a mean dose 1098.1 mL (14.9 mL/kg) and OctaplasLG 1149.5 mL (15.26 mL/kg)	Individual relative recoveries of coagulation Factors I, II, V, VII, VIII, IX, X, XI; hemostatic parameters (aPTT, PT, protein C and PI)	All coagulation and hemostatic parameters met the equivalence criterion	(no premeds) Most freq AEs: HA, paraesthesia, urticaria. 1 SAE of anaphylactic shock with OctaplasLG (withdrawn from study, recovered same day)
UNI-101 Tollofsrud et al; Norway; 1999-2001; <i>Intensive Care Med 2003</i>	Prospective; Randomized; Single-Blinded	Total n = 84 Octaplas® n=19; Uniplas n=36; No plasma n=29	Elective open heart surgery	Uniplas and Octaplas® Generation 2a, dosing according to clinical needs	aPTT, ACT, complement activation, DAT	aPTT and ACT values were comparable in the 3 active treatment groups	AEs were evenly distributed
LAS-201; Multi-center Germany; 2008-2010; <i>Publication N/A</i>	Non- Interventional; Observational	Total n = 125	any	Octaplas® Generation 2a and OctaplasLG	Objective physician assessment based on clinical or lab parameters	Efficacy conclusions could not be drawn because of the observational nature of the study	1 ADR in OctaplasLG subject (severe hypotension)
UNI-110 Jilma; Austria; 2009; <i>Publication N/A</i>	Prospective; Double blind; Cross over	30 healthy individuals; PEX after PPh	Healthy volunteers	OctaplasLG n=29 mean dose 16.2 mL/kg and Uniplas LG n=30 mean dose 16.1 mL/kg	Hemoglobin and other parameters of hemolysis, complement activation, DAT	Mean values of coagulation parameters were within the normal range and variations in their levels were similar between treatment groups	(no premeds) Most freq AEs: HA, paraesthesia, urticaria. No SAEs

<b>Study Number Investigator; Site; Study Period; Publication</b>	<b>Design</b>	<b>Number of Subjects</b>	<b>Diagnosis/Indication</b>	<b>Product Treatment Regimen</b>	<b>Evaluation Criteria</b>	<b>Results (Efficacy)</b>	<b>Results (Safety)</b>
3PLASIV90 Inbal et al; Israel; 1990-1992; <i>Blood Coagulation and Fibrinolysis 1993</i>	Prospective; Open label; Single arm	11	Hereditary Factor VII, X, or XI deficiency (n=8); Acquired coagulation disorders due to LD (n=3)	Octaplas® Generation 1, mean dose of 580 mL (range 400 to 1600 mL)	PK parameters, hemostatic efficacy (2 on-going bleeding, 8 prophylaxis prior to invasive procedure, 1 PPh)	In those with hereditary deficiency, the deficient factor showed an increase by calculated recovery, bleeding stopped or no bleeding noted during procedure	3 ADRs in 2 subjects (pruritis and urticaria, anaphylactoid reaction,
LAS-Study 1-D Hellstern et al; Germany; 1992; <i>Infusionsther Transfusionmed 1993</i>	Prospective; Open label; Single arm	30	Post-op admission to ICU and treated for DIC and/or coagulopathy due to blood volume dilution or loss (no formalized in/exclusion criteria)	Octaplas® Generation 1, mean dose 377 mL	Coagulation analysis before and within 10 to 60 min after plasma infusion (PT, fibrinogen, ATIII, aPTT, plts), VS	16/22 subjects with manifest bleeding demonstrated hemostatic effect	No ADRs reported
Study number N/A Chekrizova et al; Multi-center Ireland; 2002-2003; <i>Transfusion Medicine 2006</i>	Retrospective	A. 41 neonates  B. 38 adults  C. 15 children w/ LD and 17 adults w/ LD	A. Neonates with coagulopathy w or w/o hemorrhage B. OB/Gyn  C. LD	Uniplas and Octaplas® Generation 2a A. mean dose 18.4 mL/kg B. mean dose 15.3 mL/kg C. mean dose children 38 mL/kg; adults 10.2 mL/kg	aPTT, PT and fibrinogen	Reported decreases in mean aPTT and PT in neonates, OB/Gyn and LD patients	No ADRs reported

<b>Study Number Investigator; Site; Study Period; Publication</b>	<b>Design</b>	<b>Number of Subjects</b>	<b>Diagnosis/Indication</b>	<b>Product Treatment Regimen</b>	<b>Evaluation Criteria</b>	<b>Results (Efficacy)</b>	<b>Results (Safety)</b>
Study number N/A Scully et al; Ireland; 2003-2005; <i>Vox Sanguinis 2007</i>	Retrospective	32 subjects (50 acute TTP episodes)	Acute TTP undergoing PEX	Octaplas® Generation 2a and Cryosupernatant		Reported no difference in number of PEX to remission with cryosupernatant and Octaplas®	allergic/ urticarial and citrate reactions were more common with cryosupernatant
Study number N/A Edel et al; Germany; 1998-2006; <i>Transfusion Medicine and Hemotherapy 2010</i>	Retrospective	8	Acute TTP undergoing PEX	Octaplas® Generation 2a, median of mean dose exchanged 43.66 mL/kg	Platelet count, assessment of hemolytic anemia	Reported increase in platelet count to above 150x10 <sup>9</sup> /L and disappearance of hemolytic anemia	No ADRs reported
Study number N/A Santagostino et al; multi-center Italy; Period not specified <i>The Hematology Journal 2006</i>	Prospective; Open label; Uncontrolled	17	Inherited coagulation disorders (afibrinogenemia n=1, FV n=4, FV/FVIII n=6, FX n=1, FXI n=5) (14 elective surgery, 2 vaginal delivery, 1 emergent subdural cyst removal)	Octaplas® Generation 2a, median dose 18 mL/kg	PK of deficient factors and hemostatic efficacy	Reported treatment courses judged fully effective (actual blood loss did not exceed expected and no bleeding complications) in 13/16 cases.	1 ADR (rash)
Study number N/A Demeyere et al; Belgium; 2002-2004; <i>Vox Sanguinis 2010</i>	Prospective	40	Semi-urgent cardiac surgery	Octaplas® Generation 2a n=20 PCC n=20	Number of subjects reaching target INR (≤1.5), time to reach target after CPB, post-op bleeding	Reported PCC reversed anticoagulation faster and with less bleeding than Octaplas®	2 ADRs (oozing with Octaplas®)

*Adapted from: Octapharma Appendices to Summary of Clinical Safety, Tables 2.7.2.5 February 2011 and 2.7.3.6 November 2011*