



STATISTICAL REVIEW AND EVALUATION BLA (MID-CYCLE REVIEW)

BLA Number: STN 125416/0

Product Name: octaplasLG

Indication(s):

1. Management of preoperative or bleeding patients who require replacement of multiple plasma coagulation factors
2. Substitution of intentionally removed plasma (e.g. plasma exchange in patients with thrombotic thrombocytopenic purpura)

Applicant: Octapharma

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1. EXECUTIVE SUMMARY

The sponsor submitted a biologic licensure application for the use of octaplasLG for the following two indications: 1) management of preoperative or bleeding patients who require replacement of multiple plasma coagulation factors and 2) substitution of intentionally removed plasma (e.g., plasma exchange in patients with thrombotic thrombocytopenic purpura [TTP]).

Study reports from four clinical studies are used in support of the product's efficacy: one observational study, two Phase I PK studies (one conducted under an IND), and one Phase II study (with similarly formulated products). The review is ongoing, and this memo serves as a mid-cycle review assessment.

2. INTRODUCTION

2.1 Overview

The sponsor submitted a biologic licensure application for the use of octaplasLG for the following two indications: 1) management of preoperative or bleeding patients who require replacement of multiple plasma coagulation factors and 2) substitution of intentionally removed plasma (e.g., plasma exchange [PEX] in patients with thrombotic thrombocytopenic purpura [TTP]).

Octaplas was developed in the late 1980's and has obtained marketing authorization in 29 countries worldwide. It was developed as an alternative to single-donor fresh frozen plasma (FFP) to minimize the risk of virus transmission and improve therapeutic accuracy and reduce adverse reactions.

Octaplas is prepared from 630 to 1,520 single-donor units of FFP of the same blood group. During the manufacturing process, whole cells and cell fragments/debris are removed by filtration. Subsequently, the plasma pool is treated with a combination of solvent and detergent (S/D) to inactivate any enveloped viruses. These S/D reagents are later removed by oil and solid phase extraction. After additional filtration, Octaplas is filled into 200 mL bags and rapidly deep-frozen.

The sponsor has produced several generations of SDP: Octaplas (Generation 1), Octaplas (Generation 2a), octaplasLG (Generation 2b), Uniplas (Generation 3a) and UniplasLG (Generation 3b). This BLA is for octaplasLG (ligand gel [LG]). The manufacturing process for octaplasLG eliminates potential prion proteins and the S/D treatment has been shortened from -----(b)(4)--- resulting in higher plasmin inhibitor activities. The active ingredient (human plasma proteins) consists of all the normal components of plasma such as albumin, immunoglobulins and other globulins, coagulation factors and complement factors, and their inhibitors. The total protein concentration is 45 - 70 mg/mL and the protein distribution is within the normal range for human plasma. The coagulation

activity values are close to the corresponding values for normal human plasma. Currently, octaplasLG is approved in 11 European countries.

A Type C meeting to discuss the clinical program was held with the sponsor on December 18, 2008. During this meeting, the FDA recommended that a phase 1 PK bridging study between Octaplas and octaplasLG be conducted; subsequently, IND 13956 for substitution of intentionally removed plasma was submitted on February 18, 2009 and the FDA allowed it to proceed on May 7, 2009. The clinical study was initiated on December 01, 2009 and completed July 27, 2010.

2.2 Data Sources

All data sources are included in the sponsor's eCTD submission located in the FDA/CBER Electronic Document Room (EDR).

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Fourteen clinical studies and one observational study are cited in support of clinical efficacy (Table 1). Complete study reports (including data) from four of the studies (UNI-101, LAS-201, LAS-203 and UNI-110) are included in this application, but only with three of these four studies (LAS-201, LAS-203, and UNI-110) included the product octaplasLG. Two of the studies (LAS-203 and UNI-110) are PK studies.

The remaining clinical studies listed in Table 1 were performed on other generations of the product and the literature describing the studies are briefly summarized by the sponsor. The sponsor states that despite some differences in the composition of FFP and SDP plasma, prospective controlled and observational studies have failed to reveal any significant difference in clinical efficacy or tolerance between the 2 types of plasma and therefore considers FFP and octaplas/octaplas LG and Uniplas to be essentially equally efficacious. This efficacy review will evaluate only the four complete studies submitted by the sponsor.

Table 1: Efficacy Studies to Support the BLA

Study	Design	Product(s)	Disease	Total N
<i>Indication: Management of Preoperative or Bleeding Patients Who Require Replacement of Multiple Plasma Coagulation Factors</i>				
UNI-101 (Solheim et al)	Phase II, prospective, randomized, controlled, blinded	Octaplas (G-2a*) and Uniplas	Elective open heart surgery	84
Hellstern et al. (1998-9)	Prospective, controlled, open-label	Octaplas (G-2a) and FFP	Open heart surgery	67
Svennevig et al.	Prospective, open-label, parallel group	Octaplas (G-1**), no plasma, and FFP	Open heart surgery	66
Chekrizova et al.	Retrospective	Uniplas and Octaplas (G-2a)	Neonates with coagulopathy;	111

Study	Design	Product(s)	Disease	Total N
			OBGyn patients; liver disease	
<i>Indications: Management of Preoperative or Bleeding Patients Who Require Replacement of Multiple Plasma Coagulation Factors AND Substitution of Intentionally Removed Plasma (Plasma Exchange)</i>				
LAS-201	Observational, prospective, multi-center, sequential cohort, open-label	Octaplas (G-2a) and octaplasLG	Any	125
LAS-103 (Williamson et al)	Prospective, randomized, multi-center, open-label	Octaplas (G-2a) and FFP	Liver disease, liver transplantation, TTP	55
<i>Indication: Substitution of Intentionally Removed Plasma (Plasma Exchange)</i>				
LAS-203 (IND 13956)	Phase 1, prospective, randomized, open-label, controlled, cross-over, single center	Octaplas (G-2a) and octaplasLG	Healthy volunteers	60
UNI-110	Phase 1, prospective, randomized, double-blind, controlled, cross-over, single center	octaplasLG and UniplasLG	Healthy volunteers	30
Scully et al.	Retrospective	Octaplas (G-2a) and cryosupernatant	Acute TTP	32
Edel et al.	Retrospective	Octaplas (G-2a)	Acute TTP	8
<i>Other Indications</i>				
Inbal et al.	Prospective, open-label	Octaplas (G-1)	Hereditary or acquired coagulation factor deficiency	11
Hellstern et al. (1992)	Prospective, open-label, single center	Octaplas (G-1)	ICU patients w/ disseminated intravascular coagulation (DIC)	30
Santagostino et al	Phase 4, prospective, open-label, multi-center	Octaplas (G-2a)	Inherited coagulation disorders	17
Demeyere et al	Prospective, randomized, single center	Octaplas (G-2a) and prothrombin complex	Cardio-pulmonary bypass surgery	40

Study	Design	Product(s)	Disease	Total N
		concentrates		
LAS-1-02-D (cancelled)	Phase 4	Octaplas (G-2a) and FFP	ICU patients	7

*Generation 2a **Generation 1

3.1.1 Clinical Study UNI-101

Primary Objectives (Safety):

- 1) To show there is no additional activation of the complement system compared to normal activation during open heart surgery
- 2) To show there are no incompatibility reactions due to low titered anti-A or anti-B antibodies in Uniplas.

Secondary Objective (Safety): To show that Uniplas is safe by monitoring vital signs and recording AEs.

Secondary Objective (Efficacy): To show Uniplas is effective by measuring global coagulation parameters.

3.1.1.1 Study Design and Endpoints

This prospective phase 2, randomized, controlled, observer-blind, single center (Norway), parallel group (three treatment arms plus control) study investigated octaplas (Generation 2a) and Uniplas in 84 patients aged > 18 years undergoing elective open heart surgery (coronary bypass [single or multiple grafts], valvular surgery, or combined coronary bypass and valvular surgery). The treating anaesthesiologist was not blinded, but the primary endpoints (laboratory measurements) were assessed by blinded investigators in a different location. Subjects were evaluated up to two days post-operatively and had a six month follow-up period. Number of units administered depended on the subject's condition during surgery and the post-operative phase. Usually, two to three units at 200mL were administered in continuation.

For randomization, subjects were stratified into three blood groups: A or B (stratum 1), AB (stratum 2), or O (stratum 3). Within each stratum, the subjects were randomized (2:1 ratio) to receive either Uniplas or octaplas (blood group AB). Randomization took place before plasma infusion during surgery. In case no infusion was administered, the subject was assigned to the control group. Some subjects could (potentially) receive plasma only during the post-operative phase, but not during surgery. In these cases, randomization took place during the post-operative phase. The subject was assigned to one of three treatment groups in the same randomized manner.

Sample size was determined based on an expected difference in increases of C3bc from baseline between the treatment arms. The estimated sample size of 18 evaluable subjects would be sufficient to detect a clinically significant difference of 20 A.U. in C3bc between the treatment arms with 80% power and a Type I error of 0.05. The planned number of subjects per blood group was based on the expected frequency of

the blood groups in the target population. Thus, in stratum 1, 16 subjects were randomized to Uniplas and eight to octaplas. In stratum 2, two subjects were randomized to Uniplas and one to octaplas. For the third stratum, 18 subjects were randomized to Uniplas and nine to octaplas. Subjects who did not receive any plasma were entered in the control group, with a maximum of 18 subjects enrolled. Under this randomization scheme, 36 subjects (all blood types combined) received Uniplas, 18 subjects (all blood types combined) received octaplas, and 18 subjects were assigned to the control group.

For analysis, subjects were grouped into three treatment arms depending on their blood group and the treatment received. Arm 1 consists of subjects with blood group A, B or AB and received Uniplas, while Arm 2 has subjects with blood group O and received Uniplas. Arm 3 consists of subjects with any blood group that received Octaplas. A non-randomized control group did not receive any plasma.

The two primary safety endpoints were maximum increase in C3b3 compared to baseline and positive direct antiglobulin test (DAT) compared to baseline. Secondary safety endpoints were vital signs, AEs, laboratory parameters, urine examination, and viral markers. The two efficacy endpoints were the coagulation parameters activated partial thromboplastin time (aPTT) and activated coagulation time (ACT).

Endpoints were measured at baseline, after surgery, and post-operatively days 1 and 2; additionally, safety endpoints were measured after infusion for active treatment subjects only. Viral markers were only measured six months post-operatively. Post-infusion samples were taken within 30 minutes after the last infusion series. If further series were required, post-infusion samples were taken again within 30 minutes post-infusion. Post-operative samples were taken within 30 minutes after the end of surgery. In case further plasma units were required (most likely to happen during the first post-operative day), post-infusion samples were taken again.

An interim analysis was performed approximately 14 months after the study started (42 subjects enrolled). It was not planned a priori, but rather incorporated into the study design via a protocol amendment. The purpose of the interim analysis was not defined, but the sponsor did not plan to stop the trial based on the interim results. The sponsor did not provide information on who had access to the interim results. Adjustment of the Type I error rate for the primary safety endpoint C3bc was done using the O'Brien and Fleming procedure. This unplanned interim analysis calls into question the validity of the study results.

3.1.1.2 Patient Disposition, Demographic and Baseline Characteristics

A total of 84 subjects were enrolled: 25, 11, 19, and 29 subjects, respectively, in arms 1, 2, 3 and control. By blood group, 45 (54%) subjects were type A, 7 (8.3%) were type B, one (1.2%) type AB and 31 (37%) type O. Of these 84 subjects, 75 subjects completed the study and nine subjects (2, 1, 4 and 2, respectively) withdrew. 58% of the enrolled subjects were male.

3.1.1.3 Statistical Methods

For the efficacy variables, changes from baseline were summarized using mean, SD and range. No adjustment of the significance level for multiplicity was employed due to no hypothesis test being performed.

3.1.1.4 Results and Conclusions

Only subjects with complete datasets (measurements at all time points) were used in the analysis (73 subjects for aPTT and 67 for ACT). Analysis was conducted using the intent-to-treat principle. Missing data were not replaced.

No hypothesis tests were planned for the efficacy endpoints. Tables 2 and 3 show the changes from baseline for aPTT and ACT, respectively.

Table 2: Changes in aPTT Over Time

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

Table 3: Changes in ACT Over Time

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

3.1.2 Observational Study LAS-201

Objectives:

- Assess the effectiveness and tolerability of Octaplas (Generation 2a) and octaplasLG
- Compare the outcomes in patients treated with Octaplas (Generation 2a) with those treated with octaplasLG.

3.1.2.1 Study Design

This non-interventional, sequential cohort, observational, open-label, prospective, multicenter (five centers in Germany) study did not follow a defined protocol but rather normal clinical practice. All initially enrolled patients received Octaplas; once octaplasLG was marketed, then the remaining patients were enrolled. This sequential cohort design was chosen because it was planned that once the additional manufacturing step was implemented, Octaplas would be replaced by octaplasLG. The cohort receiving Octaplas is the comparator group.

Eligibility consisted of male and female subjects of any age who required a transfusion, as determined by the responsible physician, with octaplas or octaplasLG, taking into account the labeled contraindications and warnings and precautions. Dosage was according to the situation and individual needs of the patient.

One treatment episode was defined as the time period when either product was given. Within one treatment episode, one or more bags could be transfused. If the time difference between two transfusions was more than four hours, then the subsequent administration was considered a new treatment episode.

The sample size was based on the 95% confidence interval for the probability of observing a rare event (a patient with at least one adverse drug reaction [ADR]). For a sample size of 59 in which no events occur, the upper bound of the one-sided 95% CI for the probability of an event is 0.05 (i.e., ADRs with an incidence of at least 5% can be detected with 95% confidence). Total planned sample size was 120 patients (60 in each cohort).

The effectiveness of whether the use of the product was successful was an objective assessment by the physician based on clinical or laboratory parameters relevant for the indication. This assessment was analyzed for the following subgroups: center, gender, age, blood group, primary indication for transfusion (centrally assessed), and administration of other plasma/blood or coagulation-promoting products during transfusion. In the case of multiple episodes per patient, the last episode was analyzed. In addition, analyses of study product and administration of other plasma/blood products were planned.

The tolerability was evaluated on the basis of the number, nature, type and severity of ADRs. Only AEs with a causal relationship (definite, probable or possible) with the administration of the product were recorded as an ADR. Examination of laboratory parameters (for the last individual episode) was planned.

The observation period per patient depended on the indication treated, but was usually one to two days. The study duration was two years.

Since this was a non-interventional, observational study, informed consent was not necessary. In addition, source data verification was not performed. However, proper data recording methods on the case report forms as well as data quality crosschecks were planned.

3.1.2.2 Patient Disposition, Demographic and Baseline Characteristics

Total enrollment was 125 patients (65 Octaplas, 60 octaplasLG). Distribution of patient enrollment at the five centers was n=34, 43, 13 (all Octaplas), 25 (all Octaplas) and 10 (all octaplasLG) patients.

More male patients (n=74) than female (n=51) were enrolled. Patients were evenly divided between age > 60 years (n=62) and ≤ 60 years (n=63). Ethnicity/race information was not collected. Fifty-three patients had blood group O, 56 with blood group A, and 16 with blood group B or AB.

Patients were evenly divided concerning administration of other plasma/blood products or coagulation-promoting agents during transfusion (with: n=63, without: n=62). The primary indication for transfusion was peri-/intra-operative use (n=43), PEX (n=32), consumptive coagulopathy/DIC (n=30), non-surgical bleeding (n=11), and other (n=9).

3.1.2.3 Statistical Methodologies

No statistical hypothesis testing was planned. Methods of descriptive statistics were used for the analyses. Standard summary statistics (mean, SD, median, range, quartiles) as well as the 95% confidence interval of the mean were calculated for continuous variables. Observed and relative frequencies were presented for categorical variables.

All patients who received at least one dose were included in the analysis. Missing data was not replaced.

3.1.2.4 Results and Conclusions

Only one adverse drug reaction occurred.

3.1.3 Clinical Study LAS-203

Primary Objective: To compare the efficacy of octaplasLG with Octaplas in terms of recovery of coagulation factors and other hemostatic parameters.

Secondary Objective: To compare the safety and tolerability of octaplasLG with Octaplas in terms of hematological and clinical chemistry parameters and AE reporting

3.1.3.1 Study Design and Endpoints

This open label, randomized, single center, two-period cross-over, phase 1 IND study (13956) of substitution of intentionally removed plasma was conducted in 60 healthy volunteers (30 volunteers for each treatment sequence) at least 18 years of age. A cross-over design was chosen to minimize inter-individual variability in the endogenous plasma levels of coagulation factors and differences in response. Each subject was randomly assigned to one out of two treatment sequences (A or B). Sequence A subjects received octaplasLG followed by Octaplas. Sequence B subjects received treatment in the opposite order. Block randomization was utilized, but the block sizes were not specified.

Subjects first underwent a blood sampling, followed by standard plasmapheresis of 600mL and a second blood sampling five minutes later. The product was then infused at a dose of 1200mL. Additional blood samples to assess safety and efficacy parameters were drawn 15 minutes, two hours, 24 hours, and seven days after the end of infusion. The second infusion (of the other product) took place after a minimum washout period of four weeks. Identical blood sampling time frames were observed. Each subject's participation was seven to 10 weeks.

The primary endpoints were coagulation factors (FI, FII, FV, FVII, FVIII, FIX, FX, and FXI) and hemostatic parameters (aPTT, PT and protein C). The secondary endpoints were hematology parameters (RBC count, WBC count, platelets, hematocrit, hemoglobin, plasmin inhibitor, and protein S), clinical chemistry parameters (sodium, potassium, calcium, creatinine, ALAT, GGT, and total protein), AEs, overall tolerability, and vital signs. All laboratory assessment were done on fresh plasma at the study site.

All subjects who received at least one infusion of either treatment constituted the safety population. The intent-to-treat population consisted of all subjects with any measurements on the primary endpoint parameters. All subjects who completed both treatment periods without major protocol deviations formed the per-protocol population.

No interim analysis was planned, and imputation of missing data was not planned. Subjects were to be replaced only if more than 10% of subjects withdrew.

3.1.3.2 Statistical Methods

Descriptive statistics for the original values of the efficacy endpoints as well as their relative differences to baseline (after plasmapheresis) were planned. In addition, plots of the individual time profiles and the mean profiles per treatment were planned. To demonstrate equivalent efficacy, recoveries were analyzed by one-sided paired t-tests.

A review of the sponsor's results is ongoing.

3.1.4 Clinical Study UNI-110

Primary Objective: To compare safety and the tolerability of UniplasLG with octaplasLG.

Secondary Objective: To compare the efficacy of UniplasLG with octaplasLG.

3.1.4.1 Study Design and Endpoints

This phase 1 double-blind, randomized, cross-over study was conducted with 30 healthy volunteers (15 per treatment group) at least 18 years of age. Each subject's participation was four to five months. Each subject was randomly assigned to one out of two treatment sequences (A or B). Sequence A subjects received UniplasLG

followed by octaplasLG. Sequence B subjects received treatment in the opposite order. Block randomization was utilized, but the block sizes were not specified.

The study treatment plan was identical to that for study LAS-203 (see Section 3.1.3.1).

The primary endpoint was hemoglobin. The secondary endpoints were hemolysis parameters, complement activation, CIC, immune hematology, hematology parameters, hemostatic parameters, viral status, overall tolerability, and vital signs.

The review of this study is ongoing.

3.1.5 Comparison of Efficacy

Due to the heterogeneity of the studies, no single efficacy endpoint was used in all the efficacy trials. For the purpose of comparing the efficacy results across the studies, the sponsor chose a global coagulation parameter (either PT or aPTT).

3.2 Evaluation of Safety

In addition to the above efficacy clinical studies, the safety program consists of eight clinical studies. A review of the safety program is ongoing.

3.2.1 Clinical Study UNI-101

3.2.1.1 Study Design

See section 3.1.1.1 for a description of the study and the safety endpoints.

3.2.1.2 Statistical Methods

For the primary safety endpoint of C3bc, a one-way ANOVA test was conducted for equality of the three treatment means. For the primary safety endpoint of DAT, positive reactions graded as +, ++, +++, and ++++ were summarized by treatment arm using counts and percentages. Measured values of the secondary safety endpoints and changes from baseline were summarized using mean, SD and range. Number of subjects with values below, within, or above the reference range at different time points were tabulated. Viral markers were summarized using counts and percentages. Every subject who received active treatment was included in the safety analysis population.

This review is ongoing.

3.3 Gender, Race, Age and Other Special/Subgroup Populations

A complete review of the subgroup populations is ongoing.

4. SUMMARY AND CONCLUSIONS

This marketing application contains four efficacy studies (one observational; two Phase I and one Phase II clinical). This reviewer found several review issues in the studies included in this BLA submission:

- None of the four studies is a pivotal study. This reviewer expects OBRR to make the assessment regarding the appropriateness of the clinical studies submitted.
- For the phase 2 study UNI-101, the efficacy was described without making any inferences (i.e., there is not a statistical hypothesis with a success criterion for the primary endpoint).
- For the phase 2 study UNI-101, an interim analysis was conducted on the primary safety endpoint, C3bc, without being pre-specified in the protocol before the start of the study. In addition, the sponsor does not specify who had access to the interim analysis. This unplanned interim analysis calls into question the integrity of the study results.

The review is ongoing and this statistical review memo serves as a mid-cycle assessment for the biological license application under STN 125416.

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