



STATISTICAL REVIEW AND EVALUATION BLA (FINAL 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

Date Submitted: December 23, 2011

Review Priority: Standard

Statistical Branch: Therapeutics Evaluation Branch (TEB)

Primary Statistical Reviewer: Renée C. Rees, Ph.D., Mathematical Statistician

Concurring Reviewer (1): Jessica Kim, Ph.D., Team Leader

Concurring Reviewer (2): Boguang Zhen, Ph.D., Branch Chief

Medical Office/Division: OBRR/DH/LH

Lead Reviewer: Nancy Kirschbaum, Ph.D.

Project Manager: Pratibha Rana, Ph.D.

Table of Contents

1. EXECUTIVE SUMMARY	3
2. INTRODUCTION	3
2.1 OVERVIEW	3
2.2 DATA SOURCES	4
3. STATISTICAL EVALUATION	4
3.1 EVALUATION OF EFFICACY	4
3.2 EVALUATION OF SAFETY	16
3.3 GENDER, RACE, AGE AND OTHER SPECIAL/SUBGROUP POPULATIONS	16
4. SUMMARY AND CONCLUSIONS	16
DISTRIBUTION LIST.....	17

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]). It currently has marketing authorization in 29 countries.

The application contains 14 studies (comparing various generations of the product) for efficacy consideration; this review evaluates the four studies for which the sponsor submitted data (one observational; two Phase I PK and one Phase II clinical). Note that none of the four studies is a pivotal study, and none of the 14 studies compares octaplasLG to the US standard of care (FFP).

Due to the heterogeneity of the studies, no single primary endpoint was used in the efficacy trials reviewed. However, statistical and clinical equivalence was observed for both the PK studies for their respective primary endpoints, although in one of the PK studies, the investigator assessed the tolerability of the product as “not well tolerated” in five of the 60 subjects. For the observational study, which did not follow a defined protocol but rather normal clinical practice, the treatment was deemed successful. The Phase 2 study was not powered to detect equivalence, but it did fail to reject the null hypothesis of no additional activation of the complement system. In addition, an unplanned and unblinded interim analysis was conducted on the primary endpoint in this Phase 2 study, calling into question the integrity of this study’s results.

This reviewer has no objections to the approval of octaplasLG.

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 S/D plasma: 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.

A Blood Products Advisory Committee meeting was held on September 20, 2012 to discuss this application. Details can be found at <http://www.fda.gov/AdvisoryCommittees/Calendar/ucm313863.htm>.

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

Thirteen clinical studies and one observational study are cited in support of clinical efficacy (Table 1). Complete study reports were provided for nine of the studies (Table 2), and data are provided for four of those. Note that only three of the studies included the product octaplasLG, and that two of them 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 S/D 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 studies with raw data submitted by the sponsor (Table 2).

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
Chekizova et al.	Retrospective	Uniplas and Octaplas (G-2a)	Neonates with coagulopathy; OBGyn patients; liver disease	111
<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

Study	Design	Product(s)	Disease	Total N
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 concentrates	Cardio-pulmonary bypass surgery	40

*Generation 2a **Generation 1

Table 2: Efficacy Studies with Study Reports

Study	Raw Data Provided	octaplasLG Studied
UNI-101 (Solheim et al)	X	
Hellstern et al. (1998-9)		
Svennevig et al.		
LAS-201	X	X
LAS-103 (Williamson et al)		
LAS-203 (IND 13956)	X	X
UNI-110	X	X
Inbal et al.		
Hellstern et al. (1992)		

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 in Uniplas
- 2) To show there are no incompatibility reactions due to low titred 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 (four treatment groups) 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 as follows: stratum 1 (blood groups A or B), stratum 2 (blood group AB), and stratum 3 (blood group O). Within these strata, 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 (stratum 4). 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 stratum 1, 2 or 3 in the same randomized manner.

For analysis, subjects were grouped into four treatment arms depending on their blood group and the treatment received. Arm 1 consisted 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 consisted of subjects with any blood group that received Octaplas, while Arm 4 was the non-randomized control group that did not receive any plasma.

The two primary endpoints were defined for the study: the safety endpoints maximum increase in C3b3 and TCC compared to baseline and positive direct antiglobulin test (DAT) compared to baseline. No adjustments of the significance level to avoid multiplicity were planned. Secondary safety endpoints were vital signs, AEs, laboratory parameters, urine examination, and viral markers. Secondary 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.

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. (SD 23 A.U.) in C3bc between the treatment arms with 80% power and a one-sided Type I error rate 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.

An unblinded interim analysis was performed approximately 14 months after the study started (42 subjects enrolled). It was not planned a priori, but conducted because of slow recruitment and thus 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 for a two-stage group sequential test plan. The significance level (two-sided) will be 0.0485 in the final analysis. 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 screened and enrolled: 25, 11, 19, and 29 subjects, respectively, in treatment arms 1-4. Of these 84 subjects, 75 (89.3%) subjects completed the study and nine subjects (2, 1, 4 and 2, respectively, per arm) withdrew. 58% (49/84) of the enrolled subjects were male and the mean age (SD) was 68.2 (11.3) years (range 31 to 88 years). 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.

During one transfusion episode, the minimum dose was one bag and the maximum dose was seven bags. The maximum dose given to one subject during the study was 23 bags. One subject had six transfusion episodes.

The baseline values of C3bc were comparable in all four treatment arms.

3.1.1.3 Statistical Methods

For each subject, the increase in baseline Cb3c to all post-operative measurements was calculated, and the maximum among these increases was compared. The null hypothesis was that the maximum increase in Cb3c is the same for treatment arms 1, 2 and 3. An ANOVA model with treatment as a factor was used to test the hypothesis. If the null hypothesis was rejected, Scheffe's method of multiple comparisons would be used. The 95% CI for the difference between the treatment groups was also calculated using the MSE from the ANOVA model as the estimated SD.

Other safety endpoints were summarized descriptively, including changes from baseline as appropriate. For the efficacy variables, changes from baseline were summarized descriptively.

The analysis population was not specified. Missing data was not replaced.

3.1.1.4 Results and Conclusions

Data from all 84 subjects were used in the safety evaluation. For the primary endpoint C3bc, the mean (SD) maximum increase for the four treatment arms 1-4 was 66.68 (26.36), 81.36 (47.49), 71.06 (27.53) and 60.07 (34.74), respectively. The results of the ANOVA testing ($p=0.4522$) failed to reject the hypothesis that the maximum increase is the same for treatment arms 1-3. However, equivalence cannot be declared as the study was not powered to detect equivalence. In addition, the unplanned, unblinded interim analysis calls into question the integrity of these results.

For the second primary endpoint of DAT, there was no sign of an incompatibility reaction caused by anti-A or anti-B antibodies as there was no clear positive change between baseline and any other time point after first administration of the plasma for each treatment arm.

Five SAEs (Serious Adverse Events) occurred. Two subjects in treatment arm 3 (Octaplas) died peri-operatively. None of the deaths were causally related to either treatment.

Only subjects with complete datasets (measurements at all time points) were used in the secondary efficacy analysis (73 subjects for aPTT and 67 for ACT). Analysis was conducted using the intent-to-treat principle. No hypothesis tests were planned for the efficacy endpoints. The comparison of the aPTT and ACT between the groups on each sampling time point yielded similar values.

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, with the responsible physician deciding treatment with Octaplas was indicated, 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 subjects (65 Octaplas, 60 octaplasLG) with 163 treatment episodes (80 Octaplas, 83 octaplasLG). Distribution of subject enrollment at the five centers was n=34 (15 Octaplas, 19 octaplasLG), 43 (12 Octaplas, 31 octaplasLG), 13 (all Octaplas), 25 (all Octaplas) and 10 (all octaplasLG) patients.

Seventy-four male subjects (Octaplas n=33, octaplasLG n=41) and 51 female subjects (Octaplas n=32, octaplasLG n=19) were enrolled. The median age was 60 years (17-88 years). One subject (octaplasLG) was under 18 years, 72 subjects were aged 18 to 64 years, and 52 subjects were aged 65 years or over. Ethnicity/race information was not collected. Fifty-three subjects had blood group O, 56 with blood group A, and 16 with blood group B or AB.

More octaplasLG subjects (65%) than octaplas subjects (43.1%) received administration of other plasma/blood products or coagulation-promoting agents during transfusion. The primary indication for transfusion was peri-/intraoperative use (n=43), PEX (n=32), consumptive coagulopathy/DIC (n=30), non-surgical bleeding (n=11), and other (n=9). However, the indication for use varied considerably between the cohorts; the most frequent indication was consumptive coagulopathy/DIC for Octaplas and peri-/intraoperative use for octaplasLG.

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 subjects who received at least one dose were included in the analysis. In the Octaplas cohort, no treatment episode was terminated early, while in the octaplasLG cohort, one discontinuation of a treatment episode occurred. As no protocol deviations were identified, a per-protocol population was not used.

3.1.2.4 Results and Conclusions

No ADRs occurred in the Octaplas cohort; one ADR (possibly related severe hypotension) occurred in the octaplasLG cohort.

Overall, treatment success was 97% (64/65[98.5%] for Octaplas; 57/60 [95.0%] for octaplasLG). Treatment success was 100% for those subjects in both treatment arms with primary indication of consumptive coagulopathy/DIC, non-surgical bleeding or peri-/intraoperatively. For plasma exchange, success rates were 92.3% (12/13) for Octaplas and 89.5% (17/19) for octaplasLG. The fourth treatment failure occurred in the “other indication” category.

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, block randomized, single center, two-period cross-over, phase 1 IND study (13956) of substitution of intentionally removed plasma was conducted in healthy volunteers at least 18 years of age. Each subject was randomly assigned to one out of two treatment sequences (A or B). Sequence A subjects received Octaplas followed by octaplasLG. Sequence B subjects received treatment in the opposite order.

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 efficacy endpoints were coagulation factors (FI, FII, FV, FVII, FVIII, FIX, FX, and FXI) and hemostatic parameters (aPTT, PT and protein C). The secondary/safety 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. A 2-point subjective rating scale (“well-tolerated” or “not well tolerated”) was used by the investigator and subject to assess tolerability after infusion.

Relative recovery will be calculated for each efficacy parameter, treatment and subject to assess efficacy. It is defined as the maximum of the relative difference within two hours after infusion to the 5 minute post-plasmapheresis value divided by the value 5 minute post plasmapheresis multiplied by 100 to obtain a percentage. The analysis will attempt to demonstrate that the mean treatment difference of recovery for each of the efficacy parameters is within the interval [-10%, 10%]. Sixty subjects

(30 in each sequence) will give 80% power to detect a mean recovery difference of 5.5 (SD 14.5) for each of the efficacy parameters.

All subjects who received at least one infusion of either treatment constituted the safety population. The intent-to-treat (ITT) 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 (PP) population. The PP analysis is considered the primary analysis as this is an equivalence study.

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 Patient Disposition, Demographic and Baseline Characteristics

Sixty-three subjects were screened, 63 randomized, 60 analyzed in the ITT and safety populations (Sequence A, N=31; Sequence B, N=29), and 43 subjects in the PP population (Sequence A, N=25; Sequence B, N=18). Ten subjects withdrew and 10 subjects had insufficient dose of study drug.

In the ITT population, 35/60 (58.3%) of the subjects were male and all subjects, except one, were White. Mean age was 32.6±9.1 years (range 20 to 53). Blood group O was found in 25 (41.7%) subjects, Group A in 23 (38.3%), Group AB in 5 (8.3%), and Group B in 7 (11.7%) subjects.

Mean exposure to study drug was 15.1 mL/kg body weight for octaplasLG and 14.9 mL/kg for Octaplas.

3.1.3.3 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 the two one-sided t-tests (TOST) approach on the paired treatment differences of the coagulation factors and hemostatic parameters. In addition, 90% confidence intervals were calculated.

For the safety endpoints, frequency tabulations of AEs were grouped by SOC and preferred terms. Other safety parameters were analyzed descriptively for the two treatments including changes from baseline.

3.1.3.4 Results and Conclusions

For the coagulation factors and hemostatic parameters, all 90% CIs were within the tested interval [-10%, 10%]. Similar results were obtained for the ITT population. The results were also confirmed by paired t-tests (or non-parametric signed rank test in case of violation of normality). Thus the two plasmas are equivalent on the results for the hemostatic and coagulation parameters.

Bonferroni adjustment for multiple testing was performed on all hemostatic parameters and coagulation factors as an additional exploratory analysis. The p-values from the paired t-tests were used; the adjustment on these p-values had no influence on the results.

The amount of plasmin inhibitor in the 24 hours after plasma transfusion was higher in the octaplasLG group compared to the Octaplas group, and the differences were statistically significant at 15 minutes ($p=0.0012$) and two hours ($p=0.019$) post-transfusion for the PP population; the ITT population supported these results. Thus, the change in manufacturing process has led to an increase in plasmin inhibitor concentrations for octaplasLG (a deficiency of plasmin inhibitor can lead to excessive bleeding).

There were no deaths and one possibly related SAE (anaphylactic shock) in the octaplasLG cohort. Tolerability was assessed as “not well tolerated” five times in the octaplasLG cohort and 10 times in the Octaplas cohort by the investigator.

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, block randomized, single site, cross-over study was conducted with 30 healthy volunteers (15 per treatment group) at least 18 years of age and not blood group O. 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.

The study treatment plan was identical to that for study LAS-203 (see Section 3.1.3.1), with an additional blood sample at 12 weeks after the second infusion.

The primary endpoint was the change in hemoglobin (Hb) prior to plasmapheresis compared to 15 minutes after plasma transfusion. The secondary endpoints were hemolysis parameters, complement activation, CIC, immune hematology, hematology parameters, hemostatic parameters, viral status, overall tolerability, and vital signs.

All subjects who received at least one infusion of either treatment constituted the safety population. All subjects who completed both treatment periods without major protocol deviations formed the per-protocol (PP) population. The PP analysis is considered the primary analysis since it is an equivalence trial.

3.1.4.2 Patient Disposition, Demographic and Baseline Characteristics

Forty subjects were screened, 31 randomized and 30 treated (Sequence A, N=15; Sequence B, N=15). One subject withdrew. The PP population had 25 subjects (Sequence A, N=12; Sequence B, N=13).

Gender did not vary greatly between the treatment groups: 8/15 (53.3%) males in Sequence A and 9/15 (60%) males in Sequence B. Mean age of all subjects was 30.6±6.0 years (range 24 to 41 years) in Sequence A and 40.6±9.7 years (range 23 to 55 years) in Sequence B. One subject (Sequence A) was Asian; all other subjects were White. Exposure to treatment drug was 16.2 mL/kg body weight for UniplasLG and 16.1 mL/kg body weight for octaplasLG.

3.1.4.3 Statistical Methods

All measurements were analyzed descriptively.

To demonstrate equivalence of Hb change, a standard ANOVA model with treatment, period, sequence effects and subject effect nested within sequence was used. The square root of residual mean squares was used as an estimate of the variance and a 90% CI for the difference between treatment means were calculated. The equivalence margin was predefined as [-0.5 g/dL; +0.5 g/dL]. The null hypothesis (Hb change after Uniplas treatment was not within the equivalence range of octaplasLG treatment) was tested by the two one-sided t-test approach (TOST). The level of significance was set at 0.05.

Secondary endpoints were analyzed descriptively between the two treatments with mean treatment differences estimated along with 95% CIs for continuous parameters and shift tables for categorical variables. Any p-values for secondary endpoints were calculated only for exploratory purposes. All treatment-emergent AEs were displayed in summary tables, listings and figures. AE incidences were given as numbers and percentages of subjects within each treatment group.

3.1.4.4 Results and Conclusions

The 90% CI for Hb, [0.03859, 0.4967] in the PP population, was within the predefined limits of equivalence: [-0.5 g/dL; +0.5 g/dL]. For the safety population, the 90% CI [0.05894, 0.5203] was not within the equivalence margin; removing a potential outlier, though, did yield a 90% CI within the equivalence margin: [0.02193, 0.4771]. However, since the primary analysis is the PP population, the two plasmas are equivalent on Hb.

No SAEs occurred during the study.

3.1.5 Comparison of Efficacy

Due to the heterogeneity of the studies, no single primary endpoint was used in the efficacy trials reviewed. However, equivalence was observed for both the PK studies (LAS-201 and UNI-110) for their respective primary endpoints. For the observational study (LAS-203), the treatment was deemed successful. For the phase 2 study, ANOVA

testing failed to reject the null hypothesis that no additional activation of the complement system was observed in the primary endpoint.

3.2 Evaluation of Safety

Safety endpoints were used as primary endpoints in the above efficacy clinical studies and are discussed in Sections 3.1.1 – 3.1.4.

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

For efficacy (observational) study LAS-201, subgroup analyses by sex, age, blood groups and by administration of other plasma/blood products or coagulation-promoting agents during transfusion revealed no particular trends for treatment failures. Ethnicity data was not collected in this study.

No subgroup analyses were planned or performed for the other three efficacy studies reviewed.

4. SUMMARY AND CONCLUSIONS

This marketing application contains fourteen studies for efficacy consideration. The sponsor submitted study reports for nine of those studies, of which data was provided for four of them (one observational; two Phase I PK and one Phase II clinical). This review evaluated the four studies with data. The results from the primary endpoint analyses of those four studies are the following. Note that safety endpoints were used as primary endpoints.

- For the phase 2 study UNI-101, analysis of the primary endpoint, Cb3c, ANOVA testing failed to reject the null hypothesis that there was no additional activation of the complement system due to Uniplas when compared to treatment with Octaplas and to normal activation seen during cardiac surgery. However, equivalence cannot be declared as the study was not powered for such.
- For the observational study LAS-201, no statistical hypothesis testing was planned. Overall, treatment success was 97% (98.5% for Octaplas and 95.0% for octaplasLG).
- For the phase 1 PK study LAS-203 conducted under IND 13956, all primary endpoints (coagulation factors and hemostatic parameters) had 90% CIs within the equivalence interval.
- For the phase 1 PK study UNI-110, the 90% CI for the primary endpoint, Hb, in the PP population was within the predefined limits of equivalence; thus UniplasLG and octaplasLG are equivalent on Hb.

Several review issues were identified in the studies evaluated in this BLA submission:

- None of the four studies is a pivotal study, or compares the product (octaplasLG) to the US standard of care (FFP). This reviewer expects OBRR to make the assessment regarding the appropriateness of the clinical studies submitted.
- Due to the heterogeneity of the studies, no single primary endpoint was used in the efficacy trials reviewed. Thus, comparison across studies is not possible.

- For the phase 2 study UNI-101, an unplanned, unblinded interim analysis was conducted on the primary 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.

This reviewer has no objections to the approval of octaplasLG.

DISTRIBUTION LIST

cc:

DCC/HFM-99

HFM- 215 /Chron

Pratibha Rana, Ph.D. HFM-380

Nancy Kirschbaum, Ph.D. HFM-392

Mitchell Frost, M.D. HFM-392

Jessica Kim, Ph.D. HFM-219

Boguang Zhen, Ph.D. HFM-219

John Scott, Ph.D. HFM-219

Henry Hsu, Ph.D. HFM-215

Estelle Russek-Cohen, Ph.D. HFM-215

Christopher Egelebo HFM-215