

# Pharmacology/Toxicology Review Memo - RiaSTAP

## MEMORANDUM

**To:** File (STN 125317/0)

**From:** La'Nissa A. Brown, Ph.D., Pharmacologist, Laboratory of Hemostasis, Division of Hematology/OBRR

**Through:** Timothy Lee, Ph.D. , Acting Branch Chief, Laboratory of Hemostasis, Division of Hematology/OBRR

**Subject:** Filing of Final Pre-clinical Review of STN 125317/0 – CSL Behring's BLA for Human Fibrinogen Concentrate, Pasteurized [RiaSTAP TM]

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### I. **Background**

Afibrinogenemia is a rare coagulation disorder with an estimated incidence of one to two per million in the population. Congenital afibrinogenemia refers to a deficiency in fibrinogen that renders blood incoagulable. It is inherited as an autosomal recessive trait and occurs mostly in children from consanguineous parents. RiaSTAP TM also known as Haemocomplettan, is a sterile, virus-inactivated, lyophilized human fibrinogen concentrate, pasteurized (HFCP) indicated for the treatment of afibrinogenemia (congenital fibrinogen deficiency).

Fibrinogen (Factor I) is a soluble plasma glycoprotein dimer which consists of three pairs of polypeptide chains ( $A\alpha$ ,  $B\beta$ , and  $\gamma$ ). Fibrinogen is a physiological substrate of three enzymes: thrombin, FVIIa and plasmin. Fibrinogen is a precursor to fibrin, a fibrillar protein that is three-dimensional polymerized to form in conjunction with platelets a hemostatic clot. Ineffective fibrinogen generation predisposes the person to hemorrhage, while excessive fibrin generation may lead to thrombosis. Fibrinogen is implicated in an increased risk of thromboembolic episodes such as deep vein thrombosis, pulmonary embolism, and myocardial infarction due to clotting incidence associated with increased levels of protein.

### II. **Proposed Use and Doses**

RiaSTAP TM will be reconstituted in sterile water to be administered on-demand intravenously at 15-30 mg/kg BW (maximal dose 60-120 mg/kg BW). The initial dose and subsequent doses are determined by the treating clinician based on measurement of the patient's fibrinogen levels. However, the determination of fibrinogen levels is recommended before and during treatment with HFCP.

### III. **Recommendations**

**Recommendation on BLA:**

Based on the review of pharmacological and toxicological data presented, I recommend the filing of this Biologics License Application (BLA) STN 125317/0 for Human Fibrinogen Concentrate, Pasteurized [RiaSTAP TM].

**Recommendation for non-clinical studies:**

Due to its long-standing history in clinical applications, the safety pharmacology and toxicity of RiaSTAP TM is well established for human use. Based on review of the presented data on pharmacology and toxicology, the safety data of Riastap TM in pre-clinical studies appears sufficient to support in human use. To note, please monitor for adverse events such as thromboembolic episodes as expected with fibrinogen administration.

I have no request for any further non-clinical evaluation at this time. There is no outstanding issue that preventing this BLA according to FDA guidelines from a pre-clinical standpoint. However, I will defer the final decision to my clinical colleagues who may be aware of other safety concerns based on their previous experience with this product in this application.

**IV. General Comments**

- No teratogenic, reproductive & developmental toxicity, mutagenic, secondary pharmacodynamics, repeat dose toxicity, genotoxicity or carcinogenic studies were performed using Riastap or its predecessors in pre-clinical studies.
- Repeat dose toxicity studies were not carried out due to probable antibody induction and previous human experience with RiaSTAP TM outside the U.S..

**V. List of Non-clinical Studies in STN 125317/0**

- Study Report LMR 03/00 Influence of Haemocomplettan P on fibrinogen plasma levels and on coagulation in the LPS induced sepsis model in rats
- Study Report 165-35 Safety Pharmacological investigations with Hemocomplettan HS on -(b)(4)- dogs following intravenous administration
- Study Report 165-09 Assay on possible formation of neoantigens arising from the change in the production procedure with Haemocomplettan HS.
- Study Report PT-8r Neoantigenicity study of Haemocomplettan P
- Study Report 165.1-24 Local Toxicity study after intravenous injection of Haemocomplettan HS in rabbits
- Study Report 165.1-24.1 Local toxicity study after intraarterial injection of Haemocomplettan HS in rabbits
- Study Report 165.1-24.2 Local toxicity study after paravenous injection of Haemocomplettan HS in rabbits
- Study Report 165-11 Acute intravenous toxicity with Haemocomplettan HS in the mouse
- Study Report 165-12 Acute intravenous toxicity study with Haemocomplettan HS in the rat

**VI. Summary of Review of Studies in STN 125317/0**

| Project Number | Purpose                  | Dose                                | Study design   | Observations  | Outcome  | Animal Model                    |
|----------------|--------------------------|-------------------------------------|--|---|--|---------------------------------|
| LMR 03/00      | Pharmacodynamic/Efficacy | 25,50, 100 & 200, PC, NC mg/kg BW   | TEG; n=4/gr. (T=26 F) t=285 min; antigen LPS Abs admin. Prior to test article (DIC model)  | Dose-dependent increase in fibrinogen --> improved TEG; shortened rxn. time (ampl.) 200 mg/kg restored normal fibrinogen levels                                       | RiaSTAP restores coagulation associated w/ decrease in fibrinogen w/ severe DIC;   | Rats (Hypofibrinogenemic model) |
| 165-35         | Safety Pharmacology      | 320 mg/kg BW; 20, 100, 200 mg/kg BW | GLP i.v. at 5 mins intervals Replacement therapy, n=6/gr., 3M/3F/gr., circulation, respiration, complete serum chemistry & coagulation were monitored. | TEG, slight changes in hematology: PLT, WBC, Ery.; fibrinogen, coagulation/fibrinolysis; prolonged aPTT; all changes were dose-dept. following treatment with RiaSTAP | Test article was tolerable but requires further observation for safety as slight/mild minor changes in cardio & respiration and hematology (WBCs, platelets and eury.) occurred. | Hemophilia A -(b)(4)-           |
| 165-35         | Pharmacokinetics         | 320 mg/kg BW; 20, 100, 200          | ADME, non-rodent model (not defined in report)   | t 1/2=2.7-3.6 days, no specific studies performed in  | Close PK/PD relationship established;  | Non-rodent <i>in vitro</i>      |

| Project Number | Purpose         | Dose                            | Study design  | Observations   | Outcome   | Animal Model |
|----------------|-----------------|---------------------------------|---|--|---|--------------|
|                |                 | mg/kg BW                        |   | non-clinical PK model  | Human PK well known and established   |              |
| 165-11         | Toxicology      | 250-500 & 1000, saline mg/kg BW | GLP i.v. Acute toxicity, n=5 M/F, 2wks. 4 gr.'s; gross path, BW, clinical signs | Clinical signs, BW changes, gross path., were elevated but with no ss changes related to test article. | No toxicity with adverse rxns. and well tolerated w/o test article related changes. | Mice         |
| 165-12         | Toxicology      | 100, 200, 300, saline mg/kg BW  | GLP Bolus i.v Acute toxicity & local tolerance, n=5 M/F, 4 gr., 2 wks.          | Clinical signs, BW changes, gross path., were elevated but with no ss changes related to test article. | No toxicity and well tolerated w/o test article related changes.                    | Rat          |
| 165.1-24       | Local tolerance | 100 mg/kg;                      | i.v site, n=5/F, vs. saline (control); 30-40 days post dose                     | Blood samples, 3 notable adverse rxns. (slight-moderate hemorrhages) that were test article related    | Tolerable overall with concern for hemorrhage                                       | Rabbit       |
| 165.1-24.1     | Local tolerance | 100 mg/kg                       | i.a site, n=5/F vs. saline (control);   | No significant changes to note   | Well tolerated  | Rabbit       |
| 165.1-24.2     | Local tolerance | 100 mg/kg                       | p.v. site, n=5/F vs.  | No significant changes to cause alarm; 2   | Well tolerated  | Rabbit       |

| Project Number | Purpose         | Dose                                       | Study design  | Observations  | Outcome  | Animal Model        |
|----------------|-----------------|--|---|---|--|---------------------|
|                |                 |  | salinel (control)   | adverse rxn.'s (slight hemorrhages)   |  |                     |
| 165-09         | Neoantigenicity | 10 mg/animal/1 mL                          | s.c (rabbit n=5/gr.) 3x/wk.; 3x/wk acute i.c & i.v (guinea pig n=4/gr); 4 lots, n=20/22; PCA Freund's adjuvant (emulsifier) | There were no significant induction of antigenic determinants based on ouchterlony assay and PCA test | No neoantigens; slight immunogenicity                                  | Rabbit , Guinea pig |
| PT-8r          | Neoantigenicity | 100 mg/kg; pasteurized vs. non-pasteurized | i.v 3x immunization/wk., ~40 days; 2 lots, n=6(8total), native-western analysis   | 1 death= likely shock related, 2 anaphylatic rxn.'s as related to test article (immunogenic rxn)      | No neoantigens; slight immunogenicity caused by product administration | Rabbit              |

VII. PCA= passive cutaneous anaphylaxis PC=positive control NC=negative control LPS= E. coli antigen LPS antibodies TEG=thromboemplasty T=total ss=statistically significant rxn.= reaction

VIII. **Comments:**

IX. **The pre-clinical program for RiaSTAP TM and its predecessors appears to be sufficient with concurrence to monitor safety and toxicity post market. The extensive previous clinical experiences negate the need for any further pre-clinical studies for current indication. Due to the potential of thrombogenicity and the small safety margin in the toxicity animal studies when compared to the proposed dosage, I recommend the sponsor to monitor post-marketing clinical data from other countries and in the U.S. regarding repeat use of RiaSTAP TMat the indicated dosage. As with all biologics, it suggested that the Sponsor monitor the immunogenicity following RiaSTAP TM administration in clinical settings.**

X. **Based on review of presented pharmacology and toxicology studies and previous clinical experience, the safety of in pre-clinical studies appears**

approvable for BLA for RiaSTAP TM on-demand treatment administration in patients of congenital fibrinogen deficiency (afibrinogenemia and hypofibrinogenemia). I have no request for any further non-clinical evaluation at this time based on these data. However, FDA does retain the right to request additional specialized preclinical studies if issues arise regarding safety following RiaSTAP TM administration in humans. As with all coagulation biologic products, it suggested that the Sponsor monitor the immunogenicity and thrombogenicity following RiaSTAP TM administration in clinical settings.

- XI. -Acute toxicity (mice and rat) observations were summarized and assumed to not be related to test article. However, data and findings for all subjects in study reports should be disclosed completely to draw conclusions in unbiased fashion. Further examination of results did not reflect substantial safety concerns outside of expected toxic responses following fibrinogen administration.
- XII. -Local tolerance studies are sufficient to confirm tolerability of RiaSTAP TM with minimal adverse reactions at maximal proposed dose.
- XIII. -RiaSTAP TM appears to be effective in a dose-dependent manner for safety and therapy's targeted treatment at and well above proposed human dose.
- XIV. -Historical data indicates RiaSTAP TM is well tolerated with minimal immunogenic responses in humans in clinical settings corroborating results of pre-clinical studies for proposed indication.
- XV. -A literature reference has been compiled on RiaSTAP TM and its predecessors within the preclinical program submission that includes *in vitro* analysis and a few *in vivo* analysis studies (rat sepsis model [TEG], porcine coagulopathy model). These data were supportive of the effectiveness of RiaSTAP TM in disease animal models.
- XVI. **Executive Summary**  
RiaSTAP TM was determined to be safe based on non-clinical studies (GLP and non-GLP) and its long-standing clinical history and use. Pre-clinical studies were conducted for local tolerance and neoantigenicity (rabbit and guinea pig), acute toxicity (mouse and rat), safety pharmacology/ pharmacodynamics and efficacy (- (b)(4)-, rat sepsis model, porcine coagulopathy model), and pharmacokinetics (non-rodent) at doses ranging from the clinical dose and up to more than ten fold maximal clinical dose. The safety profile of RiaSTAP TM is sufficient to support BLA approval. There were slight immunogenic responses following RiaSTAP TM administration (dogs and rabbit) likely attributed to immune reaction to human protein which is not atypical with human biologic products. *In vitro* and *in vivo* mutagenesis and carcinogenesis studies have not been performed with RiaSTAP TM. Previous experience with fibrinogen indicates a potential for clot formation and thromboembolic events when administered in pre-disposed patients and associated with elevated levels of fibrinogen in plasma.  
The Pharm/Tox reviewer, La'Nissa Brown, recommends approval.