Global Development Plan for a Double Virus Inactivated Fibrinogen Concentrate for the Treatment of Congenital Fibrinogen Deficiency

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Abstract

Congenital afibrinogenaemia and hypofibrinogenaemia are rare inherited disorders occurring in homozygotic patients with an estimated incidence of 1 in 10^6. Patients present with frequent severe bleeding episodes since birth or early childhood. Bleeding may occur after a minor trauma or a small surgical intervention, into the skin, mucosa, muscles, gastrointestinal tract, or the brain. Therapeutic substitution with human fibrinogen concentrate may help correct the haemostatic defect and arrest the bleeding in patients with these fibrinogen deficiencies. Octafibrin is a highly purified, lyophilized, human plasma fibrinogen concentrate, without added albumin. Octafibrin, a human fibrinogen concentrate product, is double virus inactivated using 2 dedicated virus inactivation / removal steps, solvent / detergent treatment, and nanofiltration. A plan for the global development and investigation of Octafibrin has been prepared taking into account discussions with European Regulators and the FDA. This plan also involves discussions with the European pediatric committee (PDCO) which oversees the inclusion of pediatric subjects into drug development under the new EMA guidelines.

Effective management of congenital fibrinogen deficiencies in bleeding situations is necessary for the prevention of potentially life-threatening bleeding episodes. This clinical program will investigate whether fibrinogen substitution using Octafibrin is able to successfully control bleeding, increase the fibrinogen plasma levels, and reduce the amount of transfusions needed with allogeneic blood products. In addition, it will give information on the tolerability and overall safety profile of Octafibrin.

Introduction

- Octafibrin is a plasma-derived, double virus inactivated, highly purified concentrate of freeze-dried human fibrinogen
- Octafibrin's intended therapeutic indication is the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia

The production of Octafibrin leads to a highly purified fibrinogen concentrate where no stabilizers are added.

Figure 1. Chromatography of fibrinogen concentrates

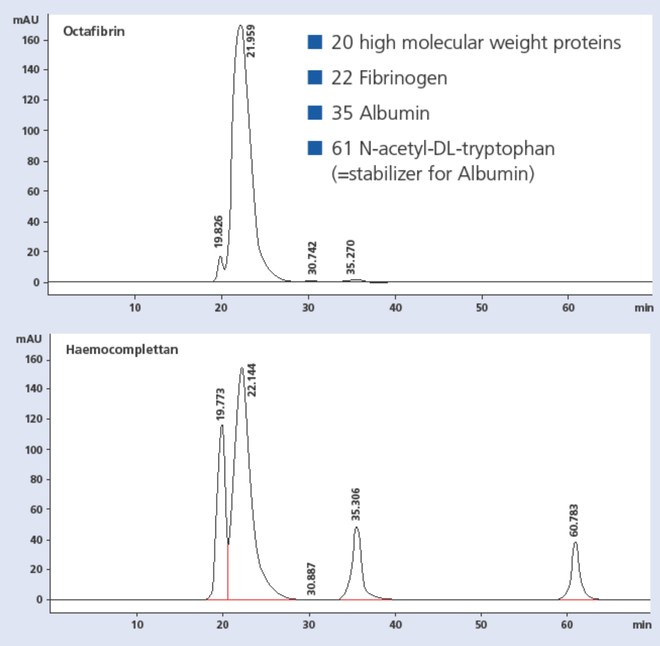
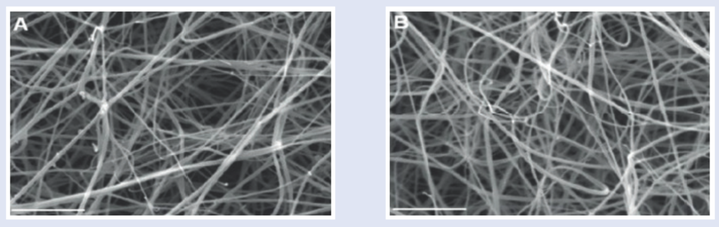


Figure 2. Octafibrin compared to international standard

Scanning electron micrographs of clots prepared from Octafibrin and from International Standard for Fibrinogen Concentrate (NIBSC 98/614)



Octafibrin | International Standard

Identical fiber thickness and crosslinking

Table 1. Octafibrin composition and pharmaceutical form

Ingredients	Quantity per mL reconstituted solution, mean values	Standard
Active ingredient		
Fibrinogen as clottable protein	20 mg	Ph. Eur.
Excipients		
Sodium chloride	6 mg	Ph. Eur.
Sodium citrate dihydrate	1.5 mg	Ph. Eur.
Glycine	10 mg	Ph. Eur.
L-Arginine hydrochloride	10 mg	Ph. Eur.

The package of the final product (Octafibrin 1gr) contains freeze-dried powder with the active ingredient to be reconstituted with 50 mL water for injection (WFI).

Octafibrin is double virus inactivated using 2 virus safe guarding steps, solvent / detergent treatment and nanofiltration. Table 2 and 3 show the virus reduction factors achieved.

Table 2. S/D Treatment for the inactivation of enveloped viruses

Virus (Model for)	S/D treatment [$\log_{10}$]
HIV (HIV-1/HIV-2)	≥ 7.5
PRV (HBV/CMV)	≥ 8.5
SBV (HCV/WNV)	≥ 8.6

HIV-1, 2 = Human immunodeficiency virus type I, II; PRV = Pseudorabies virus; HBV = Hepatitis B virus CMV = Cytomegalovirus; SBV = Sindbis virus; HCV = Hepatitis C virus; WNV = West Nile virus

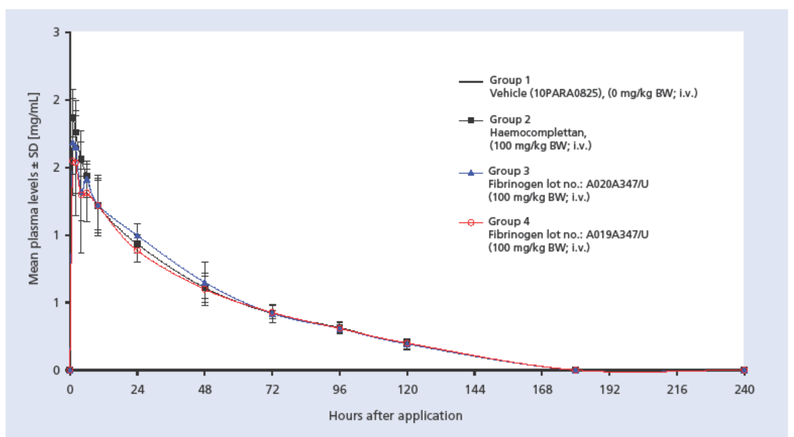
Table 3. Removal of non-enveloped viruses by nanofiltration

Virus reduction factor [log]					
Virus	**HIV-1/2**	**BVDV**	**PRV**	**HAV**	**PPV**
Run 1	≥ 6.82	≥ 5.55	≥ 6.56	≥ 5.61	5.06
Run 2	≥ 6.34	≥ 5.55	≥ 6.67	≥ 5.49	4.82

- The Planova 20N filter was specifically developed for this product.
- Nanofiltration is effective for removing even very small enveloped and non-enveloped viruses under conditions where 90-95% of protein activity is recovered

A pharmacokinetic study (PK) was performed in rabbits after a single i.v. dose of fibrinogen. Two batches of Octafibrin were tested in comparison to one batch of Haemocomplettan® P / RiaSTAP™ at a dose of 100 mg/kg body weight (BW) using a group size of 6 animals.

Figure 3. Comparative PK in rabbits



- Acute toxicity studies revealed no adverse or toxic effects
- Extensive pharmacology studies to evaluate safety were performed in dogs and rabbits assessing the cardiovascular, respiratory, neurological and coagulation system. No adverse effects and no signs of increased thrombogenicity were observed.

Clinical development of Octafibrin

- A marketing authorization application is planned for Octafibrin in Europe and the US for the indication of "treatment of bleeding in patients with congenital fibrinogen deficiency disorders"
- No specific guidelines for the clinical development of fibrinogen concentrates in the proposed indication from either the EU or USA
- The clinical program is based on the "Guidelines on the Clinical Investigation of Human Plasma-Derived and Recombinant Factor IX products", published by the EMA
- Congenital fibrinogen deficiencies are much rarer than factor IX [FIX] deficiency
- The development program for Octafibrin includes a comparative study with Haemocomplettan® P / RiaSTAP™ (FORMA 01)

Three studies are planned for investigation of the product in patients with congenital fibrinogen deficiency including:

FORMA 01

- A phase II comparative study (with Haemocomplettan® P / RiaSTAP™ as the comparator) to enroll 18 evaluable patients

FORMA 02

- An open, uncontrolled phase III efficacy study will evaluate efficacy and safety of Octafibrin in patients with acute or traumatic bleeding and surgery

FORMA 04

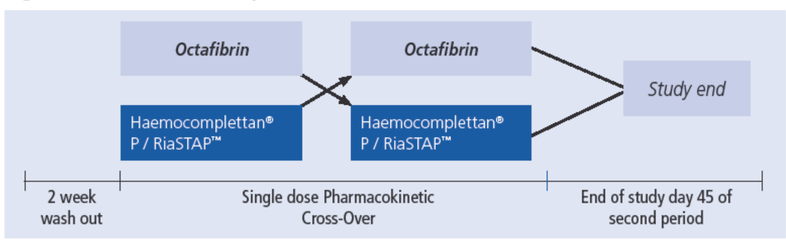
- A phase IIIb study to evaluate the efficacy and safety of Octafibrin in acute bleeding in patients aged < 12 years
- This study is to be conducted post market authorization in order to meet the requirements of the European Medicines Agency Pediatric Committee

FORMA 01

A prospective, controlled, randomised, cross-over study investigating the pharmacokinetic properties, surrogate efficacy and safety of Octafibrin compared to Haemocomplettan® P / RiaSTAP™ in subjects with congenital fibrinogen deficiency.

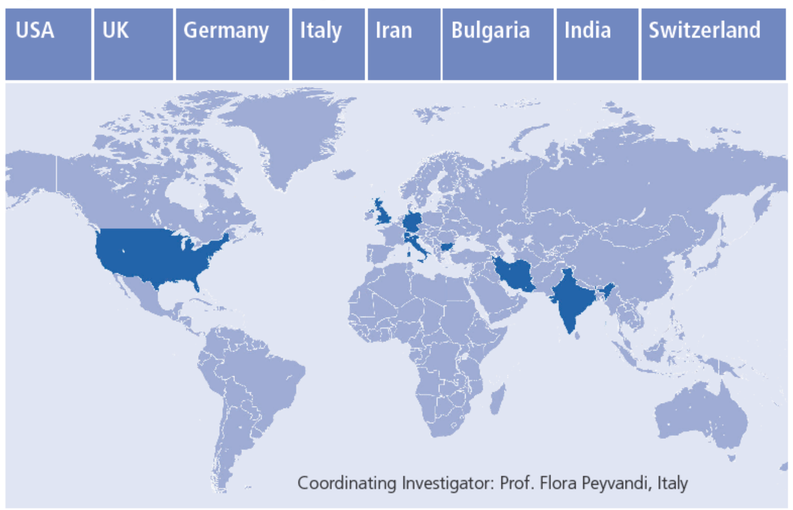
- Primary endpoint:
  A comparison of the area under the concentration curve between Octafibrin and Haemocomplettan® P / RiaSTAP™
- Surrogate endpoint for hemostatic efficacy:
  Comparison of Maximum Clot Firmness between Octafibrin and Haemocomplettan® P / RiaSTAP™ at 1 hour post-infusion
- Secondary endpoints:
  - To compare the *in vivo* recovery between Octafibrin and Haemocomplettan® P / RiaSTAP™
  - To compare the pharmacokinetics between Octafibrin and Haemocomplettan® P / RiaSTAP™
  - To evaluate the safety of Octafibrin

Figure 4. FORMA 01 Study outline



- Study will consist of two periods. Each study period consist of 45 days. Subjects will be randomised to receive a single infusion of Octafibrin or Haemocomplettan® P / RiaSTAP™ in both study periods. Crossover will be performed at the end of the first study period
- Single intravenous infusion of 70 mg/kg body weight of Octafibrin and Haemocomplettan® P / RiaSTAP™

Figure 5. FORMA 01 participating countries



Current status

- FORMA 01 enrollment was started in Q1 2013 with 7 sites initiated in 6 countries
- 17 patients have been enrolled as of April 2014
- No serious or related adverse events have been seen to date
- FORMA 02 study of the safety and efficacy in bleeding and surgery is in the initiation process and will begin shortly.

Conclusions

- Effective management of congenital fibrinogen deficiencies in bleeding situations is necessary for the prevention of potentially life-threatening bleeding episodes.
- This clinical program will investigate whether fibrinogen substitution using Octafibrin is able to:
  - successfully control bleeding,
  - increase the fibrinogen plasma levels,
  - be effective in the treatment of bleeds and in prophylaxis during and after surgery.
- This study will provide information on the tolerability and overall safety profile of Octafibrin.

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