Pharmacokinetic (PK) Comparison of Two Fibrinogen Concentrates for the Treatment of Congenital Fibrinogen Deficiency

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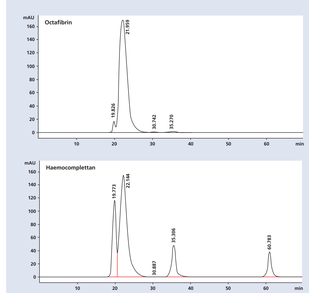
Background

Patients with congenital afibrinogenaemia and hypofibrinogenaemia experience frequent severe bleeding episodes starting at birth or early childhood. Bleeding may occur after a minor trauma or a small surgical intervention, into the skin, mucosa, muscles, gastrointestinal tract, or brain. Therapeutic substitution with human fibrinogen concentrate can correct the haemostatic defect and arrest the bleeding in patients with these fibrinogen deficiencies. In this first study in man, the (PK) profile of a new fibrinogen concentrate, Octafibrin, was compared to a commercially available product (Haemocomplettan® P / RiaSTAP™).

Introduction

- Octafibrin is a plasma-derived, double virus inactivated (SD and nanofiltration), highly purified concentrate of freeze-dried human fibrinogen.
- The production of Octafibrin leads to a highly purified fibrinogen concentrate where no stabilizers are added (Figure 1).

Figure 1. Chromatography of fibrinogen concentrates



- 20 high molecular weight proteins
- 22 Fibrinogen
- 35 Albumin
- 61 N-acetyl-DL-tryptophan (=stabilizer for Albumin)

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).

Clinical Development of Octafibrin

The following three studies are planned for investigation of the product in patients with congenital fibrinogen deficiency:

FORMA 01
- A phase II comparative study (with Haemocomplettan® P / RiaSTAP™ as the comparator) in 18 evaluable patients

FORMA 02
- An open, uncontrolled phase III efficacy study to evaluate the efficacy and safety of Octafibrin in 24 evaluable 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 6 evaluable patients aged < 12 years

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FORMA 01 Study

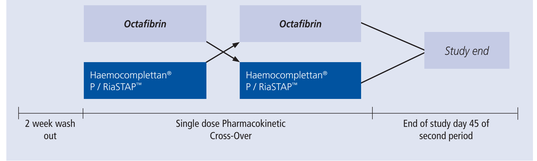
This study was a prospective, controlled, randomised, cross-over study investigating the pharmacokinetic properties, surrogate efficacy, and safety of Octafibrin compared to Haemocomplettan® P / RiaSTAP™ in subjects with congenital fibrinogen deficiency. The study was performed in the USA, the EU, and Asia.

Primary endpoints:
- To compare the area under the concentration curve between Octafibrin and Haemocomplettan® P / RiaSTAP™
- To compare Maximum Clot Firmness (MCF, ROTEM®) between Octafibrin and Haemocomplettan® P / RiaSTAP™ at 1 hour post-infusion (surrogate for haemostatic efficacy)

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

Study outline:
- The study consisted of two periods of 45 days each. Subjects were randomized to receive a single infusion of Octafibrin or Haemocomplettan® P / RiaSTAP™ in both study periods. Cross-over was performed at the end of the first study period (Figure 2).

Figure 2. FORMA 01 Study outline



- Single intravenous infusion of 70 mg/kg body weight of Octafibrin and Haemocomplettan® P / RiaSTAP™ was followed by blood samples for the PK analyses taken at baseline, 0.5, 1, 2, 4, 8, 24, 48, 96, 144, 216, and 312 hours post-infusion.

Primary inclusion criteria:
- Age ≥12 years
- Documented congenital fibrinogen deficiency (afibrinogenaemia - plasma fibrinogen activity and antigen at screening below detection limit, i.e., <20 mg/dL)

Primary exculsion criteria:
- Bleeding disorder other than congenital fibrinogen deficiency
- Dysfibrinogenaemia
- Treatment with any fibrinogen concentrate or other fibrinogen-containing blood product in the 2 weeks prior to enrolment and/or treatment

Methods:

PK
Fibrinogen activity assay was used to determine the actual potency of all Octafibrin and Haemocomplettan® P / RiaSTAP™ batches used. The actual potencies of the two concentrates were used to assess AUC, in vivo $T_{1/2}$, IVR, C_{max}, T_{max}, MRT, V_{SS}, and CL.

Recovery
Incremental and classical IVRs were calculated as the maximum increase in plasma fibrinogen activity within 4 hours following infusion as compared with preinfusion plasma fibrinogen levels.

Efficacy
Rotational thromboelastometry (ROTEM®) was used to measure MCF (surrogate marker of efficacy) at 1 hour after administration of either concentrate.

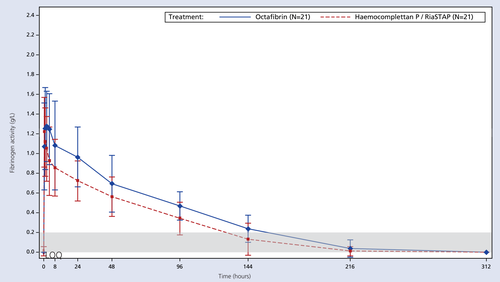
Safety
Thrombogenicity measurements included prothrombin fragment 1 (F1) + prothrombin fragment 2 (F2) and D-dimer performed prior to the PK infusion and at 0.5, 1, 2, 4, and 8 hours post-infusion on Day 1 of both study periods.

Virus safety assessments included testing for HIV-1 and -2, HAV, HBV, HCV, and parvovirus B19 (parvo B19) by serology and PCR assessments.

Results

Pharmacokinetics
PK parameters were assessed in 21 patients who completed both PK periods in accordance with the protocol. PK data presented are based on fibrinogen activity. At baseline, fibrinogen concentrations were at or below the limit of detection of the assays. Concentrations peaked at 0.5 to 8 hours after administration and had decreased to the pre-infusion levels by 216 hours (i.e. Day 9) (Figure 3). Over the first 144 hours, Octafibrin showed consistently higher blood concentrations than Haemocomplettan® P / RiaSTAP™.

Figure 3. Mean (± SD) fibrinogen activity (g/L) during PK assessment after Octafibrin and Haemocomplettan®P / RiaSTAP™ administration (n=21)



PK, pharmacokinetic; LOQ, limit of quantification; SD, standard deviation.

Primary PK endpoint
The primary endpoint, AUC_{norm} for fibrinogen activity, was significantly higher for Octafibrin than for Haemocomplettan® P / RiaSTAP™ (p=0.0002; Table 1). The ratio of Octafibrin to Haemocomplettan® P / RiaSTAP™ for AUC_{norm} was 1.196 (90% CI, 1.117 to 1.281), i.e., the bioequivalence criterion (90% CI, 80% to 125%) was not met.

Table 1. AUC_{norm} (fibrinogen activity) for Octafibrin and Haemocomplettan® P / RiaSTAP™ (n=21)

Parameter	Mean	SD	Median	Range	p value*
AUC_{norm}, h•kg•g/L/mg					
Octafibrin	1.62	0.45	1.59	0.85–2.51	0.0002
Haemocomplettan® P / RiaSTAP™	1.38	0.47	1.24	0.76–2.46	
AUC_{norm}, standardised to 70 mg/kg, g•h/L					
Octafibrin	113.7	31.54	111.14	59.7–175.51	
Haemocomplettan® P / RiaSTAP™	96.39	32.89	87.03	53.36–172.16	

* p values for treatment effect from the ANOVA type 3 tests of fixed effects AUC_{norm}, area under the curve normalised to the dose administered; SD, standard deviation

Secondary PK endpoints
ANOVA showed no significant differences between concentrates for most secondary PK parameters except clearance (CL), which was significantly lower for Octafibrin (p=0.0002; Table 2).

Table 2. Selected secondary PK parameters (fibrinogen activity) for Octafibrin and Haemocomplettan®P/ RiaSTAP™ (n=21)

Parameter	Mean	SD	Median	Range	p value*
IVR, mg/dL/(mg/kg)					
Octafibrin	1.787	0.458	1.766	1.08–2.62	0.9089
Haemocomplettan® P / RiaSTAP™	1.77	0.442	1.7	1.21–2.84	
$T_{1/2}$, h					
Octafibrin	75.94	23.831	72.854	40.03–156.96	0.2981
Haemocomplettan® P / RiaSTAP™	69.378	16.006	64.644	48.6–101.94	
CL, mL/h/kg					
Octafibrin	0.665	0.197	0.63	0.4–1.17	0.0002
Haemocomplettan® P / RiaSTAP™	0.804	0.255	0.804	0.41–1.31	

* p values for treatment effect from the ANOVA type 3 tests of fixed effects
PK, pharmacokinetics; IVR, in vivo recovery; $T_{1/2}$, half-life; CL, clearance; SD, standard deviation

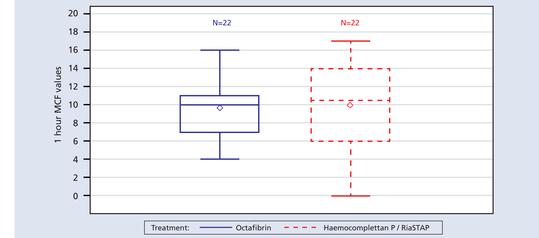
Primary efficacy endpoint
The primary segregate efficacy analysis was performed on the full analysis set (n=22). The MCF change from pre-infusion was significant with both concentrates (Table 3). At 1 hour post-infusion, ANOVA showed no significant difference between Octafibrin and Haemocomplettan® P / RiaSTAP™ (mean difference: –0.32 mm; 95% CI –1.7 to 1.07) (Figure 4).

Table 3. MCF pre-infusion and 1 hour post-infusion (n=22)

Concentrate	Pre-infusion MCF (mm)		1 hour post-infusion MCF (mm)		Increase in MCF from pre- to 1 hour post-infusion (mm)	
	Mean (SD)	Median (range)	Mean (SD)	Median (range)	95% CI	p value*
Octafibrin	0 (0)	0 (0–0)	9.68 (2.95)	10 (4–16)	8.37; 10.99	<0.0001
Haemocomplettan® P / RiaSTAP™	0 (0)	0 (0–0)	10 (4.353)	10.5 (0–17)	8.07; 11.93	<0.0001

* Two-sided p-value at 5% significance level using paired t-test
MCF, maximum clot firmness; SD, standard deviation; CI, confidence interval

Figure 4. Box plot of MCF change from baseline to 1 hour after Octafibrin and Haemocomplettan®P / RiaSTAP™ administration (n=22)



The box plot shows the median (horizontal line), mean (diamond), upper and lower quartiles (box ends), and minima and maxima (whiskers) within 1.5* interquartile range.

Safety
The safety dataset included all patients who received at least one dose of Octafibrin or Haemocomplettan® P / RiaSTAP™ (n=22). The incidence and nature of AEs after administration of Octafibrin and Haemocomplettan® P / RiaSTAP™ were similar. One AE (mild pyrexia) was considered possibly related to Octafibrin. One patient experienced 2 SAEs (abdominal pain, vaginal haemorrhage) on the same day, which were not considered treatment-related. No deaths, cases of thromboembolism, treatment-related allergic reactions, or seroconversions for HIV, HAV, HBV, HCV, or parvovirus B19 were observed after infusion of Octafibrin.

Conclusions

- The primary endpoint, AUC_{norm}, was significantly higher statistically for Octafibrin than for Haemocomplettan®P / RiaSTAP™ (p=0.0002). No significant differences between concentrates was found for most secondary PK parameters except clearance, which was statistically significantly lower for Octafibrin.
- The increases in MCF after infusion were statistically similar between products and were within the range considered to indicate sufficient fibrin polymerisation and good clot formation in relation to the administered dose.
- The safety data for Octafibrin do not indicate any safety concerns with no related serious AEs or thrombotic events after single-dose administration in patients with congenital fibrinogen deficiency.

We would like to thank all investigators, site staff, and patients who participated in the study

Toshko Lissitchkov, Sofia, Bulgaria
Cecil Ross, Bangalore, India
Suchitra Acharya, New Hyde Park, USA
Marylin Manco-Johnson, Aurora, USA
Savita Rangarajan, London, UK
Mehran Karimi, Shiraz, Iran
Alok Srivastava, Vellore, India

Poster number 199