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

Bruce Schwartz (1), Savita Rangarajan (2), Mehran Karimi (3), Sigurd Knaub (4), Flora Peyvandi (5)

(1) CRBD, Octapharma USA, Hoboken, United States, (2) Consultant Haematologist, Southern Hemophilia Network, Basingstoke, United Kingdom, (3) Hematology Research Center, Nemazi Hospital, Shiraz, Iran (4) CRBD, Octapharma, Lachen, Switzerland, (5) Centro Emofilia & Tombolo Angela Bianchi Bonomi, Milano, Italy

**Background**

Patients with congenital alloimmunization and hypofibrinogenemia experience frequent spontaneous intracranial bleeding and oozing from any minor trauma or a small surgical intervention. Rare bleeding disorders may occur after a minor trauma or a small surgical intervention, into the skin, mucosa, ocular, 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 nonfibrinogen), 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).

**FORMA 01 Study**

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

**Primary endpoints:**

- To compare the concentration curve between Octafibrin and Haemocomplettan® P / RiaSTAP™.
- To compare Maximum Coagulation Force (MCF) between Octafibrin and Haemocomplettan® P / RiaSTAP™ at 1 hour post-infusion (suitable for haemostatic monitoring).

**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 final study period (Figure 2).

**Figure 1.** Chronology of fibrinogen concentrates.

The package of the final product (Octafibrin 1g) 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 (both Haemocomplettan® P / RiaSTAP™ as the comparator) in 18 evaluable patients.

**FORMA 02**
- A phase II placebo-controlled trial phase II 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 III study to evaluate the efficacy and safety of Octafibrin in acute bleeding in 26 evaluable patients aged ≥ 12 years.

**Results**

**Pharmacokinetics**

PK parameters were calculated in 21 patients who completed both PK periods in accordance with the protocol. PK data presented are based on fibrinogen activity. All studied fibrinogen concentrations were at or below the limit of detection of measurements. Concentrations peaked at 0.5 to 4 hours after administration and had decreased to the pre-infusion levels by 216 hours (Figure 3). Over the first 144 hours, Octafibrin showed consistently higher blood concentrations than Haemocomplettan® P / RiaSTAP™. Concentrations peaked at 0.5 to 8 hours after administration and had decreased to the pre-infusion levels by 216 hours (Figure 3). Over the first 144 hours, Octafibrin showed consistently higher blood concentrations than Haemocomplettan® P / RiaSTAP™. The increases in MCF after infusion were statistically similar between products in the 2 weeks prior to enrolment and/or treatment.

**Primary PK endpoint**

The primary endpoint, AUC<sub>0-216</sub> for fibrinogen activity, was significantly higher for Octafibrin than for Haemocomplettan® P / RiaSTAP™ (p < 0.0001; Table 1). The ratio of Octafibrin to Haemocomplettan® P / RiaSTAP™ on day 1 was 198 (90% CI, 1.17 to 1.28), i.e., the bioavailability ratio (90% CI, 90% to 125%) was not met.

**Figure 2.** PK study outline.

**Table 1.** AUC<sub>0-216</sub> for fibrinogen activity for Octafibrin and Haemocomplettan®P / RiaSTAP™ (n=21).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (SD)</th>
<th>Median (range)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octafibrin</td>
<td>1.42 (0.43)</td>
<td>1.40 (1.1)</td>
<td>0.028</td>
</tr>
<tr>
<td>Haemocomplettan® P / RiaSTAP™</td>
<td>1.38 (0.47)</td>
<td>1.24 (0.76)</td>
<td>0.693</td>
</tr>
</tbody>
</table>

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

- No significant differences between products for most secondary PK parameters except clearance (CL), which was significantly lower for Octafibrin (p = 0.022; Table 2).

**Secondary PK endpoints**

ANOVA showed no significant differences between concentrates for most secondary PK parameters except clearance, which was statistically significantly lower for Octafibrin.

**Safety**

The safety dataset included all patients who received at least one dose of Octafibrin or Haemocomplettan® P / RiaSTAP™. The median and range of all adverse events were: 68% (0–100%) for Octafibrin, 76% (0–100%) for Haemocomplettan® P / RiaSTAP™. One AE considered possibly related to Octafibrin and one AE considered possibly related to Haemocomplettan® P / RiaSTAP™ were serious. The two AEs of abdominal pain and vaginal haemorrhage were considered possibly related to Octafibrin. No deaths, cases of thrombosis, new thrombosis-related adverse reactions, or seroconversions for HIV (HIV, HBV, HCV) or parvovirus B19 were observed after infusion of Octafibrin.

**Conclusions**

- The primary endpoint, AUC<sub>0-216</sub>, was significantly higher statistically for Octafibrin than for Haemocomplettan® P / RiaSTAP™ (p < 0.0001). No significant differences between concentrates were 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. The increase in MCF considered to indicate sufficient fibrin polymerization and good clot formation in relation to the administered dose.
- The safety data for Octafibrin did not induce any safety concerns related to the serious AEs or thrombotic events after single-dose administration in patients with congenital fibrinogen deficiency.

**Primary efficacy endpoint**

The primary efficacy endpoint analysis was performed on the full analysis set (n=22). The primary efficacy analysis was performed with both concentrate (Table 3). AUC<sub>0-216</sub> was statistically significantly higher for Octafibrin than for Haemocomplettan® P / RiaSTAP™ (mean difference –0.32 mm; 95% CI: –1.7 to 1.07; p = 0.45).

**Table 3.** AUC<sub>0-216</sub> for fibrinogen activity for Octafibrin and Haemocomplettan®P / RiaSTAP™ (n=22).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Octafibrin</th>
<th>Haemocomplettan® P / RiaSTAP™</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;0-216&lt;/sub&gt;</td>
<td>0.804</td>
<td>0.804</td>
<td>0.996</td>
</tr>
</tbody>
</table>

**Table 4.** MCF (mm) on day 1 post-infusion (n=22).

<table>
<thead>
<tr>
<th>Concentrate</th>
<th>Mean (SD)</th>
<th>Median (range)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octafibrin</td>
<td>9.68 (2.95)</td>
<td>10 (4–16)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Haemocomplettan® P / RiaSTAP™</td>
<td>8.37 (2.43)</td>
<td>8 (4–15)</td>
<td>0.484</td>
</tr>
</tbody>
</table>

The box plot shows the median (horizontal line), mean (diamond), upper and lower fence lines (wa), and inner and outer fence values (out) in a box-and-whisker plot.