Efficacy of human fibrinogen concentrate for on-demand treatment of acute bleeding and to prevent bleeding during and after surgery in subjects with congenital fibrinogen deficiency

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Background and Objectives

Patients with the rare congenital conditions afibrinogenemia and hypofibrinogenemia frequently experience severe bleeding episodes (BEs) after minor trauma or surgical intervention.¹ BEs start at birth or early childhood and commonly occur in the joint spaces, mucosa, muscles, and gastrointestinal tract.¹ Therapeutic substitution with human fibrinogen concentrate corrects the haemostatic defect and arrests bleeding in these patients.^{2,3}

Here, we investigate the safety and efficacy of *Octafibrin* (Octapharma AG, Lachen, Switzerland), a new plasma-derived, highly purified, lyophilized fibrinogen concentrate with two dedicated virus inactivation/removal steps, in the on-demand treatment of BEs and surgical prophylaxis.

Methods

- Planned interim analysis of a prospective, open-label, multinational, phase III study (NCT02267226) in adult and adolescent a- or hypofibrinogenemic patients
- All patients received ≥ 1 dose *Octafibrin* to treat acute BEs or as surgical prophylaxis, to achieve a target plasma fibrinogen level of 100 mg/dL (accepted lower limit 80 mg/dL) for minor bleeding/surgery and 150 mg/dL (accepted lower limit 130 mg/dL) for major bleeding/surgery
- Efficacy was assessed using a 4-point objective scale by the investigator and adjudicated by an independent data monitoring and endpoint adjudication committee (IDMEAC)

Results: On-Demand Treatment of BEs

- A total of 13 patients (11 adults and 2 adolescents) with afibrinogenemia were included in the analysis
- Of these, 11 experienced a total of 23 minor BEs; 16 BEs (69.6%) were spontaneous and 7 (30.4%) were traumatic
- The majority of BEs (21/23) required 1 infusion of *Octafibrin* (91.3%) and 2 (8.7%) required 2 infusions
- The median (range) dose of *Octafibrin* administered for all BEs was 57.5 (33.9–71.4) mg/kg per infusion and 58.8 (33.9–101.7) mg/kg per BE
- For all BEs, the success rate (efficacy rating of excellent or good) was 100% (90% CI: 0.88, 1.00) as rated by the IDMEAC and 95.7% (90% CI: 0.81, 1.00) as rated by the investigator (one missing rating, considered a failure) (**Table 1**)

Table 1. Hemostatic efficacy of *Octafibrin* for treatment of BEs (n=23 BEs in 11 patients)

Efficacy rating: 4-point efficacy scale	Investigator N (%)	IDMEAC N (%)
Excellent	19 (82.6)	23 (100)
Good	3 (13.0)	0
Moderate	0	0
None	0	0
Missing	1 (4.4%)	-

- Maximum clot firmness (MCF) was determined in frozen plasma at the central laboratory using thromboelastometry (ROTEM®) for the first infusion administered for treatment of all 23 BEs
- Mean ($\pm$ SD) change in MCF from baseline to 1 h after the first infusion of *Octafibrin* was 6.5 mm ($\pm$ 2.0) ($p < 0.0001$) (**Figure 1**)

Figure 1. Maximum clot firmness at baseline and 1 hour after first *Octafibrin* infusion (n=23 BEs in 11 patients)

Results: Surgical Prophylaxis

- Four patients underwent 4 surgeries: 1 major and 3 minor
- The intra- and postoperative success rates (haemostatic efficacy rated as excellent or good) were 100% (90% CI 0.5, 1.0) (**Figures 2 and 3**)

Figure 2. Intra-operative assessment of *Octafibrin* efficacy in surgical prophylaxis (n=4 surgeries in 4 patients)

Figure 3. Post-operative assessment of *Octafibrin* efficacy in surgical prophylaxis (n=4 surgeries in 4 patients)

Results: Safety

- No deaths or thrombotic events were reported and no patients developed anti-fibrinogen antibodies during the study
- In total, 16 adverse events in seven patients (53.8%) were reported but assessed as unrelated to the treatment; the majority (13/16, 81.3%) were mild. One moderate AE (arthropod sting) and two serious AEs (ligament rupture and patella fracture due to a fall) were reported

Conclusions

- Octafibrin* demonstrated 100% haemostatic efficacy in on-demand treatment in bleeding patients with congenital fibrinogen deficiency
- Haemostatic efficacy in surgical prophylaxis was rated excellent/good in 100% of surgeries
- MCF increased significantly post-infusion in all patients after administration, reflecting the successful treatment of bleeding events
- No safety concerns relating to the use of *Octafibrin* were identified in this study