ORIGINAL ARTICLE

Fibrinogen concentrate for treatment of bleeding and surgical prophylaxis in congenital fibrinogen deficiency patients

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Abstract

Background: Congenital fibrinogen deficiency is an ultra-rare disorder in which patients can experience severe and/or frequent bleeding episodes (BEs). Here, we present the largest prospective study to date on the treatment of this disorder.

Methods: Hemostatic efficacy of human fibrinogen concentrate (HFC; FIBRYGA®, Octapharma AG) for treatment of bleeding or surgical prophylaxis was assessed by investigators and adjudicated by an independent data monitoring and endpoint adjudication committee (IDMEAC) according to a four-point scale, using objective criteria. Thromboelastometry maximum clot firmness (MCF) was also determined.

Results: Twenty-five afibrinogenemia patients were treated with HFC: 24 for on-demand treatment of 89 BEs, and nine as prophylaxis for 12 surgeries. For BEs, treatment success (rating of excellent or good) evaluated by investigators was 96.6% (90% confidence interval [CI], 0.92-0.99; two missing ratings, classified as failures) and by the IDMEAC was 98.9% (90% CI, 0.95-0.999). Mean ± standard deviation (SD) increase in MCF was 5.8 ± 2.5 mm one hour after the first HFC infusion (mean ± SD dose, 61.88 ± 11.73 mg/kg). For the 12 surgeries (median [range] HFC dose/surgery, 85.80 mg/kg [34.09-225.36]), intraoperative and postoperative treatment success were both rated 100% (90% CI, 0.82-1.00) by investigators and the IDMEAC. Three adverse events were possibly treatment related, including a moderate case of thrombosis. There were no deaths, no severe allergic or hypersensitivity reactions, and no clinical evidence of neutralizing antifibrinogen antibodies.

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Conclusions: Human fibrinogen concentrate was efficacious for on-demand treatment of bleeding and as surgical prophylaxis, with a favorable safety profile, in patients with congenital afibrinogenemia.

KEYWORDS

afibrinogenemia, fibrinogen, hemostasis, thrombelastography, surgical prophylaxis

1 | INTRODUCTION

Fibrinogen, a 340 kDa glycoprotein, plays a central role in hemostasis, specifically in clot formation and stabilization.[1] Congenital fibrinogen disorders are rare, affecting approximately 1 to 2 in every million people in the general population.[2] Whereas healthy individuals have a plasma fibrinogen level ranging from 150-450 mg/dL,[3] those with afibrinogenemia and hypofibrinogenemia have an absence or low level (<150 mg/dL) of circulating fibrinogen, respectively.[4] The incidence of spontaneous or trauma-related bleeding episodes (BEs) associated with congenital fibrinogen deficiency is variable, with the severity ranging from mild to catastrophic.[2,4] Afibrinogenemia and/or more severe hypofibrinogenemia (ie, fibrinogen < 10 mg/dL) are often associated with bleeding in the nose, gastrointestinal tract, joints, and uterus (heavy menstrual bleeding).[2] Despite low levels of fibrinogen activity, annual incidence of bleeding in some patients with inherited afibrinogenemia or hypofibrinogenemia can be low, typically less than once per year.[2]

Standard treatment for bleeding patients with congenital fibrinogen deficiency is fibrinogen replacement, targeted to a plasma fibrinogen level of 100-150 mg/dL.[4,5] Therapies include fresh-frozen plasma (FFP), cryoprecipitate, and human fibrinogen concentrate (HFC). FFP requires thawing and donor–recipient ABO compatibility blood matching before administration and it has a low and variable fibrinogen content (and variable levels of other coagulation factors), which prevents precise dosing.[6] Fibrinogen replacement with FFP necessitates a large transfusion volume, which is associated with a risk of volume overload.[5,6] Furthermore, FFP most often does not undergo pathogen inactivation, and therefore carries a risk of pathogen infection, and contains antigens and antibodies, which could elicit adverse immunological or allergic reactions including the risk of transfusion-related acute lung injury.[6] Cryoprecipitate is a human plasma derivative that requires cross-matching and thawing prior to administration and has a higher and slightly less variable fibrinogen concentration than FFP.[6,7] Cryoprecipitate is pooled from multiple donors and is therefore associated with safety concerns, including risk of pathogen transmission (no viral inactivation) and transfusion-related acute lung injury.[5-7] Consequently, cryoprecipitate has been withdrawn from most European countries, although it remains available in several others, for example the United States, the UK, and Canada.[6,7]

Owing to the limitations of FFP and cryoprecipitate, HFC has become the preferred option for replacement of fibrinogen in cases of congenital fibrinogen deficiency,[5] and the replacement therapy

Essentials

- This the largest prospective interventional study in congenital fibrinogen deficiency to date.
- Hemostatic efficacy of human fibrinogen concentrate (HFC) is assessed in afibrinogenemia patients.
- HFC was efficacious for both on-demand treatment of bleeding and surgical prophylaxis (n = 25).
- HFC had a favorable safety profile in patients with congenital afibrinogenemia.

of choice in patients with afibrinogenemia.[8] Advantages of HFC over FFP and cryoprecipitate include faster preparation (no thawing required; no need for blood matching), faster administration (low infusion volume), and greater purity.[6] Furthermore, the fibrinogen content of HFC is more consistent and can be accurately determined, thereby allowing standardized dosing.[6] HFC can be considered safer than FFP and cryoprecipitate, with no risk of volume overload and reduced risk of pathogen transmission.[6]

Fibrinogen concentrates have been shown to be efficacious for the treatment of bleeding and surgical prophylaxis, while demonstrating a good safety profile.[9-12] The HFC used in this trial was a state-of-the-art lyophilized plasma-derived concentrate (FIBRYGA®, Octapharma AG) that provides high purity and pathogen safety through two virus inactivation/elimination steps (solvent/detergent treatment and nanofiltration).[5,13] The pharmacokinetic (PK) profile of this HFC was previously investigated in a randomized, cross-over comparative study. The PK properties were broadly comparable between the new HFC and a currently marketed comparator HFC (Haemocomplettan® P [RiaSTAP®]), with the exception of AUC_{norm}, which was significantly larger, and clearance, which was significantly slower, for the new HFC in patients with afibrinogenemia.[14] The HFC used in this study is now licensed in multiple countries for the treatment of acute bleeding and for surgical prophylaxis in patients with fibrinogen deficiency, with approval obtained on the basis of a planned interim analysis of the present study.[15] Here, we report the results from the final analysis, which aims to evaluate the efficacy and safety of HFC for on-demand treatment of acute bleeding episodes in the largest

data collection available to date from a prospective interventional study of patients with congenital fibrinogen deficiency.

2 | METHODS

2.1 | Study design

This study (FORMA-02, NCT02267226) was a prospective, multicenter, open label, uncontrolled Phase 3 efficacy and safety study in patients with congenital fibrinogen deficiency. Twelve centers across Bulgaria, India, Iran, Lebanon, Russia, Saudi Arabia, Turkey, the United States, and the UK participated in this study between October 2014 and February 2018. Patients received HFC (FIBRYGA®; Octapharma AG) via intravenous infusion for on-demand treatment of bleeding or as surgical prophylaxis. HFC dosing was individually calculated for each patient based on baseline fibrinogen activity levels measured at the local laboratory and target plasma fibrinogen concentrations of 100 mg/dL (recommended lower limit of 80 mg/dL) for minor bleeding or minor surgery and 150 mg/dL (recommended lower limit of 130 mg/dL) for major bleeding or major surgery. The final decision on dosing was at the discretion of the treating physician. After each infusion, patients were monitored for ≥3 days for minor bleeding or minor surgery or ≥7 days for major bleeding or major surgery. Patients treated on-demand for bleeding were monitored for a 30-day safety follow-up period.

The study was conducted in accordance with Good Clinical Practice (CPMP/ICH/135/95), the Declaration of Helsinki and its amendments, and national law. The study protocol received approval from the appropriate national regulatory bodies, institutional review boards, and independent ethics committees for each institution. All patients provided written informed consent before participating.

2.2 | Study population

Patients ≥12 years old (≥18 years in Russia) were enrolled if they had documented congenital afibrinogenemia or severe hypofibrinogenemia (defined as historical plasma fibrinogen activity of <50 mg/dL, or levels below the limit of detection of the local assay method) and were expected to require on-demand treatment for an acute BE or were planning to undergo surgery. Key exclusion criteria were a bleeding disorder other than congenital fibrinogen deficiency, including dysfibrinogenemia; life expectancy of <6 months; any coagulation-active drug within 1 week prior to start of treatment; hypersensitivity to human plasma proteins; deep vein thrombosis (DVT), pulmonary embolism, or arterial thrombosis within 1 year prior to start of treatment; diagnosis or suspicion of neutralizing antifibrinogen antibody currently or in the past; and regular prophylaxis with a fibrinogen-containing product.

2.3 | Evaluation of hemostatic efficacy

The investigator's clinical assessment of hemostatic efficacy for all BEs treated with HFC during the study period was based on a 4-point objective scale (excellent, good, moderate, and none; Table S1). Previous studies demonstrated the utility of objective criteria for the clinical investigation of other congenital bleeding disorders.[16,17] All clinical efficacy assessments were adjudicated by an independent data monitoring and endpoint adjudication committee (IDMEAC) according to the same 4-point objective scale using data collected from the case report forms and information provided by the investigator. Overall treatment success was defined as a rating of excellent or good.

The primary endpoint was efficacy in the treatment of the first BE for each patient. To evaluate the efficacy of HFC for surgical prophylaxis, intraoperative and postoperative efficacy were assessed by the surgeon and hematologist, based on objective 4-point scales, which included a comparison of predicted and actual blood loss (Tables S2 and S3). Efficacy ratings were additionally adjudicated by the IDMEAC. Overall treatment success was defined as a rating of excellent or good.

2.4 | Clot strength

Maximum clot firmness (MCF) was assessed as a surrogate measure of hemostatic efficacy. Plasma samples were prepared from blood taken prior to the first infusion for treatment of BEs and at 1 hour after the end of the infusion. For consistency, frozen samples were transferred to a central laboratory for testing. MCF was determined by performing thromboelastometry (ROTEM) on thawed plasma samples, as previously described.[10,14]

2.5 | Fibrinogen level and in vivo recovery

Fibrinogen plasma level was evaluated at the central laboratory using the Clauss assay. Incremental in vivo recovery (IVR) was calculated as the maximum increase in plasma fibrinogen between pre-infusion and 1 hour post-infusion, divided by the exact dose of HFC.

2.6 | Safety

All adverse events (AEs) occurring during the study period were recorded. Treatment-emergent AEs (TEAEs) were defined as AEs occurring between the start of the first HFC infusion and the end of each 30-day observation and follow-up period or during the surgical observation period, and were absent prior to treatment or worsened relative to the pre-treatment state. Non-TEAEs were those that occurred outside of follow-up periods.

Thrombogenicity measurements were performed at the central laboratory on plasma samples prepared from blood taken prior to the first infusion of HFC, 1 hour and 3 hours post-infusion and 1 day after last infusion. Prothrombin fragments 1 and 2 (F1 + F2) and D-dimer levels were assessed.

Blood was drawn for immunogenicity testing on Day 1, prior to the first infusion of HFC, and Days 14 and 30 after infusion. An experimental enzyme-linked immunosorbent assay (ELISA) was developed for identification of antifibrinogen antibodies, with analysis performed at the central laboratory. Specific tests for neutralizing antifibrinogen antibodies were not performed.

2.7 | Statistical analysis

Categorical variables are presented as absolute values and percentages. Continuous variables are presented as mean ± standard deviation (SD) or median (range). For evaluation of hemostatic efficacy, the lower limit of the two-sided 90% confidence intervals (CI) for success rate were calculated according to Blyth–Still–Casella interval for the proportion of patients with successful hemostatic efficacy (rating of excellent or good). Missing assessments were counted as failures. As the number of patients with this indication is very low, no formal sample size calculation was carried out; however, comparing the probabilities for different outcomes gave a success rate of 90% for a total of 24 patients together with respective 90% CIs. Statistical analysis was performed using SAS version 9.3.

3 | RESULTS

3.1 | Patient characteristics

Thirty-three patients were enrolled in the study, 25 of whom received at least one infusion of HFC (Safety Population; Figure 1). Of these, 24 patients received HFC for treatment of one or more BEs (Bleeding Population; 89 BEs in total) and nine received HFC as
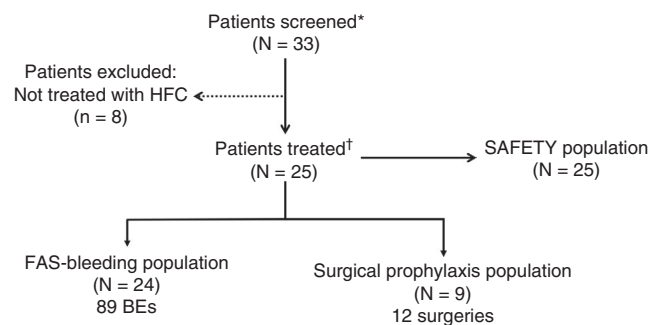

FIGURE 1 Patient disposition and analysis populations. *Patients who were screened and gave consent; †Patients who received at least one infusion of fibrinogen concentrate for treatment of a BE or surgical prophylaxis. Eight patients were included in both the Bleeding and Surgical Prophylaxis populations. BE, bleeding episode; N, number of patients

surgical prophylaxis (Surgical Prophylaxis Population; 12 surgeries in total). Eight patients received HFC for bleeding and surgery, while one was treated for surgery only. The study was open for patients with hypofibrinogenemia or afibrinogenemia, but only patients with afibrinogenemia were enrolled.

The median (range) age of the Safety Population was 27 years (12-54), with six patients (24%) aged 12-17 years (Table 1). Fourteen patients (56%) were male. All patients (100%) had afibrinogenemia.

3.2 | Hemostatic efficacy for on-demand treatment of bleeding

Of the 89 BEs treated with HFC, 87 were classed as minor. A full list of all BEs is given in Table S4. These included hemarthrosis or superficial muscle, soft tissue, or oral bleeding. Two BEs were classed as major: a spontaneous intracranial hemorrhage and a spontaneous occult gastrointestinal bleed. Sixty-seven BEs were spontaneous and 22 were due to trauma. The mean (±SD) first dose of HFC administered per BE was 61.88 mg/kg (±11.73), while the total dose per BE was 65.51 mg/kg (±26.47; Table 2). In total, 100 infusions were administered, with 93.3% of BEs treated with a single infusion.

Investigator-assessed hemostatic efficacy was excellent for 70 BEs (78.7%), good for 16 (18.0%), and moderate for one BE (1.1%) (Figure 2). Efficacy ratings by the investigator were missing for two BEs, one simultaneous with surgery, and one lost to follow-up. The IDMEAC was able to assess hemostatic efficacy for all 89 BEs. The

TABLE 1 Patient characteristics

	N = 25	
	Mean ± SD	**Median (range)**
Age at informed consent (years)	29.0 ± 13.0	27 (12-54)
Height (cm)	163.3 ± 11.7	165 (138-190)
Weight (kg)	67.2 ± 19.9	68 (28-101)
BMI (kg/m^2)	25.0 ± 6.7	25.2 (12.6-39.6)
	n (%)	
Age <18 years*	6 (24.0)	
Sex		
Male	14 (56.0)	
Female	11 (44.0)	
Race		
White	19 (76.0)	
Asian	5 (20.0)	
Arab/Middle Eastern	1 (4.0)	
Congenital fibrinogen deficiency		
Afibrinogenemia	25 (100.0)	

Abbreviations: BMI, body mass index; SD, standard deviation

*Age at first HFC infusion.

TABLE 2 Summary of fibrinogen concentrate dosages for treatment of bleeding episodes and for surgical prophylaxis

	No. BEs/ surgeries	No. infusions	Mean ± SD (mg/kg)	Median (range) (mg/kg)
Bleeding (N = 24)				
Dose of first infusion	89	89	61.88 ± 11.73	58.82 (32.12-102.60)
Dose per infusion	89	100	58.30 ± 15.45	57.47 (11.54-102.60)
Total dose per BE	89	100	65.51 ± 26.47	59.41 (32.12-273.80)
Total dose for major bleeds[a]	2	9	209.49 ± 90.94	209.49 (145.18-273.79)
Total dose for minor bleeds[a]	87	91	62.20 ± 11.31	58.82 (32.12-101.69)
Surgical prophylaxis (N = 9)				
Total dose per surgery	12	31	104.49 ± 54.86[b]	85.80 (34.09-225.36)
Preoperative loading dose	12	11[c]	77.39 ± 20.22	70.00 (58.46-127.91)
Maintenance dose	12	20[d]	20.13 ± 7.49	16.97 (10.59-34.09)
Dose per infusion	12	31	40.45 ± 30.78	28.99 (10.59-127.91)

Abbreviations: BE, bleeding episode; SD, standard deviation.

[a]Minor bleeding was treated to achieve a recommended target fibrinogen plasma level of 100 mg/dL, with a recommended lower limit of 80 mg/dL. Major bleeding was treated to achieve a recommended target fibrinogen plasma level of 150 mg/dL, with a recommended lower limit of 130 mg/dL.

[b]The major surgery was treated with a total dose of 225.36 mg/kg via a preoperative loading dose plus seven maintenance infusions.

[c]One patient did not receive a loading dose for one surgery as they had received fibrinogen concentrate for treatment of a BE shortly beforehand and their plasma fibrinogen level was deemed to be acceptable.

[d]Administered across a total of six surgeries (five minor, one major).

IDMEAC rated hemostatic efficacy as excellent for 81 BEs (91.0%), good for 7 (7.9%), and moderate for one (1.1%, based on a decrease in hemoglobin level, as per the objective rating scale; additional
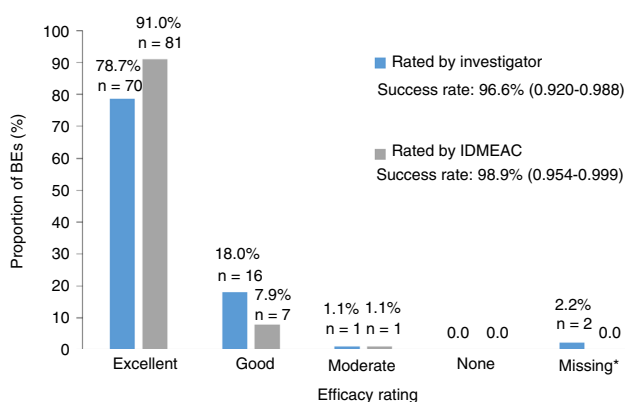

FIGURE 2 Efficacy of fibrinogen concentrate for on-demand treatment of bleeding episodes (Bleeding Population). *Two BEs with missing investigator assessments were adjudicated/scored by the IDMEAC. The success rate is a rating of excellent/good, with 90% confidence intervals calculated according to Blyth–Still–Casella interval for the proportion of patients with successful hemostatic efficacy. N = 89 BEs in 24 patients. BE, bleeding episode; IDMEAC, independent data monitoring and endpoint adjudication committee

hemostatic intervention was not required in this patient). Treatment was therefore classified as success (rating of excellent or good) for 96.6% (90% CI: 0.92-0.99) of patients by the investigator and 98.9% (90% CI: 0.95-0.999) by the IDMEAC (Figure 2).

For the subset of six adolescent patients (<18 years) with 11 BEs, investigator-assessed hemostatic efficacy was rated excellent for 100% of BEs, while the IDMEAC assessed the treatment of 72.7% of BEs as excellent and 27.3% as good. Treatment of all BEs (100%) was therefore categorized as successful in this population.

For the total Bleeding Population, there was a significant increase in MCF tested in frozen plasma from 0 mm at baseline to 1 hour after the first HFC infusion, with a mean (±SD) change of 5.79 mm (±2.53; P < .001). For the six adolescent patients, mean (±SD) change in MCF for the 11 treated BEs was also significant (P < .001), but slightly lower, at 4.00 mm (±2.14). The mean value in adolescent patients included two postinfusion measurements of 0.0 mm, which were likely due to pre-analytical sample issues because there was a measurable plasma fibrinogen level in both cases. For all bleeds, the mean (SD) increase in MCF from baseline to 1 hour postinfusion was 6.48 mm (3.07). An additional post hoc analysis was performed examining the relationship between MCF increase and age, body weight, or body surface area. Using a Pearson correlation from multilevel regression models,

the results suggested a significant association with change in MCF for both weight and body surface area (BSA; $P < .001$) but not for height ($P = .05$) or age ($P = .46$).

3.3 | Hemostatic efficacy for surgical prophylaxis

Nine patients received surgical prophylaxis for a total of 12 surgeries. Surgical procedures comprised one major (eye enucleation with socket reconstruction) and 11 minor (knee radioisotope synovectomy [n = 2], dental extraction [n = 3], root canal operation [n = 1], circumcision [n = 2], excision of scar bud of circumcision [n = 1], skin biopsy [n = 1], and debridement of superficial necrosis [n = 1]).

A total of 31 infusions were administered for the 12 surgeries, with a median dose of 28.99 mg/kg HFC per infusion (Table 2). The median (range) dose per surgery was 85.80 mg/kg (34.09-225.36) and when considering only the 11 minor surgeries, was 78.57 mg/kg (34.09-161.17). More than one infusion was administered for five of the minor surgeries, with a median (range) of three (1-4) maintenance infusions. Seven daily maintenance infusions were administered for the major surgery; these were given at the discretion of the treating physician based on assessment of the clinical situation even though the measured plasma fibrinogen levels were between 117 and 136 mg/dL over postoperative Days 2-6.

Intraoperative and postoperative hemostatic prophylaxis was rated a success in 100% of cases by the investigator and IDMEAC (Figure 3). The individual intraoperative efficacy was rated as excellent for 91.7% and good for 8.3% of surgeries, by both the investigator and the IDMEAC. Postoperative efficacy was rated as excellent for 100% of surgeries by the investigator (Figure 3A and B); the IDMEAC rated postoperative efficacy as excellent for 91.7% of surgeries and good for 8.3%. Postoperative hemostatic efficacy for the major surgery was classified as good by the IDMEAC, owing to postoperative oozing from the wound. Actual blood loss did not exceed the maximum expected blood loss, as

assessed prior to surgery, for any procedure. In addition, no intraoperative or postoperative transfusions were necessary.

3.4 | Fibrinogen level and in vivo recovery

Fibrinogen plasma level increased from baseline after HFC infusion in all patients for treatment of all BEs, reaching maximum values at 1 or 3 hours (Figure 4). The mean (±SD) fibrinogen level at 1 hour post-infusion was 109.01 mg/dL (±24.38), with a median (range) of 109.00 mg/dL (0.00-204.00), following a mean (±SD) first infusion dose of 61.88 mg/kg (±11.73). Four patients had post-infusion fibrinogen plasma levels below the lower limit of 80 mg/dL recommended for minor BEs, including one patient who was significantly under-dosed for the first BE (33.9 mg/kg; 54% of planned dose). One post-infusion fibrinogen value from the central laboratory was recorded as zero, likely due to pre-analytical sample issues, with the local laboratory analysis providing a value of 105.00 mg/dL at the same time point. Hemoglobin levels remained stable following HFC infusion for the majority of patients (Figure 4). A single patient, with a history of anemia, experienced a drop in hemoglobin of more than 20%. For the six adolescent patients, the mean (±SD) fibrinogen level was 98.55 mg/dL (±10.43) at 1 hour after the first HFC infusion for treatment of all 11 BEs.

The mean (±SD) incremental IVR calculated after the first infusion of HFC for treatment of BEs was 1.82 mg/dL/[mg/kg] (±0.42). When calculated for the 11 BEs in the six adolescent patients, the mean was lower, at 1.29 mg/dL/[mg/kg] (±0.24). The mean (±SD) IVR calculated after the loading dose for each of the 11 surgeries was 1.44 mg/dL/(mg/kg) (±0.58).

3.5 | Safety

In total, 91 AEs occurred in 19 patients (76.0%), of which, 43 AEs in 15 patients were TEAEs. Three AEs in three patients were considered possibly related to treatment: a moderate AE reported as exacerbation of a
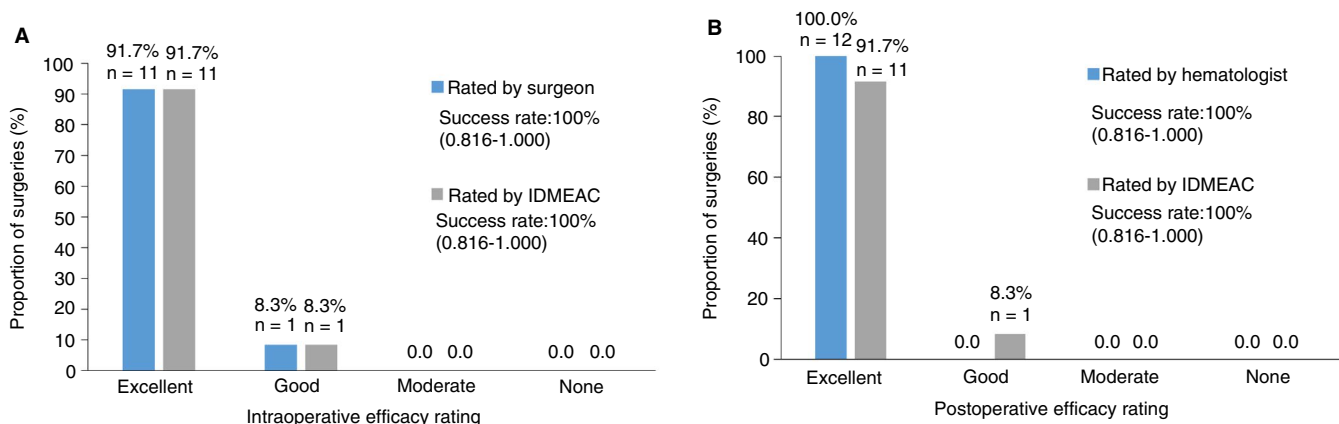

FIGURE 3 Efficacy of fibrinogen concentrate in surgical prophylaxis (Surgical Prophylaxis Population). A, Intraoperative efficacy; B, Postoperative efficacy. Surgical Prophylaxis population (N = 9; 12 surgeries). IDMEAC, independent data monitoring and endpoint adjudication committee. The success rate is a rating of excellent/good, with 90% confidence intervals calculated according to Blyth–Still–Casella interval for the proportion of patients with successful hemostatic efficacy
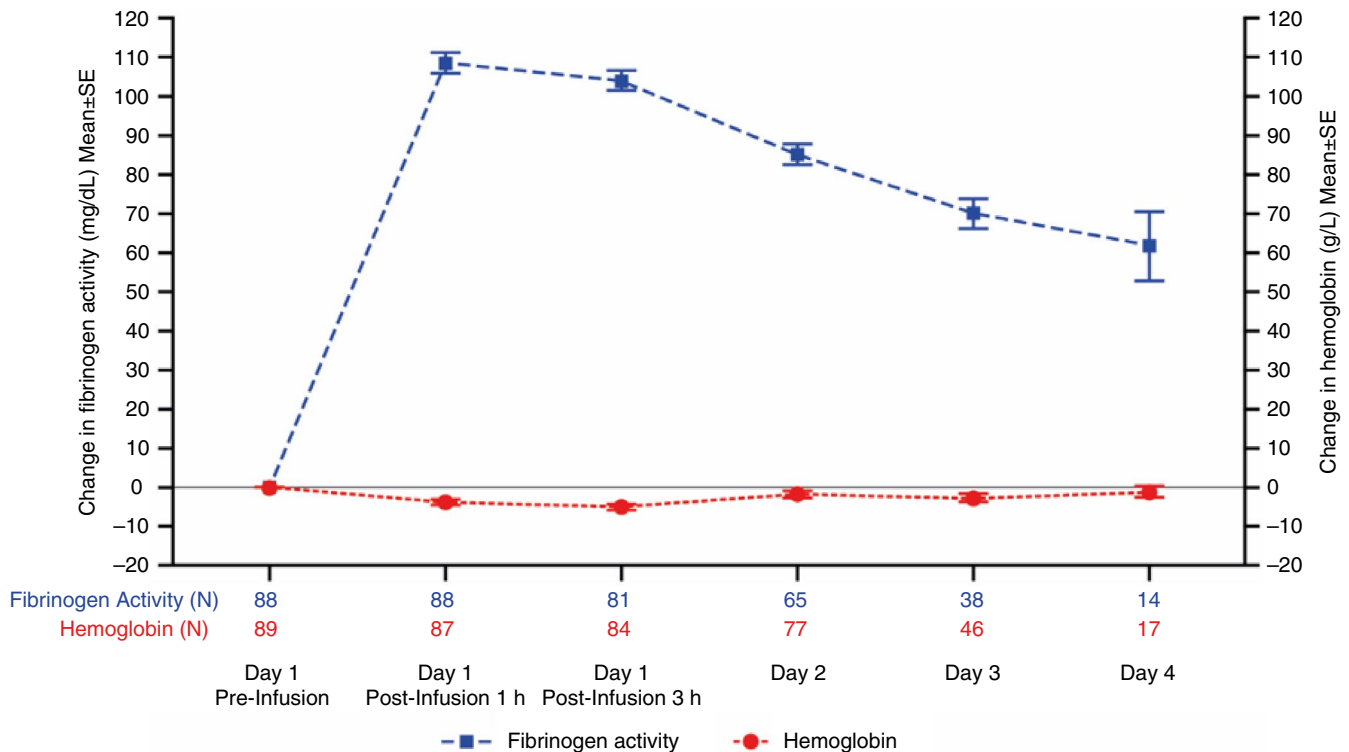
FIGURE 4 Change in plasma fibrinogen and hemoglobin levels before and after administration of fibrinogen concentrate for on-demand treatment of bleeding (Bleeding Population). Note that the number of available data values (N) diminishes markedly after Day 2 as most patients were only observed for this period. BE, bleeding episode; N, number of BEs for which data were available at the indicated time point; SE, standard error of the mean

pre-existing condition of peripheral ischemia due to digital microthrombi, a mild skin reaction, and a mild AE reported as peripheral phlebitis of the upper limbs; all of which resolved (Table 3). The ischemia due to digital microthrombi was classified as a serious event. The patient presented with toe discoloration and pain 2 days after a 66.05 mg/kg (3962.7 mg) infusion of HFC and one day after an additional dose of 13.21 mg/kg (792.5 mg) for treatment of a minor BE (vaginal bleeding). The patient received treatment with acetylsalicylic acid and analgesics and reported that the discoloration was resolved two months later (full details of laboratory data at each time point are given in Table S5). In total, 15 serious AEs were reported in five patients, one of which was considered possibly related to treatment (Table S6). There were no deaths during this study.

3.6 | Thrombogenicity markers

Fifteen patients had an increased level of prothrombin F1 + F2 at baseline. For five patients, levels appeared to increase following the first infusion of HFC. A single patient had an increased D-dimer level at baseline, with this remaining above the reference limit throughout the study. Of the patients with normal levels at baseline, four had an increased level after the first HFC infusion. One patient with elevated thrombogenicity markers experienced a documented thrombotic event after treatment with HFC (ischemia due to digital microthrombi, as noted above).

3.7 | Immunogenicity

A positive antifibrinogen antibody test was obtained for six patients. In three patients, antibodies were already detected before the first HFC infusion. In the other three patients, antibodies were detected at various time points during the study. For these patients the positive testing was not constant and mostly at the threshold of positivity of the assay. In cases in which the test indicated the presence of de novo antibodies, these did not appear

TABLE 3 Summary of adverse events possibly or probably related to treatment

Event description	Preferred term	Serious (Yes/No)	Severity	Resolved (Yes/No)	Causality
Mild skin reaction (itchiness and redness)	Drug eruption	No	Mild	Yes	Possibly related
Ischemia due to digital microthrombi	Thrombosis	Yes	Moderate	Yes	Possibly related
Peripheral phlebitis upper limbs	Phlebitis	No	Mild	Yes	Possibly related

Note: Adverse events defined according to MedDRA version 18.1. MedDRA, Medical Dictionary for Regulatory Activities.

to be neutralizing as there was no observable effect on fibrinogen levels or efficacy.

4 | DISCUSSION

This prospective, multinational study in patients with congenital fibrinogen deficiency represents the largest prospective data collection to date in this indication. HFC was successful in the treatment of BEs and as surgical prophylaxis, demonstrating adjudicated hemostatic efficacy (treatment success) for 98.9% of BEs and 100% of surgical procedures. In addition, the change in MCF from baseline, which has been used as a surrogate marker for hemostatic efficacy,[18] showed a statistically significant increase after treatment and was in good agreement with the efficacy rating given by the investigators and IDMEAC. A favorable safety profile was demonstrated, with no severe allergic or hypersensitivity reactions and no clinical evidence of de novo neutralizing antifibrinogen antibodies.

The high success rate for treatment of bleeding demonstrated here is comparable with that previously reported for other fibrinogen concentrates. A retrospective analysis of 12 patients with congenital fibrinogen deficiency treated with Haemocomplettan® P rated hemostatic efficacy as very good (the highest rating) for all 26 BEs; however, these data were based on a subjective scoring system without independent adjudication.[9] In a postauthorization study of Clottafact®, five patients with afibrinogenemia received 48 infusions for treatment of 49 hemorrhagic events, with efficacy rated as excellent for 27 and good for 21 infusions, giving a success rate (rating of excellent/good) of 100% using an objective 4-point scale.[11]

In the present study, the change in MCF from baseline to 1 hour after the first infusion of HFC was evaluated as a surrogate marker of efficacy. The statistically significant increase in MCF coincided with the 98.9% successful efficacy rating given by the IDMEAC, utilizing an objective 4-point scale. Manco-Johnson et al also demonstrated a statistically significant increase in MCF pre- and post-infusion of Haemocomplettan® P, using the same methodology.[10] In a comparison of the HFC investigated in the present study and Haemocomplettan® P, equivalent increases in MCF were observed on administration of a single infusion of the respective fibrinogen concentrates.[14] Taken together, data from previous studies demonstrate that MCF measured in plasma is suitable for use as a surrogate measure of efficacy in the administration of fibrinogen concentrate for treatment of bleeding in patients with congenital fibrinogen deficiency.

Six patients aged 12-17 years received HFC for treatment of a total of 11 BEs. Hemostatic efficacy was classified as successful for all BEs. There was also a significant increase in MCF from baseline to 1 hour after HFC infusion in this population. These results suggest no difference in the efficacy of HFC for treatment of bleeding in the adult and the adolescent patients studied; however, the small number of patients aged <18 years that were enrolled, with none under 12 years, should be taken into consideration. Data regarding the response of adolescent and pediatric patients to fibrinogen concentrate are scarce, with previous studies not including a sufficient number of patients to allow a meaningful comparison of the different age groups. A study evaluating Clottafact® as prophylaxis demonstrated clinical efficacy of 98.8% for patients aged under 12 years and 100% for those aged 12 years or older; however, there were only four and five patients in these age groups, respectively.[11]

After administration of HFC, fibrinogen plasma level increased in all patients. The mean incremental IVR for HFC (1.82 mg/dL/[mg/kg]) found in this study is comparable to those reported in an earlier PK study comparing it to Haemocomplettan® P (1.79 and 1.77 mg/dL/[mg/kg], respectively).[14] Manco-Johnson et al reported a similar value for Haemocomplettan® P (1.7 mg/dL/[mg/kg]).[10] Kreuz et al calculated a slightly lower value of 1.5 mg/dL/[mg/kg]; however, the majority of patients received Haemocomplettan® P as routine prophylaxis or prior to surgery and so the results cannot be directly compared with those reported here.[9]

The HFC used in this study demonstrated 100% hemostatic efficacy (treatment rated as success) for surgical prophylaxis. Success rates were comparable with published data on Haemocomplettan® P, where fibrinogen concentrate was administered as prophylaxis for 11 surgical procedures in patients with congenital fibrinogen deficiency.[9] Clinical efficacy based on subjective criteria was reported to be very good, which was the highest efficacy rating, for all but one surgery.

Of the 91 AEs that occurred in 19 patients, three were assessed as being possibly related to HFC. One of these was a thrombotic event, ie, ischemia due to digital microthrombi. This occurred 1 day after the second infusion of HFC for treatment of a BE. This patient displayed elevated levels of prothrombin F1 + F2 prior to receiving HFC for treatment of all four BEs and the single surgery that they were treated for during the study, with variable levels post-infusion. Other fibrinogen concentrates have also been associated with thromboembolic events. A severe thrombosis of the subclavian vein was reported for a patient following intensification of prophylactic treatment with Clottafact®,[11] and a venous thrombosis and a nonfatal lung embolism were observed during treatment with Haemocomplettan® P.[9] However, overall, the incidence of thromboembolic events in patients treated with fibrinogen concentrates is low.[12] It should also be noted that patients with congenital fibrinogen disorders may experience thrombotic events in the absence of treatment with fibrinogen concentrate. Coagulation studies in vivo showed increased thrombus formation in the absence of fibrinogen in an afibrinogenaemic patient, with thrombi that were larger and more loosely packed than those formed with fibrinogen leaving patients potentially at thrombotic risk.[19] Although this has mainly been noted for patients with dysfibrinogenemia, a number of cases have been reported for patients with hypo- or afibrinogenemia.[20] It has been suggested that the absence of fibrinogen in blood may result in increased levels of other procoagulants, thereby increasing the general risk of thrombosis.[20] Furthermore, data from a fibrinogen gene-knockout mouse model have shown that such thrombi are unstable,[21]

while increasing plasma fibrinogen levels by supplementation with fibrinogen concentrate may inhibit platelet adhesion and reduce the risk of thrombosis.[20,22]

Allergic or hypersensitivity reactions are a known risk of fibrinogen and other coagulation factor concentrates, with anaphylactic shock, urticaria, and rash all having been previously reported.[9,11,12,14] In the present study, a single mild skin reaction was reported. The patient received treatment with diphenhydramine and hydrocortisone and the event resolved. The same patient received two further HFC infusions, with prophylactic treatment with diphenhydramine and hydrocortisone administered each time, and did not experience any further reactions.

Because there is no standard test for fibrinogen inhibitors, an experimental nonstandard antifibrinogen ELISA was developed for the purpose of this study to identify the presence and/or development of antifibrinogen antibodies. Although a number of patients displayed positive results for such antibodies, none appeared to have neutralizing activity, with hemostatic efficacy and plasma fibrinogen level not being affected.

This large prospective study evaluating the treatment of congenital fibrinogen deficiency, an ultra-rare condition, showed that HFC is able to treat BEs and prevent surgical bleeding, leading to significant increases in fibrinogen blood levels and markers of global hemostasis. This study also used robust objective criteria for efficacy as well as adjudication by an independent committee of experts to assess the hemostatic efficacy for treatment of bleeding and for surgical prophylaxis. This assessment showed overwhelming success of the treatment in the patients studied. Limitations of the study included the relatively low number of adolescent patients (n = 6), which made it difficult to identify any differences in efficacy between age groups. Given the low median age of the study, it is also a limitation that further differences in older age groups could not be identified, given concerns regarding underlying thrombosis in older patients. The frequency and variability of bleeding symptoms reflects the variability seen in congenital fibrinogen deficiency, as despite low or no measurable fibrinogen levels, patients do not always experience frequent bleeding.[2] The low numbers of major BEs and major surgeries might also be considered limitations, but the incidence of these is consistent with the ultra-rare setting and the nature of the disorder. With regard to the use of MCF as a surrogate measure of efficacy, a post hoc analysis identified a significant association with change in MCF for both weight and BSA but not for height or age. As this is a non-powered post hoc analysis, the significant *P*-values are likely to be the result of chance, as no pathophysiological mechanism could be identified for this result.

In conclusion, this was the largest prospective study to date evaluating the treatment of patients with congenital fibrinogen deficiency. HFC was efficacious for on-demand treatment of bleeding and for surgical prophylaxis in patients with this condition. One patient experienced a single thrombotic event, while none experienced a severe allergic or hypersensitivity reaction and there was no clinical evidence of neutralizing antifibrinogen antibodies, demonstrating the favorable safety profile of the HFC used in this study.

AUTHOR CONTRIBUTIONS

B. A. Schwartz, F. Peyvandi, and S. Knaub conceived the study and contributed to data interpretation. Cristina Solomon contributed to data interpretation. K. Kavakli, N. Zozulya, A. Almomen, B. Madan, C. D. Khayat, C. Ross, G. R. De Angulo, M. Karimi, T. Lissitchkov, K. Subramanian, F. D'Souza, A. Viswabandya, H. Hoorfar contributed to data collection. All authors reviewed the manuscript for important intellectual content and approved the final version to be submitted to the JTH. All authors have access to the primary clinical trial data.

CONFLICTS OF INTEREST

Bruce A. Schwartz, Cristina Solomon, and Sigurd Knaub are employees of Octapharma. Flora Peyvandi has received investigator fees from Octapharma, and honoraria or fees for participation in a speaker's bureau from Kedrion Biopharma, Ablynx, Grifols, Novo Nordisk, Shire, Sobi, and F. Hoffmann-La Roche. Kaan Kavakli has received investigator fees from Octapharma. Nadezhda Zozulya has received research support from Octapharma, Baxalta, CSL Behring, and Generium, and personal fees from Octapharma, Baxalta, CSL Behring, Generium, Sobi, Novo Nordisk, and F. Hoffmann-La Roche. Toshko Lissitchkov has received investigator fees from Octapharma, Bayer, CSL Behring, Novo Nordisk, and Sanofi, and honoraria or fees for participation in advisory boards from Bayer, F. Hoffmann-La Roche, Shire, and Sobi. Abdulkareem Almomen, Auro Viswabandya, Bella Madan, Claudia Djambas Khayat, Cecil Ross, Fulton D'Souza, Guillermo R. De Angulo, Hamid Hoorfar, Kannon Subramanian, and Mehran Karimi have disclosed no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.