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HEMOSTASIS

TRANSFUSION

Efficacy and safety of fibrinogen concentrate for perioperative prophylaxis of bleeding in adult, adolescent, and pediatric patients with congenital fibrinogen deficiency: FORMA-02 and FORMA-04 clinical trials

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Abstract

Background: Congenital fibrinogen deficiency (CFD) is a rare coagulation disorder placing patients at increased bleeding risk. Human fibrinogen concentrate (HFC) represents current standard of care for fibrinogen replacement in CFD, however, limited data are available on HFC for prophylactic administration before/during surgery. Here, we report results and dosing considerations for HFC treatment in perioperative bleeding management in adult, adolescent, and pediatric patients with CFD.

Study Design and Methods: FORMA-02/FORMA-04 were multinational, prospective, open-label, uncontrolled Phase 3 HFC efficacy/safety studies for surgical bleeding prophylaxis in adult/adolescent (≥12 years) and pediatric patients (<12 years) respectively. HFC dosing was calculated to achieve pre-established target fibrinogen plasma levels. Overall hemostatic efficacy was assessed as success/failure by an Independent Data Monitoring and Endpoint Adjudication Committee (IDMEAC) according to objective criteria.

Results: Twelve patients (≥12 years, $N = 9$; <12 years, $N = 3$) received HFC for surgical prophylaxis (15 surgeries; 13 minor, 2 major). Eleven minor surgeries in patients aged ≥12 years required a median of 1 infusion (range; 1–5), with a mean (±SD) dose of 93.50 mg/kg [±41.43] and two minor surgeries in patients <12 years required 1 infusion (91.55 mg/kg [±23.40]). The major surgery in an adult patient required eight infusions (225.3 mg/kg total dose). The major surgery in a pediatric patient required six infusions (450.4 mg/kg). All surgeries were rated successful by the IDMEAC.

Discussion: In adults/adolescents and pediatric patients with fibrinogen deficiency, HFC treatment for hemostatic management during/after minor and major surgery was successful, with efficacy comparable across the different age groups.

KEYWORDS
blood component preparations, blood management, coagulation factor therapy, hemostasis, transfusion practices (adult), transfusion practices (neonatal, pediatrics), transfusion practices (surgical)

1 | INTRODUCTION

Congenital fibrinogen deficiency (CFD) is a rare blood coagulation disorder affecting 1–2 individuals per million in the general population.[1] There are three types of CFD; afibrinogenemia (complete absence of fibrinogen), hypofibrinogenemia (decreased fibrinogen functional activity and antigenic levels), and dysfibrinogenemia (qualitative defect affecting fibrinogen functionality).[2] As fibrinogen deficiency impairs blood clot formation, CFD places patients at increased risk of bleeding, whether spontaneous or related to trauma or surgery.[3,4]

Fibrinogen replacement therapy is used to replete fibrinogen in patients with CFD. Historically, this has been through cryoprecipitate or fresh frozen plasma infusion; however, these allogeneic blood products have limitations, such as variable fibrinogen content and the requirement for crossmatching and preparation/thawing before use, as well as the potential for pathogen transmission.[5–9] Plasma-derived, pathogen-inactivated human fibrinogen concentrate (HFC) represents the current standard of care for fibrinogen replacement in CFD, with benefits including rapid preparation time, well-defined fibrinogen content enabling accurate/standardized dosing, fewer extraneous proteins, and a smaller infusion volume.[5–7,9] HFCs are highly efficacious with favorable benefit/risk balance in patients with CFD,[10–15] and can be administered prophylactically before and during surgery to prevent blood loss.[5,6] However, limited data have been published on this application.

We previously reported results from two Phase 3 studies on HFC efficacy and safety (*Fibryga*, Octapharma AG) in adults/adolescents (FORMA-02; $n = 25$),[14] and in pediatric patients (FORMA-04; $n = 14$) with CFD.[12] In both studies, this HFC was efficacious for on-demand bleeding episode (BE) treatment and surgical prophylaxis, and exhibited a favorable safety profile. Here, we report results of HFC treatment to prevent perioperative bleeding in adult, adolescent, and pediatric patients with CFD in FORMA-02 and FORMA-04, with a detailed insight into dosing and target fibrinogen plasma levels for minor/major surgeries across all age groups. Efficacy and safety outcomes are presented for all surgical patients, with four individual cases (minor and major surgeries in adult and pediatric patients) also presented, providing detailed information regarding dosing considerations and optimal HFC use for perioperative hemostatic management in distinct clinical CFD surgical scenarios.

2 | METHODS

2.1 | Study design

FORMA-02 (NCT02267226), performed in adults/adolescents (aged ≥12 years),[14] and FORMA-04 (NCT02408484), performed in children (aged <12 years),[12] were multinational, multicenter, prospective, open-label, uncontrolled Phase 3 studies to assess HFC efficacy and safety for the on-demand treatment of bleeding episodes (BEs) and surgical prophylaxis in patients with CFD. Designs of these trials have been described previously.[12,14] Data presented herein are for all surgical patients included across these two studies.

2.2 | Eligibility criteria

The inclusion/exclusion criteria have been described previously,[12,14] which differed mainly in their age requirements. All patients presented had a documented diagnosis of congenital afibrinogenemia/severe hypofibrinogenemia (historical plasma fibrinogen activity <50 mg/dl or below the lower detection limit of the local assay) and were to undergo surgery deemed to require prophylactic fibrinogen supplementation.

2.3 | Dosing for surgery

Each surgical patient treated received an HFC (*Fibryga*, Octapharma AG) loading infusion within 3 h prior to surgery. As previously described, HFC dosing for surgical prophylaxis was individually calculated based on the patient's fibrinogen plasma level to achieve a recommended target fibrinogen plasma level dependent on surgery type (minor/major).[16,17] The recommended target fibrinogen plasma level for minor surgery was 100 mg/dl, with an accepted lower limit of 80 mg/dl; the recommended target fibrinogen plasma level for major surgery was 150 mg/dl, with an accepted lower limit of 130 mg/

dl. Dosing targets and accepted lower limits were informed by published data from a survey of 34 physicians from 10 different countries describing HFC treatment for 517 BEs and 74 surgical procedures in 100 a- or hypofibrinogenemia patients.[4] In addition, in cases where multiple vial sizes were used, doses could be rounded to full/half vials. Final dosing decisions were at the treating physician's discretion. Additional HFC doses were given at the treating physician's discretion.

2.4 | Fibrinogen levels

Fibrinogen levels were measured 1 and 3 h after the initial HFC infusion. Postoperative fibrinogen activity was measured daily during the surgical observation period (minor surgery, ≥3 postoperative days; major surgery, ≥7 postoperative days). Fibrinogen levels were also measured before and within 1 h after each additional HFC infusion, if required, to guide dosing in order to achieve pre-established target fibrinogen plasma levels (see Section 2.3). Fibrinogen activity was measured by the Clauss assay performed at local laboratories.

2.5 | Hemostatic efficacy evaluations

HFC hemostatic efficacy evaluation for surgical prophylaxis was conducted using objective 4-point Likert scales (excellent, good, moderate, and none), as previously described.[12,14] Intraoperative efficacy was assessed by the surgeon at end of surgery (after last suture), and postoperative efficacy by the hematologist on the last postoperative day (at least Day 4 for minor surgery, at least Day 8 for major surgery, or the day of the last postoperative infusion if this came later). All clinical efficacy assessments were adjudicated by an Independent Data Monitoring and Endpoint Adjudication Committee (IDMEAC). Overall hemostatic efficacy was assessed using a 2-point scale: treatment success or failure.[12,14]

2.6 | Safety

All adverse events (AEs) and serious AEs (SAEs), including thromboembolic events (TEEs) and signs of allergic/hypersensitivity reactions that occurred or worsened from the start of the preoperative HFC loading infusion to the last postoperative day of the surgical observation period were recorded as treatment-emergent AEs (TEAEs). AEs that occurred outside the surgical observation period were non-TEAEs.

2.7 | Statistics

HFC hemostatic efficacy and safety in surgical prophylaxis were evaluated by descriptive statistics. Categorical variables are presented as absolute values and percentages; continuous variables are presented as mean ± SD or median (range). As prespecified, the primary analysis of hemostatic efficacy was performed using IDMEAC assessments. Missing assessments were counted as failures.

3 | RESULTS

3.1 | Patient characteristics

Patient disposition and analysis populations in FORMA-02 and FORMA-04 have been described previously.[12,14] Baseline characteristics of the full surgical populations in each study are shown in Table 1. All patients had a diagnosis of congenital afibrinogenemia. In FORMA-02, most surgical patients were male (7/9, 78%) and of White (5/9, 56%) or Asian (3/9, 33%) race; one patient was adolescent, and the median (range) age was 30 years (12–49). All three surgical patients in FORMA-04 were white males, with a median (range) age of 3 years[1–5] at study enrollment. Most surgeries across both studies (13/15, 87%) were minor; two were major.

In total, 12 patients received HFC prior to 15 surgeries; 12 surgeries in 9 adult/adolescent patients, and three surgeries in three pediatric patients (Figure 1). One adult patient (a 38-year-old female) received on-demand treatment with HFC for an acute BE and underwent minor surgery (dental extraction) shortly afterwards. Her fibrinogen activity prior to surgery was 87 mg/dL (above the recommended lower limit for minor surgery) and the investigator deemed it unnecessary to administer an HFC loading dose before surgery. The characteristics of each surgical prophylaxis patient reported herein, including the surgical procedures they underwent, are listed in Table 2 (also see Table S1). One adult and one pediatric patient received HFC for surgery only, while all other surgical patients were also treated for other BEs.

3.2 | Hemostatic efficacy for surgical prophylaxis

For all surgeries (100%) in both studies, prophylactic treatment with HFC to prevent bleeding during/after surgery was successful, as previously described.[12,14] Intraoperative and postoperative hemostatic efficacy were rated excellent by the IDMEAC for all surgeries except one

TABLE 1 Baseline characteristics of the surgical populations included in the FORMA-02 and FORMA-04 clinical trials

	FORMA-02 surgical population (*N*=9[a])		FORMA-04 surgical population (*N* = 3)	
Parameter	**Mean (±SD)**	**Median (range)**	**Mean (±SD)**	**Median (range)**
Age at informed consent signed (years)	31.0 (±11.54)	30.0 (12.0–49.0)	3.0 (±2.0)	3.0 (1.0–5.0)
Height (cm)	164.33 (±11.24)	167.0 (149.0–183.0)	96.7 (±14.5)	97.0 (82.0–111.0)
Weight (kg)	72.8 (±19.09)	78.0 (36.2–101.0)	14.8 (±2.86)	15.0 (11.8–17.5)
BMI (kg/m^2)	26.81 (±6.52)	26.12 (15.88–39.64)	15.9 (±1.66)	15.9 (14.2–17.5)
	N	**%**	**N**	**%**
Age category				
<6 years	0	0	3	100.0
≥6–<12 years	0	0	0	0
≥12–<18 years	1	11.1	0	0
≥18 years	8	88.9	0	0
Gender				
Male	7	77.8	3	100.0
Female	2	22.2	0	0
Race				
White	5	55.6	3	100.0
Asian	3	33.3	0	0
Arab/Middle Eastern	1	11.1	0	0
Congenital fibrinogen deficiency				
Afibrinogenemia	9	100.0	3	100.0
Hypofibrinogenemia	0	0	0	0

Abbreviations: BMI, body mass index; N, number of patients.
[a]Includes one adult patient who received on-demand treatment with HFC for acute bleeding prior to undergoing minor surgery; the patient did not receive a loading dose specifically for surgical prophylaxis.

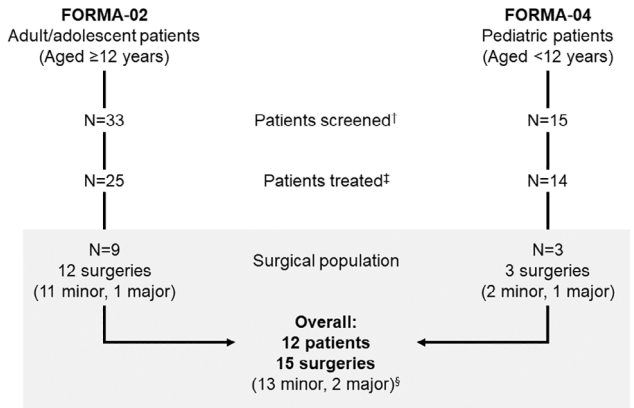

FIGURE 1 Patient disposition and surgical populations in the FORMA-02 and FORMA-04 clinical trials. † Patients who were screened and gave consent. ‡ Patients who received HFC for pharmacokinetic analysis, treatment of a bleeding episode or surgical prophylaxis. § One adult patient received on-demand treatment with HFC for a bleeding episode and underwent minor surgery shortly afterwards and thus did not receive a loading dose specifically for surgical prophylaxis. HFC, human fibrinogen concentrate; N, number of patients

major surgery in an adult patient (described below), for which intraoperative and postoperative efficacy were rated as good (Table S2). For the same surgery, the excellent postoperative efficacy rating by the hematologist was recorded as good upon IDMEAC adjudication; all other IDMEAC ratings were in agreement with investigator assessments. HFC hemostatic efficacy for surgical prophylaxis was comparable for all age groups. HFC dosing for surgical prophylaxis across both studies are shown in Table 3.

3.3 | Minor surgeries

For the 13 minor surgeries, the mean (±SD) HFC loading dose was 74.30 mg/kg (±22.64); 74.87 mg/kg (±19.41) for patients aged ≥12 years, and 91.50 mg/kg (±23.33) for patients aged <12 years. Nine minor surgeries required only one HFC infusion to achieve pre-established target fibrinogen plasma levels, with a mean (±SD) dose of 75.56 mg/kg (±27.59). Four minor surgeries in adult

TABLE 2 Details of each patient and the surgeries they underwent in FORMA-02 and FORMA-04

Surgery number	Patient age/gender	Surgery severity	Episode number	Procedure
FORMA-02 (12 surgeries in 9 patients)				
1	42/Male	Minor	1	Radioisotope synovectomy left knee
2		Minor	2	Radioisotope synovectomy left knee
3		Minor	3	Tooth extraction
4	49/Male	Minor	1	Root canal operation
5	38/Female[a]	Minor	1	Dental extraction
6	26/Male	Minor	1	Ritual circumcision
7		Minor	2	Circumcision revision
8	36/Male	Major	1	Circumcision
9	12/Male	Minor	1	Extraction of tooth 36 dental scaling
10	19/Male	Major	1	Right eye enucleation with socket reconstruction
11	30/Female	Minor	1	Skin biopsy
12	26/Male	Minor	1	Debridement for superficial necrosis on left third toe
FORMA-04 (3 surgeries in 3 patients)				
1	01/Male	Minor	1	Circumcision
2	05[b]/Male	Major	1	Splenectomy
3	03[c]/Male	Minor	1	Pulpectomy for tooth 74 and tooth 85

[a]Patient received on-demand treatment with HFC for a bleeding episode and underwent minor surgery shortly afterwards and, therefore, did not receive a loading dose specifically for surgical prophylaxis.
[b]Patient was 6 years old at the time of surgery.
[c]Patient was 4 years old at the time of surgery.

TABLE 3 HFC dosing for surgical prophylaxis in FORMA-02 and FORMA-04

	FORMA-02 $N = 9$ patients (11 minor surgeries, 1 major surgery)		FORMA-04 $N = 3$ patients (2 minor surgeries, 1 major surgery)	
Dose (mg/kg)	**Mean (±SD)**	**Median (range)**	**Mean (±SD)**	**Median (range)**
Total dose per surgery	104.49 (±54.86)	85.80 (34.09–225.36)	211.16 (±207.84)	108.09 (75.00–450.39)
Total dose per minor surgery	93.50 (±41.43)	78.57 (34.09–161.17)	91.55 (±23.40)	91.55 (75.00–108.09)
Total dose per major surgery	225.33 (n/a)	225.33 (n/a)	450.40 (n/a)	450.40 (n/a)
Dose per infusion for all surgeries	40.45 (±30.78)	28.99 (10.59–127.91)	79.19 (±20.56)	78.75 (52.50–108.09)
Preoperative loading dose (first infusion) per all surgeries[a]	77.39 (±20.22)	70.00 (58.46–127.91)	78.50 (±27.96)	75.00 (52.50–108.09)
Preoperative loading dose (first infusion) per minor surgery[a]	74.87 (±19.41)	69.89 (58.46–127.91)	91.50 (±23.40)	91.50 (75.0–108.09)
Preoperative loading dose (first infusion) per major surgery	102.56 (n/a)	102.56 (n/a)	52.50 (n/a)	52.50 n/a

Abbreviation: n/a, not applicable.
[a]The patient who did not receive a loading dose specifically for surgical prophylaxis was not included for these calculations.

patients required additional HFC infusions, with 2–5 total doses administered, and a mean (±SD) dose of 132.87 mg/kg (±29.06). Two cases, which are typical examples of an adult or pediatric patient undergoing minor surgery, are described below.

3.3.1 | HFC prophylaxis in an adult patient undergoing minor surgery

A 36-year-old male patient underwent circumcision under local anesthesia. Fibrinogen activity (Figure 2) was

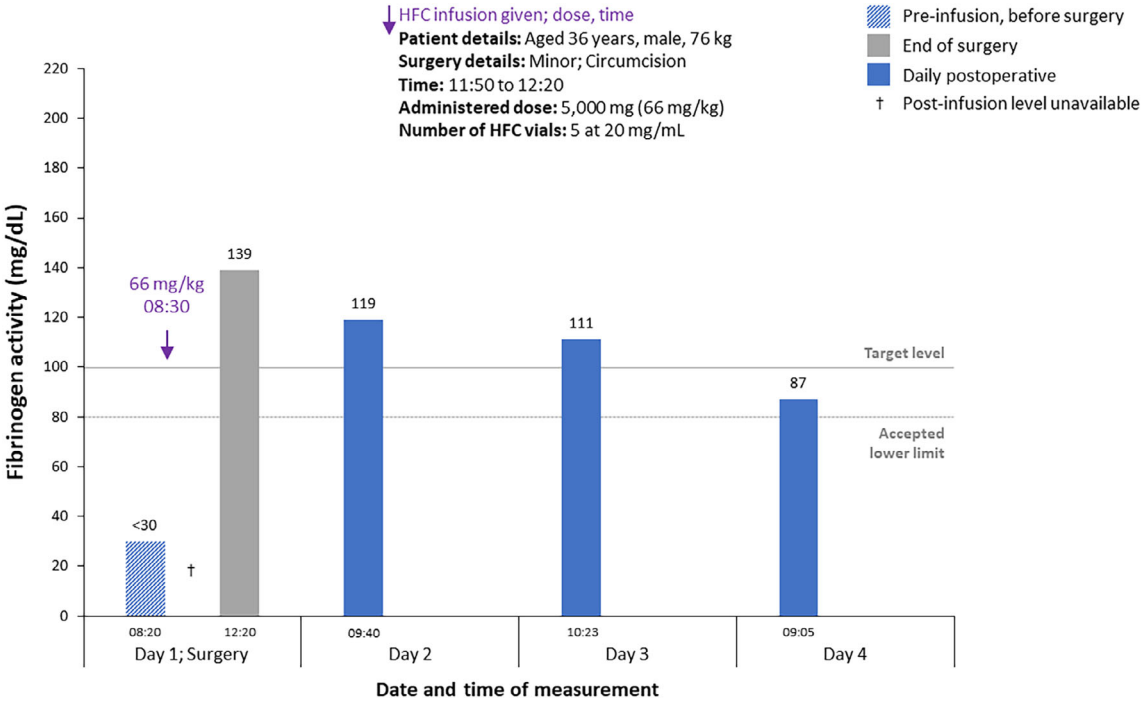

FIGURE 2 Fibrinogen activity in an adult male patient who received a single dose of HFC as surgical prophylaxis for a successful minor surgery. Solid gray line indicates recommended target level of 100 mg/dl for plasma fibrinogen activity for minor surgery; dashed gray line indicates accepted lower limit of 80 mg/dl. HFC, human fibrinogen concentrate. [Color figure can be viewed at wileyonlinelibrary.com]

undetectable prior to surgery and a 5000 mg (66 mg/kg) HFC loading dose (equivalent to 5 full HFC vials; batch provided as 1000 mg per vial at 20 mg/ml) was administered. Fibrinogen activity at 1-h post-infusion was not available from the local laboratory. Blood loss during the 30-min surgery was 8 ml; lower than the predicted 15–30 ml. Fibrinogen activity at end of surgery was 139 mg/dl. There was no bleeding/oozing from the surgical wound at the Day 2 assessment and no additional HFC infusions were needed, with fibrinogen activity levels remaining above target on Day 2 (119 mg/dl) and on Day 3 (111 mg/dl), and above the recommended lower limit for minor surgery on Day 4 (87 mg/dl). Based on laboratory results and overall health status, the patient was deemed to have responded very well to treatment, with a single HFC infusion being sufficient. The surgeon, hematologist, and IDMEAC all rated HFC hemostatic efficacy for this surgery as excellent. No AEs were recorded.

3.3.2 | HFC prophylaxis in a pediatric patient undergoing minor surgery

Pulpectomy of two teeth (numbers 74 and 85) was performed in a male patient aged 4 years old at the time of surgery. Fibrinogen activity (Figure 3) was undetectable 90 min before surgery and the patient was administered a 1838 mg (108 mg/kg) HFC loading dose at the investigator's discretion. Post-infusion, fibrinogen activity at the start of surgery was 185 mg/dl, above the target level. Surgery lasted 80 min and daily postoperative measurements showed fibrinogen activity levels of 135 mg/dl on Day 2 and 73 mg/dl on Day 3. There was no bleeding/oozing after surgery and the wound condition was deemed excellent. No additional HFC infusions were required. Treatment was successful, with intraoperative and postoperative HFC hemostatic efficacy rated excellent by the surgeon, hematologist, and IDMEAC. No AEs were recorded.

3.4 | Major surgeries

Two surgeries were classed as major; one was ocular surgery in an adult patient and the other was splenectomy in a pediatric patient. These cases are described below.

3.4.1 | HFC prophylaxis in an adult patient undergoing major surgery

A 19-year-old male patient underwent enucleation of the right eye with socket reconstruction (expected duration 120 min; actual duration 135 min). The patient had

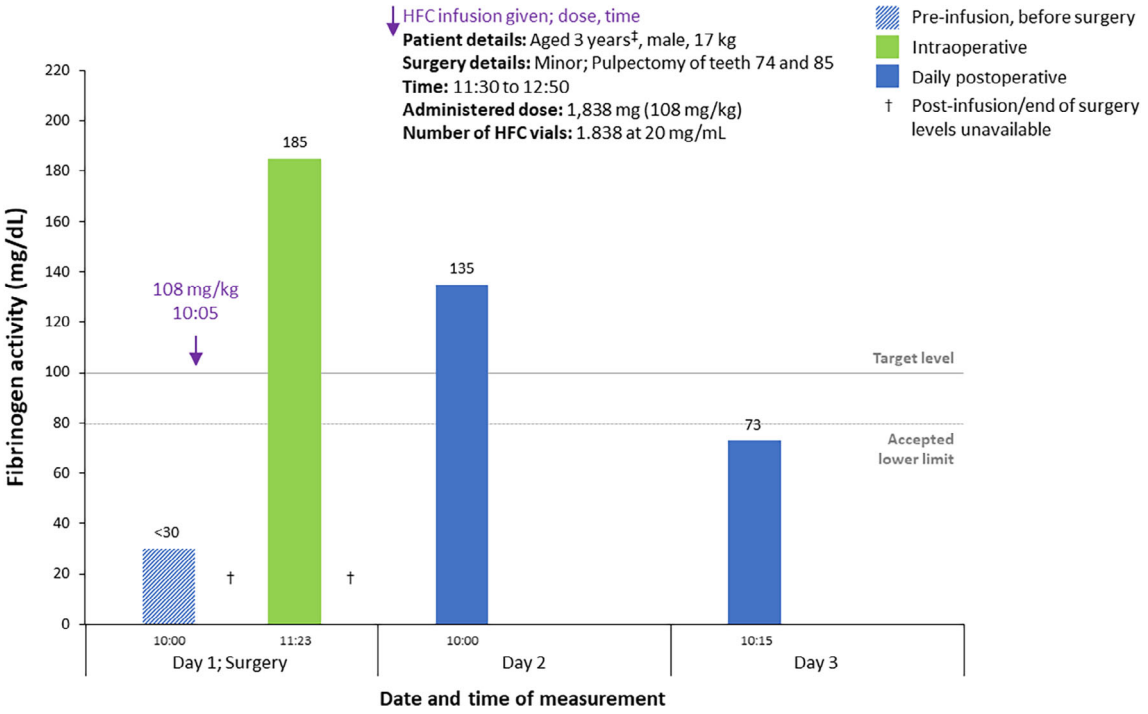

FIGURE 3 Fibrinogen activity in a pediatric male patient who received a single dose of HFC as surgical prophylaxis for a successful minor surgery. Solid gray line indicates recommended target level of 100 mg/dl for plasma fibrinogen activity for minor surgery; dashed gray line indicates accepted lower limit of 80 mg/dl. ‡ Patient was aged 3 years at the time of inclusion in the study and was aged 4 years at the time of surgery. HFC, human fibrinogen concentrate [Color figure can be viewed at wileyonlinelibrary.com]

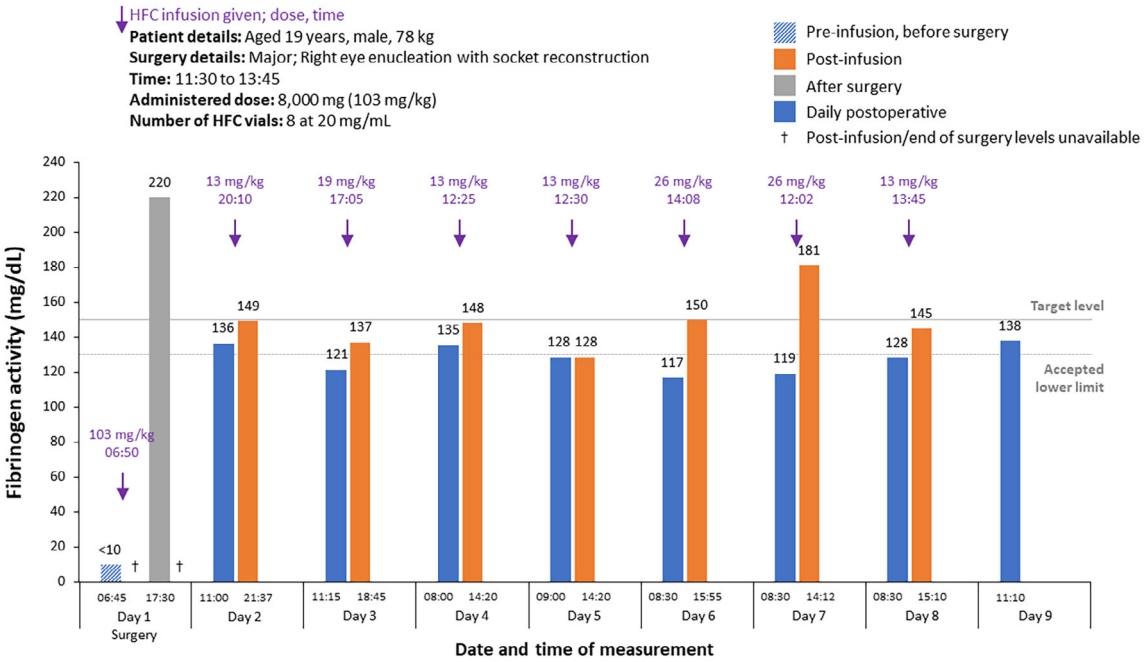

FIGURE 4 Fibrinogen activity in an adult male patient who received multiple doses of HFC as surgical prophylaxis for a major surgery. Solid gray line indicates recommended target level of 150 mg/dl for plasma fibrinogen activity for major surgery; dashed gray line indicates accepted lower limit of 130 mg/dl. The investigator noted that bleeding and oozing were more than usual on Day 2, prompting HFC infusion, with a further dose given on Day 4, even though the patient's fibrinogen activity was above the accepted lower limit of 130 mg/dl. Oozing was absent from Day 4 onwards. HFC, human fibrinogen concentrate [Color figure can be viewed at wileyonlinelibrary.com]

experienced diminished vision since the age of 10 years following a fall, and his medical history included right-eye buphthalmos and symblepharon, and entropion of the lower lid, as well as traumatic glaucoma of the right eye. Bleeding history at screening was two severe BEs per year and the patient previously received on-demand cryoprecipitate treatment. Fibrinogen activity (Figure 4) was undetectable prior to surgery and the patient was infused with a 8000 mg (103 mg/kg; equivalent to eight full vials) HFC loading dose. Fibrinogen activity at 1-hour post-infusion was not available from the local laboratory. At end of surgery, fibrinogen activity was 220 mg/dl and blood loss was 60 ml (maximum of 100 ml expected). Expected transfusion requirements for this type of surgery were a maximum of 400 ml packed red blood cells (RBCs), which were available on standby, along with cryoprecipitate; neither were required.

On Day 2, the investigator noted that bleeding and oozing (8 ml) were more than usual for this procedure and although fibrinogen activity level (136 mg/dl) was still above the accepted lower limit for major surgery, a maintenance HFC dose (1000 mg, 13 mg/kg) was administered, which elevated fibrinogen activity to 149 mg/dl (very close to the target level). Oozing decreased on Day 3 (2 ml) and was absent from Day 4. Fibrinogen activity was below 130 mg/dl on postoperative Days 3–8 (except for Day 4: 135 mg/dl), prompting further daily HFC maintenance doses. In all, eight HFC infusions were given for hemostatic management, with a loading dose of 103 mg/kg followed by seven maintenance doses ranging from 13–26 mg/kg (overall total dose: 225.3 mg/kg). For all eight infusions, the actual HFC dose administered was mostly rounded up to the next half or full vial, with a maximum increase of 24% from the initial calculated dose.

On Day 10, surgery outcome was deemed successful and without complication. The surgeon and IDMEAC rated intraoperative HFC efficacy as good; the hematologist rated postoperative efficacy as excellent, whereas the IDMEAC rating was good. Three AEs (vomiting, incision site pain, and constipation on Days 1, 2, and 3, respectively) were recorded, all of which were mild, deemed unrelated to HFC, and resolved with treatment.

3.4.2 | HFC prophylaxis in a pediatric patient undergoing major surgery

A male patient who was 5 years old at the time of study inclusion experienced spleen rupture at the age of 6 years, which included major intraperitoneal bleeding originating from the spleen due to ongoing fibrinogen deficiency and resulted in hospitalization. Four HFC infusions were administered across 9 days for this BE

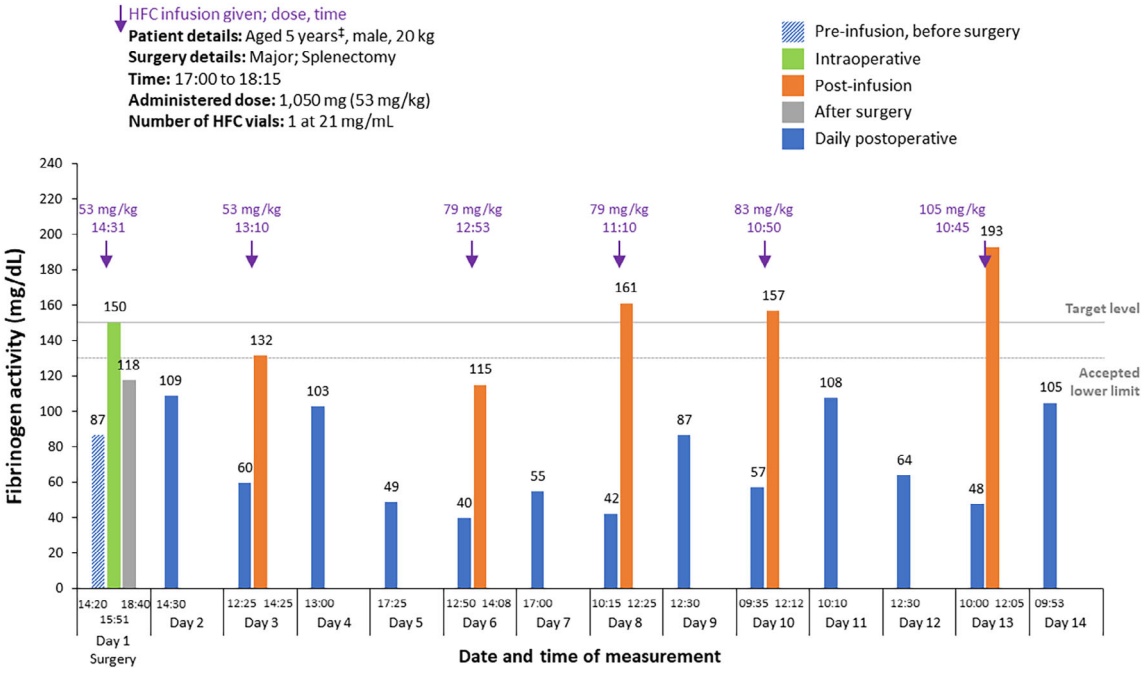

FIGURE 5 Fibrinogen activity in a pediatric male patient who received multiple doses of HFC as surgical prophylaxis for a major surgery. Solid gray line indicates recommended target level of 150 mg/dl for plasma fibrinogen activity for minor surgery; dashed gray line indicates accepted lower limit of 130 mg/dl. ‡ Patient was aged 5 years at the time of inclusion in the study and was aged 6 years at the time of surgery. HFC, human fibrinogen concentrate [Color figure can be viewed at wileyonlinelibrary.com]

treatment. On the eleventh day, splenectomy was performed. Fibrinogen activity (Figure 5) prior to surgery was 87 mg/dl and the patient was due to receive 711 mg (36 mg/kg; 0.7 vial) of HFC. An initial infusion of 1050 mg (53 mg/kg; equivalent to 1 full vial [HFC batch provided as 1050 mg per vial at 21 mg/ml]; +32.3% dose-rounding) was administered at the investigator's discretion, targeting a level of 150 mg/dl, which was attained during surgery. Fibrinogen activity at end of surgery was 118 mg/dl, below the recommended lower limit. Surgery duration was 75 min (expected: 90 min) and blood loss was 50 ml (expected maximum 100 ml). The expected transfusion requirement for this surgery was 200 ml of packed RBCs, but no transfusions were needed.

Fibrinogen activity was below 130 mg/dl on Days 2–8, however, there was no postoperative bleeding and the patient continued to be observed. Additional HFC doses were administered preventively for wound healing on Days 3, 6, 8, 10, and 13. On Day 3, 1050 mg (53 mg/kg; 1 vial of HFC) was administered. On Days 6, 8, and 10,1575 mg (79 mg/kg; 1.5 vials of HFC) was administered and on Day 13, 2100 mg (105 mg/kg; 2 vials of HFC) was administered. Fibrinogen activity increased following each infusion, exceeding the lower limit on Day 3 and achieving the target level on Days 8, 10, and 13. In all, six HFC infusions were given perioperatively for this major surgery, with a loading dose of 53 mg/kg followed by five maintenance doses ranging from 53–105 mg/kg (overall total dose: 450.4 mg/kg). For all six infusions, the actual HFC dose administered was rounded up to the next half or full vial, with a maximum increase of 45% from the initial calculated dose. The surgeon, hematologist, and IDMEAC all recorded that HFC provided excellent hemostatic efficacy for this major surgery.

The patient experienced two AEs that were deemed possibly related to treatment; portal vein thrombosis (PVT) and fever (pyrexia). PVT was confirmed by ultrasound on Day 6 and was an SAE of severe intensity, occurring following splenectomy for a spontaneous spleen rupture. The SAE was assessed as possibly related to HFC, while taking into consideration that PVT is a regular complication of splenectomy. The patient also experienced another AE, procedural pain, on the day of surgery, which was not classified as serious or related to HFC.

3.5 | Safety

In FORMA-02, 11 SAEs occurred in three patients, all of whom received HFC for both BE treatment and surgical prophylaxis. Of these SAEs, four (Dengue fever, hypocalcemia, iron-deficiency anemia, and upper gastrointestinal hemorrhage) occurred after receiving HFC for surgical prophylaxis, all of which occurred in the same patient and were considered unrelated to HFC treatment. One surgical patient in FORMA-04 experienced a single SAE considered possibly related to HFC; PVT in a patient aged 6 years who underwent major surgery (splenectomy), as described above. There were no deaths, severe allergic/hypersensitivity reactions, or clinical signs of neutralizing anti-fibrinogen antibodies in any patients during the studies.

4 | DISCUSSION

Data collected from FORMA-02 and FORMA-04 demonstrated HFC efficacy and safety for surgical prophylaxis in adult, adolescent, and pediatric patients with CFD.[12,14] This article describes in detail the surgical patient population across both studies. For all 15 surgeries performed in 12 patients, treatment with HFC for hemostatic management during/after surgery was successful, with comparable efficacy across age groups. The overall HFC safety profile was favorable in the treatment of surgical patients with CFD.

The 100% success rate observed with HFC for surgical prophylactic treatment in FORMA-02 and FORMA-04 is consistent with the hemostatic efficacy reported in studies with other HFCs.[10,11,13,18] Clinical efficacy of HFC for surgical prophylaxis in FORMA-02 and FORMA-04 coincided with post-infusion increases/maintenance of fibrinogen activity levels, as exemplified by the four typical cases described herein. For most minor surgeries (69.2%), a single infusion before surgery was sufficient, while six and eight perioperative doses were used for the two major surgeries. Among the 13 minor surgeries, the mean HFC loading dose was higher in children aged <12 years (92 mg/kg) and the one adolescent patient aged 12 years (128 mg/kg) than in adults (65 mg/kg). It has been noted previously that pharmacokinetic (PK) parameters differ in children compared with adults/adolescents.[12,19] The PK profile for patients in the FORMA-04 pediatric study (<12 years) compared with adults/adolescents (aged ≥12 years) in the FORMA-01 study, particularly in the youngest age subgroup (aged <6 years) demonstrated a lower in vivo recovery (IVR), shorter half-life, and faster clearance (CL) in the younger group.[12,19] This is consistent with what is known for other fibrinogen concentrates. For instance, for *FibCLOT*, IVR and area under the curve were lower, and CL was higher, in patients aged ≤6 years compared with patients aged 7–12 years.[10] Such numerical differences between age groups are expected due to physiological differences in body size and pharmacodynamics.[20] Consequently, higher HFC doses may be required for younger pediatric patients in clinical practice.[4,5,7]

This study demonstrates that some adult/adolescent patients received higher doses than recommended by the study protocol. This is possibly due to two reasons: in adults/adolescents, calculated doses were occasionally rounded up to half /whole vials for practical reasons; in addition, in pediatric patients, investigators administered higher doses that were calculated using a lower IVR value than generated from the previous adult/adolescent data, acknowledging differences between IVRs in adults and children observed with other HFCs or coagulation factor concentrates. Final dosing decisions were at the discretion of the investigator based upon their judgment of the patient's condition. For example, in the adult patient who underwent major ocular surgery, the investigator noted that bleeding/oozing was more than usual on the first postoperative day and gave additional HFC doses, despite the patient's fibrinogen activity being above the accepted lower limit of the target level. Oozing diminished after these additional infusions and was absent from Day 4 onwards.

Safety data indicated a favorable benefit–risk profile for HFC in this population of surgical patients with CFD. One TEE occurred; PVT, which was assessed as possibly related to treatment and occurred in a pediatric patient who underwent splenectomy following an intra-peritoneal bleed resulting from a spontaneous spleen rupture. Patients with prior splenectomy have been noted to experience a high PVT incidence.[21] Furthermore, although CFD is a bleeding diathesis, it can also be accompanied by thrombotic manifestations,[22,23] and PVT has been reported in cases of congenital dysfibrinogenemia.[22,24,25] It is of note that fibrinogen activity of the patient who experienced PVT was not elevated around the time PVT occurred (Day 6), as it remained below target level on Days 2–7. The same patient also had fever, likely a clinical manifestation of the PVT.[12,26,27] Overall, a low rate of TEEs has been observed across the studies performed to-date with the HFC used in FORMA-02 and FORMA-04.[12,14,19] No other AEs in the surgical prophylaxis patients within these studies were considered possibly related to HFC treatment.

Data presented herein describes a population of 12 patients with afibrinogenemia who underwent surgery across two clinical studies. Small study populations are unavoidable in this rare disease setting, and there were only two major surgeries and one adolescent patient included, and only three patients aged <6 years. Other limitations include that HFC dosing was occasionally adapted according to the investigator's decision. For patients requiring multiple HFC doses for surgical prophylaxis, the data reported herein supports the use of an age-group-specific dosing formula, that is, an IVR of 1.8 and 1.4 mg/dl/(mg/kg) for patients aged ≥12 years and <12 years respectively.[28]

In summary, HFC administration demonstrated a 100% success rate for perioperative prophylaxis and a favorable safety profile in adult, adolescent, and pediatric patients with CFD undergoing a range of elective surgical procedures of differing location, type, severity, and duration. Monitoring fibrinogen activity and achieving target plasma levels guided decision-making around the need for additional HFC doses, which should lead to achieving effective hemostasis in this population.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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