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ORIGINAL ARTICLE

Rare bleeding disorders

Analysis of fibrinogen concentrate pharmacokinetics and dosing for bleeds and surgery in adults, adolescents, and children with congenital afibrinogenaemia and hypofibrinogenaemia

Claudia Djambas Khayat[1] | Sunil D. Lohade[2] | Omid R. Zekavat[3] | Irina Kruzhkova[4] | Cristina Solomon[4] | Sigurd Knaub[4] | Flora Peyvandi[5,6]

[1]Hotel Dieu de France Hospital, Beirut, Lebanon

[2]Sahyadri Specialty Hospital, Pune, India

[3]Hematology Research Center, Nemazee Hospital, Shiraz University of Medical Sciences, Shiraz, Iran

[4]Research & Development Department, Octapharma, Lachen, Switzerland

[5]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Milan, Italy

[6]Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy

Correspondence
Claudia Djambas Khayat, Hotel Dieu de France Beirut Saint Joseph University, Alfred Naccache Street, Beirut, Lebanon.
Email: claudiakhayat@yahoo.fr

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Octapharma

Abstract

Introduction: Congenital afibrinogenaemia and hypofibrinogenaemia are rare coagulation disorders where clotting is impaired due to a lack of fibrinogen. Consequent bleeding episodes (BEs) are treated using human fibrinogen concentrate (HFC).

Aim: This post-hoc analysis compared HFC pharmacokinetics (PK) and dosing between patient age groups and defined the in vivo recovery (IVR) for children with a- and hypofibrinogenaemia.

Methods: The analysis used data from the FORMA-01 (Phase 2), FORMA-02 and FORMA-04 (Phase 3) multinational, prospective, open-label studies in patients with a- and hypofibrinogenaemia. HFC PK in adults/adolescents (≥12 years; FORMA-01) and children (<12 years; FORMA-04) was examined. Haemostatic efficacy in BE treatment and perioperative prophylaxis was examined in FORMA-02 and FORMA-04 using an objective 4-point scale, with success defined as excellent/good.

Results: Median (range) age was 23 years for FORMA-01 (12–53; $n = 22$), 26.5 years for FORMA-02 (12–54; $n = 25$), and 6 years for FORMA-04 (1–10; $n = 13$). Mean PK parameters were lower for children (AUC, C_{max}, IVR; $p = .02$), while clearance was higher. Median (range) total dose of HFC for all BEs was 59.41 mg/kg (32.12–273.80) in adults/adolescents and was 24% higher (ns) in children at 73.91 mg/kg (47.45–262.50). Treatment was successful in 98.9% of the 89 BEs in adults/adolescents and in 100% of the 10 BEs in children, with comparable results for perioperative prophylaxis.

Conclusion: As expected, HFC PK differed between adults/adolescents and children. However, with the higher doses given to children, HFC showed similar efficacy across age groups. Dose adaptation based on age groups appears recommendable.

KEYWORDS

adults, afibrinogenemia, children, fibrinogen, haemostasis, human fibrinogen concentrate, pharmacokinetics

1 | INTRODUCTION

Congenital fibrinogen deficiency (CFD) is a rare coagulation disorder where clotting is impaired due to an inherited lack of functional fibrinogen, with fibrinogen being either decreased or absent (a- and hypofibrinogenemia) or defective (dysfibrinogenaemia).[1] Patients with CFD can experience life-threatening bleeding episodes (BEs) requiring acute care.[1] CFD treatment currently includes use of cryoprecipitate and human fibrinogen concentrates (HFCs).[2] The latter confers several advantages, such as standardised fibrinogen concentration, rapid reconstitution, purified, and viral inactivation to reduce transfusion complications.[3] Moreover, HFC is well documented for fibrinogen replacement in congenital and acquired fibrinogen deficiency disorders.[4]

Fibryga® (Octapharma AG), hereinafter referred to as HFC, has been investigated in several studies in patients with CFD, specifically with afibrinogenaemia and hypofibrinogenaemia. FORMA-01, a multinational, prospective, randomised, controlled Phase 2 study, examined HFC pharmacokinetics (PK) and safety for adult/adolescent patients (≥12 years) with a- or hypofibrinogenaemia versus a marketed fibrinogen concentrate as a control.

FORMA-02 and FORMA-04 were multinational, prospective, open-label, uncontrolled Phase 3 studies investigating HFC haemostatic efficacy and safety for BE treatment and perioperative prophylaxis in adult/adolescent (≥12 years old) and children (<12 years old), respectively, with a- or hypofibrinogenaemia.[5,6] In FORMA-02 and FORMA-04, HFC dosing was calculated using a formula that included the actual plasma fibrinogen level, the desired fibrinogen level (100 mg/dL for minor BEs and surgery; 150 mg/dL for major BEs and surgery), body weight, and the incremental in vivo recovery (IVR) value based on FORMA-01 adult/adolescent data, as follows:

$$\text{Fibrinogen dose (mg/kg body weight)} = \frac{(\text{Target peak plasma level [mg/dL]} - \text{measured level [mg/dL]}^{\ddagger})}{\text{Median response}^{\dagger}\ \text{(mg/dL per mg/kg bodyweight)}}$$

Results of FORMA-02 (which included six adolescent patients aged 12–17 years and 19 adults aged ≥18–54) and FORMA-04 (which included 14 children aged 1–10 years), all with afibrinogenaemia demonstrated HFC to be efficacious for BE treatment and perioperative prophylaxis in patients with CFD, with comparable efficacy in children versus adult/adolescent patients. In FORMA-02, $n = 87$ (97.8%) BEs were minor and $n = 2$ (2.2%) were major; in FORMA-04, $n = 8$ (80.0%) BEs were minor and $n = 2$ (20.0%) were major. Minor BEs in both studies included mild hemarthrosis, superficial muscle, soft tissue, oral, and vaginal bleeding. Major bleeding in FORMA-02 included an occult gastrointestinal bleed and an intracranial haemorrhage, while major bleeding in FORMA-04 included left knee and thigh bleed and an intraperitoneal bleed from the spleen. For surgeries, both FORMA-02 and FORMA-04 contained data on one major surgery each (eye enucleation with socket reconstruction and splenectomy, respectively); the remaining surgeries were minor and included synovectomy, dental extraction, circumcision, and excision of scar bud of circumcision, skin biopsy, and debridement of superficial necrosis. HFC was well tolerated in both FORMA-02 and FORMA-04 studies, with a favourable safety profile demonstrated.[5,6] FORMA-04 also examined the single-dose PK profile of HFC in children with CFD.[5] Initial comparison of data from FORMA-01 and FORMA-04 suggested that most PK parameters were numerically lower in children compared with adults/adolescents, and that children received numerically higher HFC doses.[6,7]

Herein, we provide a detailed examination of HFC PK data for adults, adolescents, and children from FORMA-01, FORMA-02, and FORMA-04, and investigate dosing differences between age groups to assess the impact of dose recalculation using age-group-specific IVR values to define an IVR specific for children.

2 | MATERIALS AND METHODS

2.1 | Study design

PK assessments of HFC (*Fibryga*®, Octapharma AG) in FORMA-01 and FORMA-04 have been previously described.[6,7] In both studies, patients were required to undergo a 14-day wash-out period where no fibrinogen-containing products were administered. Haemostatic efficacy in FORMA-02 and FORMA-04 was assessed using an objective 4-point scale (excellent, good, moderate, none) with treatment success defined as excellent/good.[5,6] BEs were assessed by the treating physician and efficacy for perioperative prophylaxis was evaluated by the surgeon (end of surgery) and the haematologist (post-operatively). Bleeding and surgical efficacy assessments were adjudicated by an Independent Data Monitoring and Endpoint Adjudication Committee (IDMEAC). All adverse events (AEs) during the study periods were recorded.

2.2 | Fibrinogen activity measurements

In FORMA-01 and FORMA-04, fibrinogen activity was measured using a modified Clauss fibrinogen assay. In FORMA-01, fibrinogen levels were measured pre-infusion (baseline) and post-infusion at 11 time

†The median response in this dose calculation formula is the incremental IVR of 1.77 mg/dL/[mg/kg]

‡The measured level for the first infusion was the historical level for that patient after a washout or, if below the limit of detection of the local assay, 0 mg/dL was used

points over 13 days.[7] In FORMA-04, fibrinogen was measured over eight time points: baseline, 1 and 3 h post-infusion, and on post-infusion Days 2, 5, 7, 10, and 14, including before and within 1 h after subsequent HFC infusions.[6]

2.3 | PK measurements

The following PK endpoints were assessed in FORMA-01 and FORMA-04 after a single infusion of 70 mg/kg per body weight of HFC:[6,7] area under the concentration-time curve (AUC), AUC normalised to the dose administered according to the measured actual potency (AUC_{norm}), AUC standardised to 70 mg/kg (g*h/L; AUC_{stand}), in vivo half-life ($T_{1/2}$), incremental IVR, maximum plasma concentration (C_{max}), C_{max} normalised to the dose administered according to measured actual potency ($C_{maxnorm}$), C_{max} standardised to 70 mg/kg (g*h/L; $C_{maxstand}$), time to reach maximum plasma concentration (T_{max}), mean residence time (MRT), volume of distribution at steady state (V_{SS}) and clearance (CL). Incremental IVR was calculated as maximum increase in plasma fibrinogen activity (within 4 h for FORMA-01 and within 3 h for FORMA-04) post-infusion when compared with pre-infusion levels.

2.4 | HFC dosing

For BE treatment and perioperative prophylaxis with HFC in FORMA-02 and FORMA-04, a dosing formula incorporating body weight, plasma fibrinogen levels, and IVR was recommended. An IVR of 1.77 mg/dL/(mg/kg) was derived from FORMA-01 data, with final dosing decisions made by the treating physician.

For the current analysis, the recorded dosage was recalculated using median age-group-specific IVR values calculated based on PK data from FORMA-01 and FORMA-04. In FORMA-02, an IVR of 1.8 mg/dL/(mg/kg) was used for all patients ≥12 years, and in FORMA-04, an IVR of 1.4 mg/dL/(mg/kg) was used for all patients <12 years. In age sub-group analyses, the following IVRs were used; 1.7 mg/dL/(mg/kg) for patients ≥18 years, 2.0 mg/dL/(mg/kg) for patients ≥12–< 18 years, 1.4 mg/dL/(mg/kg) for patients ≥6–< 12 years, and 1.3 mg/dL/(mg/kg) for patients <6 years.

2.5 | Statistical analysis

Post-hoc analysis of PK parameters between FORMA-01 and FORMA-04, and HFC dosing between FORMA-02 and FORMA-04, was performed using the unpaired *t*-test. Analysis of Variance and multilevel regression were applied when analysing the differences between the subgroups (≥18 years, ≥12–< 18 years, ≥6–< 12 years, <6 years). In FORMA-02 and FORMA-04, statistical analysis was performed for all BEs and surgeries in each patient. Confidence intervals (CI) of mean data were calculated using a *t*-test, and *p*-values were calculated using a paired *t*-test.[5,6] For comparison of different dosing measurements, analysis was performed using the Wilcoxon matched-pairs test. For dose comparison between age groups, analysis was performed using the Mann-Whitney test. *p*-Values <.05 were considered statistically significant.

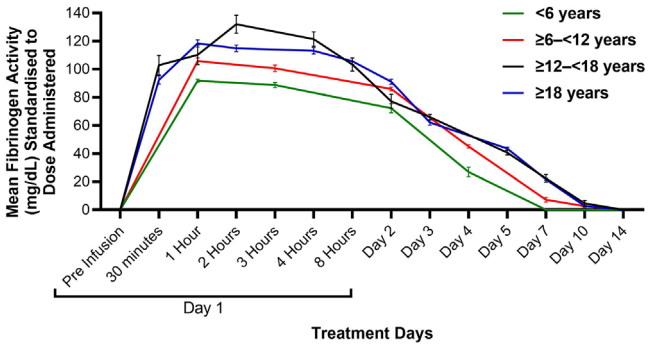

FIGURE 1 Fibrinogen activity in adults/adolescents and children with CFD. Fibrinogen activity (mg/dL) measurements standardised to 70 mg/kg mean (±SE) over time by age group for $n = 21$ patients ≥12 years in FORMA-01 and $n = 13$ patients <12 years in FORMA-04 (PK population). Values <30 mg/dL (below detectable limit) were considered as zero. CFD, congenital fibrinogen deficiency; PK, pharmacokinetic; SE, standard error

3 | RESULTS

3.1 | Patient demographics

In FORMA-01, 22 adult/adolescent patients underwent PK assessment. The median (range) age was 23.0 years (12–53) (≥12–<18 years, $n = 6$; ≥18 years, n = 16). The median (range) weight was 69.1 kg (33–107). PK analyses were performed on 21 patients; one was excluded as they received <90% of the planned total dose of HFC.

In FORMA-02, the median (range) age was 26.5 years (12–54) (≥12–<18 years, $n = 6$; ≥18 years, $n = 18$). Data was collected on 89 BEs ($n = 24$ patients) and 12 surgeries ($n = 9$ patients).

In FORMA-04, the median (range) age was 6.0 years (1–10) (<6 years, $n = 5$; ≥6–<12 years, $n = 8$). The median (range) weight was 17.5 kg (11–35). Thirteen children underwent PK assessment. Patient characteristics from FORMA-01 and FORMA-04 PK studies are detailed in Table 1. Data was also collected on 10 BEs ($n = 8$ patients) and three surgeries ($n = 3$ patients) in FORMA-04.

3.2 | Fibrinogen activity level

For the PK populations in FORMA-01 and FORMA-04, fibrinogen activity (mg/dL) standardised to 70 mg/kg mean (±SE) over time by age group is shown in Figure 1. In FORMA-01, mean (±SE) fibrinogen concentration, normalised to the actual dose administered, peaked within 2-h post infusion at 132.0 mg/dL (±6.44) for patients ≥12–18 years, and for patients ≥18 years peaked at 1-h post infusion at 118.4 mg/dL (±2.65; Figure 1). In FORMA-04, mean (±SE) fibrinogen concentration

TABLE 1 Demographic and clinical characteristics of the PK populations in FORMA-01 and FORMA-04

	FORMA-01 PK population (*N* = 21 adults/adolescents)		FORMA-04 PK population (*N* = 13 children)	
Parameter	**Mean ± SD**	**Median (range)**	**Mean ± SD**	**Median (range)**
Age at informed consent (years)	26.6 ± 12.8	23.0 (12–53)	6.2 ± 2.6	6.0 (1–10)
Height (cm)	162.9 ± 13.7	161.0 (130–190)	112.1 ± 15.7	111.0 (82–139)
Weight (kg)	67.1 ± 17.0	69.1 (33–107)	20.2 ± 7.1	17.5 (12–35)
BMI (kg/m^2)	25.2 ± 4.8	25.6 (14–34)	15.8 ± 2.9	15.9 (12–23)
	N	**%**	**N**	**%**
Age	**<18 years**, 5 **≥18 years**, 16	**<18 years**, 23.8 **≥18 years**, 76.2	**<6 years**, 5 **≥6–<12 years**, 8	**<6 years**, 38.5 **≥6–<12 years**, 61.5
Gender				
Female	14	66.7	7	53.8
Male	7	33.3	6	46.2
Race				
Asian	7	33.3	4	30.8
White	14	66.7	9	69.2

Abbreviations: BMI, body mass index; *N*, number of patients; PK, pharmacokinetics; SD, standard deviation.

normalised to the actual dose administered peaked at 1-h post infusion for both age sub-groups; 91.8 mg/dL (±1.02) for patients <6 years and 105.7 mg/dL (±2.32) for patients ≥6–<12 years (Figure 1). Fibrinogen plasma level returned to baseline by Day 7 for the <6 years age group and almost returned to baseline by Day 10 for all other age groups, returning to baseline completely by Day 14.

3.3 | PK comparison

PK parameters for patients aged <12 years were numerically different to those in patients ≥12 years (Table 2). Mean values for C_{max}, $C_{maxnorm}$, and IVR were numerically higher in patients ≥12 years versus patients <12 years; V_{SS} was also comparatively higher in patients ≥12 years. AUC, AUC_{stand}, and AUC_{norm} were higher, MRT and $T_{1/2}$ were longer, and CL was slower in patients ≥12 years compared with those < 12 years (Table 2). *Post-hoc* statistical analyses of the differences in PK parameters between all patients demonstrated significant differences in AUC, C_{max} standardised to 70 mg/kg and incremental IVR ($p = .02$ for all; Table 2).

PK parameters also differed between the four age subgroups (Table 3). In general, there was a trend for numerically lower recovery (IVR) and faster elimination ($T_{1/2}$) in younger patients. *Post-hoc* statistical analyses showed that only C_{max} varied significantly across the four age subgroups ($p = .03$; Table 3).

3.4 | HFC dosing

Across the two efficacy studies, FORMA-02 and FORMA-04, there were 89 BEs and 12 surgeries in patients ≥12 years, and 10 BEs and three surgeries in patients <12 years. For BE treatment, the median (range) total dose of HFC was 59.41 mg/kg (32.12–273.80) in patients ≥12 years and 73.91 mg/kg (47.45–262.50) in patients <12 years (Table 4). Although HFC dosing appeared higher in patients <12 years (24% higher median total dose in patients <12 years compared to patients ≥12 years), there was no statistical significance in the total dose administered for the treatment of all BEs, the dose administered for the first infusion for all BEs, or the dose administered per infusion for all BEs (Table 4).

Statistical analysis of dosing across the four age subgroups suggested that patients in the ≥12–<18 years subgroup and the <6 years subgroup were administered the highest doses, and that patients in the ≥18 years and ≥6–<12 years subgroups had the lowest doses, for all three dosing measurements (Table 5).

For perioperative prophylaxis, the median (range) loading dose was 70.00 mg/kg (58.46–127.91) for patients ≥12 years and 75.00 mg/kg (52.50–108.10) for patients <12 years, with a median total dose per surgery of 85.80 mg/kg and 108.10 mg/kg, respectively.

3.5 | HFC efficacy

For treatment of the 89 BEs (≥12 years; $n = 24$), HFC was rated as 98.9% successful (90% CI, 95.4–99.9) by the IDMEAC. For the treatment of the 10 BEs (<12 years; $n = 8$), HFC was rated as 100% successful (95% CI, 69.15–100.0) by the IDMEAC. For perioperative prophylaxis, the IDMEAC rated HFC as 100% successful for all 12 surgeries (≥12 years; $n = 9$) and for all three surgeries in the younger cohort (<12 years; $n = 3$).

TABLE 2 PK parameters for HFC determined by fibrinogen activity for patients in FORMA-01 and FORMA-04

FORMA-01		AUC	AUC_{norm}	AUC_{stand}	C_{max}	$C_{maxnorm}$	$C_{maxstand}$	IVR	T_{max}	$T_{1/2}$	MRT	CL	V_{SS}
All patients (≥12 years [*N* = 21])[a]	Mean ± SD	124.8 ± 34.58	1.624 ± .564	113.7 ± 31.54	1.266 ± .338	.018 ± .005	1.266 ± .338	1.787 ± .458	2.148 ± 1.475	75.94 ± 23.831	106.3 ± 30.927	.665 ± .197	70.19 ± 29.86
	Median (range)	119.4 (65.74–193.32)	1.588 (.85–2.51)	111.14 (59.70–175.51)	1.236 (.75–1.96)	.018 (.01–.03)	1.236 (.75–1.96)	1.766 (1.08–2.62)	2.000 (.50–4.08)	72.854 (40.03–156.96)	98.975 (58.72–205.47)	.63 (.40–1.17)	61.037 (36.89–149.11)
FORMA-04		**AUC[b]**	**AUC_{norm}[b]**	**AUC_{stand}[b]**	C_{max}	$C_{maxnorm}$	$C_{maxstand}$	IVR	T_{max}	**$T_{1/2}$[b]**	**MRT[b]**	**CL[b]**	**V_{SS}[b]**
All patients (<12 years [*N* = 13])	Mean ± SD	96.595 ± 21.003	1.314 ± .286	91.987 ± 20.010	1.072 ± .168	.015 ± .002	1.021 ± .160	1.459 ± .229	1.462 ± .877	63.339 ± 11.975	88.031 ± 16.818	.790 ± .151	67.632 ± 7.069
	Median (range)	92.514 (73.207–140.949)	1.259 (.996–1.918)	88.100 (69.689–134.237)	1.020 (.930–1.540)	.014 (.013–.021)	.971 (.886–1.467)	1.387 (1.265–2.095)	1.000 (1.000–3.000)	59.635 (45.574–91.649)	82.317 (63.625–126.656)	.796 (.521–1.004)	67.749 (52.783–76.803)
p-Value[c]		**.02**	.11	.06	.06	.05	**.02**	**.02**	.14	.13	.09	.09	.79

Notes: PK parameters were calculated using actual times relative to the end of infusion. The exact doses, calculated by use of actual potencies, were used for the PK analysis.

Abbreviations: AUC, area under the curve (g*h/L); AUC_{norm}, AUC normalised to the dose administered (h*kg*g/L/mg); AUC_{stand}, AUC standardised to 70 mg/kg (g*h/L); CL, clearance (mL/h/kg); C_{max}, maximum plasma concentration (g/L); $C_{maxnorm}$, maximum plasma concentration normalised to the dose administered (kg*g/L/mg); $C_{maxstand}$, C_{max} standardised to 70 mg/kg (g*h/L); IVR, incremental in vivo recovery (mg/dL/[mg/kg]); MRT, mean residence time (h); PK, pharmacokinetics; SD, standard deviation; $T_{1/2}$, half-life (h); T_{max}, time to reach maximum plasma concentration (h); V_{SS}, volume of distribution at steady state (mL/kg).

[a] Pharmacokinetic analyses were performed on 21 out of 22 patients. This excluded one patient who received <90% of the planned total dose of study medication.

[b] PK parameters for three patients were not calculated in FORMA-04 due to an insufficient number of quantifiable values. Fibrinogen concentrations below the limit of quantification were set to missing.

[c] *p*-Value represents the difference between mean FORMA-01 and FORMA-04 PK values, determined using an unpaired *t*-test; statistically significant *p*-values (<.05) are highlighted in bold.

TABLE 3 PK parameters for HFC determined by fibrinogen activity for the four age subgroups in FORMA-01 and FORMA-04

FORMA-01		AUC	AUC_{norm}	AUC_{stand}	C_{max}	$C_{maxnorm}$	$C_{maxstand}$	IVR	T_{max}	$T_{1/2}$	MRT	CL	V_{SS}
Adults (≥18 years [*n* = 16])	Mean ± SD	126.2 ± 35.81	1.64 ± .466	114.81 ± 32.61	1.346 ± .382	.005 ± .017	1.225 ± .348	1.737 ± .472	2.002 ± 1.520	76.91 ± 26.08	108.01 ± 33.98	.661 ± .208	71.64 ± 34.09
	Median (range)	121.24 (65.74–193.32)	1.593 (.84–2.51)	111.52 (59.70–175.51)	1.335 (.83–2.16)	.017 (.01–.03)	1.219 (.75–1.96)	1.741 (1.08–2.62)	1.542 (.50–4.08)	70.674 (40.03–156.96)	99.78 (58.72–205.47)	.628 (.40–1.17)	57.94 (36.89–149.11)
Adolescents (≥12–<18 years [*n* = 5])	Mean ± SD	120.46 ± 33.75	1.573 ± .444	110.13 ± 31.09	1.528 ± .323	.020 ± .004	1.396 ± .298	1.947 ± .410	2.613 ± 1.366	72.84 ± 16.52	100.71 ± 20.06	.675 ± .180	65.41 ± 7.947
	Median (range)	112.77 (85.79–171.06)	1.475 (1.11–2.22)	103.25 (88.74–155.50)	1.650 (1.16–1.94)	.021 (.01–.03)	1.500 (1.05–1.76)	1.953 (1.50–2.52)	2.017 (1.00–4.08)	72.85 (52.63–98.12)	98.975 (76.27–131.90)	.678 (.45–.90)	57.875 (55.15–74.72)
FORMA-04		**AUC[a]**	**AUC_{norm}[a]**	**AUC_{stand}[a]**	**C_{max}**	**$C_{maxnorm}$**	**$C_{maxstand}$**	**IVR**	**T_{max}**	**$T_{1/2}$[a]**	**MRT[a]**	**CL[a]**	**V_{SS}[a]**
Children (≥6–<12 years [*n* = 8])	Mean ± SD	102.07 ± (22.23)	1.389 ± (.303)	97.21 ± (21.17)	1.124 ± (.198)	.015 ± (.0027)	1.070 ± (.188)	1.529 ± (.269)	1.500 ± (.926)	66.093 ± (12.117)	92.173 ± (17.090)	.747 ± (.148)	67.233 ± (8.234)
	Median (range)	95.791 (78.16–140.95)	1.303 (1.063–1.918)	91.21 (74.43–134.24)	1.045 (.930–1.540)	.014 (.013–.021)	.995 (.886–1.467)	1.422 (1.265–2.095)	1.000 (1.000–3.000)	59.718 (57.74–91.65)	82.690 (79.75–126.66)	.767 (.521–.940)	66.439 (52.78–76.80)
Children (<6 years [*n* = 5])	Mean ± SD	83.82 ± (12.37)	1.140 ± (.169)	79.81 ± (11.80)	.990 ± (.049)	.013 ± (.0007)	.943 ± (.048)	1.347 ± (.066)	1.400 ± (.894)	56.914 ± (14.019)	78.368 ± (14.019)	.889 ± (.126)	68.561± (4.425)
	Median (range)	80.45 (73.21–97.40)	1.099 (.996–1.325)	76.962 (69.69–92.78)	.970 (.940–1.060)	.013 (.013–.014)	.925 (.895–1.009)	1.322 (1.278–1.442)	1.000 (1.000–3.000)	58.121 (45.57–67.05)	79.494 (63.63–91.53)	.910 (.754–1.004)	69.058 (63.91–72.72)
p-Value[b]		.13	.23	.23	**.03**	.08	.07	.08	.40	.43	.32	.82	.96

Notes: PK parameters were calculated using actual times relative to the end of infusion. The exact doses, calculated by use of actual potencies, were used for the PK analysis.

Abbreviations: AUC, area under the curve (g*h/L); AUC_{norm}, AUC normalised to the dose administered (h*kg*g/L/mg); AUC_{stand}, AUC standardised to 70 mg/kg (g*h/L); CL, clearance (mL/h/kg); C_{max}, maximum plasma concentration (g/L); $C_{maxnorm}$, maximum plasma concentration normalised to the dose administered (kg*g/L/mg); $C_{maxstand}$, C_{max} standardised to 70 mg/kg (g*h/L); IVR, incremental in vivo recovery (mg/dL/[mg/kg]); MRT, mean residence time (h); PK, pharmacokinetics; SD, standard deviation; $T_{1/2}$, half-life (h); T_{max}, time to reach maximum plasma concentration (h); V_{SS}, volume of distribution at steady state (mL/kg).

[a] PK parameters for three patients were not calculated in FORMA-04 due to an insufficient number of quantifiable values. Fibrinogen concentrations below the limit of quantification were set to missing.

[b] *p*-Value represents the difference in mean PK values across the four age subgroups, determined using Analysis of Variance; statistically significant *p*-values (<.05) are highlighted in bold.

TABLE 4 HFC dose administered for the treatment of BEs in FORMA-02 and FORMA-04

	FORMA-02 (100 infusions for $N = 89$ BEs in 24 patients)		FORMA-04 (15 infusions for $N = 10$ BEs in eight patients)		Dosing difference
HFC dose (mg/kg)	Mean ± SD	Median (range)	Mean ± SD	Median (range)	*p*-value
Total dose administered for the treatment of all BEs	65.51 ± 26.47	59.41 (32.12–273.80)	93.78 ± 64.60	73.91 (47.45–262.50)	.05[a]
Dose administered for the first infusion for all BEs	61.88 ± 11.73	58.82 (32.12–102.60)	70.78 ± 17.88	73.91 (47.45–98.44)	.23[a]
Dose administered per infusion for all BEs	58.30 ± 15.45	57.47 (11.54–102.60)	62.52 ± 22.56	70.21 (23.13–98.44)	.69[b]

Abbreviations: BEs, bleeding episodes; HFC, human fibrinogen concentrate; SD, standard deviation.
[a]*p*-Value represents the difference in dose, performed using one observation per BE using a two-level multilevel regression model.
[b]*p*-Value represents the difference in dose, performed using one observation per infusion using a three-level multilevel regression model.

3.6 | HFC dose recalculation using age-group-specific IVR values

As expected, for patients ≥12 years, dose recalculation for BE treatment and perioperative prophylaxis resulted in minor changes to the calculated dose, as age-group-specific IVR values were similar to the original IVR value for this age group (Table 6 and Table 7). For patients <12 years, recalculation of HFC dosing for BE treatment and perioperative prophylaxis using age-group-specific IVR values provided higher values than those calculated using the IVR from FORMA-01, as the recalculation used lower IVR values. However, as higher doses were mostly administered than those calculated using the IVR from FORMA-01, there was good alignment between the recalculated doses and the exact doses actually administered in FORMA-04 (Table 6 and Table 7).

4 | DISCUSSION

This study provides a detailed examination of HFC PK and dosing characteristics for adults/adolescents and children with CFD. Comparison of PK data suggested that most PK parameters were numerically lower in children versus adults/adolescents. Detailed analysis revealed lower AUC and recovery, shorter $T_{1/2}$, and faster CL in children compared with adults/adolescents. Children received numerically higher HFC doses compared to adults/adolescents for BE treatment and perioperative prophylaxis when dosing was calculated using an adult-specific IVR value from FORMA-01. Recalculation of these doses using paediatric-specific IVR values obtained in FORMA-04 brought them broadly in line with the higher doses that were administered to these patients, suggesting that an age-group-adjusted formula in children is recommendable.

The PK data presented herein are comparable to observations in previously published studies. HFC PK data for adults/adolescents from FORMA-01 were broadly comparable with data on other fibrinogen concentrates. One study examined the use of *Haemocomplettan*® *P* in adult/adolescents ≥8–65 years (mean, 30 years) and a subgroup aged ≥16–<65 years ($n = 10$).[8] While median values for some PK parameters were numerically different (higher $T_{1/2}$ and AUC_{stand}; lower CL and V_{ss}) in this subgroup compared with the age-equivalent group in FORMA-01 ($n = 16$; ≥18 years), other PK parameters were similar (C_{max} and MRT). Incremental IVR for the full analysis population ($n = 14$) in the *Haemocomplettan*® *P* study was 1.7 mg/dL/(mg/kg), with no statistically relevant difference by age, consistent with FORMA-01.[7,8] In a study of *FibCLOT*®, median values for PK parameters in 14 adults/adolescents, including 12 patients aged ≥13 years showed some differences to those reported for patients ≥12 years in FORMA-01 (e.g., $T_{1/2}$, 67.9 vs. 72.9 h; MRT, 94.7 vs. 98.9 h; CL, .57 vs. .63 mL/h/kg; V_{ss}, 53.5 vs. 61.0 mL/kg; IVR 2.22 vs. 1.77 mg/dL/[mg/kg]).[7,9] However, it should be noted that the difference in PK parameters between studies are difficult to interpret due to potential differences in the population, the PK sampling approach, the statistical analyses and outcome, and importantly, between plasma fibrinogen tests used for PK determination. For instance, the tests used in FORMA-01 and in the *FibCLOT*® study have been shown to provide considerably different results for the same sample in similar clinical settings, with the Multifibren test measuring fibrinogen levels that were significantly different ($p < .05$) to fibrinogen values obtained with other types of measurement.[10] Therefore, it is conceivable that only a PK study with a cross-over design and the same methodology for assessing PK could confirm the extent to which the different fibrinogen concentrates are comparable.[7–9]

Regarding PK data for HFC in children, the *Haemocomplettan*® *P* study examined a subgroup of four patients aged 8–14 years.[8] This subgroup had numerically higher median $T_{1/2}$ (69.1 vs. 59.6 h), C_{max} (1.4 vs. 1.0 g/L), and AUC (91.4 vs. 88.1 g*h/L [standardised to 70 mg/kg]), and numerically lower MRT (74.7 vs. 82.3 h) and V_{SS} (57.9 vs. 67.7 mL/kg) values compared with children (<12 years) in FORMA-04, with CL being similar between the studies (.77 vs. .79 mL/h/kg).[6,8] PK parameters of *FibCLOT*® in 12 patients with afibrinogenaemia ≤12 years ($n = 6$, ≤6 years; $n = 6$, 7–12 years) also showed some differences to HFC in FORMA-04; median PK parameters were 84.5 versus 92.5 g*h/L for AUC, 50.3 versus 59.6 h for $T_{1/2}$, 72.6 versus 82.3 h for MRT, .71 versus .80 mL/h/kg for CL, 53.9 versus 67.75 mL/kg for V_{SS}, and 1.85 versus 1.39 mg/dL/(mg/kg) for the IVR.[6,11] However, as discussed above, a direct comparison of these PK parameters is impaired by the

TABLE 5 HFC dose administered for the treatment of BEs in the four age subgroups of FORMA-02 and FORMA-04

	FORMA-02 (*N* = 89 BEs in 24 patients)		FORMA-04 (*N* = 10 BEs in eight patients)		Dosing difference
HFC dose (mg/kg)	≥18 years Mean ± SD Median (range) (*n* = 78 BEs in 18 patients)	≥12–<18 years Mean ± SD Median (range) (*n* = 11 BEs in six patients)	≥6–<12 years Mean ± SD Median (range) (*n* = 5 BEs in four patients)	<6 years Mean ± SD Median (range) (*n* = 5 BEs in four patients)	*p*-Value
Total dose administered for the treatment of all BEs	64.31 ± 24.54 58.01 (32.12–273.80)	73.98 ± 15.39 78.57 (37.78–91.30)	68.44 ± 35.42 47.73 (47.45–129.32)	119.12 ± 80.80 86.84 (73.50–262.50)	**.008**[a]
Dose administered for the first infusion for all BEs	60.17 ± 10.13 57.58 (32.12–102.65)	73.98 ± 15.39 78.57 (37.78–91.30)	59.18 ± 16.57 47.73 (47.45–83.06)	82.37 ± 10.43 78.75 (73.50–98.44)	**.001**[a]
Dose administered per infusion for all BEs	56.36 ± 14.40 57.07 (11.54–102.65)	73.98 ± 15.39 78.57 (37.78–91.30)	48.88 ± 22.19 47.47 (23.13–83.06)	74.45 ± 15.72 76.54 (52.50–98.44)	<**.001**[b]

Abbreviations: BE, bleeding episode; HFC, human fibrinogen concentrate; SD, standard deviation.
[a]*p*-value represents the difference in dose, performed using one observation per BE using a two-level multilevel regression model.
[b]*p*-value represents the difference in dose, performed using one observation per infusion using a three-level multilevel regression model.

differences in PK setting, which can be overcome only by a cross-over PK study. Finally, it is important to note that both the *FibCLOT*® and FORMA-04 studies reported numerically higher CL and V_{ss}, and lower AUC and MRT in the younger group (<6 years, or <7 years) than in older groups (6–11 years, or 7–12 years).[6,11] The *FibCLOT*® study in children also revealed a lower IVR and a shorter $T_{1/2}$ compared with adults/adolescents.[11] Comparison of data across these studies is hampered by differences in assays and age group boundaries, small sample sizes, and wide estimate intervals. The age group comparisons described in studies with other HFCs[8,11] and in the analyses herein consistently indicate differences in PK parameters, such as decreased AUC and MRT, and increased CL, in children versus adolescents/adults with CFD.

FORMA-02 did not fully assess HFC PK but did include measurement of IVR. The mean (±SD) IVR in adult/adolescent patients in FORMA-02, 1.82 mg/dL/(mg/kg) (±.42),[5] was comparable to that for adult/adolescent patients reported in FORMA-01,[7] and was higher than reported for children in FORMA-04; 1.4 mg/dL/(mg/kg).[6] Conversely, mean (±SD) IVR in patients aged ≥12–<18 years (*n* = 6) in FORMA-02, 1.29 mg/dL/(mg/kg) (±.24),[5] was lower than in FORMA-01 and FORMA-04.[6,7] These studies provide further evidence of different PK characteristics between adult/adolescent and children, and the potential need for age-group-specific HFC dosing.

For the HFC assessed in this study, lower PK values were expected owing to physiological differences in body size and pharmacodynamics between adults/adolescents and children.[12] Similar numerical PK differences have been described for other coagulation factor concentrates, including human-cl rhFVIII.[13,14] Several factors, such as age, body weight, type of congenital disease, HFC dosing, type of Clauss assay, and the statistical analysis performed, must be considered when comparing PK data from separate studies. Therefore, it is likely that PK data may not be transferrable and that direct product comparisons, as performed in FORMA-01, are required.[7]

Despite the differences observed in PK parameters in this study, treatment with HFC was shown to be efficacious in all age groups. Haemostatic efficacy for BE treatment was successful for 98.9% and 100% of BEs in FORMA-02 and FORMA-04, respectively, and intra-operative and post-operative haemostatic efficacy was 100% successful in both studies.[5,6]

The PK profiles of many drugs are different in children compared with adults; therefore, dosing in children cannot always be extrapolated directly from adult/adolescent data.[15] Weight-based versus fixed dosing can reduce inter-patient variability and overexposure.[16,17] Comparison of weight-based and age-based dosing is limited by the high correlation of weight and age; however, results are comparable.[17] Based on the FORMA-04 data, an IVR value of 1.4 mg/dL per mg/kg body weight may be included in the dosing formula of HFC for a- and hypofibrinogenaemia patients <12 years old.

4.1 | Limitations

Statistical significance in this analysis should be interpreted with caution due to low sample size and the fact that these studies were not appropriately powered for such statistical determination. Increasing sample size to determine statistical significance was not feasible due to the rarity of CFD, particularly in patients <12 years old. Importantly, the total number of surgeries (FORMA-02, *n* = 12; FORMA-04, *n* = 3) was considerably lower than the number of BEs; therefore, the results of dosing calculations for surgeries should be interpreted with caution.

5 | CONCLUSION

This analysis confirms the known differences in PK parameters between adults/adolescents and children. However, despite observed

TABLE 6 Comparison of calculated, recalculated, nominal, and exact HFC dose administered for the treatment of all BEs in FORMA-02 and FORMA-04

HFC dose comparison (mg/kg)	Total calculated dose according to protocol formula[a]		Dose recalculation using: IVR 1.8[b] (patients ≥12 years); IVR 1.7[b] (patients ≥18 years); IVR 2.0[b] (patients ≥12–<18 years)				Total nominal dose administered[b]				Exact total dose administered[a]			
	Mean ± SD	Median (range)	Mean ± SD	Median (range)	Average % dose	*p*-Value[c]	Mean ± SD	Median (range)	Average % dose	*p*-Value[c]	Mean ± SD	Median (range)	Average % dose	*p*-value[c]
FORMA-02														
All patients ≥12 years (*N* = 89 BEs in 24 patients)	55.13 ± 20.75	55.93 (22.60–211.29)	54.21 ± 20.40	55.00 (22.22–207.78)	98	<.001	65.23 ± 25.10	59.41 (32.12–261.50)	118	<.001	65.38 ± 25.45	59.41 (32.12–262.26)	119	<.001
Patients ≥18 years (*n* = 78 BEs in 18 patients)	55.37 ± 21.71	53.95 (22.60–211.29)	57.87 ± 22.68	57.65 (23.53–222.00	105	<.001	64.72 ± 26.51	58.01 (32.12–261.50)	117	<.001	64.16 ± 26.41	58.01 (32.12–262.26)	116	<.001
Patients ≥12–<18 years (*n* = 11 BEs in six patients)	51.87 ± 10.96	56.50 (22.60–56.50)	45.91 ± 9.70	50.00 (20.00–50.00)	89	.002	71.92 ± 14.72	71.43 (39.77–88.24)	139	.01	73.98 ± 15.39	78.57 (37.78–91.30)	143	.008
p-value[d]	.11		<.001				.007				.001			
HFC dose comparison (mg/kg)	**Total calculated dose according to protocol formula** [a]		**Dose recalculation using: IVR 1.4[b] (patient <12 years); IVR 1.4[b] (patients ≥6–<12); IVR 1.3[b] (patients <6 years)**				**Total nominal dose administered[a]**				**Exact total dose administered[a]**			
FORMA-04														
All patients <12 years (*N* = 10 BEs in eight patients)	78.30 ± 61.83	56.50 (45.20–241.81)	103.55 ± 84.31	76.92 (57.14–329.22)	132	.005	88.21 ± 62.04	68.33 (43.88–250.00)	113	.02	93.78 ± 64.60	73.91 (47.75–262.50)	120	.005
Patients ≥6–<12 years (*n* = 5 BEs in four patients)	63.05 ± 33.96	45.20 (45.20–123.16)	79.71 ± 42.93	57.14 (57.14–155.71)	126	.04	64.55 ± 34.46	45.45 (43.88–124.40)	102	.50	68.44 ± 35.42	47.73 (47.45–129.32)	109	.04
Patients <6 years (*n* = 5 BEs in four patients)	93.56 ± 82.87	56.50 (56.50–241.81)	127.38 ± 112.83	76.92 (76.92–329.22)	136	.03	111.87 ± 77.92	78.95 (66.67–250.00)	120	.04	119.12 ± 80.80	86.84 (73.50–262.50)	127	.04
p-Value[d]	.14		.06				.08				.08			

Notes: Nominal dose is the HFC dose administered to patients based on the nominal potency as provided on the product vial. Exact dose is the dose of HFC administered to patients based on the actual potency of individual HFC batches infused.

Abbreviations: BEs, bleeding episodes; HFC, human fibrinogen concentrate; IVR, in vivo recovery; SD, standard deviation.

[a]Dosing values shown here were calculated using an IVR of 1.77 mg/dL/(mg/kg) and are reported in the relevant clinical study reports for FORMA-02 and FORMA-04.

[b]mg/dL/(mg/kg).

[c]Statistical difference to the total calculated dose according to protocol formula (Wilcoxon matched-pairs test).

[d]Statistical difference between the two age subgroups within each study (≥18 years and ≥12–<18 years in FORMA-02; ≥6–<12 years and <6 years in FORMA-04; Mann-Whitney test).

TABLE 7 Comparison of calculated, recalculated, nominal, and exact HFC dose administered for perioperative prophylaxis in FORMA-02 and FORMA-04

HFC dose comparison (mg/kg)	Total calculated dose according to protocol formula[b]		Dose recalculation using: IVR 1.8[c] (patients ≥12 years); IVR 1.7[c] (patients ≥18 years); IVR 2.0[c] (patients ≥12–<18 years)			Total nominal dose administered[b]			Exact total dose administered[b]		
	Mean ± SD	Median (range)	Mean ± SD	Median (range)	Average % dose	Mean ± SD	Median (range)	Average % dose	Mean ± SD	Median (range)	Average % dose
FORMA-02											
All patients ≥12 years[a] (*N* = 8 surgeries in eight patients)	100.28 ± 59.85	66.10 (50.85–205.09)	96.39 ± 57.29	65.00 (50.00–201.67)	96	109.71 ± 52.24	93.03 (58.46–225.35)	109	111.41 ± 52.66	93.03 (58.46–225.33)	111
Patients ≥18 years[a] (*n* = 7 surgeries in seven patients)	105.15 ± 61.35	75.71 (50.85–205.09)	107.03 ± 61.95	74.44 (52.94–213.53)	102	109.05 ± 55.02	85.80 (58.46–225.35)	104	108.38 ± 54.36	85.80 (58.46–225.33)	103
Patients ≥12–<18 years (*n* = 1 surgery in one patient)	56.50 ± 0	56.50 (n/a)	50.00 ± 0	50.00 (n/a)	88	116.28 ± 0	116.28 (n/a)	206	127.91 ± 0	127.91 (n/a)	226
HFC dose comparison(mg/kg)	**Total calculated dose according to protocol formula[b]**		**Dose recalculation using: IVR 1.4[c] (patient <12 years); IVR 1.4[c] (patients ≥6–<12); IVR 1.3[c] (patients <6 years)**			**Total nominal dose administered[b]**			**Exact total dose administered[b]**		
FORMA-04											
All patients <12 years (*N* = 3 surgeries in three patients)	153.47 ± 144.19	84.75 (56.50–319.17)	209.23 ± 196.80	115.38 (76.92–435.38)	136	201.11 ± 197.95	102.94 (71.43–428.95)	131	211.67 ± 208.79	108.00 (75.00–450.00)	138
Patients ≥6–<12 years (*n* = 0)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Patients < 6 years (*n* = 3 surgeries in three patients)	153.47 ± 144.19	84.75 (56.50–319.17)	209.23 ± 196.80	115.38 (76.92–435.38)	136	201.11 ± 197.95	102.94 (71.43–428.95)	131	211.67 ± 208.79	108.00 (75.00–450.00)	138

Notes: Statistical analysis was not performed for perioperative prophylaxis due to the limited sample size. Nominal dose is the HFC dose administered to patients based on the nominal potency as provided on the product vial. Exact dose is the dose of HFC administered to patients based on the actual potency of individual HFC batches infused.

Abbreviations: BEs, bleeding episodes; HFC, human fibrinogen concentrate; IVR, in vivo recovery; n/a, not applicable; SD, standard deviation.

[a]Dosing values associated with acceptable local fibrinogen levels (≥100 mg/dL for minor events and ≥150 mg/dL for major events) were excluded from dose recalculations (*n* = 1).

[b]Dosing values shown here were calculated using an IVR of 1.77 mg/dL/(mg/kg) and are reported in the relevant clinical study reports for FORMA-02 and FORMA-04.

[c]mg/dL/(mg/kg).

differences in HFC PK and dosing, the efficacy of HFC for BE treatment and perioperative prophylaxis in children were comparable to adults/adolescents. Numerically higher doses of HFC were administered to children (at the discretion of the treating physicians) compared with adults/adolescents; therefore, age-group-specific IVR values for HFC dosing calculations in children are recommended. The median IVR of 1.4 mg/dL per mg/kg body weight for patients <12 years, as determined in FORMA-04, appears appropriate for HFC dose calculation in this age group.

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CONFLICTS OF INTEREST

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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