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ORIGINAL ARTICLE

Population pharmacokinetics of a triple-secured fibrinogen concentrate administered to afibrinogenaemic patients: Observed age- and body weight-related differences and consequences for dose adjustment in children

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Aims: The pharmacokinetics (PK) of a triple-secured fibrinogen concentrate (FC) was assessed in patients ≥40 kg by noncompartmental analysis over a period of 14 days with multiple blood samples. Limited PK time point assessments in children lead to consideration of using Bayesian estimation for paediatric data. The objectives were (i) to define the population PK of FC in patients with afibrinogenaemia; (ii) to detect age- and body weight-related differences and consequences for dose adjustment.

Methods: A population PK model was built using plasma fibrinogen activity data collected in 31 patients aged 1 to 48 years who had participated in a single-dose PK study with FC 0.06 g kg^{-1}.

Results: A 1-compartment model with allometric scaling accounting for body weight was found to best describe the kinetics of FC. Addition of age and sex as covariates did not improve the model. Incremental in vivo recovery assessed at the end of infusion with the predicted maximal concentrations was lower, weight-adjusted clearance was higher, and fibrinogen elimination half-life was shorter in patients <40 kg than patients ≥40 kg. Interpatient variability was similar in both groups.

Conclusion: Dosing in patients ≥40 kg based on the previous empirical finding using noncompartmental analysis where FC 1 g kg^{-1} raises the plasma fibrinogen activity by 23 g L^{-1} was confirmed. In patients <40 kg, (covering the age range from birth up to about 12 years old) FC 1 g kg^{-1} raises the plasma fibrinogen by 19 g L^{-1}. Dosing should be adapted accordingly unless therapy is individualized.

KEYWORDS

coagulation, congenital disorders, NONMEM, paediatrics, population analysis

No principal investigator is listed as an author. This paper describes the development of a population PK model to characterize a fibrinogen concentrate in using specific data from 3 clinical studies and there was no direct implication of study investigators. Results from each of study were or will be published in separate papers.

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1 | INTRODUCTION

Afibrinogenaemia is a rare congenital coagulation disorder characterized by a complete quantitative deficiency in plasma fibrinogen[1] transmitted as autosomal recessive traits in both sexes. The prevalence of fibrinogen deficiency in the population is estimated to be about 1 case per million.[2] This estimate includes both afibrinogenaemia and hypofibrinogenaemia, the latter being a less severe form with low plasma levels as compared to normal levels (2.0–4.0 g L^{-1}).[3] Disease is often diagnosed at birth, when the neonate experiences bleeding from the head or from the umbilical cord or at time of circumcision. The bleeding tendency is highly variable in afibrinogenaemia, ranging from very few to several bleeding events per year, even among patients with the same mutation.[4,5]

The goal of treatment with fibrinogen concentrate is to provide the specific clotting factor needed while reducing the possibility of overdosing with ancillary clotting proteins and blood-borne pathogen transmission. Also of importance in patients with fibrinogen deficiency is the fibrinogen incremental in vivo recovery measurement which evaluates the improvement in plasma fibrinogen level following FC treatment. This parameter is known to differ between individuals and between age groups.[6]

CLOTTAFACT, also marketed under the trade name FibCLOT in some countries, is a fibrinogen concentrate (FC) manufactured by LFB, Les Ulis, France. It is recovered from the supernatant fraction of cryoprecipitate and involves in its manufacturing process 3 viral inactivation or removal steps. The drug product is presented as a freeze-dried powder to be dissolved in water at a concentration of 15 g L^{-1} and administered intravenously.

The pharmacokinetic (PK) properties of the product were previously studied using noncompartmental analyses (NCA) after a single dose of 0.06 g kg^{-1} in 5 afibrinogenaemic adult patients[7] and then in 14 patients ≥40 kg.[8] Fibrinogen concentrations, expressed as antigen and activity, were assessed up to 14 days to capture approximately 4 half-lives of fibrinogen. The distribution was mainly restricted to the intravascular compartment and the elimination was slow and linear. The PK of FC was further assessed in 12 paediatric patients aged ≤12 years with afibrinogenaemia during a multicentre clinical study conducted between 2014 and 2015 (trial FGTW-1004, registered on clinicaltrials.gov under number NCT02094430). Children received the same single dose of 0.06 g kg^{-1} for the clinical pharmacology part of the study. Due to the ages of the patients, low volumes of blood were collected and only 3 postinfusion samples per patient were drawn across 5 days. With this sparse sampling, NCA was not possible; therefore, a population PK model was planned using all fibrinogen concentration data available from the 3 clinical studies. Population PK models are used to describe the time course of drug exposure in patients as well as to investigate sources of variability in patients. This approach considers the population study sample, rather than the individual, as a unit of analysis for the estimation of the distribution of parameters and their relationships with covariates within the population.[9] This method provides estimates of population characteristics that define the population distribution of the PK parameters.[10,11]

What is already known about this subject

- Patients with congenital fibrinogen deficiency were managed by replacement therapy with fibrinogen concentrate with dosing based on pharmacokinetic (PK) properties of the product.
- The PK of a triple-secured fibrinogen concentrate was investigated by a traditional noncompartmental approach in adults.
- No population PK model has been undertaken to simultaneously analyse fibrinogen concentration in patients of all ages.

What this study adds

- A population PK model was built to predict parameters and optimize dosing for paediatric patients
- For the first time in the congenital fibrinogen deficiency, data show the need to adjust treatment in children <40 kg.

The aim of the article is to characterize the PK of FC after development of a population PK model. In addition, relationships with age and body weight were used to define the best way to calculate the required dose of FC in paediatric populations.

2 | MATERIALS AND METHODS

2.1 | Study population and data collection

Individual fibrinogen concentrations were available in activity and in antigen from 31 patients with afibrinogenaemia recruited in 3 clinical studies, performed between 2004 and 2015, which had all been separately approved by the ethics committees (Table 1). Each study was conducted in accordance with Good Clinical Practice and ethical principles that have their origin in the Declaration of Helsinki. Written informed consent was obtained from each subject or legal representatives or parents before enrolment in the studies and before performance of any study-related procedure.

Patients were aged from 17 months to 48 years. They had not received fibrinogen substitution for at least 2 weeks prior to fibrinogen administration for PK purposes and they were in nonbleeding state. All patients received a single dose of 0.06 g kg^{-1} of FC administered at a maximum rate of 4 mL/min. The median infusion length was 1.0 h (range 13 min to 2 h) according to the volume to be infused. In studies 1 and 2, blood samples were collected in patients ≥40 kg before infusion and at 1, 3, 6 and 24 h, and 3, 6, 10 and 14 days after the end of infusion. In study 3, blood samples were collected in children aged ≤12 years (all <40 kg) before infusion and at 1 h and 3 and

TABLE 1 Study and patient characteristics of the clinical pharmacology part of the 3 studies pooled to define the overall population (*n* = 31)

	Study 1	Study 2	Study 3
Variable	***n* = 5**	***n* = 14**	***n* = 12**
Study phase	I/II	II/III	II/III
Study design	Open-label, multicentre	Open-label, multicentre	Open-label, multicentre
Inclusion criteria	Afibrinogenaemia >18 y and ≤65 y	Afibrinogenaemia ≥40 kg	Afibrinogenaemia ≤12 y
Dose infused (g kg^{-1})	0.06	0.06	0.06
Postinfusion samples per patient	8	8	3
Sex, male/female	3/2	8/6	7/5
Body weight (kg) Median (range)	72.4 (65.0–87.9)	64.0 (44.0–93.5)	20.0 (10.8–39.0)
<40 kg (*n* patients)	0	0	12
<40 kg and <6 y	0	0	6
<40 kg and 7–12 y	0	0	6
≥40 kg (*n* patients)	5	14	0
≥40 kg and 7–12 y	0	2	0
≥40 kg and >12 y	5	12	0
Age (y) Median (range)	31.9 (28.5–48.7)	21.9 (11.7–38.0)	7.1 (1.5–12.0)
≤12/ >12 y	0/5	2/12	12/0
Body mass index (kg m^{-2}) Median (range)	23.3 (21.7–28.3)	23.1 (18.7–37.0)	15.9 (12.8–22.7)

5 days after the end of infusion. Blood samples were always taken within predefined time windows and actual times of sample collections were used in the analysis.

2.2 | Bioanalytical method

Clauss assay was used to determine the fibrinogen activity in plasma samples.[12,13] The method quantifies functional fibrinogen concentration by measuring the rate of fibrinogen conversion in diluted samples under the influence of an excess of thrombin. The concentration is inversely proportional to clotting time. All fibrinogen activity determinations were performed on frozen plasma samples using the STA-R coagulometer and reagents (Diagnostica Stago, Asnières, France). Assays were conducted by Prof. Alessi, La Timone Hospital, Marseille, France for the first study,[7] then by Biomnis, Ivry-sur-Seine, France for the second and third studies. The lower limit of quantification (LLOQ) was 0.09 g L^{-1} in the first laboratory. The LLOQs at the second laboratory were 0.12 or 0.3 g L^{-1}, respectively depending on usual dilutions at 1/2 or 1/5 (low or high calibration curve). The method was validated over a range of 0.12–1.45 g L^{-1} for the low calibration curve and 0.3–3.15 g L^{-1} for the high calibration curve assays. The within-day coefficient of variation (CV) of this assay was ≤3% for 1/2 diluted samples and ≤6% for 1/5 diluted sample. The between-day CV was ≤4% and ≤6% for 1/2 and 1/5 diluted samples, respectively.

Fibrinogen antigen levels were determined by the same laboratories in charge of measuring fibrinogen activity using a validated nephelometry-based method. This method relies on the specific detection of fibrinogen with anti-fibrinogen antibodies and formation of immune complexes. These complexes scatter a beam of light passed through the samples whereby the intensity of scattered light is proportional to the concentration of fibrinogen.[14] These samples were analysed on a BN II automated nephelometer system (Siemens Healthcare Diagnostics, Marburg, Germany). The LLOQ was 0.01 g L^{-1} in the first study and 0.1 g L^{-1} in the 2 subsequent studies.

2.3 | PK modelling

A stepwise-forward approach was used to build the population PK model. As the goal was to study FC characteristics in paediatric patients, and that body weight is one of the most important parameter in this population, the base model was first developed with allometric scaling added a priori in the equations. This allowed accounting for body mass increase with age in the paediatric population. This approach also included determination of interindividual variability (IIV) and residual error. The differences in objective function value (OFV) were employed to discriminate between hierarchical models. A ΔOFV between any 2 models approximates a χ^2 distribution. In model building and covariate search, it was considered statistically significant if ΔOFV exceeded 3.84 ($P < .05$) for forward-addition steps and 6.63 ($P < .01$) for backward elimination steps. Covariates were then added to the base model to improve the model, i.e. diminishing OFV. A

validation of the final model was then performed using visual predictive checks (VPC). Predictions were made for each subject using individual weight and the actual dose administered. All steps followed established regulatory guidance.[9] Modelling was performed using NONMEM 7.3 with Fortran 5 Digital compiler, the PDxPop 5.1 interface and R 3.2.2 software for post processing (ICON Development Solutions, Ellicott City, MD, USA).[15] Excel was used to draw goodness of fit (GOF) plots.

2.3.1 | Base model

The base model using data measured in activity described the distribution and elimination of FC following intravenous infusion, any IIV on the parameters and, any residual error. The best model was selected both on the OFV (difference in OFV of −2-log likelihood) and GOF and included allometric exponents on each primary PK parameters equation. Any concentration reported as below the limit of quantification (BLQ) was not imputed or accounted for in the model, except for the first-BLQ postinfusion time point, which was reported as half the LLOQ.[16] In total, 177 postinfusion fibrinogen concentrations from 31 unique patients were included in the analysis. Of them, 16 concentrations under BLQ were imputed as half the LLOQ. Appropriateness of the model was evaluated using a 1- or 2-compartment PK model. IIV of the PK parameters was assumed to be log-normally distributed and was estimated for clearance (CL) and volume of distribution (V) using exponential models. For the residual error, a proportional error model, a constant additive error model, and a combination of both models were evaluated and the proportional error model was selected. Three different variance parameters were then estimated for the variance of the residual error relating to different Clauss assay calibration curves. Results were not significantly different, which led to estimation of only 1 residual error value.

2.3.2 | Selection of covariates of interest

An assessment of covariates of interest was performed with the aim to identify significant determinants of IIV. Covariates were selected based on scientific and clinical interest. The effect of age, sex and body size were to be evaluated on the PK parameters. However, since body weight was part of the allometric model a priori, only sex (categorical variable) and age (continuous variable) were further investigated. Using a stepwise forward approach, a covariate was retained in the model if it significantly reduced the OFV (i.e. ΔOFV of >3.84 for 1 degree of freedom at a risk ≤0.05).

2.3.3 | Validation of the final model using VPCs

The performance of the final model was evaluated by VPC using Monte Carlo simulations of the entire dataset.[17] Two thousand simulations were performed per virtual subject. The simulations were performed using NONMEM 7.3. Perl speaks NONMEM, Xpose 4.5.3, and R 3.3.1 software programs were used to process and produce the VPC plots (Consult-2-deliver, Nottingham, UK). VPCs were nonsmoothed in order to obtain a better image of the confidence intervals at each time point. Observations and the 5^{th}, 50^{th} and 95^{th} percentiles of observed data were superimposed with the 5^{th}, 50^{th} and 95^{th} percentiles of simulated data and compared visually, respectively.

2.4 | Population PK parameters

The following PK variables were derived individually using Bayesian estimation: CL, volume of distribution at steady state, area under the curve to infinity, elimination half-life, mean residence time, and maximum concentration (C_{max}) for fibrinogen activity and antigen at time of C_{max} (T_{max}), which was considered to be the end of infusion. Geometric means of individual conditional estimates of PK parameters and incremental recovery (IR) were calculated in the total cohort as well as by age subgroups. Categories of age were ≤6 years and 7–12 years for children, 13–<18 years for adolescents, and ≥18 years for adults, where age was defined as age at time of PK infusion. An additional analysis was performed by body weight subgroups (<40 kg and ≥40 kg). In general, <40 kg covers the age range from birth up to age about 12 years. Body weight subgroups were compared using a Student *t* test for 2 independent samples ($\alpha = 0.05$) with a common variance based on Satterthwaite approximation. Incremental recovery at T_{max} was calculated using the following formula, expressed as g L^{-1} per g kg^{-1}:

IR = concentration at T_{max} (g L^{-1}) /dose infused (g kg^{-1}).

2.5 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY with link for fibrinogen as endogenous peptide in humans https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=6749.

3 | RESULTS

Fibrinogen activity over time following infusion of the studied FC is displayed by body weight subgroups in Figure 1. Fibrinogen activity showed monoexponential decay for both groups. Mean plasma fibrinogen concentrations measured in the paediatric population <40 kg which corresponds also to patients aged ≤12 years showed lower values than those observed in adolescent and adult patients ≥40 kg.

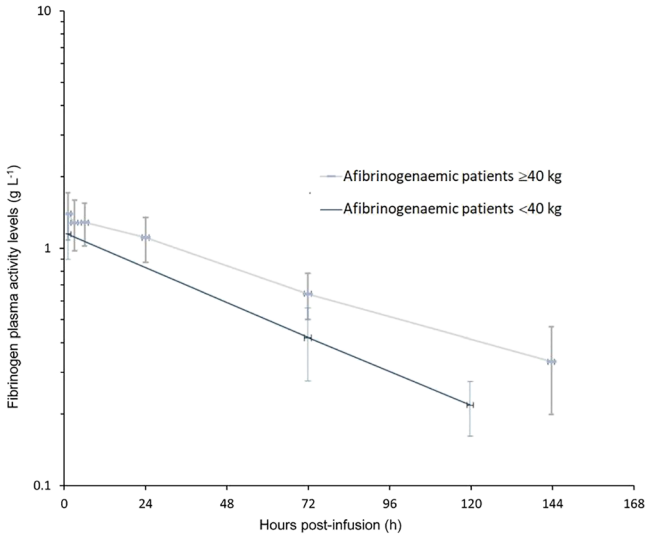

FIGURE 1 Mean (standard deviation) values of fibrinogen plasma activity over time stratified by body weight

3.1 | Structural model development

Time profiles of fibrinogen activity from all 31 patients were best described by a 1-compartment PK model with allometric scaling and exponential function to describe IIV for CL and V.

$$CL = TVCL^{\eta 1} \quad (1)$$

$$V = TVV^{\eta 2} \quad (2)$$

where TV is the typical value.

Allometric exponents were estimated and actual patient body weight on the day of PK assessment was used in the equations of CL without centring. Correlation between CL and V was low at approximately 75% (<95%); therefore, the estimation of covariance was not necessary. As mentioned above, only 1 proportional residual error with identical variance for the different Clauss assays was used.

$$Y = F*(1+\varepsilon 1) \quad (3)$$

Covariate selection analyses are summarized in the online supplementary material as Table S1. Sex was explored as a categorical covariate and age as a continuous covariate using linear relations. Based on the absence of significant change in OFV (ΔOFV <3.84 corresponding to $P > 0.05$), none of them proved to significantly affect the PK. Parameters of the final PK model were estimated with reasonable precision (% relative standard error of the estimates <20%; Table 2). Due to the low number of patients, precision of the IIV and residual error were not determined.

GOF plots of the final PK model for predicted and observed fibrinogen concentrations are presented over time in Figure S1. Population and individual predictions were distributed around the identity line with observations as shown in Figure S2. Weighted residuals *vs* time or *vs* population predictions were distributed equally over the zero line that suggests absence of model misspecification (Figure S3). However, larger residuals (in absolute value) were observed for low predictions (close to LLOQ).

The final fibrinogen population PK model equations for CL and V are as follows:

$$TVCL = 0.00288*WT^{0.556} \quad (4)$$

$$TVV = 0.0960*WT^{0.808} \quad (5)$$

where WT is the body weight

3.2 | Model validation

The VPC results confirmed the robustness of the model stability and PK parameters were estimated with good precision. In total, 2000 simulations were performed per virtual subject: 90% of the observed values lie within the 5th and 95th percentiles of the simulated data suggesting good prediction of the data by the model (Figure 2). In

TABLE 2 Parameter estimates of the final model for fibrinogen activity assay

Parameter		Estimate	RSE	95% CI	CV
Clearance (L/h) = $\Theta 1^* WT^{\Theta 3}$					
	Θ_1	0.00288	19.3%	(0.00179; 0.00397)	
Allometric exponent	Θ_3	0.556	9.7%	(0.45; 0.662)	
Proportional interindividual variability	Ω_1^2	0.0387	ND	(0.0187; 0.0587)	19.7%
Volume of distribution (L) = $\Theta 2^* WT^{\Theta 4}$					
	Θ_2	0.0960	16.9%	(0.0642; 0.128)	
Allometric exponent	Θ_4	0.808	5.7%	(0.717; 0.899)	
Proportional interindividual variability	Ω_2^2	0.0250	ND	(0.0107; 0.0393)	15.8%
Proportional residual error σ^2		0.0120	ND	(0.00524; 0.0188)	11.0%

RSE, relative standard error of the estimate; CI, confidence interval; CV, coefficient of variation; WT, body weight; ND, not determined.

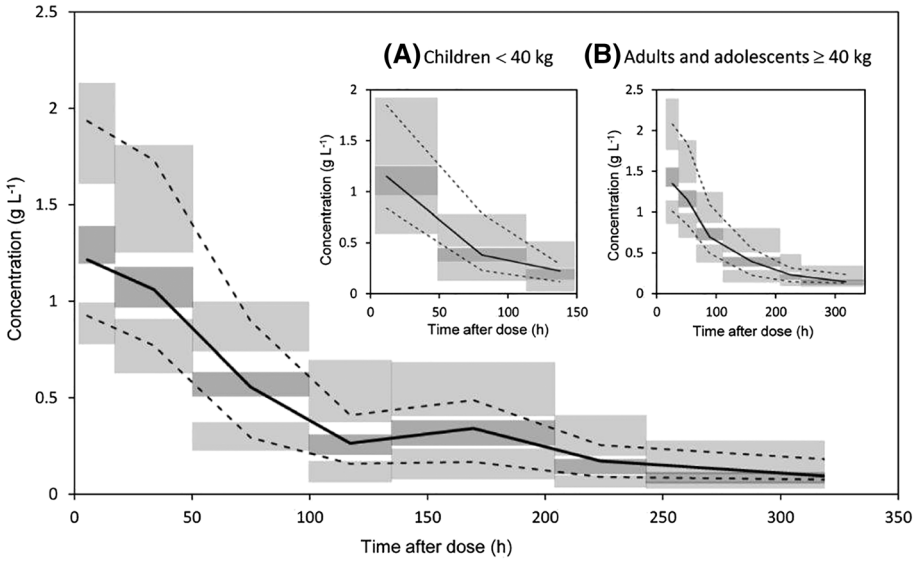

FIGURE 2 Visual predictive check plot for the final FC activity population pharmacokinetic population model for the entire population and stratified by body weight: (A) subjects <40 kg and (B) subjects ≥40 kg. In total, 2000 simulations were performed per virtual subject. Dotted lines represent quantiles Q95 and Q5 of the observed values; full line represents the Q50. Grey shaded areas are 95% confidence intervals of simulated 5th, 50th and 95th percentiles

addition, when classified by body weight as subjects <40 kg (A) and ≥40 kg (B), PK was adequately described by the model.

3.3 | PK parameters for fibrinogen activity data based on individual Bayes estimates

PK parameters estimated from the population PK model are presented by age groups in Table 3, by body weight groups in Table 4, and by study in Table S2. Children had higher CL, larger volume of distribution at steady state, shorter half-life and lower IR than both adolescents and adults following a single dose of 0.06 g kg^{-1}. Geometric mean exposure in term of area under the curve to infinity was 81.3 g h L^{-1} for patients <40 kg and 133.4 g h L^{-1} for patients ≥40 kg body weight. Clearance standardized to body weight (kg) in patients <40 kg was increased by 64% compared to the rest of the population. Predicted IR was 18.5 g L^{-1} per g kg^{-1} for patients <40 kg and 23.1 g L^{-1} per g kg^{-1} for patients ≥40 kg with forest plots showing a 95% confidence interval ranging, respectively, from 17.8 to 19.3 and 22.7 to 23.6 g L^{-1} per g kg^{-1} (Figure 3). The difference of the means was significant between the 2 groups with a *P*-value <.0001.

As a consequence, 1 g (kg body weight)$^{-1}$ of FC showed a geometric mean of 18.5 g L^{-1} (geometric CV 6.4%) fibrinogen activity increase in young patients (up to approximately 12 years) *vs* 23.1 g L^{-1} (geometric CV 4.1%) in older patients.

3.4 | PK parameters for fibrinogen antigen data

A high correlation was calculated at 98.7% (R^2 of 0.975) between activity and antigen concentrations indicating that the infused protein is fully functional (Figure 4). Taking this fact into consideration, the

TABLE 3 Summary of pharmacokinetic parameters and incremental recovery for fibrinogen activity based on individual Bayes estimates from population pharmacokinetic analysis by age groups and overall

Variable			Children ≤6 y (*n* = 6)	Children 7–12 y (*n* = 8)	Adolescents 13–<18 y (*n* = 3)	Adults ≥18 y (*n* = 14)	Overall (*n* = 31)
Mean dose of FC infused		(g kg^{-1})	0.060	0.060	0.061	0.060	0.060
Pharmacokinetic parameters							
Geometric mean (geometric CV (%))	CL	(mL h^{-1} kg^{-1})	0.81 (15.4)	0.65 (23.3)	0.43 (26.8)	0.44 (25.1)	0.54 (34.8)
	V_{ss}	(mL kg^{-1})	54.4 (10.3)	48.6 (18.7)	39.5 (19.0)	43.8 (18.0)	46.5 (19.1)
	AUC_{inf}	(g h L^{-1})	74.2 (15.4)	92.8 (23.4)	143.7 (29.9)	135.9 (25.6)	110.1 (35.1)
	$t_{1/2}$	(h)	46.6 (9.8)	52.1 (10.4)	64.2 (9.9)	69.3 (19.7)	59.2 (22.5)
	MRT	(h)	67.3 (9.8)	75. 2 (10.4)	92.6 (9.9)	100.0 (19.7)	85.4 (22.5)
	C_{max}	(g L^{-1})	1.06 (4.2)	1.20 (5.9)	1.42 (9.1)	1.39 (4.1)	1.27 (12.3)
Incremental recovery at T_{max}		(g L^{-1} per g kg^{-1})	17.7 (4.2)	20.0 (5.9)	23.1 (5.3)	23.3 (3.2)	21.2 (12.1)

CV, coefficient of variation; CL, clearance; V_{ss}, volume of distribution at steady state; AUC_{inf}, area under the concentration time curve to infinity; $t_{1/2}$, elimination half-life; MRT, mean residence time; IR, incremental recovery; C_{max}, maximum concentration for fibrinogen activity; T_{max}, time at C_{max} (considered the end of infusion).

TABLE 4 Summary of pharmacokinetic parameters and incremental recovery for fibrinogen activity and antigen based on individual Bayes estimates from population pharmacokinetic analysis by body weight groups

			<40 kg		≥40 kg	
			(*n* = 12)		(*n* = 19)	
Variable			Fibrinogen activity	Fibrinogen antigen	Fibrinogen activity	Fibrinogen antigen
Mean dose of FC infused		(g kg^{-1})	0.060	0.064	0.060	0.064
Pharmacokinetic parameters						
Geometric mean (geometric CV (%))	CL	(mL h^{-1} kg^{-1})	0.74 (22.6)	0.61 (16.1)	0.45 (24.8)	0.37 (18.8)
	V_{ss}	(mL kg^{-1})	52.2 (15.9)	55.0 (13.9)	43.2 (17.3)	46.2 (15.7)
	AUC_{inf}	(g h L^{-1})	81.3 (22.6)	105.4 (16.3)	133.4 (25.6)	169.9 (20.3)
	$t_{1/2}$	(h)	49.0 (11.6)	62.4 (7.7)	66.7 (19.0)	85.9 (15.5)
	MRT	(h)	70.7 (11.6)	90.1 (7.7)	96.2 (19.0)	123.9 (15.5)
	C_{max}	(g L^{-1})	1.11 (6.4)	1.14 (5.8)	1.39 (5.2)	1.33 (4.7)
Incremental recovery at T_{max}		(g L^{-1} per g kg^{-1})	18.5 (6.4)	17.8 (5.8)	23.1 (4.1)	21.1 (6.1)

CV, coefficient of variation; CL, clearance; V_{ss}, volume of distribution at steady state; AUC_{inf}, area under the concentration time curve to infinity; $t_{1/2}$, elimination half-life; MRT, mean residence time; IR, incremental recovery; C_{max}, maximum concentration for fibrinogen activity and antigen; T_{max}, time at C_{max} (considered the end of infusion).

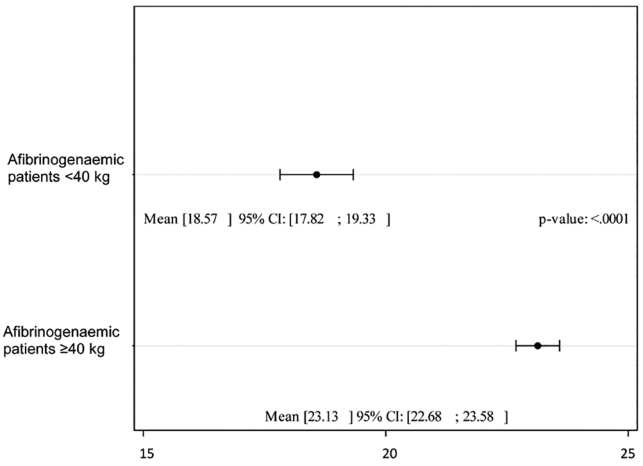

FIGURE 3 Forest plots of the incremental recovery at Tmax for fibrinogen activity comparing patients <40 kg with patients ≥40 kg. The dot corresponds to the mean. The left vertical line corresponds to 2.5% of confidence interval (CI); the right vertical line corresponds to 97.5% of CI

same population PK model was applied to antigen data and GOF plots were satisfactory (not shown). Individual conditional estimates were then determined. Geometric means of the PK parameters obtained on fibrinogen antigen are presented in Table 4 and are in the same order of magnitude than those obtained on fibrinogen activity.

4 | DISCUSSION

A population PK model for this triple secured fibrinogen was developed based on data from paediatric, adolescent, and adult afibrinogenaemic patients who participated in the clinical pharmacology part of 3 clinical studies. Even though performed in 2 different central laboratories, each laboratory used the same methodologies for fibrinogen activity and antigen, i.e. the Clauss method and nephelometry, respectively. For activity measurement, the LLOQ was slightly different between the 2 laboratories (0.09 g L^{-1} in the first study and 0.12 g L^{-1} in the 2 subsequent studies), but no substantial impact on the PK results was foreseen. This type of PK analysis was chosen due to the low number of samples allowed to be drawn in the paediatric study. The population PK model was best described by a 1-compartment model with allometric scaling noncentred on body weight. Due to the wide range of body weights (10.8–93.5 kg), the estimation of allometric exponents was possible. The effect of body weight on fibrinogen CL and V were estimated with allometric exponent of 0.556 and 0.808, respectively. The model identified sources of IIV in CL and V. The covariates sex and age did not affect the PK model significantly but there was a high correlation between body weight and age during growth which prevented a direct evaluation of age. The model was validated using VPC on the overall population and on the 2 subgroups (patients <40 kg and patients ≥40 kg). Overall, the observed concentrations lie within the band of simulated data. Moreover, after calculation, 90% of the observed values were within the 90% confidence interval (within the 5^{th} and 95^{th} percentiles), confirming that the values predicted by the model can be considered valid.

The model was first created using fibrinogen activity. Correlation between activity and antigen concentrations following fibrinogen administration is very high, demonstrating an absence of dissociation between fibrinogen activity and antigen over time. Parameters were determined using population PK analysis for both fibrinogen activity and antigen and for the different patient populations studied. The PK parameters estimated by the population PK model in patients ≥40 kg are consistent with those calculated by NCA in previous studies for the same population.[7,8] No handling effect of population PK model was seen compared to NCA

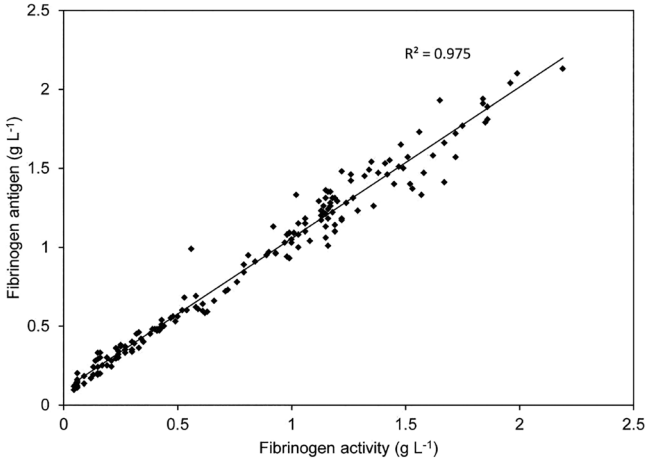

FIGURE 4 Correlation between fibrinogen antigen and fibrinogen activity concentrations for all clinical samples from all clinical studies

approach in study 1 for clearance (0.38 *vs* 0.41 mL h^{-1} kg^{-1}), volume of distribution (44.5 *vs* 47.2 mL kg^{-1}) and half-life (80.7 *vs* 82.0 h) as well as in study 2 for clearance (0.48 *vs* 0.53 mL h^{-1} kg^{-1}), volume of distribution (42.7 *vs* 50.7 mL kg^{-1}) and half-life (62.3 *vs* 69.3 h). Conversely, in 12 paediatric patients aged ≤12 years and <40 kg, the majority of estimated PK parameters were found dissimilar: clearance standardized to body weight was increased by 64%, half-life was shorter and C_{max} and IR predicted by the model were lower than in patients ≥40 kg. Such reduced half-life and higher CL rate per kg body weight of fibrinogen had already been suggested for another fibrinogen concentrate by Manco-Johnson *et al*. in 4 subjects aged <14 years.[6] The model was built with data from afibrinogenaemic patients without hepatic or renal impairment as well as in nonpregnant women. Extended covariate searches regarding these nonstudied populations including also patients with hypo- or dysfibrinogenaemia could be of importance to improve the model.

5 | CLINICAL IMPLICATIONS

Higher clearance together with lower half-life and lower recovery do suggest a need to review the dose to be administered in children <40 kg. The following algorithm, as mentioned in the fibrinogen core summary of product characteristics (SmPC), applies to LFB's FC to calculate the first dose to administer in case of surgical procedures or to treat a bleeding episode.[18]

Dose (g) = [desired levels (g/L) – baseline level (g/L)] × 1/recovery (g/L per g/kg) × body weight (kg), with product specific information on recovery.

In patients ≥40 kg, the geometric mean IR was predicted at 23 g L^{-1} per g kg^{-1}, and reciprocal is therefore 0.043, which was the same value as determined at 1 h given in the previous FibCLOT/CLOTTAFACT SmPC. With 12 paediatric patients ≤12 years old and < 40 kg, the authors are presenting a substantial number of paediatric afibrinogenaemic patients in a prospective clinical study. Incremental recovery in those 12 paediatric patients <40 kg was predicted by the model at 19 g L^{-1} per g kg^{-1} (geometric mean) at T_{max}. The corresponding reciprocal is 0.053. This calculation does not impede the need to obtain the actual IR of the paediatric patient (as is usually done in standard care) but the multiplying factor of 0.053 is a better first estimate than 0.043 in the dose algorithm and thus should be the number to consider for the paediatric population <40 kg. This should avoid underdosing of FC in this specific population. The FibCLOT/CLOTTAFACT SmPC was updated accordingly.

In summary, population and individual values predicted by the model correlated well with the observed clinical PK data. Weighted residuals *vs* time or *vs* population predictions do not suggest model misspecification. Altogether, this population PK model appears suitable to predict fibrinogen activity levels in afibrinogenaemic patients. While population PK analysis take IIV into account, data indicate differences in recovery of approximately 20% across 2 body weight subgroups <40 kg and ≥ 40 kg. These data highlight the potential impact for dosing and may support the need for higher doses in children than in adolescents and adults. These assumptions do not necessarily apply to very young patients, and further studies in this group are needed.

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CONTRIBUTORS

A.B. and E.F. conceived the PK modelling and contributed to the analysis of pharmacological data. A.B., F.B. and C.H. contributed to the analysis, interpretation of data, and wrote the manuscript. In addition, F.B. and C.H. edited the manuscript. O.R. was responsible for bioanalytical results. J.L. was responsible for statistical support and programming management. W.S. supervised the project. A.D., M.B.T. and D.G. were responsible for the acquisition, verification and accuracy of clinical data of each study.

All authors reviewed and approved the final manuscript.

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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SUPPORTING INFORMATION

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

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