Clinical Pharmacology Supplemental BLA Review

Division of Clinical Evaluation and Pharmacology/Toxicology

Office of Tissues and Advanced Therapy

BLA	125612/67
Product	FIBRYGA® [human fibrinogen], Powder for Solution for Intravenous Injection, 20 mg/mL
Sponsor	OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.
Indication	Treatment of acute bleeding episodes (b) (4) in adults, adolescents and children with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia
Date Received	June 26, 2020
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Table of Contents

1 Executive Summary 2

2 Introduction/Background 2

3 Summary of Important Clinical Pharmacology Findings 3

4 Clinical Pharmacology Labeling Comments 5

5 Recommendations 8

6 Study #1: FORMA-04 9

1 EXECUTIVE SUMMARY

On June 26, 2020, OCTAPHARMA Pharmazeutika Produktionsges.m.b.H. submitted a Supplemental Biological License Application (sBLA) for FIBRYGA®, seeking approval for 1) the addition of a pediatric age group for the treatment of acute bleeding episodes, and 2) the addition of (b) (4) to the approved indication. FIBRYGA® is individually dosed to achieve a recommended target fibrinogen plasma level dependent on the type of bleeding or surgery. The dose is calculated as following: dose (mg/kg body weight) = [target fibrinogen level (mg/dL) – measured fibrinogen level (mg/dL)]/Incremental in vivo recovery (IVR) (mg/dL per mg/kg body weight). The recommended target fibrinogen plasma level is 100 mg/dL for minor bleeding and 150 mg/dL for major bleeding.

FIBRYGA® is a plasma-derived, double virus inactivated/eliminated, highly purified concentrate of freeze-dried human fibrinogen intended for intravenous injection. It is supplied as a powder for reconstitution and intravenous injection. On June 07, 2017, FIBRYGA was licensed in the US for the treatment of acute bleeding episodes (Bes) in adults and adolescents ≥ 12 years of age with congenital fibrinogen deficiency (CFD), including afibrinogenemia and hypofibrinogenemia.

In the current sBLA, the applicant submitted data from two clinical studies (FORMA-02 and FORMA-04) to support the additional indications and to fulfill the Pediatric Research Equity Act (PREA) postmarketing requirement (PMR). Study FORMA-04 evaluated the efficacy, safety, and pharmacokinetics of FIBRYGA® for on-demand treatment of acute bleeding and to prevent bleeding during and after surgery in pediatric subjects with congenital fibrinogen deficiency. The PK results of Study FORMA-04 indicated that pediatric subjects (1 to < 12 years of age) had numerically lower recovery, shorter half-life and faster clearance, compared to adults and adolescents. Other PK parameters, such as Cmax and AUC were also lower in children. Due to the differences of incremental IVR values observed between pediatric subjects and adults and adolescents, pediatric patients (1 to < 12 years of age) should be given a higher dose of FIBRYGA using the incremental IVR of 1.4 (mg/dL per mg/kg body weight) to achieve target fibrinogen plasma levels.

Based on the pharmacokinetic (PK) results of Study FORMA-04, this sBLA is acceptable from a clinical pharmacology perspective.

2 INTRODUCTION/BACKGROUND

Human fibrinogen is a plasma glycoprotein synthesized in the liver, and it circulates in the plasma at a concentration of 2.9–4.5 g/L. Fibrinogen is essential for hemostasis, wound healing, fibrinolysis, inflammation, angiogenesis, cellular and matrix interactions, and neoplasia. These processes involve the conversion of fibrinogen into fibrin, and often the interaction of fibrinogen with various proteins and cells. The plasma level of clottable fibrinogen may be markedly decreased or even undetectable in various congenital or acquired conditions. Therapeutic

substitution with human fibrinogen concentrate can correct the hemostatic defect and arrest bleeding in patients with these fibrinogen deficiencies.

FIBRYGA® is a plasma-derived, highly purified, double virus inactivated concentrated of freeze-dried active human Fibrinogen. FIBRYGA® was developed with the aim of providing a purified and potentially safer fibrinogen concentrate than currently marketed products. It is supplied as a powder for reconstitution and intravenous injection. The final drug product contains 1 g Fibrinogen per vial. On June 07, 2017, FIBRYGA was licensed in the US for the treatment of acute bleeding episodes (BEs) in adults and adolescents ≥ 12 years of age with congenital fibrinogen deficiency (CFD), including afibrinogenemia and hypofibrinogenemia.

FIBRYGA® is individually dosed to achieve a recommended target fibrinogen plasma level dependent on the type of bleeding or surgery. The dose is calculated as following:

$$\text{Fibrinogen dose (mg/kg body weight)} = \frac{\text{[Target peak plasma level (mg/dL) − Measured level (mg/dL)**]}}{\text{Median response* (mg/dL per mg/kg body weight)}}$$

The recommended target fibrinogen plasma level is 100 mg/dL for minor bleeding and 150 mg/dL for major bleeding. When the fibrinogen level is unknown, the recommended dose is 70 mg/kg body weight. The incremental IVR is 1.8 mg/dL per mg/kg body weight for adults and adolescents.

In the current supplemental BLA, the applicant submitted data from two clinical studies (FORMA-02 and FORMA-04) and proposed labeling changes to fulfill the Pediatric Research Equity Act (PREA) postmarketing requirement (PMR).

- Study FORMA-02: Prospective, open-label, uncontrolled, phase 3 study to assess the efficacy and safety of FIBRYGA® for on-demand treatment of acute bleeding and to prevent bleeding during and after surgery in subjects with congenital fibrinogen deficiency.

- Study FORM-04: Prospective, open-label, uncontrolled, phase 3 study to assess the efficacy, safety, and pharmacokinetics of FIBRYGA® for on-demand treatment of acute bleeding and to prevent bleeding during and after surgery in pediatric subjects with congenital fibrinogen deficiency.

The pharmacokinetics in pediatric subjects was evaluated in Study FORMA-04.

3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

1. Pediatric subjects (1 to < 12 years of age) had numerically lower recovery, shorter half-life and faster clearance of FYBRYGA®, compared to adults and adolescents. Other PK parameters, such as Cmax and AUC were also lower in children.

2. The incremental IVR of 1.4 mg/dL per mg/kg body weight as determined in Study FORMA-04 for pediatric subjects is recommended to be used for dose calculation of FIBRYGA® for pediatric patients (1 to < 12 years of age):

   Dose (mg/kg body weight) = [target fibrinogen level (mg/dL) - measured fibrinogen level (mg/dL)] / 1.4 (mg/dL per mg/kg body weight)

4 CLINICAL PHARMACOLOGY LABELING COMMENTS

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fibrinogen (Factor I) is a soluble plasma protein that, during the coagulation process, is converted to fibrin, one of the key components of the blood clot. Fibrinogen is a heterohexamer with a molecular weight of 340 kDa and composed of two sets of A*alpha*, B*beta*, and *gamma* polypeptide chains.

Following coagulation activation and thrombin generation, fibrinogen is cleaved by thrombin at specific sites on the A*alpha* and B*beta* chains to remove fibrinopeptide A (FPA) and fibrinopeptide B (FPB). The removal of FPA and FPB exposes binding sites on the fibrinogen molecule and leads to the formation of fibrin monomers that subsequently undergo polymerization. The resulting fibrin is stabilized by activated factor XIII. Factor XIIIa acts on fibrin to form cross links between fibrin polymers and renders the fibrin clot more resistant to fibrinolysis. The end product of the coagulation cascade is cross-linked fibrin which stabilizes the primary platelet plug and achieves secondary hemostasis.

12.2 Pharmacodynamics

Administration of FIBRYGA to patients with congenital fibrinogen deficiency supplements the missing coagulation factor or increases low plasma fibrinogen levels. Normal plasma fibrinogen level is in the range of 200-450 mg/dL.

An open-label, prospective, randomized, controlled, two-arm, cross-over study was conducted in 22 subjects with congenital fibrinogen deficiency (afibrinogenemia), ranging in age from 12 to 53 years (6 adolescents, 16 adults). Each subject received a single intravenous 70 mg/kg dose of FIBRYGA and the comparator product. Blood samples were drawn from the patients to measure the fibrinogen activity at baseline and up to 14 days after the infusion. Maximum Clot Firmness (MCF) was measured by thromboelastometry (ROTEM).

For each subject, MCF was determined before (baseline) and one hour after the single dose administration of FIBRYGA. In this cross-over study, the results were compared with another fibrinogen concentrate available on the US market. The results of the study demonstrated that the MCF values were significantly higher after administration of FIBRYGA than at baseline (*see Table 2*). The mean change from pre-infusion to 1 hour post-infusion was 9.7 mm in the primary analysis (9.0 mm for subjects < 18 years old and 9.9 mm for subjects ≥ 18 to < 65 years old).

Table 2: MCF [mm] (ITT population) n=22

Time point	**Mean ± SD**	**Median**

		(range)
Pre-infusion	0 ± 0	0 (0-0)
1 hour post-infusion	9.7 ± 3.0	10.0 (4.0-16.0)
Mean change (primary analysis)[a]	9.7 ± 3.0	10.0 (4.0-16.0)

MCF = maximum clot firmness; mm = millimeter; ITT = intention-to-treat.

[a] p-value was <0.0001, 95% CI 8.37, 10.99

12.3 Pharmacokinetics

An open-label, prospective, randomized, controlled, two-arm, cross-over study was conducted in 22 subjects with congenital fibrinogen deficiency (afibrinogenemia), ranging in age from 12 to 53 years (6 adolescents, 16 adults), where each subject received a single intravenous 70 mg/kg dose of FIBRYGA and the comparator product. In addition, a prospective, open-label, uncontrolled, multicenter clinical study was conducted in 14 pediatric subjects with afibrinogenemia, ranging in age from 1 to 10 years. Thirteen subjects each received a single intravenous 70 mg/kg dose of FIBRYGA. In both studies, blood samples were drawn from the subjects to determine the fibrinogen activity at baseline and up to 14 days after the infusion. The pharmacokinetic parameters of FIBRYGA (n=34) are summarized in Table 3.

In the study of adult and adolescent subjects, the incremental *in vivo* recovery (IVR) was determined from levels obtained up to 4 hours post-infusion. The median incremental IVR was a 1.8 mg/dL (range 1.1-2.6 mg/dL) increase per mg/kg. The median *in vivo* recovery indicates that a dose of 70 mg/kg will increase patients' fibrinogen plasma concentration by approximately 125 mg/dL. In pediatric subjects, the incremental *in vivo* recovery (IVR) was determined from levels obtained up to 3 hours post-infusion. The median incremental IVR was a ~~1.5~~ 1.4 mg/dL (range 1.3-2.1 mg/dL) increase per mg/kg.

Reviewer's Comments:

Please list the PK parameters of pediatric subjects as two age groups: < 6 years of age and 6 to < 12 years of age.

Table 3: Pharmacokinetic Parameters for Fibrinogen Activity

Parameters	**Mean ± SD (range)**	
	Adult and adolescent subjects (n=21*)	**Pediatric subjects (n=13*)**
Half-life [hr]	75.9 ± 23.8 (40.0-157.0)	63.3 ± 12.0 (45.6-91.6)
Cmax [mg/dL]	139.0 ± 36.9 (83.0-216.0)	107.2 ± 16.8 (93.0-154.0)
AUC [mg*hr/mL]	124.8 ± 34.6 (65.7-193.3)	96.6 ± 21.0 (73.2-140.9)
AUC_{norm} for dose of 70 mg/kg [mg*hr/mL]	113.7± 31.5 (59.7-175.5)	92.0 ± 20.0 (69.7-134.2)

Clearance [mL/hr/kg]	0.7 ± 0.2 (0.4-1.2)	0.8 ± 0.2 (0.5-1.0)
Mean residence time [hr]	106.3 ± 30.9 (58.7-205.5)	88.0 ± 16.8 (63.6-126.7)
Volume of distribution at steady state [mL/kg]	70.2 ± 29.9 (36.9-149.1)	67.6 ± 7.1 (52.8-76.8)

C_{max} = maximum plasma concentration; AUC = area under the curve; AUC_{norm} = area under the curve normalized to the dose administered; SD = standard deviation

* One subject in each study did not undergo PK analysis.

No difference in fibrinogen activity was observed between males and females. There was no difference in the pharmacokinetics of FIBRYGA between adults and adolescents (12-17 years of age). Lower recovery, shorter half-life and faster clearance were observed in children aged 1 to < 12 years, compared to adults and adolescents. Other parameters, such as C_{max} (maximum plasma concentration), AUC (area under the curve) and AUC_{norm} (area under the curve normalized to the dose administered), were also lower in children. Such differences may be expected for the younger age subgroup owing to physiological differences in body size and composition.

5 RECOMMENDATIONS

Based on the pharmacokinetic (PK) results of Study FORMA-04, clinical pharmacology reviewer recommends approval for this sBLA for the expansion of the indication to the pediatric population < 12 years of age.

6 STUDY #1: FORMA-04

Study Title: Prospective, open-label, uncontrolled, phase 3 study to access the efficacy, safety, and pharmacokinetics of *Octafibrin*[1] for on-demand treatment of acute bleeding and to prevent bleeding during and after surgery in pediatric subjects with congenital fibrinogen deficiency (Study No. FORMA-04).

Objectives:

Primary Objective

- To demonstrate the efficacy of *Octafibrin* for on-demand treatment of acute bleeding episodes (BE) (spontaneous or after trauma)

Secondary Objectives

- To determine the single-dose pharmacokinetics of *Octafibrin* in pediatric subjects with congenital fibrinogen deficiency
- To investigate an association between the overall clinical assessment of hemostatic efficacy and the surrogate endpoint "clot strength" or "clot firmness" (referred to as "maximum clot firmness" [MCF] in this protocol) via thromboelastometry (ROTEM). Therefore, MCF as surrogate efficacy parameter will be determined before and after the first infusion of *Octafibrin* for treatment of a bleeding episode.
- To achieve a peak target plasma fibrinogen level of 100 mg/dL in minor bleeds and 150 mg/mL for major bleeds 1 hour post-infusion
- To determine the response to *Octafibrin* based on incremental in vivo recovery (IVR)
- To demonstrate the efficacy of *Octafibrin* in preventing bleeding during and after surgery
- To access the safety of *Octafibrin* in subjects with congenital fibrinogen deficiency, including immunogenicity, thromboembolic complications, and early signs of allergic or hypersensitivity reactions

Study Design:

This was a phase 3, multinational, multicenter, prospective, open-label, uncontrolled study in pediatric subjects with congenital fibrinogen deficiency.

For pharmacokinetic (PK) assessments, within 2 weeks after initial screening, subjects received a single infusion of 70 mg/kg dose of *Octafibrin* on Day 1 of PK testing (PK-Day-1). Before the start of the PK phase there was a 14-day wash-out period for any fibrinogen containing products. Blood samples were collected for PK assessments, which comprised measurements of *Octafibrin* activity and antigen levels. The sampling schedule was as follows: Day 1: pre-infusion, one and three hours post-infusion, Day 2, Day 4, Day 7, Day 10 and Day 14.

[1] In Study FORMA-04, FYBRYGA® is referred to as *Octafibrin*.

Plasma levels of fibrinogen were measured using both fibrinogen activity and antigen assays. Pharmacokinetic parameters were calculated by non-compartmental analysis (NCA).

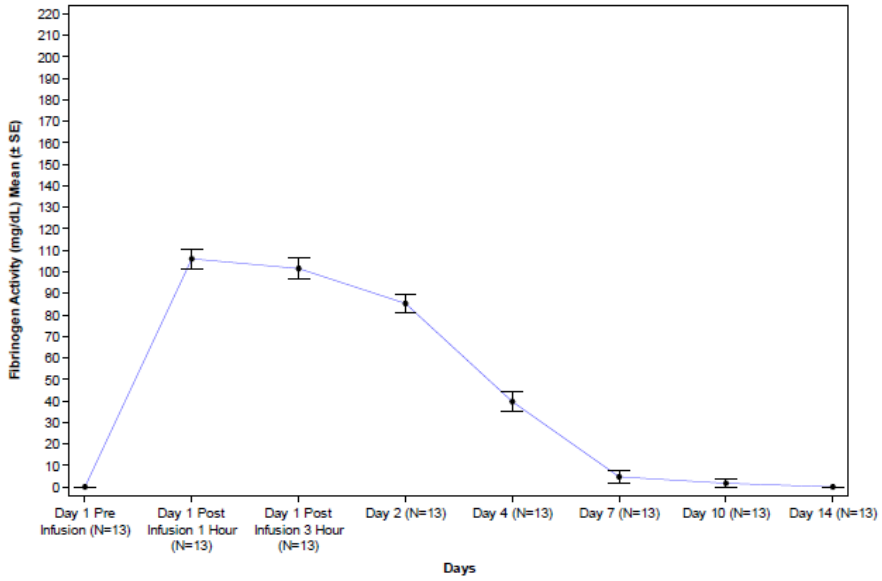
Results

A total of 14 pediatric subjects (1 to 10 years old) with confirmed congenital fibrinogen deficiency received at least one administration of *Octafibrin*. The PK analysis population included all subjects who started the PK assessment with at least one valid post-baseline fibrinogen activity level. PK analysis population included 13 subjects. All subjects in PK analysis population received an exact dose of 73.5 mg/kg of body weight *Octafibrin*.

Pharmacokinetics

As illustrated in Figure 1, after the washout period of at least 14 days and before administration of *Octafibrin*, plasma fibrinogen activity levels were at or below the limit of detection of the assays, as expected in subjects with afibrinogenaemia. After administration, peak levels of fibrinogen were achieved around 1 to 3 hours post-infusion. The mean (±SD) fibrinogen concentrations were 106.1 mg/dL (±17.04) and 101.5 mg/dL ((±17.36) for 1 hour and 3 hours post-infusion, respectively. By 7 days following infusion, fibrinogen levels decreased to nearly baseline.

Figure 1. Mean (±SE) Fibrinogen Activity (g/L) During PK Assessment After FIBRYGA (*Octafibrin*) Administration



Data presents actual values for fibrinogen activity. Values <30 mg/dL (below the detectable limit of the assay) were considered as zero for the calculation.
The time point on the x-axis represents the days based on the dates fibrinogen activity assays were performed by the central laboratory.
N represents number of observations of fibrinogen activity available (central laboratory).
LOQ = limit of quantification; PK = pharmacokinetic; PP = per-protocol; SE = standard error.

Source: sBLA submission. FORMA-04 study report Figure 2.

PK parameters of *Octafibrin* are listed in Table 1 (fibrinogen activity assay) and Table 2 (fibrinogen antigen assay).

Lower recovery, shorter half-life and faster clearance were observed in children aged 1 to < 12 years, compared to adults and adolescents. Other parameters, such as C_{max} (maximum plasma concentration), AUC (area under the curve) and AUC_{norm} (area under the curve normalized to the dose administered), were also lower in children. Such differences may be expected for the younger age subgroup owing to physiological differences in body size and composition.

The incremental *in vivo* recovery (IVR) was determined from levels obtained up to 3 hours post-infusion. Compared to adult and adolescent subjects, pediatric subjects had lower incremental IVRs. The median incremental IVR were 1.8 mg/dL/(mg/kg) and 1.4 mg/dL/(mg/kg) for adults/adolescent subjects and pediatric subjects, respectively (fibrinogen activity).

Table 1. PK Parameters for FIBRYGA (Fibrinogen Activity)

Parameter	n	Mean	SD	Median	Range
AUC, g*h/L	10*	96.595	21.0025	92.514	73.207–140.949
AUC_{norm} h*kg*g/L/mg	10*	1.314	0.2859	1.259	0.996–1.918
AUC standardized to 70 mg/kg g*h/L	10*	91.987	20.010	88.100	69.689–134.237
C_{max}, g/L	13	1.072	0.1680	1.020	0.930–1.540
$C_{maxnorm}$, kg·g/L/mg	13	0.015	0.0023	0.014	0.013–0.021
C_{max}, standardised to 70 mg/kg (g·h/L)	13	1.021	0.1599	0.971	0.886–1.467
Incremental IVR, mg/dL/(mg/kg)	13	1.459	0.2285	1.387	1.265–2.095
T_{max}, h	13	1.462	0.8771	1.000	1.000–3.000
$T_{1/2}$, h	10*	63.339	11.9747	59.635	45.574–91.649
MRT, h	10*	88.031	16.8182	82.317	63.625–126.656
CL, mL/h/kg	10*	0.790	0.1511	0.796	0.521–1.004
V_{ss}, mL/kg	10*	67.632	7.0685	67.749	52.783–76.803

* PK parameters for three subjects were not calculated because of insufficient number of quantifiable values. Fibrinogen concentrations below the limit of quantification were set to missing
PK parameters were determined from the actual values for fibrinogen activity measured pre- and post-infusion. The exact doses, calculated by use of actual activity potencies were used for the PK analysis
AUC = area under the curve; C_{max} = maximum plasma concentration; $C_{maxnorm}$ = maximum plasma concentration normalised to the dose administered; CL = clearance; IVR = in vivo recovery; MRT = mean residence time; PK = pharmacokinetics; PP = per-protocol; SD = standard deviation; $T_{1/2}$ = half-life; T_{max} = time to reach maximum plasma concentration; V_{ss} = volume of distribution at steady state.

Source: sBLA submission. FORMA-04 study report Table 16.

Table 2. PK Parameters for FIBRYGA (Fibrinogen Antigen)

Parameter	n	Mean	SD	Median	Range
AUC, g*h/L	13	106.824	36.8896	98.365	64.665–193.045
AUC_{norm} h*kg*g/L/mg	13	1.419	0.4385	1.298	0.940–2.375
AUC standardized to 70 mg/kg g*h/L	13	99.358	30.6982	90.882	65.818–166.226
C_{max}, g/L	13	1.559	0.3183	1.560	1.120–2.190
$C_{maxnorm}$, kg·g/L/mg	13	0.016	0.0033	0.016	0.012–0.023
C_{max}, standardised to 70 mg/kg (g·h/L)	13	1.126	0.2298	1.126	0.809–1.581
Incremental IVR, mg/dL/(mg/kg)	13	1.592	0.3224	1.599	1.155–2.259
T_{max}, h	13	1.154	0.5547	1.000	1.000–3.000
$T_{1/2}$, h	13	84.356	34.2658	72.233	57.456–181.027
MRT, h	13	114.332	37.9732	102.554	78.583–221.358
CL, mL/h/kg	13	0.756	0.1872	0.770	0.421–1.064
V_{ss}, mL/kg	13	81.651	15.2735	74.663	62.563–113.297

PK parameters were determined from the actual values for fibrinogen activity measured pre- and post-infusion. The exact doses, calculated by use of actual potencies were used for the PK analysis.
AUC = area under the curve; C_{max} = maximum plasma concentration; $C_{maxnorm}$ = maximum plasma concentration normalised to the dose administered; CL = clearance; IVR = in vivo recovery; MRT = mean residence time; PK = pharmacokinetics; PP = per-protocol; SD = standard deviation; $T_{1/2}$ = half-life; T_{max} = time to reach maximum plasma concentration; V_{ss} = volume of distribution at steady state.

Source: sBLA submission. FORMA-04 study report Table 17.

Reviewer's Comments:

FIBRYGA® is individually dosed to achieve a recommended target fibrinogen plasma level dependent on the type of bleeding or surgery. The dose is calculated as following:

$$\text{Fibrinogen dose (mg/kg body weight)} = \frac{\text{[Target peak plasma level (mg/dL) – Measured level (mg/dL)**]}}{\text{Median response* (mg/dL per mg/kg body weight)}}$$

The recommended target fibrinogen plasma level is 100 mg/dL for minor bleeding and 150 mg/dL for major bleeding. The incremental IVR is 1.8 mg/dL per mg/kg body weight for adults and adolescents. When the fibrinogen level is unknown, the recommended dose is 70 mg/kg body weight.

Based on the incremental IVR values determined in Study FORMA-04, the median incremental IVR was 1.4 mg/dL per mg/kg body weight for pediatric subjects < 12 years of age. Therefore, to achieve the same target fibrinogen level, pediatric subjects should receive a higher dose of FIBRYGA than adults and adolescents.

In the dose recommendation section of the labeling, the incremental IVR of 1.4 is recommended in dose calculation for pediatric subjects less than 12 years of age.

Therefore, the recommended dose (per kg) of FYBRYGA for pediatric patients (< 12 years of age) is about 29% higher than the recommended dose for adults and adolescents based on calculations per labeling.

Subgroup Analysis of FIBRYGA Pharmacokinetics – Fibrinogen Activity Assay

The demographic characteristics of the full analysis set (FAS) and PK populations are shown in Table 3.

Table 3. Demographic and Clinical Characteristics of Study Populations (Study FORMA-04)

	FAS Population (N=14)		PK Population (N=13)	
Parameter	**Mean±SD**	**Median (range)**	**Mean±SD**	**Median (range)**
Age at informed consent signed (years)	6.0±2.57	6.0 (1.0–10.0)	6.2±2.61	6.0 (1.0–10.0)
Height (cm)	111.3±15.37	111.0 (82.0–139.0)	112.1±15.70	111.0 (82.0–139.0)
Weight (kg)	19.8±6.93	17.0 (11.8–35.0)	20.2±7.06	17.5 (11.8–35.0)
BMI (kg/m^2)	15.7±2.82	15.3 (12.0–22.8)	15.8±2.91	15.9 (12.0–22.8)
	N	**%**	**N**	**%**
Age category				
<6 years	6	42.9	5	38.5
6–<12 years	8	57.1	8	61.5
Gender				
Female	8	57.1	7	53.8
Male	6	42.9	6	46.2
Race				
Asian	4	28.6	4	30.8
White	10	71.4	9	69.2

BMI = body mass index; FAS = full analysis set; PK = pharmacokinetic; SD = standard deviation.
FAS: Full analysis set; PK/PK-PP: PK per protocol analysis set
Source: sBLA submission. FORMA-04 study report Table 14.

Table 4 shows PK parameters for *Octafibrin* activity by age subgroup. Compared to subjects 6 to < 12 years of age, subjects aged < 6 years (n=5) had numerically lower PK parameters except higher clearance and volume of distribution at steady-state.

Table 4. PK Parameters for FIBRYGA (*Octafibrin*) by Age Subgroup (Fibrinogen Activity)

	Age <6 years					Age ≥6–12 years				
Parameter	**n**	**Mean**	**SD**	**Median**	**Range**	**n**	**Mean**	**SD**	**Median**	**Range**
AUC, g*h/L	3	83.817	12.3655	80.847	73.207–97.397	7	102.071	22.2276	95.791	78.155–140.949
C_{max}, g/L	5	0.990	0.0490	0.970	0.940–1.060	8	1.124	0.1979	1.045	0.930–1.540
$C_{maxnorm}$, kg·g/L/mg	5	0.013	0.0007	0.013	0.013–0.014	8	0.015	0.0027	0.014	0.013–0.021
C_{max}, standardised to 70 mg/kg (g·h/L)	5	0.943	0.0467	0.925	0.895–1.009	8	1.070	0.1884	0.995	0.886–1.467
Incremental IVR, mg/dL/(mg/kg)	5	1.347	0.0663	1.322	1.278–1.442	8	1.529	0.2693	1.422	1.265–2.095
T_{max}, h	5	1.400	0.8944	1.000	1.000–3.000	8	1.500	0.9258	1.000	1.000–3.000
$T_{1/2}$, h	3	56.914	10.7868	58.121	45.574–67.046	7	66.093	12.1167	59.718	57.741–91.649
MRT, h	3	78.368	14.0189	79.949	63.625–91.529	7	92.173	17.0899	82.690	79.745–126.656
CL, mL/h/kg	3	0.889	0.1262	0.910	0.754–1.004	7	0.747	0.767	0.1478	0.521–0.940
V_{ss}, mL/kg	3	68.561	4.4247	69.058	63.909–72.716	7	67.233	8.2342	66.439	52.783–76.803

AUC = area under the curve; C_{max} = maximum plasma concentration; $C_{maxnorm}$ = maximum plasma concentration normalised to the dose administered; CL = clearance; IVR = in vivo recovery; MRT = mean residence time; PK = pharmacokinetics; PP = per-protocol; SD = standard deviation; $T_{1/2}$ = half-life; T_{max} = time to reach maximum plasma concentration; V_{ss} = volume of distribution at steady state.
The exact doses, calculated by use of actual activity potencies were used for the PK analysis.

Source: sBLA submission. Summary of Clinical Pharmacology Studies Table 12.

All PK parameters were numerically lower for male subjects versus female subjects, except for clearance and the volume of distribution at steady-state, which were numerically higher. The observed difference of PK parameters between male and female subjects can be explained by the age differences between the two subgroups. Female subjects had a median (range) age of 7 (5-10) years compared to male subjects who had a median age of 4.5 (1-8). The physiological differences in body size and composition likely contributed to the PK differences observed between male and female subjects.

PK parameters of *Octafibrin* activity were similar between Asian (n=4) and White (n=9) subjects, except for Tmax. The median (range) Tmax values were 2.0 hour (1.0 – 3.0 hours) and 1.0 (1.0 – 3.0 hours) for Asian and White subjects, respectively. The data on subgroups is limited such that no conclusions can be drawn in this regard.

In Vivo Recovery

In addition to the PK assessments, the incremental in vivo recovery was also evaluated in subjects with on-demand treatment of bleeding episodes (BEs) and surgery prophylaxis. IVR values observed in the above populations were similar to IVR values determined in the PK assessment population (Table 5).

Table 5. Incremental IVR Values (mg/dL per mg/kg body weight) for the Treatment of Bleeding Episodes

Population	N	n	Mean±SD	Median (range)
firstBLEED/firstBLEED-PP, first BE	8	8	1.5±0.29	1.4 (1.1–1.9)
BLEED/BLEED-PP, all BEs	8	10	1.5±0.34	1.4 (1.1–2.1)
SURG/SURG-PP	3	3	1.3±0.22	1.3 (1.0–1.4)

BE = bleeding episode; IVR = in vivo recovery; N = number of patients; n = number of BEs; PP = per-protocol; SD = standard deviation.

Source: sBLA submission. Summary of Clinical Pharmacology Studies Table 9.

Conclusions:

- Pediatric subjects (1 to < 12 years of age) had numerically lower recovery, shorter half-life and faster clearance of FYBRYGA®, compared to adults and adolescents. Other PK parameters, such as Cmax, AUC were also lower in children.

- The incremental IVR (1.4 (mg/dL per mg/kg body weight)) determined in Study FORMA-04 for pediatric subjects is recommended be used for dose calculation of FIBRYGA® for pediatric patients (1 to < 12 years of age):

  Dose (mg/kg body weight) = [Target fibrinogen level (mg/dL) - measured fibrinogen level (mg/dL)] / 1.4 (mg/dL per mg/kg body weight)