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Division / Office	OTAT
Committee Chair	Karl Kasamon, M.D.
Clinical Reviewer(s)	Karl Kasamon, M.D.
Project Manager	Nadia Whitt, M.S.
Priority Review	6-month review
Reviewer Name(s)	Lin Huo, Ph.D.
Review Completion Date / Stamped Date	
Supervisory Concurrence	Renée C. Rees, Ph.D., Team Leader, Therapeutics Evaluation Branch
	Boguang Zhen, Ph.D., Branch Chief, Therapeutics Evaluation Branch
Applicant	OCTAPHARMA Pharmazeutika Produktionsges. m.b.H
Established Name	Fibrinogen (Human)
(Proposed) Trade Name	FIBRYGA
Pharmacologic Class	
Dosage Form(s) and Route(s) of Administration	A sterile, lyophilized powder for reconstitution for intravenous injection
Dosing Regimen	70 mg/kg body weight for unknown fibrinogen level. Recommended target fibrinogen plasma level is 100 mg/dL for minor bleeding or minor surgery and 150 mg/dL for major bleeding or major surgery.
Indication(s) and Intended Population(s)	For the treatment of acute bleeding episodes (b) (4) in adult and pediatric patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia.

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GLOSSARY

AE	Adverse Event
BE	Bleeding Episode
BLA	Biologics License Application
CI	Confidence interval
CRF	Case Report Form
CSR	Clinical Study Report
EMA	European Medicines Agency
FAS	Full analysis set
FDA	Food and Drug Administration
IDMEAC	Independent Data Monitoring & Endpoint Adjudication Committee
IMP	Investigational Medicinal Product
IND	Investigation new drug
ITT	Intent- to-treat
IVR	In Vivo Recovery
MCF	Maximum Clot Firmness (‘clot strength’)
PK	Pharmacokinetic
PMR	Postmarketing requirement
ROTEM	Rotational Thromboelastometry
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SURG	Surgery analysis set
TEE	Thromboembolic Event
US	United States

1. Executive Summary

This is a labeling supplement for the applicant's human fibrinogen concentrate FIBRYGA (also referred as Octafibrin in this memo). FIBRYGA was licensed under biologics license application (BLA) 125586 on 07 June 2017 by the US Food and Drug Administration (FDA). It is currently indicated for the treatment of acute bleeding episodes (BEs) in adults and adolescents with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia.

This submission contains the applicant's proposed revisions to the FIBRYGA prescribing information, the addition of the age group children (b) (4) to the approved indication as follows:

FIBRYGA is a human fibrinogen concentrate indicated for the treatment of acute bleeding episodes (b) (4) *in adults, adolescents and children with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia.*

The label extension is based on the final results of two completed clinical studies: FORMA-02 and FORMA-04. This memo focuses on reviewing FORMA-04 and the updated results of FORMA-02.

FORMA-02 is an open label, uncontrolled Phase 3 efficacy study that assessed the efficacy and safety of Octafibrin in the on-demand treatment of bleeding episodes and as surgical prophylaxis in subjects with congenital fibrinogen deficiency aged 12 years or older. Twenty-four subjects received FIBRYGA for treatment of a total of 89 bleeding episodes, 87 were minor and 2 were major. Sixty-seven (75.3%) BEs were spontaneous and 22 (24.7%) were traumatic.

Of the 89 evaluable bleeding episodes, 86 (96.6%) were assessed as having a successful efficacy outcome (rating of good or excellent efficacy) by the investigator and 88 (98.9%) by an independent adjudication committee. When considering only the first bleeding episode in each subject, all 24 BEs (100%) were assessed as successful by both the investigator and the independent adjudication committee. For the 6 subjects 12 to < 18 years of age, all 11 BEs were classified as successful by both the investigator and the independent adjudication committee.

Nine subjects received FIBRYGA as prophylaxis for a total of 12 surgeries, 11 were minor and one was major. A median (range) loading dose of 70.0 mg/kg (58.5-127.9) (mean [±SD]: 77.4 mg/kg [±20.2]) was administered for 11 surgeries. The median (range) dose of FIBRYGA per surgery was 85.8 mg/kg (34.1-225.4). For the 11 minor surgeries, the median (range) dose per surgery was 78.6 mg/kg (34.1-161.2). The one major surgery was treated with a total dose of 225.4 mg/kg.

FORMA-04 is a multicenter, prospective, open-label, uncontrolled, Phase III study to assess the efficacy, safety, and pharmacokinetics (PK) of Octafibrin for on-demand treatment of acute bleeding and surgical prophylaxis in

pediatric subjects with congenital fibrinogen deficiency. A total of 15 subjects were enrolled and 14 were included in the full analysis set (6 were under age 6 years and 8 were 6 to <12 years of age). Eight subjects received FIBRYGA for treatment of a total of 10 bleeding episodes, 8 were minor and 2 were major. Five BEs were spontaneous and 5 were traumatic.

Of the 10 evaluable bleeding episodes, 8 were assessed as having a successful efficacy outcome by the investigator, while one moderate efficacy rating and one missing assessment were counted as failures. All 10 BEs were assessed to be successful (rating of good or excellent efficacy) by an independent adjudication committee. When considering only the first bleeding episode in each subject, 6 BEs (75%) were assessed as to be successful by the investigator, while one moderate efficacy rating and one missing assessment were counted as failures. All 8 first BEs were assessed to be successful by the independent adjudication committee.

Three subjects received FIBRYGA as prophylaxis for a total of 3 surgeries, 2 were minor and one was major. A median (range) loading dose of 75.0 mg/kg (52.5-108.1) (mean [±SD] 78.5 mg/kg [±28.0]) was administered for the 3 surgeries. The median (range) dose of FIBRYGA per surgery was 75.0 mg/kg (52.5-108.1); 91.50mg/kg (75.0-108.0) per infusion for the 2 minor surgeries and 450.40 mg/kg for the one major surgery.

All the updated efficacy results of the FORMA-02 study and the primary efficacy endpoints and key secondary efficacy endpoints of the FORMA-04 study were reviewed and verified. No discrepancies were found. (b) (4) I defer to the clinical reviewer regarding its adequacy in assessing efficacy.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Congenital fibrinogen deficiency is an inherited coagulation disorder with considerably higher incidence in consanguineous marriages. Conditions of congenital fibrinogen deficiency include afibrinogenaemia (complete absence of plasma fibrinogen), hypofibrinogenaemia (reduced concentration of plasma fibrinogen) and dysfibrinogenaemia (presence of abnormal or dysfunctional fibrinogen). Affected individuals with afibrinogenaemia have a highly variable bleeding tendency that can be severe, including life-threatening bleeding and spontaneous/trauma-related bleeds. Afibrinogenaemia has an estimated prevalence of around 1:1,000,000.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Historically, the principal source for treatment of congenital fibrinogen deficiency has been cryoprecipitate. Plasma-derived and viral-inactivated fibrinogen concentrates were shown by Dr. Arturo Pereira in 2007[4] to be safer and more specific in the treatment of congenital fibrinogen deficiency compared to cryoprecipitate.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

The FIBRYNA development program was conducted under Investigational New Drug (IND) 14777. The original BLA 125612/0 was approved in the United States (US) for the treatment of acute bleeding episodes in adults and adolescents with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia. The approval letter for the original BLA 125612/0, states that "A prospective observational study of patients ≥12 years of age with congenital afibrinogenemia and hypofibrinogenemia treated with FIBRYNA for at least 10 major bleeding events to further characterize the risk of thromboembolic events following Fibryna treatment" was a postmarketing requirement (PMR); the results for FORMA-04 in this supplement satisfies this requirement.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

The submission was adequately organized for conducting a complete statistical review.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

There are two clinical studies in this submission. FORMA-02 was an open label, uncontrolled Phase 3 efficacy study that assessed the efficacy and safety of Octafibrin for the on-demand treatment of bleeding episodes and as surgical prophylaxis in subjects with congenital fibrinogen deficiency aged 12 years or older. FORMA-04 was an open label, uncontrolled Phase 3 efficacy study that assessed the efficacy, PK and safety of Octafibrin for the on-demand treatment of bleeding episodes and as surgical prophylaxis in subjects with congenital fibrinogen deficiency who were younger than 12 years of age. An interim clinical study report for the FORMA-02 study was reviewed in the original submission (see BLA 125612/0, statistical review memo, dated on May 16, 2017). Therefore, study FORMA-04 will be reviewed in detail and FORMA-02 will be briefly discussed with updated results only.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

- Original submission under BLA 125612/67
  - Module 1.14: Labeling
  - Module 2.5: Clinical Overview
  - Module 2.7: Clinical Summary
  - Module 5.3.5.2: Clinical Study Reports (CSRs) for FORMA-02 and FORMA-04, Statistical Analysis Plans (SAPs) and tabulation data

    <u>FORMA-02</u>
    - The CSR (962 pages), dated March 1, 2019, with 95-page main text.
    - The Protocol (203 pages), Version 4.0, dated February 13, 2014.
    - The SAP (32 pages), Version 2.0, dated July 11, 2016.

FORMA-04

- The CSR (902 pages), dated January 10, 2020, with 90-page main text.
- The Protocol (215 pages), Version 1.0, dated January 12, 2015.
- The SAP (40 pages), Version 4.0, dated June 2, 2017.

5.3 Table of Studies/Clinical Trials

The following clinical studies, summarized in Table 1, are included in the submission.

Table 1. Summary of Registration Clinical Studies with *Octafibrin*

Study No. Status	Population/ No. of Patients/ Planned Age (Enrolled Age)	Design/ Study Site/ Location/ Study Period	Endpoints
FORMA-02 Completed	Patients with congenital fibrinogen deficiency N=25 ≥12 years (≥18 in Russia) (12–54 years)	Multinational Multicentre Prospective Open-label Uncontrolled Phase 3 12 centres in Bulgaria, India, Iran, Lebanon, Russia, Saudi Arabia, Turkey, UK and USA Start: 13-Oct-2014 End: 14-Feb-2018	*Primary endpoint* Efficacy in treating the first documented bleeding episode of each patient *Secondary endpoints* *Efficacy*: MCF, haemostatic efficacy in all bleeding episodes, surgical prophylaxis, fibrinogen plasma concentration, IVR *Safety*: Safety and tolerability
FORMA-04 Completed	Patients with congenital fibrinogen deficiency N=14 <12 years (1–10 years)	Multinational Multicentre Prospective Open-label Uncontrolled Phase 3 5 centres in India, Iran and Lebanon Start: 15-Dec-2015 End: to 11-Jun-2019	*Primary endpoint* Efficacy in treating the first documented bleeding episode of each patient *Secondary endpoints* *PK:* AUC, C_{max}, IVR, T_{max}, $T_{1/2}$, MRT, V_{ss} and CL *Efficacy*: MCF, haemostatic efficacy in all bleeding episodes, surgical prophylaxis, fibrinogen plasma concentration, IVR *Safety*: Safety and tolerability

Source: Adapted from BLA 125612/67; Clinical Overview, V1.0, Table 1

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 FORMA-02 Study

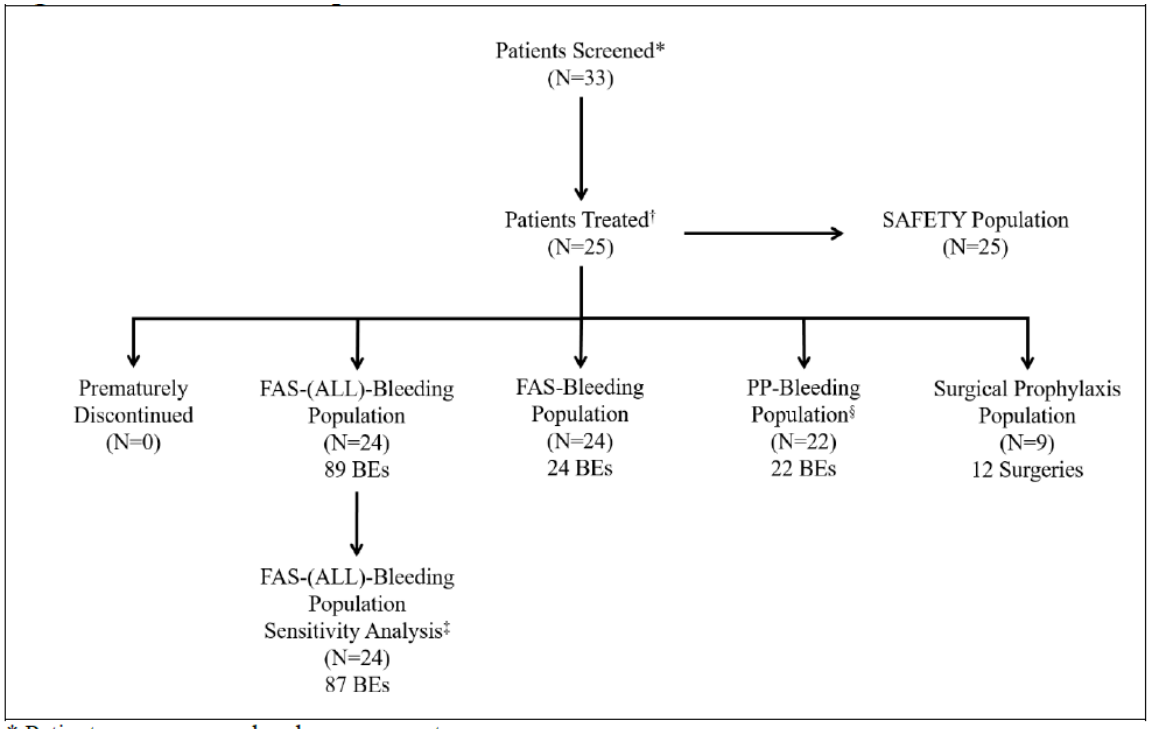
FORMA-02 was an open, uncontrolled Phase 3 efficacy study that assessed the efficacy and safety of Octafibrin in the on-demand treatment of bleeding episodes and as surgical prophylaxis in subjects with congenital fibrinogen deficiency aged 12 years or older. The primary efficacy endpoint for acute bleeding was the proportion of subjects with treatment success for treated first BEs. For a complete description of the study design, please refer to the statistical review memo for BLA 125612/0, dated on May 16, 2017.

6.1.10 Study Population and Disposition

6.1.10.1.3 Subject Disposition

A summary of subject disposition is presented in Figure 1. A total of 33 subjects were screened, all of whom met the enrollment criteria. Eight of these subjects were not treated with Octafibrin during the study period. Of the 25 subjects that received Octafibrin, 7 did not complete the study. The reasons for these premature discontinuations were investigator decision (N=1), Sponsor request (N=4) and the investigator decided to close the site (N=2).

Figure 1. Subject Disposition



* Patients were screened and gave consent.
† Patients received *Octafibrin* for treatment of a BE or surgical prophylaxis.
‡ Excludes 2 BEs that were not treated according to protocol (under-dosed).
§ Excludes 2 patients whose first BE was not treated according to protocol (under-dosed).
BE = bleeding episode; FAS = full analysis set; N = number of patients; PP = per-protocol
Source: Original from BLA 125612/67; Clinical Study Report FORMA-02, V2.0, Figure 1.

6.1.11 Efficacy Analyses (Updated results)

Twenty-four subjects received FIBRYGA for treatment of a total of 89 bleeding episodes, 87 of which were minor and 2 of which were major. Minor bleeding included mild hemarthrosis or superficial muscle, soft tissue or oral bleeding. Major bleeding included an occult gastrointestinal bleed and a spontaneous intracranial hemorrhage. Sixty-seven (75.3%) BEs were spontaneous and 22 (24.7%) BEs were traumatic.

Of the 89 evaluable bleeding episodes, 86 (96.6%) were assessed as having a successful efficacy outcome (rating of good or excellent efficacy) by the investigator and 88 (98.9%) were assessed as successful by an independent adjudication committee. For two bleeding episodes, the investigator's assessments were missing and were therefore classified as failures. When considering only the first bleeding episode in each subject, all 24 BEs (100%) were assessed as having a successful efficacy outcome by both the investigator and the independent adjudication committee. Hemostatic efficacy of FIBRYGA for treatment of 11 BEs in the 6 subjects 12 to < 18 years of age was classified as successful in all cases by both the investigator and the independent adjudication committee.

Nine subjects received FIBRYGA as prophylaxis for a total of 12 surgeries, 11 of which were minor (including knee radioisotope synovectomy [2], dental extraction [3], root canal operation, circumcision [2], excision of scar bud of circumcision, skin biopsy[1], and debridement of superficial necrosis[1]) and one major (right eye enucleation with socket reconstruction). A median (range) loading dose of 70.0 mg/kg (58.5-127.9) (mean [±standard deviation {SD}]: 77.4 mg/kg [±20.2]) was administered for 11 surgeries, with one subject having received an infusion of FIBRYGA for treatment of a bleeding episode shortly before the surgery and therefore not requiring an additional dose. Maintenance infusions were administered for five of the minor surgeries, with the median (range) number of maintenance doses being 3 (1-4). Seven maintenance doses were administered for the major surgery. The median (range) dose of FIBRYGA per surgery was 85.8 mg/kg (34.1-225.4). For the 11 minor surgeries, the median (range) dose per surgery was 78.6 mg/kg (34.1-161.2). The one major surgery was treated with a total dose of 225.4 mg/kg.

Reviewer Comment: (b) (4) *I defer to the clinical reviewer regarding its adequacy.*

6.2 FORMA-04 Study

FORMA-04 study is titled "Prospective, open-label, uncontrolled, phase III study to assess the efficacy, safety, and pharmacokinetics of *Octafibrin* for on-demand treatment of acute bleeding and to prevent bleeding during and after surgery in pediatric subjects with congenital fibrinogen deficiency".

6.2.1 Objectives (Primary, Secondary, etc)

Primary objective:
To demonstrate the efficacy of *Octafibrin* for on-demand treatment of acute BEs (spontaneous or after trauma).

Secondary objectives:

- To determine the single-dose PK 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 memo) via thrombolastometry (ROTEM). Therefore, MCF as surrogate efficacy parameter will be determined before and after the first infusion of investigational medicinal product (IMP) for treatment of a bleeding episode
- To achieve a peak target plasma fibrinogen level of 100 mg/dL in minor bleeds and 150 mg/dL 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 assess the safety of *Octafibrin* in subjects with congenital fibrinogen deficiency, including immunogenicity, thromboembolic complications, and early signs of allergic or hypersensitivity reactions

6.2.2 Design Overview

The study was a multinational, multi-center, prospective, open-label, uncontrolled, Phase III study to assess the efficacy, safety, and PK of Octafibrin for on-demand treatment of acute bleeding and surgical prophylaxis in pediatric subjects with congenital fibrinogen deficiency.

<u>On-demand Treatment of Acute Bleeding</u>
Each subject received at least 1 infusion of Octafibrin for the treatment of acute bleeding on Day 1. The individual observation and follow-up period for each documented episode started with the first dose of Octafibrin administered for on-demand treatment of an acute bleeding episode (Day 1) and was followed up to at least Day 30.

Each subject's treatment observation period was defined according to the severity of the event and lasted at least 3 days for minor and 7 days for major BEs. During the treatment observation period (i.e., 3 days for minor and 7 days for major bleeding), fibrinogen plasma levels were measured daily to determine whether additional infusions of Octafibrin were needed. Additional infusions of Octafibrin were administered if the actual fibrinogen plasma level measured on these days was below the accepted lower limit of the target level (80 mg/dL for minor bleeding, 130 mg/dL for major bleeding). If the actual fibrinogen plasma level was above the accepted lower limit of

the target level, Octafibrin was not administered. The actual treatment duration was determined by the investigator based on his/her judgement of the subject's condition.

All adverse events (AEs), including thromboembolic events (TEEs) and early signs of allergic or hypersensitivity reactions, occurring between the start of the first Octafibrin infusion and the end of each 30-day observation and follow-up period were recorded. The detection of TEEs was supported by completing a TEE questionnaire at each study visit for the treatment of BEs and for surgeries. Concomitant medications were also recorded throughout each 30-day observation and follow-up period.

All severe AEs (SAEs) occurring after the first IMP infusion were documented and reported throughout the duration of the subject's participation in the study or as required to meet local regulations. Any concomitant medications used to treat an SAE were also recorded.

At the end of the study all subjects who received any IMP were asked to return for a Study Completion Visit.

Surgical Prophylaxis

Subjects planning to undergo elective surgery were also enrolled in the study.

Within 3 hours prior to surgery, each subject received a loading infusion of Octafibrin to achieve a recommended fibrinogen plasma level of 100 mg/dL for minor surgeries and 150 mg/dL for major surgeries. Each subject's surgical observation period started with the first dose of Octafibrin administered prior to elective surgery (Day 1) and, depending on the severity of the event, lasted at least 3 post-operative days for minor and 7 post-operative days for major surgeries or until the day of the last post-operative infusion, whichever came last.

On each post-operative day, fibrinogen plasma levels were measured (i.e., at least 3 or 7 days for minor/major surgeries) to determine whether additional infusions of Octafibrin were needed. Additional infusions of Octafibrin were administered if the actual fibrinogen plasma level measured on subsequent days was below the accepted lower limit of the target level (80 mg/dL for minor surgeries, 130 mg/dL for major surgery). If the fibrinogen plasma level was greater than or equal to the accepted lower limit of the target fibrinogen plasma level, Octafibrin was not administered. The actual treatment duration was determined by the investigator based on his/her judgement of the patient's condition.

6.2.3 Population

Subject eligibility criteria:

1. Aged < 12 years (at the start of treatment)
2. Documented diagnosis of congenital fibrinogen deficiency, expected to require on-demand treatment for bleeding or surgical prophylaxis:

- Fribrinogen deficiency manifested as afibrinogenaemia or sever hypofibrinogenaemia
- Historical plasma fribrinogen activity of <50 mg/dL or levels below the limit of detection of the local assay method

3. Expected to have an acute BE (spontaneous or after trauma) or planning to undergo elective surgery
4. Informed consent signed by the subject's legal guardian

6.2.4 Study Treatments

Octafibrin Treatment Dose Calculation

Octafibrin was individually dosed to achieve a recommended target fibrinogen plasma level dependent on the type of bleeding or surgery (minor or major). The dose was calculated individually as follows:

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

*The median response in this dose calculation formula is the median incremental in vivo recovery reported in the final analysis of study FORMA-01.
**The measured level for the first infusion will be the historical level for that patient after a washout or, if below the limit of detection of the local assay, zero (0) will be used.

Dosing for On-Demand Treatment of Bleeding

Octafibrin was individually dosed to achieve a recommended target fibrinogen plasma level dependent on the bleeding type (minor or major).

- **Minor bleeding** was treated to achieve a recommended target fibrinogen plasma level of 100 mg/dL and an accepted lower limit of 80 mg/dL.
- **Major bleeding** was treated to achieve a recommended target fibrinogen plasma level of 150 mg/dL and an accepted lower limit of 130 mg/dL.

Dosing for Surgery

For each surgery treated as part of the study, within 3 hours prior to surgery, each subject received a loading infusion of *Octafibrin*. *Octafibrin* was individually dosed to achieve a recommended target fibrinogen plasma level dependent on the surgery type (minor or major).

- Subjects undergoing **minor surgery** were treated to achieve a recommended target fibrinogen plasma level of 100 mg/dL and an accepted lower limit of 80 mg/dL
- Subjects undergoing **major surgery** were treated to achieve a recommended target fibrinogen plasma level of 150 mg/dl and accepted lower limit of 130 mg/dL

6.2.6 Sites and Centers

The study was conducted in five investigational centers in the following countries: India, Islamic Republic of Iran, and Lebanon.

6.2.8 Endpoints and Criteria for Study Success

Primary efficacy variable:

- The overall clinical assessment of the hemostatic efficacy of Octafibrin in treating the first documented BE of each subject.
  The first BE covered the time period from the first Octafibrin infusion until 24 hours (i.e., 1 day) after the last infusion or the end of the treatment observation period, whichever came last. The investigator's overall clinical assessment of hemostatic efficacy was based on a 4-point hemostatic efficacy scale (Table 2). The Independent Data Monitoring & Endpoint Adjudication Committee (IDMEAC) conducted an independent adjudication of all hemostatic efficacy results and evaluated the investigator's assessments of the efficacy in the treatment of each BE. The IDMEAC analyzed data from case report forms (CRFs) and information provided by the investigator. In the event that any assessment differed between the investigator's and the IDMEAC's adjudicated assessment, the endpoint was based on the adjudicated assessment.

Table 2. Overall Clinical Assessment of Hemostatic Efficacy for On-Demand Treatment of Bleeding

Category	Definition
Excellent	Immediate and complete cessation of bleeding in the absence of other haemostatic intervention as clinically assessed by the treating physician; and/or <10% drop in haemoglobin compared to pre-infusion.
Good	Eventual complete cessation of bleeding in the absence of other haemostatic intervention as clinically assessed by the treating physician; and/or <20% drop in haemoglobin compared to pre-infusion.
Moderate	Incomplete cessation of bleeding and additional haemostatic intervention required, as clinically assessed by the treating physician; and/or between 20 and 25% drop in haemoglobin compared to pre-infusion.
None	No cessation of bleeding and alternative haemostatic intervention required, as clinically assessed by the treating physician; and/or >25% drop in haemoglobin compared to pre-infusion.

Source: Original from BLA 125612/67; Clinical Study Report FORMA-04, V1.0, Table 6.

Secondary efficacy variables:

- Efficacy in the treatment of all BEs.
- Fibrinogen and hemoglobin plasma concentrations for the first BE of each subject
- Fibrinogen plasma concentrations for all BEs
- Efficacy in surgical prophylaxis, based on an overall assessment intra-operatively (at the end of surgery = after last suture) by the surgeon and post-operatively (at the last post-operative day) by the hematologist using two 4-point efficacy scales. The overall surgical

efficacy was adjudicated by the IDMEAC who evaluated the surgeon's and investigator's assessments in conjunction with a review of the surgical case.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Sample size determination

The number of subjects was limited by the very low prevalence of this indication. The minimum number of pediatric subjects with a hemostatic outcome assessment for the on-demand treatment of a BE was agreed with the pediatric committee of the European Medicines Agency (EMA) to be 6. No confirmatory test was carried out and therefore, no sample size estimation was provided.

Analysis populations

Safety Set: All subjects who received at least one infusion of Octafibrin. The analysis of safety will be based on this population.

Full Analysis Set: The full analysis set (FAS) defined according to the intention-to-treat (ITT) principle will include subjects who fulfill all the following conditions:

- received at least one infusion of the IMP
- entered the study with a confirmed congenital fibrinogen deficiency

*First bleeding analysis set (*firstBLEED*):* subjects of the FAS who have at least one episode of acute bleeding treated with Octafibrin. The analysis of the primary endpoint was to be provided with the FirstBLEED population.

First bleeding per protocol analysis set (BLEED-PP): All patients from the FirstBLEED analysis set who fulfil the following conditions:

- Provide valid, i.e., non-missing, hemostatic efficacy data for their first bleeding
- Received ≥ 90% of the planned total dose of the IMP in the first infusion for their first bleeding
- Received ≥ 80% of the calculated dose (if no dose was calculated, 0% will be assumed) of the IMP over all further infusions of the first bleeding according to the treatment schedule
- Did not meet any of the following exclusion criteria:
  – Bleeding disorder other than congenital fibrinogen deficiency
  – End-stage liver disease (i.e., Child-Pugh-score B or C)
  – Suspicion of an anti-fibrinogen inhibitor as indicated by previous IVR, if available <0.5 (mg/dL)/(mg/kg)
  – Treatment with any fibrinogen concentrate or other fibrinogen-containing blood product within 2 weeks prior to start of treatment for the bleeding episode.
- Did not use any coagulation-active drug (i.e., non-steroidal anti-inflammatory drugs, warfarin, coumarin derivatives, platelet aggregation inhibitors) within 1 week prior to start of treatment for the

first bleeding episode, or as a planned or expected medication during the time period from Day 1 until 24 hours (i.e., 1 day) after the last Octafibrin infusion

Bleeding analysis set (BLEED): all documented BEs treated with Octafibrin in subjects of the FAS.

Surgery analysis set (SURG): all documented surgical interventions with a need for at least one infusion of the IMP during the time period from the day of surgery until day of overall clinical assessment of post-operative efficacy in subjects of the FAS.

Subgroup analysis
The subgroups based on the following categories were to be examined:

- Severity of bleeding: minor versus major
- Age 0 to < 6 years versus 6 to < 12 years

Handling of missing data
In general, missing data values were not to be replaced.

Statistical methodology
The statistical analysis of the primary, secondary and safety endpoints was to be understood in the exploratory sense. Therefore, no confirmative statistical analysis was planned.

The efficacy was to be evaluated by descriptive statistics and all results were to be presented stratified by the age groups (2-<6 years, 6-12 years), if appropriate, and in total. The stratification was to be done according to the age of the subjects at the screening assessment and subjects would stay in the respective stratum for all analyses even when the age of the subject crosses the border of the first stratum.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

Of the 15 subjects screened, 14 had confirmed congenital fibrinogen deficiency and received at least one administration of Octafibrin. Therefore, the FAS consisted of 14 subjects.

The BLEED analysis dataset included 8 subjects who experienced 10 BEs, whereas the firstBLEED analysis dataset included 8 BEs in 8 subjects.

The SURG analysis dataset included all subjects who received Octafibrin for surgical procedures (N=3).

The SAFETY population included all subjects who received at least one dose of Octafibrin (N=14).

6.2.10.1.1 Demographics

The demographic characteristics of the FAS population are shown in Table 3. The median (range) age was 6.0 (1.0 – 10.0) years. Six subjects were <6 years of age and eight were 6 to <12 years of age. Of the 14 patients in the FAS population, 10 were classified as White race and 4 were classified as Asian.

Table 3. Demographic and Clinical Characteristics of Study Populations (FAS)

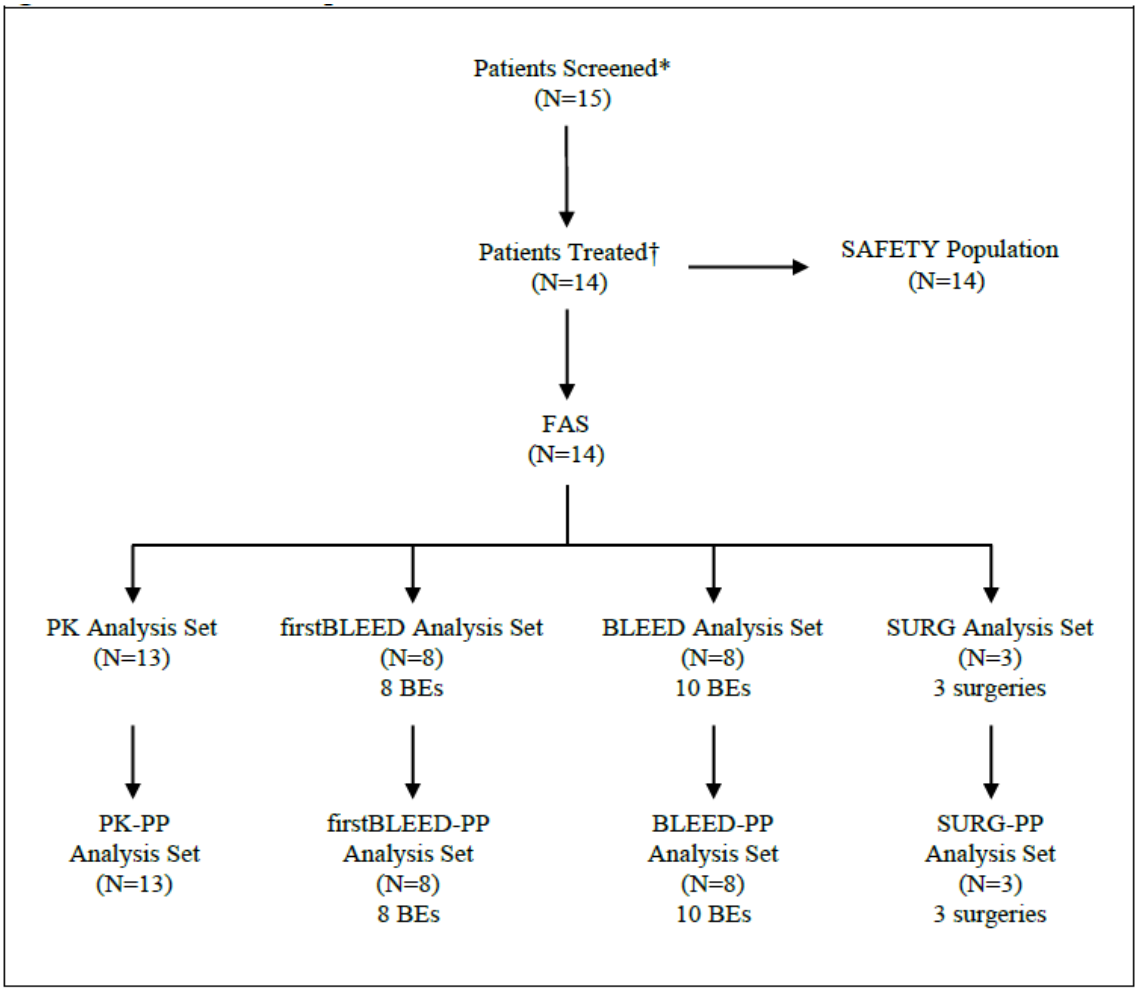
	FAS Population (N=14)	
Parameter	**Mean±SD**	**Median (range)**
Age at informed consent signed (years)	6.0±2.57	6.0 (1.0–10.0)
Height (cm)	111.3±15.37	111.0 (82.0–139.0)
Weight (kg)	19.8±6.93	17.0 (11.8–35.0)
BMI (kg/m^2)	15.7±2.82	15.3 (12.0–22.8)
	N	**%**
Age category		
<6 years	6	42.9
6–<12 years	8	57.1
Gender		
Female	8	57.1
Male	6	42.9
Race		
Asian	4	28.6
White	10	71.4

Source: Original from BLA 125612/67; Clinical Study Report FORMA-04, V1.0, Table 14.

6.2.10.1.3 Subject Disposition

A summary of subject disposition is presented in Figure 2. A total of 15 subjects were screened, all of whom met the enrollment criteria. One of these subjects was not treated with Octafibrin during the study period. Of the 14 subjects who received Octafibrin, 11 completed the study. Three subjects discontinued the study prematurely due to withdrawal of consent (N=2) and adverse event (N=1).

Figure 2. Subject Disposition



* Patients were screened and gave consent.
† Patients received *Octafibrin* for PK analysis, treatment of a BE or surgical prophylaxis.
BE = bleeding episode; FAS = full analysis set; N = number of patients; PP = per-protocol; PK = pharmacokinetic
Source: Original from BLA 125612/67; Clinical Study Report FORMA-04, V1.0, Figure 1.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

The severity of the first BE was classed as minor for six subjects (including oral, vaginal [first menarche], scrotal cutaneous and left haemocoel, left arm, and right arm bleeds, and a subcutaneous facial hematoma) and major for two subjects (Subject #(b) (6): left knee and thigh bleed, and Subject #(b) (6): intraperitoneal bleed from spleen). Of the eight first BEs, four were spontaneous and four were due to trauma. All subjects with minor bleeds, six received a single Octafibrin infusion, while of the two subjects with major bleeds, one received three infusions and one four infusions. The mean (±SD) total Octafibrin dose per infusion administered for the treatment of the first BE of each subject was 61.81 mg/kg (±22.91), with a median (range) of 70.21 mg/kg (23.13–98.44). The mean (±SD) Octafibrin dose for the first infusion

administered for the treatment of the first BE of each subject was 71.68 mg/kg (±17.19), with a median (range) of 73.91 mg/kg (47.45–98.44).

The IDMEAC assessments of the hemostatic efficacy of Octafibrin differed slightly from the investigator's assessments. The IDMEAC rated efficacy as excellent in six BEs and good in two (one major and one minor BE) (Table 4), whereas the investigator rated efficacy as excellent for five BEs, good for one BE and moderate for one BE. The investigator's efficacy rating was missing for one BE, thus the rating was considered as none for the purpose of this analysis. Overall, hemostatic efficacy of Octafibrin was successful (rating of excellent or good) for the treatment of all eight (100%) first BEs (95% confidence interval [CI] 63.06–100.00) according to the IDMEAC and six (75%) first BEs (95% CI 34.91–96.81) according to the investigator (Table 4).

The discrepancy between the physician and IDMEAC efficacy assessment was due to a discordant efficacy rating in one subject and a missing efficacy rating by the investigator in another subject. A rating of moderate was given by the investigator for the first BE for Subject #(b) (6) for the treatment of a major BE; this rating was adjudicated by the IDMEAC as excellent. The BE for which the efficacy rating was missing (Subject #(b) (6)) was adjudicated as good by the IDMEAC.

Reviewer Comment: Notice that subject #(b) (6) was rated as moderate by the investigator but as excellent by the IDMEAC, the discrepancy was adjudicated together with a couple of other cases by the clinical reviewer, for details, please refer to the clinical review memo.

Table 4. Efficacy Assessment for Treatment of the First Bleeding Episode According to the Investigator and the IDMEAC (firstBLEED, N=8 BEs in 8 Subjects)

Efficacy rating	Investigator		IDMEAC	
4-Point Efficacy Scale	**N (%)**		**N (%)**	
Excellent	5 (62.5%)		6 (75%)	
Good	1 (12.5%)		2 (25%)	
Moderate	1 (12.5%)		0 (0.0%)	
None	1 (12.5%)†		0 (0.0%)	
2-Point Efficacy Scale*	**N (%)**	**95% CI‡**	**N (%)**	**95% CI‡**
Success	6 (75.0%)	34.91–96.81	8 (100.0%)	63.06–100.00
Failure	2 (25.0%)		0 (0.0%)	

* Efficacy rating of excellent or good indicated success and efficacy rating of moderate or none indicated failure.
† For subject(b) (6) Haemostatic Efficacy Assessment was missing. Thus, it is considered as 'None' for analysis.
‡ 95% CI for the success rate were calculated by Clopper Pearson Method.
BE = bleeding episode; CI = confidence interval; FAS = full analysis set; IDMEAC = Independent Data Monitoring & Endpoint Adjudication Committee; N = number of BEs.
Source: Original from BLA 125612/67; Clinical Study Report FORMA-04, V1.0, Table 15.

6.2.11.2 Analyses of Secondary Endpoints

Hemostatic Efficacy in the Treatment of All Bleeding Episodes

Of the overall 10 BEs treated during the study, 5 were spontaneous and 5 were due to trauma. A total of 8 (80.0%) BEs were considered minor (including oral, vaginal [first menarche], scrotal cutaneous and left haemocoel, left arm, right arm, and intra-tibia bleeds, subcutaneous bleeding in the left foot, and a subcutaneous facial hematoma) and major for two subjects (Subject #(b) (6); left knee and thigh bleed, and Subject #(b) (6); intraperitoneal bleed from spleen). The median number of infusions per BE was 1.0 (range 1.0–4.0) (Table 5). All minor BEs (8/10, 80.0%) required only one infusion, while of the two major BEs, one (10.0%) required three infusions and one (10.0%) required four infusions.

The mean (±SD) Octafibrin dose per infusion administered for the treatment of all BEs was 62.52 mg/kg (±22.56), with a median (range) of 70.21 mg/kg (23.13–98.44). The mean (±SD) total Octafibrin dose administered for the first infusion for the treatment of all BEs was 70.78 mg/kg (±17.88), with a median (range) of 73.91 mg/kg (47.45–98.44) (Table 18). The mean (±SD) infusion rate for Octafibrin infusions for the treatment of all BEs was 4.3 mL/min (±1.05), with a median (range) of 4.7 mL/min (1.9–5.0). Only two BEs were treated with more than 100 mg/kg of Octafibrin; one BE was treated with three infusions, with a total dose of 129 mg/kg BW, while another BE was treated with four infusions, with a total dose of 264 mg/kg BW.

Table 5. Octafibrin Dosages for Treatment of All Bleeding Episodes (BLEED/BLEED-PP Population, N=10 BEs [15 Infusions] in 8 Subjects)

Parameter	Mean±SD	Median (range)
Number of exposure days/infusions	1.50±1.08	1.00 (1.00–4.00)
Dose of *Octafibrin* for the first infusion per BE, mg	1517.14±717.68	1575.00 (759.15–3300.00)
Dose of *Octafibrin* for the first infusion per BE, mg/kg	70.78±17.88	73.91 (47.45–98.44)
Dose of *Octafibrin* per BE, mg	1978.09±1399.03	1575.00 (759.15-5250.00)
Dose of *Octafibrin* per BE, mg/kg	93.78±64.60	73.91 (47.45-262.50)
Dose of *Octafibrin* per infusion, mg	1318.72±691.24	1176.00 (467.25–3300.00)
Dose of *Octafibrin* per infusion, mg/kg	62.52±22.56	70.21 (23.13–98.44)

BE = bleeding episode; FAS = full analysis set; SD = standard deviation.

Source: Original from BLA 125612/67; Clinical Study Report FORMA-04, V1.0, Table 18.

Efficacy assessments by the investigator were available for nine BEs and one was missing (excellent for seven BEs, good for one BE and moderate for one BE). Efficacy assessments by the IDMEAC were available for all 10 BEs (excellent for 8 BEs, good for 2 BEs). The proportion of BEs where treatment was considered successful (excellent or good rating) by the investigator was

80.0% (95% CI 44.39–97.48) (Table 6). Treatment was considered successful for 100.0% (95% CI 69.15–100.00) of BEs by the IDMEAC. The discrepancy between the physician and IDMEAC efficacy assessment was due to discordant efficacy ratings in one subject and a missing efficacy rating from the investigator in another subject.

Table 6. Efficacy Assessment for Treatment of All Bleeding Episodes According to the Investigator and the IDMEAC (BLEED/BLEED-PP Population, N=10 BEs in 8 Subjects)

Efficacy rating	Investigator		IDMEAC	
4-Point Efficacy Scale	**N (%)**		**N (%)**	
Excellent	7 (70.0%)		8 (80.0%)	
Good	1 (10.0%)		2 (20.0%)	
Moderate	1 (10.0%)		0 (0.0%)	
None	1 (10.0%)†		0 (0.0%)	
2-Point Efficacy Scale*	**N (%)**	**95% CI‡**	**N (%)**	**95% CI‡**
Success	8 (80.0%)	44.39–97.48	10 (100.0%)	69.15–100.00
Failure	2 (20.0%)		0 (0.0%)	

* Efficacy rating of excellent or good indicated success and efficacy rating of moderate or none indicated failure.
† For subject #(b) (6) the haemostatic efficacy assessment was missing. Thus, the rating was considered as 'None' for this analysis.
‡ 95% CI for the success rate were calculated by Clopper Pearson Method.
BE = bleeding episode; CI = confidence interval; FAS = full analysis set; IDMEAC = Independent Data Monitoring & Endpoint Adjudication Committee; N = number of BEs.
Source: Original from BLA 125612/67; Clinical Study Report FORMA-04, V1.0, Table 19.

Hemostatic Efficacy in Surgical Prophylaxis

Hemostatic efficacy of Octafibrin in prevention of bleeding during and after surgery was assessed in three subjects in a total of three surgeries: one major surgery(splenectomy) and two minor surgeries (circumcision and pulpectomy for tooth 74 and 85). All three subjects undergoing surgery were <6 years of age.

Reviewer Comment: (b) (4) *I defer to the clinical reviewer regarding its adequacy in assessing efficacy.*

A loading dose prior to surgery was administered for three surgical procedures. The mean (±SD) dose per surgery was 78.53 mg/kg (±27.96), with a median (range) of 75.00 mg/kg (52.50– 108.09) (Table 7).

Following the loading dose, no further post-operative infusions were administered for the two minor surgeries. The subject undergoing major surgery (Subject #(b) (6)) received a total of six infusions. This subject received a loading dose of 53 mg/kg (1050 mg) of Octafibrin, with additional infusions of 1000 to 2100 mg administered on Days 3, 6, 8, 10 and 13. These additional infusions were given at the discretion of the treating physician based on local laboratory values for fibrinogen levels, which ranged from a

minimum of <30 mg/dL on Day 6 to a maximum of 161 mg/dL on Day 13 (1-hour post infusion).

Table 7. Summary of Exposure Days and Dosages Administered for Surgeries (SURG/SURG-PP Population, N=3 Surgeries in 3 Subjects)

Parameter	N	n	Mean±SD	Median (range)
Total dose per surgery, mg	3	3	1312.50±454.66	1050.00 (1050.00–1837.50)
Total dose per surgery, mg/kg	3	3	78.53±27.96	75.00 (52.50–108.09)
Pre-operative loading dose, mg/kg	3	3	78.5±27.96	75.0 (52.5–108.1)
Post-operative dose, mg/kg*	1	5	79.6±18.65	78.8 (52.5–105.0)
Total dose per infusion/ED, mg	3	8	1476.56±395.31	1575.0 (1050.0–2100.0)
Total dose per infusion/ED, mg/kg	3	8	79.19±20.56	78.75 (52.50–108.09)

* Administered to patient #(b) (6) on Days 3, 6, 8, 10 and 13 after surgery.
ED = exposure day; FAS = full analysis set; N = number of surgeries; n = number of infusions; SD = standard deviation.

Source: Original from BLA 125612/67; Clinical Study Report FORMA-04, V1.0, Table 23.

For all three surgeries, intra-operative treatment with Octafibrin was successful (hemostatic efficacy rating of excellent or good) (95% CI: 29.24%-100.00%) (Table 8). Both the surgeon and the IDMEAC rated hemostatic efficacy as excellent for all three surgeries. The same results were obtained for post-operative hemostatic efficacy.

Table 8. Intra-operative Assessment of Octafibrin Efficacy in Surgical Prophylaxis as Assessed by the Surgeon and the IDMEAC (SURG/SURG-PP Population, N=3 Surgeries in 3 Subjects)

Type of surgery				
Efficacy rating	Surgeon		IDMEAC	
4-Point Efficacy Scale	N (%)		N (%)	
Excellent	3 (100.0)		3 (100.0)	
Good	0 (0.0)		0 (0.0)	
Moderate	0 (0.0)		0 (0.0)	
None	0 (0.0)		0 (0.0)	
2-Point Efficacy Scale*	N (%)	95% CI†	N (%)	95% CI†
Success	3 (100.0)	29.24–100.00	3 (100.0)	29.24–100.00
Failure	0 (0.0)		0 (0.0)	

* Efficacy rating of excellent or good indicated success and efficacy rating of moderate or none indicated failure.
† 95% CI for the success rate were calculated by Clopper Pearson Method.
CI = confidence interval; FAS = full analysis set; IDMEAC = Independent Data Monitoring & Endpoint Adjudication Committee; N = number of surgeries.

Source: Original from BLA 125612/67; Clinical Study Report FORMA-04, V1.0, Table 24.

6.2.11.3 Subpopulation Analyses

Hemostatic Efficacy in the On-Demand Treatment of the First BE by Age Group

Hemostatic efficacy of Octafibrin in the on-demand treatment of the first BE was examined in four subjects aged <6 years and four subjects aged 6 to <12 years. For subjects aged <6 years, hemostatic efficacy was rated as excellent by the investigator for two BEs, good for one BE and one rating was missing. Hemostatic efficacy was rated by the IDMEAC as excellent for three BEs and good for one BE (Table 9).

For subjects aged 6 to <12 years the rate of success was similar, with hemostatic efficacy rated by the investigator as excellent for three BEs, moderate for one BE, and rated by the IDMEAC as excellent for three BEs and good for one BE (Table 9).

Table 9. Efficacy Assessment for Treatment of the First Bleeding Episode According to the Investigator and the IDMEAC by Age Subgroup (firstBLEED/firstBLEED-PP Population, N=8 BEs in 8 Subjects)

	Efficacy rating	Investigator		IDMEAC	
Age <6 years (N=4)	**4-Point Efficacy Scale**	**N (%)**		**N (%)**	
	Excellent	2 (50.0)		3 (75.0)	
	Good	1 (25.0)		1 (25.0)	
	Moderate	0 (0.0)		0 (0.0)	
	None	1 (25.0) †		0 (0.0)	
	2-Point Efficacy Scale*	**N (%)**	**95% CI‡**	**N (%)**	**95% CI‡**
	Success	3 (75.0)	19.41–99.37	4 (100.0)	39.76–100.00
	Failure	1 (25.0)		0 (0.0)	
Age ≥6–12 years (N=4)	**4-Point Efficacy Scale**	**N (%)**		**N (%)**	
	Excellent	3 (75.0)		3 (75.0)	
	Good	0 (0.0)		1 (25.0)	
	Moderate	1 (25.0)		0 (0.0)	
	None	0 (0.0)		0 (0.0)	
	2-Point Efficacy Scale*	**N (%)**	**95% CI‡**	**N (%)**	**95% CI‡**
	Success	3 (75.0)	19.41–99.37	4 (100.0)	39.76–100.00
	Failure	1 (25.0)		0 (0.0)	

* Efficacy rating of excellent or good indicated success and efficacy rating of moderate or none indicated failure.
† For subject #(b) (6) the haemostatic efficacy assessment was missing. Thus, the rating was considered as 'None' for this analysis.
‡ 95% CI for the success rate were calculated by Clopper Pearson Method.
BE = bleeding episode; CI = confidence interval; FAS = full analysis set; IDMEAC = Independent Data Monitoring & Endpoint Adjudication Committee; N = number of BEs.
Source: Original from BLA 125612/67; Clinical Study Report FORMA-04, V1.0, Table 27.

Hemostatic Efficacy for All BEs by Age

Hemostatic efficacy of Octafibrin in the on-demand treatment of all BEs

was examined in four subjects <6 years of age for five BEs and four subjects aged 6 to <12 years for five BEs. For subjects aged <6 years, hemostatic efficacy was rated as excellent by the investigator for three BEs, good for one BE, and one rating was missing. Hemostatic efficacy was rated by the IDMEAC as excellent for four BEs and good for one BE (Table 10).

For subjects aged 6 to <12 years the rate of success was similar, with hemostatic efficacy rated by the investigator as excellent for four BEs, moderate for one BE, and rated by the IDMEAC as excellent for four BEs and good for one1 BE (Table 10).

Table 10. Efficacy Assessment for Treatment of all BEs According to the Investigator and the IDMEAC by Age Subgroup (BLEED Population, N=10 BEs in 8 Subjects)

	Efficacy rating	Investigator		IDMEAC	
Age <6 years (N=5)	**4-Point Efficacy Scale**	**N (%)**		**N (%)**	
	Excellent	3 (60.0)		4 (80.0)	
	Good	1 (20.0)		1 (20.0)	
	Moderate	0 (0.0)		0 (0.0)	
	None	1 (20.0)†		0 (0.0)	
	2-Point Efficacy Scale*	**N (%)**	**95% CI‡**	**N (%)**	**95% CI‡**
	Success	4 (80.0)	28.36–99.49	5 (100.0)	47.82–100.00
	Failure	1 (20.0)		0 (0.0)	
Age ≥6–12 years (N=5)	**4-Point Efficacy Scale**	**N (%)**		**N (%)**	
	Excellent	4 (80.0)		4 (80.0)	
	Good	0 (0.0)		1 (20.0)	
	Moderate	1 (20.0)		0 (0.0)	
	None	0 (0.0)		0 (0.0)	
	2-Point Efficacy Scale*	**N (%)**	**95% CI‡**	**N (%)**	**95% CI‡**
	Success	4 (80.0)	28.36–99.49	5 (100.0)	47.82–100.00
	Failure	1 (20.0)		0 (0.0)	

* Efficacy rating of excellent or good indicated success and efficacy rating of moderate or none indicated failure.
† For subject #(b) (6) the haemostatic efficacy assessment was missing. Thus, the rating was considered as 'None' for this analysis.
‡ 95% CI for the success rate were calculated by Clopper Pearson Method.
BE = bleeding episode; CI = confidence interval; FAS = full analysis set; IDMEAC = Independent Data Monitoring & Endpoint Adjudication Committee; N = number of BEs.
Source: Original from BLA 125612/67; Clinical Study Report FORMA-04, V1.0, Table 29.

6.2.12 Safety Analyses

6.2.12.3 Deaths

No subjects died during the study.

6.2.12.4 Nonfatal Serious Adverse Events

One SAE occurred during the study and is shown in Table 11.

Table 11. Listing of SAEs

Patient	MedDRA preferred term	Reason for seriousness	Outcome	Causality
(b) (6)	Portal vein thrombosis	Hospitalisation or prolongation of existing hospitalisation	Not recovered	Possible*

* As assessed by the Sponsor
MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event.
Source: Original from BLA 125612/67; Clinical Study Report FORMA-04, V1.0, Table 34.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

I verified the final efficacy results for the FORMA-02 study and the primary and key second efficacy results for the FORMA-04 study.

Updated (Final) Efficacy Results of FORMA-02 Study

Twenty-four subjects received FIBRYGA for treatment of a total of 89 BEs, 87 were minor and 2 were major. Sixty-seven (75.3%) BEs were spontaneous and 22 (24.7%) BEs were traumatic.

Of the 89 evaluable BEs, 86 (96.6%) were assessed as having a successful efficacy outcome (rating of good or excellent efficacy) by the investigator and 88 (98.9%) were assessed as successful by an independent adjudication committee. For two BEs, the investigator's assessments were missing and were therefore classified as failures. When considering only the first BE in each subject, all 24 BEs (100%) were assessed as having a successful efficacy outcome by both the investigator and the independent adjudication committee. Hemostatic efficacy of FIBRYGA for treatment of 11 BEs in the 6 subjects 12 to < 18 years of age was classified as successful in all cases by both the investigator and the independent adjudication committee.

Nine subjects received FIBRYGA as prophylaxis for a total of 12 surgeries, 11 were minor and one was major. A median (range) loading dose of 70.0 mg/kg (58.5-127.9) (mean [±SD]: 77.4 mg/kg [±20.2]) was administered for 11 surgeries. Maintenance infusions were administered for five of the minor surgeries, with the median (range) number of maintenance doses being 3 (1-4). Seven maintenance doses were administered for the major surgery. The median (range) dose of FIBRYGA per surgery was 85.8 mg/kg (34.1-225.4). For the 11 minor surgeries, the median (range) dose per surgery was 78.6 mg/kg (34.1-161.2). The one major surgery was treated with a total dose of 225.4 mg/kg.

Efficacy Results for FORMA-04 Study

Eight subjects received FIBRYGA for treatment of a total of 10 BEs, 8 were minor and 2 were major. Five BEs were spontaneous and five were traumatic.

The median (range) number of infusions per BE was 1 (1-4). Of the two major BEs, one required three infusions, while the other was treated with four

infusions. The median dose of FIBRYGA per infusion for the treatment of all BEs was 70.2 mg/kg.

Of the 10 evaluable BEs, eight were assessed as having a successful efficacy outcome by the investigator, while one moderate efficacy rating and one missing assessment were counted as failures. All 10 BEs were assessed to be successful by an independent adjudication committee. When considering only the first BE in each subject, 6 BEs (75%) were assessed as having a successful efficacy outcome by the investigator, while one moderate efficacy rating and one missing assessment were counted as failures. All eight first BEs (100.0%) were assessed to be successful by the independent adjudication committee.

Three subjects received FIBRYGA as prophylaxis for a total of three surgeries, two were minor and one was major. A median (range) loading dose of 75.0 mg/kg (52.5-108.1) (mean [±SD] 78.5 mg/kg [±28.0]) was administered for the three surgeries. Five maintenance doses were administered for the major surgery; the two minor surgeries did not require maintenance infusions. The median (range) dose of FIBRYGA per surgery was 75.0 mg/kg (52.5-108.1); 91.50mg/kg (75.0-108.0) per infusion for the two minor surgeries and 450.40 mg/kg for the one major surgery.

10.2 Conclusions and Recommendations

All the updated (final) efficacy results of the FORMA-02 study and the primary efficacy endpoints and key secondary efficacy endpoints of the FORMA-04 study were reviewed and verified. No discrepancies were found. (b) (4) I defer to the clinical reviewer regarding its adequacy for assessing efficacy.