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BLA Clinical and Clinical Pharmacology Review Memorandum

Application Type	Original BLA
STN	BLA 125833/0
CBER Received Date	December 27, 2024
PDUFA Goal Date	December 27, 2025
Division / Office	DCEH/OTP
Priority Review (Yes/No)	No
Clinical Reviewer	Jennifer Dotson, DO
Clinical Pharmacology Reviewer	Xing Jing, PhD.
Acting Clinical Pharmacology Team Leader	Xiaofei Wang, PhD.
Labeling Reviewer Acting Associate Director for Labeling	Afsah Amin, MD, MPH
Review Completion Date / Stamped Date	12/16/25
Supervisory Concurrence	Bindu George, MD Megha Kaushal, MD
Applicant	Grifols
Established Name	FESILTY
(Proposed) Trade Name	FESILTY
Pharmacologic Class	Fibrinogen concentrate (human)
Formulation(s), including Adjuvants, etc.	Intravenous injection
Dosage Form(s) and Route(s) of Administration	Lyophilized powder for solution for intravenous injection. FESILTY is provided as one single-dose glass vial containing nominally 1 gram of human fibrinogen and one 50 mL glass vial of Sterile Water for Injection, USP.
Dosing Regimen	When fibrinogen level is known: Patients ≥ 6 years: [Target fibrinogen level (mg/dL)) – measured fibrinogen level (mg/dL)]/1.8 (mg/dL per mg/dL), patients <6 years: [Target fibrinogen level (mg/dL)) – measured fibrinogen level (mg/dL)]/1.6 (mg/dL per mg/dL) or 70mg/kg body weight if fibrinogen level is not known

Indication(s) and Intended Population(s)	Treatment of acute bleeding episodes in pediatric and adult patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia
Orphan Designated (Yes/No)	No

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GLOSSARY

AE Adverse Event
AESI Adverse Event of Special Interest
ALAT Alanine Aminotransferase (syn. ALT or GPT)
AP Alkaline Phosphatase
APE All-Patients Enrolled Set
aPTT Activated Partial Thromboplastin Time
AR Adverse Reaction
ASAT Aspartate Aminotransferase (syn. AST or GOT)
AUC Area Under the Curve
BLA Biologics License Application
BMI Body Mass Index
BW Body Weight
CBER Center for Biologics Evaluation and Research
CI Confidence Interval
CL Clearance
C_{max} Maximum Concentration
COVID-19 Coronavirus Disease 2019
CRO Contract Research Organization
CRF Case Report Form
CS Clinically significant
CSP Clinical Study Protocol
CV Coefficient of Variation
DMC Data Monitoring Committee
DSMB Data Safety Monitoring Board
DVT Deep Vein Thrombosis
ECG Electrocardiogram
eCRF electronic Case Report Form
(b) (4)
EMA European Medicines Agency
EoI End of Infusion
FAS Full Analysis Set
FBE Full Bleeding Event Set
FCP Fibrinogen-Containing Product(s)
FFP Fresh Frozen Plasma
FiAc Fibrinogen Activity
FiAg Fibrinogen Antigen
HAV Hepatitis A Virus
HBV Hepatitis B Virus
HCV Hepatitis C Virus
HIV Human Immunodeficiency Virus
ICH International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICF Informed Consent Form
IEC Independent Ethics Committee
Ig Immunoglobulin
IIV Interindividual Variability
IMP Investigational Medicinal Product

INR International Normalized Ratio
IR Incremental Recovery
IRAE Immediately Reportable Adverse Event
IRB Institutional Review Board
IR_{obs} Incremental Recovery Based on Observations
IR_{pred} Incremental Recovery Based on Predictions
IRR Infusion-Related Reaction
ISI International Sensitivity Index
ITT Intent-to-Treat Set
LLOQ Lower Limit of Quantification
max Maximum
MCF Maximum Clot Firmness
MedDRA Medical Dictionary for Regulatory Activities
Mm Millimeter
ODP On-Demand Prophylaxis (with FESILTY)
ODT On-Demand Treatment (with FESILTY)
OHR Overall Hemostatic Response
PD Pharmacodynamic(s)
PE Pulmonary Embolism
PIP Pediatric Investigational Plan
PK Pharmacokinetic(s)
PP Per Protocol Set
PPBE Per-Protocol Bleeding Event Set
PT Prothrombin Time
RBC Red Blood Cell
(b) (4)
SAE Serious Adverse Event
SAF Safety Analysis Set
SAR Serious Adverse Reaction
SAP Statistical Analysis Plan
SAS Statistical Analysis Software
SD Standard Deviation
SOC System Organ Class
SUSAR Suspected Unexpected Adverse Drug Reaction
t_{1/2} terminal elimination half-life
TEAE Treatment Emergent Adverse Event
TEE Thromboembolic Event
TESAE Treatment-Emergent Serious Adverse Event
t_{max} or T_{max} Time to Reach Maximum Concentration

1. EXECUTIVE SUMMARY

Grifols submitted this Biologics License Application (BLA), STN 125833/0 on December 27, 2024 for the licensure of FESILTY (human fibrinogen, with trade name of FESILTY for two proposed indications for use:

- Treatment and prophylaxis in pediatric and adult patients with congenital hypo- or afibrinogenemia with bleeding tendency
- As fibrinogen supplementation in patients with acquired fibrinogen deficiency.

FESILTY is a lyophilized, heat-treated fibrinogen concentrate manufactured from human plasma. Virus inactivation is achieved by means of aluminum hydroxide $\text{Al}(\text{OH})_3$ (b) (4), the solvent/detergent procedure with polysorbate 80/(b) (4) (TNBP), UVC irradiation, and dry heat treatment. The manufacturing process also includes cation exchange chromatography for further purification of the fibrinogen (contributing to the removal of prions). FESILTY is not currently approved in the United States. FESILTY is a combination product with the Nextaro transfer device. The Nextaro device was not used during the clinical studies but will be used in commercial manufacturing of FESILTY.

During the review process, the FDA review team identified substantive issues (b) (4) that were communicated to the Applicant for the acquired fibrinogen deficiency indication and this indication (b) (4).

To support safety and effectiveness of FESILTY for the treatment of congenital fibrinogen deficiency, the applicant conducted a prospective, open-label, single arm, multicenter trial, Study 984, and was also supported by preclinical studies. The study enrolled 67 patients total across two study parts: Part I focused on pharmacokinetic (PK)/pharmacodynamic (PD) evaluation of a single 70 mg/kg dose of FESILTY in 27 patients, while Part II evaluated efficacy and safety of on-demand treatment and on-demand prophylaxis of FESILTY in 36 patients for surgical procedures, spontaneous or post-traumatic severe bleeding) with 175 bleeding events. On-demand prophylaxis is given for surgical procedures only. A total of 45 patients were received FESILTY in parts I and II. There were 27 patients in part I and 36 patients in part II, with 18 patients participating in both parts I and II. The study evaluated patients in all age groups including 6 children <6 years, 12 children 6-12 years, 6 adolescents 12 to less than 18 years, and 21 adults 18-75 years. Part I evaluated 14-day single dose PK/PD and maximum clot firmness as a surrogate efficacy parameter. Eighteen of the 27 patients from part I participated in part II. Part II evaluated efficacy and safety of repetitive administrations of FESILTY during different bleeding events (eg, elective surgical procedures, spontaneous or traumatic bleeding) and had follow-up for a minimum of twelve months.

To provide supportive evidence for dosing in the pediatric population who had limited samples, a two-compartment population pharmacokinetic (popPK) model was fit for integrated assessment of fibrinogen antigen (FiAg) and fibrinogen activity (FiAc) levels. The model adequately described the FiAg and FiAc levels across a wide age range (1 – 40 years). The popPK model-based simulation demonstrated 28% and 14% lower median AUC for the <6 and 6-<12 year old age groups as compared to adults, respectively, but had wide prediction intervals. Cmax was comparable across all age groups.

Key clinical efficacy results reported that the mean change in maximum [OBT] infusion during bleeding events was 10.76 mm for the overall population. The mean change in MCF 1 hour after FESILTY infusion was 8.7, 11.1 and 9.8 mm in patients <6 years, 6 to 12 years, and 12 to <18 years, respectively. The mean change in MCF was significant for all age groups, though due to small numbers of patients <6 years, a p-value was not able to be calculated. Additional clinical efficacy endpoint of overall hemostatic response (OHR) was rated by the investigator after FESILTY

administration during a bleeding event on a 4-point scale (“none,” “moderate,” “good” or “excellent.”) For the overall population of adults and pediatric patients, the majority of bleeding events were reported as excellent (85.7%) or good (13.1%) OHR, with no notable differences between age groups or between major and minor bleeding events. The safety profile was consistent with the underlying disease and expected profile for human fibrinogen products, with 73.3% of patients experiencing treatment-emergent adverse events. The most common adverse reactions occurring in >2% of patients included pain in extremity (7%), back pain (7%), hypersensitivity reactions (7%), pyrexia (4%), thrombosis (4%), fibrin D-dimer increased (4%), headache (4%), and vomiting (4%). Serious adverse reactions included thrombosis in 2 patients (portal vein thrombosis and deep vein thrombosis in one subject each), pain in extremity with clinically suspected thrombosis in one patient, and one patient with epilepsy and extradural hematoma four weeks after FESILTY administration, which was fatal.

The overall benefit-risk assessment was considered favorable. The applicant has provided substantial evidence of effectiveness and safety in study 984 which includes the pharmacokinetics, pharmacodynamics and clinically meaningful endpoints of hemostasis and supported by preclinical studies. The review team recommends traditional approval of FESILTY for the treatment of acute bleeding episodes in pediatric and adult patients with congenital fibrinogen deficiency, including hypo- or afibrinogenemia.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

This Phase I/III clinical trial enrolled 67 patients with congenital fibrinogen deficiency across 6 sites in 5 countries (Lebanon, Egypt, Tunisia, and Bulgaria) from March 2013 to May 2020. There were 45 patients who received FESILTY and completed the study. The overall patient population (parts I and II of the study) included 21 adults (18-75 years, 46.7%), 6 (13.3%) patients age <6 years, 12 (26.7%) patients age 6 to <12 years, and 6 (13.3%) patients age 12 to <18 years, with a slight male predominance overall (ranging from 52% to 61% across study parts). All patients were non-Hispanic/Latino and predominantly white (96% and 100% in both parts), with the vast majority (94% and 100%) having afibrinogenemia and the remainder having severe hypofibrinogenemia. Study demographics are shown in **tables 1-3**.

The study was divided into part I and part II.

Table 1. Study Demographics

	Part I % (n) n=27 patients	Part II % (n) n=36 patients	Overall % (n) n=45 patients
Male	52% (14)	61% (22)	49% (22)
Female	48% (13)	39% (14)	51% (23)
White	96% (26)	100% (36)	98% (44)
Black or African American	4% (1)	0	2% (1)
Age (years), median (range)	18 (range 1-40)	18 (range 1-46)	14 (1-46)
Afibrinogenemia	100% (27)	94% (34)	96% (43)
Hypofibrinogenemia	0	6% (2)	4% (2)

Abbreviations: n = number of patients, % = percentage.

Table 2. Age Demographics

Age Group	Part I (SAF I) N=27	Part II (SAF II) N=36	Overall* N=45
	n (%)	n (%)	n (%)
< 6 years	6 (22.2)	3 (8.3)	6 (13.3)
6 to < 12 years	3 (11.1)	9 (25.0)	12 (26.7)
12 to < 18 years	3 (11.1)	4 (11.1)	6 (13.3)
18 to 75 years	15 (55.6)	20 (55.6)	21 (46.7)

Table 3. Number of Patients Per Study Site (FAS I and II)

	Site Identifier	Number of Patients n (%)
Lebanon	1	30 (67)
Egypt	11	6 (13)
Tunisia	12, 14	7 (16)
Bulgaria	15	2 (4)
Germany	16	0
Total		45

Abbreviations: FAS = Full Analysis Set; n = number of patients; % = percentage.

*Note: Germany (site #16) enrolled 1 patient onto part II, but this patient did not receive the investigative product.

Please reference section 6.1.10.1.1 Demographics for further information on demographics.

Reviewer comment: The sample size was limited mostly to patients of white ethnicity. Since the predilection for clinical bleeding in congenital fibrinogen deficiency is usually dependent upon baseline fibrinogen levels, it is reasonable to extrapolate efficacy data from the population in white patients to other ethnic groups. The sample size in the pediatric population including patients <6 years was also limited in number (6 patients in part I and 3 patients in part II).

FDA sent an information request to the applicant regarding applicability of foreign data to the United States population. The applicant reported that treatment modalities for congenital fibrinogen deficiency do not differ globally. Classification of congenital fibrinogen deficiency is also dependent upon clinical phenotype and functional fibrinogen levels, which is not impacted by ethnicity. Therefore, the foreign study population is Study 984 is comparable to the United States population.

1.2 Patient Experience Data

There was no patient experience data in Study 984.

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
<input type="checkbox"/>	Patient-reported outcome	
<input type="checkbox"/>	Observer-reported outcome	
<input type="checkbox"/>	Clinician-reported outcome	
<input type="checkbox"/>	Performance outcome	
<input type="checkbox"/>	Patient-focused drug development meeting summary	
<input type="checkbox"/>	FDA Patient Listening Session	
<input type="checkbox"/>	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
<input type="checkbox"/>	Observational survey studies	
<input type="checkbox"/>	Natural history studies	
<input type="checkbox"/>	Patient preference studies	
<input type="checkbox"/>	Other: (please specify)	
<input checked="" type="checkbox"/>	If no patient experience data were submitted by Applicant, indicate here.	

Check if Considered	Type of Data	Section Where Discussed, if Applicable
<input type="checkbox"/>	Perspectives shared at patient stakeholder meeting	
<input type="checkbox"/>	Patient-focused drug development meeting	
<input type="checkbox"/>	FDA Patient Listening Session	
<input type="checkbox"/>	Other stakeholder meeting summary report	
<input type="checkbox"/>	Observational survey studies	
<input type="checkbox"/>	Other: (please specify)	

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Congenital fibrinogen disorders (CFD) are rare bleeding disorders caused by mutations in the FGA, FGB, and FGG genes on chromosome 4, which encode the three polypeptide chains that form fibrinogen, a crucial 340 kDa glycoprotein produced in the liver. These disorders are classified into quantitative deficiencies (afibrinogenemia with complete absence of fibrinogen, and hypofibrinogenemia with reduced levels) and qualitative deficiencies (dysfibrinogenemia with normal antigen but decreased activity, and hypodysfibrinogenemia with disproportional decreases in both). The clinical severity correlates with fibrinogen activity levels, ranging from asymptomatic patients with levels above 100 mg/dL to severe spontaneous bleeding in those with levels below 20 mg/dL. Afibrinogenemia, the rarest form with a prevalence of 1 in 1 million, typically presents with severe bleeding including cutaneous bleeding, hematomas, and umbilical cord bleeding, while hypofibrinogenemia and dysfibrinogenemia more commonly manifest as menorrhagia and postpartum

hemorrhage. Patients may also experience thrombotic complications (8-11% across all types) and significant obstetric complications, particularly spontaneous abortions occurring in 31% of pregnancies.

Treatment approaches vary based on the specific type and severity of CFD, with fibrinogen concentrate being the most frequently used product (55% of treated patients), particularly for quantitative deficiencies. Other treatment options include cryoprecipitate (15%), fresh frozen plasma (15%), and antifibrinolytic drugs, which are especially common in dysfibrinogenemia (50%). Most patients receive on-demand treatment (78%), while prophylaxis is reserved for more severe cases, particularly in afibrinogenemia (40% of cases) and some dysfibrinogenemia patients (19%). All afibrinogenemic patients require treatment due to their severe bleeding risk, and prophylaxis is predominantly prescribed in Europe and the United States, with a relatively low risk of thrombosis (5% in prophylaxis patients). The heterogeneous nature of these disorders necessitates individualized treatment strategies based on bleeding severity, genetic subtype, and patient-specific factors including pregnancy and surgical needs (Mohsenian, S et al. 2024)

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

Treatment approaches for congenital fibrinogen deficiency (CFD) include fibrinogen concentrates, cryoprecipitate, fresh frozen plasma, and anti-fibrinolytic drugs. The currently approved products for CFD are shown in table 4. Other products have been used for treatment of CFD are considered as off-label use.

Table 4. Approved Products for Congenital Fibrinogen Deficiency

Product Name	Generic Name	Approval Date	Indication
RiaSTAP	Fibrinogen concentrate (human)	2009	Treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia
Fibryga	Fibrinogen concentrate (human)	2017	Treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia

2.3 Safety and Efficacy of Pharmacologically Related Products

Riastap was evaluated in subjects in patients with congenital fibrinogen deficiency. Patients were administered a single dose of 70mg/kg and the mean change in the maximum clot firmness (MCF) pre- and 1-hour post-infusion without a pre-specified study success was evaluated. The results of the study demonstrated that the mean change in MCF values closely approximately levels expected from adding known amounts of fibrinogen to plasma in-vitro. Pharmacokinetic studies were evaluated in

children and adults and provided data in support of efficacy. The safety profile was acceptable with adverse reactions including thrombosis, fever and headache.

Fibryga was evaluated in subjects with congenital fibrinogen deficiency in two prospective, open-label, uncontrolled clinical studies. Efficacy of Fibryga was measured using an objective 4-point efficacy scale based on criteria such as bleeding cessation, changes in hemoglobin and use of any other hemostatic means. The treatment of bleeding events was considered successful for 86 of 87 (98.9%) of evaluable bleeding events (8 ratings of good and 78 ratings of excellent efficacy). The safety profile was acceptable with the most common adverse reactions of nausea, vomiting, pyrexia and thrombocytosis. There was also an additional risk of thrombosis, which was reported in patients with congenital fibrinogen deficiency.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

There is no previous human experience with FESILTY. Clinical study reports for Trial 984 have been submitted to the BLA and will be reviewed herein.

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

The Applicant does not have an active IND in the United States for FESILTY. All amendments made prior to the BLA submission were under PTS# 007549.

The following table lists regulatory activity related to the submission.

Table 5. Regulatory Activities Related to the Submission

Date	Type of Meeting/Interaction
September 8, 2022	Pre-IND Type C Meeting – Written Response
April 2, 2024	Submission of Initial Pediatric Study Plans (iPSP)
September 19, 2024	Type B Pre-BLA Meeting Acceptance of Agreed iPSP
September 20, 2024	Agreement Letter for Initial Pediatric Study Plan for Congenital Fibrinogen Deficiency

- April 26, 2022 – Pre-IND Type C Written Response Only
 - To discuss the quality, nonclinical and clinical development of Fibrinogen Concentrate (FESILTY). Biotest wanted to discuss the acceptance of foreign clinical data not conducted under an IND (Study 984) to obtain biologics license application approval in the US in the proposed indications “Treatment and prophylaxis of bleeding in patients with congenital hypo-, dys- or afibrinogenemia with bleeding tendency.” The FDA stated that the results of Study 984 will be evaluated during the BLA process.
- September 19, 2024 – Type B Pre-BLA Meeting
 - The applicant submitted the proposed plan for format and content of the BLA submission for congenital fibrinogen deficiency for FESILTY, which the agency agreed was reasonable.
- September 20, 2024 – Agreement Letter for Initial Pediatric Study Plan for Congenital Fibrinogen Deficiency

- The agency agreed with submission of a pediatric assessment for the pediatric population age 0 to <17 years.

2.6 Other Relevant Background Information

Not applicable.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The BLA submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty. Inadequacies were resolved via use of information requests (IRs). On January 31, 2025, the applicant submitted omitted case report forms via email and to module 5.3.5.2.

3.2 Compliance With Good Clinical Practices And Submission Integrity

The applicant stated that the trials were completed in multiple centers overseas in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines, the most recent version of the Declaration of Helsinki, with local regulatory requirements (17th version, 2013), and in accordance with standard operating procedures (SOPs) for clinical research at Biotest AG and the contract research organizations (CRO) (b) (4)

The clinical trials included provisions for obtaining informed consent by all study subjects, and for ethical treatment of study subjects.

One bioresearch monitoring (BIMO) inspection was completed. There were a few issues with patient record retention, IP records and CI oversight during the inspection. However, after review, these issues did not affect patient safety or integrity. No significant inspectional findings impacting data integrity were noted in the completed EIRs, and the preliminary draft summary reports. No FDA form 483s were issued for this inspection.

Protocol Deviations

There were five patients with 9 major protocol deviations in the overall study, reported in table 5.

Table 6. Major Protocol Deviations

Deviation	Part I N=6 n (%)	Part II N=3 n (%)
Total patients	27	36
Major protocol deviation	3 (11.1)	3 (8.3)
Deviation from medical assessment	1 (3.7)	3 (8.3)
Deviation from lab assessment	2 (7.4)	0

Abbreviations: N=number of deviations; n=number of patients with at least one deviation; %=percentage of patients with a deviation.

In part I, there were 6 major protocol deviations in 3 (11.1%) out of 27 patients. One patient (b) (6) had deviation from medical assessment when they were given clopidogrel on pharmacokinetic follow-up day 7. Two patients (b) (6) had deviations from lab assessments.

In part II, there were 3 major protocol deviations in 3 patients (b) (6). In all three deviations, Exacyl (also known as tranexamic acid), a prohibited medication was dispensed. Exacyl was dispensed on the day of FESILTY administration in two patients, and three days after FESILTY administration in another patient. For patient (b) (6), tranexamic acid (TXA) was administered during one bleeding event as a concomitant medication on the same day as FESILTY administration. It is not clear if TXA was administered before, during or after FESILTY. For patient (b) (6), they received FESILTY as surgical on-demand prophylaxis for surgery for spontaneous hematoma of left maxillary sinus. They received TXA approximately 3 days after FESILTY infusion for indication "local hemostasis at bandage change." Epistaxis at bandage change was noted as an adverse event and there was no action taken with FESILTY. For patient (b) (6), the patient received on-demand treatment with one infusion of FESILTY due to bleeding from wound dehiscence. The patient also received TXA on the same day as FESILTY administration until 2 days later. All three patients with TXA use during use of FESILTY had bleeding events excluded from the Per Protocol Set

Reviewer comment: Protocol deviations did not affect the overall efficacy evaluation for FESILTY. There were patients who had missing pre-dose values for maximum clot firmness (MCF) in part I and part II. However, those patients with missing pre-dose values were not counted in the final calculations to evaluate change at hour after infusion for MCF.

There were three protocol deviations where tranexamic acid was given at the time of FESILTY administration. However, these patients were not included in the Per Protocol Set and therefore, did not affect efficacy evaluations.

3.3 Financial Disclosures

Covered clinical study (name and/or number):984
Was a list of clinical investigators provided? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (Request list from applicant)
Total number of investigators identified: <u>6</u>
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____

Significant payments of other sorts: _____

Proprietary interest in the product tested held by investigator: _____

Significant equity interest held by investigator in sponsor of covered study: _____

Is an attachment provided with details of the disclosable financial interests/arrangements? ☐ Yes ☐ No (Request details from applicant)

Is a description of the steps taken to minimize potential bias provided? ☐ Yes ☐ No (Request information from applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0

Is an attachment provided with the reason? ☐ Yes ☐ No (Request explanation from applicant)

Reviewer comment: There were no conflicts of interests for the investigators for study 984.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Fibrinogen (Human) (FESILTY) drug substance is manufactured out of human source plasma according to 21 CFR Part 640 Subpart G and USP, under germ reduced conditions, in a GMP controlled environment.

Single plasma donations are pooled to obtain a representative plasma pool from which the cryoprecipitate is separated. The intermediate cryoprecipitate is sourced and pooled from qualified contract manufacturers, purified and subjected to virus inactivation with polysorbate 80 / (b) (4). Following virus inactivation, fibrinogen is further purified by anion exchange chromatography (AEX) and glycine precipitation. After the glycine precipitation and storage, the glycine paste is (b) (4). UV-C irradiation for further virus inactivation is performed. Subsequently, a cation exchange chromatography (CEX) is performed and the elution fraction is subjected to an (b) (4) step in order to concentrate the protein solution. For formulation, polysorbate 80 and trehalose dihydrate are added. After adjusting the pH and protein concentration as well as (b) (4) filtration, Fibrinogen (Human) (FESILTY) drug substance is processed directly to the drug product.

Additionally, FESILTY was utilized in clinical study 984 with the (b) (4) device. The applicant proposed use of Nextaro v, 20/20 Transfer Device which was introduced after completion of the clinical study.

Please see CMC memo for further details.

4.2 Assay Validation

Please see CMC memo for further information.

4.3 Nonclinical Pharmacology/Toxicology

The non-clinical data package included primary and secondary pharmacokinetics, a study on the effects on cardiovascular and respiratory functions to anesthetized rabbits, study on the thrombogenic effect in the anesthetized rabbit after single administration, and local tolerance study in rabbits. The applicant notes there are no suitable animal models for investigations of primary pharmacodynamic effects of FESILTY. Biotest conducted in vitro investigations with PPQ batches of Fibrinogen concentrate (FESILTY) manufacturing according to process P2. Secondary pharmacodynamics are assessed by the (b) (4) assay in the (b) (4) device.

For the study on effects of cardiovascular and respiratory functions in rabbits, no mortality was observed following administration of FESILTY or Haemocomplettan P at each dose level tested. For study report AB04757 evaluating thrombogenic effects in rabbits, several small thrombi were observed for all animals treated with both FESILTY and reference item, except one animal who was treated with the reference item. For study AB04758, local tolerance study in rabbits, there was no mortality or morbidity in the study. There were no treatment-related histologic findings from intravenous administration of FESILTY. The animals gained weight throughout the study. Developmental and reproductive toxicology studies were not conducted. The applicant notes that pharmacokinetics in non-human primates is difficult to assess as primates have endogenous fibrinogen molecules with a high sequence homology that are analytically difficult to discriminate. The PK properties of FESILTY were investigated in a single dose PK study in rabbits and compared to characteristics of Haemocomplettan.

Please see pharmacology/toxicology memo for more information.

4.4 Clinical Pharmacology

FESILTY is a lyophilized, heat treated human fibrinogen concentrate manufactured from human plasma. Human plasma used for manufacture of FESILTY complies with the recommendations in (b) (4)

and with the US Code of Federal Regulations (CFR) Title 21 Parts 606 and 640.

According to the applicant, pharmacological effects were studied in vitro because there are no suitable animal models available for measuring human fibrinogen activity. Functional tests for the relevant primary mode of action (clot formation) were performed in vitro. The fibrinogen potency assays (b) (4) (requirement according to (b) (4) and (b) (4) assay (additional assay) are based on the first steps in fibrinogen activation whereby (b) (4) FESILTY is brought to coagulation

by addition of (b) (4) of thrombin. In terms of the assay described in the (b) (4) the amount of clotted (active) fibrinogen is determined whereby in the (b) (4) assay the coagulation time depends on the fibrinogen content. Both tests, the assay based on (b) (4) (refer to 3.2.P.5.2.1) and the (b) (4) assay have been performed for a substantial number of batches. Additionally, secondary pharmacological functions (b) (4) were also investigated.

4.4.1 Mechanism of Action

Because of its natural human origin, Fibrinogen (Human) (FESILTY) drug substance should show the biological and immunological characteristics of plasma fibrinogen. Fibrinogen is part of the coagulation cascade of proteins. The activation by thrombin is the rationale for the use of fibrinogen in the intended indications in deficiencies of this protein. Thrombin rapidly proteolyzes fibrinogen and releases fibrinopeptide A and subsequently fibrinopeptide B. An insoluble (b) (4) is formed by polymerization. The resulting insoluble fibrin aggregates appear as clots.

4.4.2 Human Pharmacokinetics (PK)

The PK and primary PD of FESILTY were reported by the Applicant as fibrinogen antigen (FiAg) and fibrinogen activity (FiAc) levels, respectively, in plasma after single IV administration of 70 mg/kg BW FESILTY in children, adolescents, and adults with congenital afibrinogenemia or severe congenital hypofibrinogenemia in Trial 984. No additional PK or PD evaluations were performed in subjects with acquired fibrinogen deficiency in Trial 995.

Reviewer Comment: For dosing and product labeling of plasma-derived replacement therapies including fibrinogen products, “activity” has been an established acceptable PK endpoint rather than “antigen”. Therefore, the relevant PK refers to the FiAc level.

Of note, sparse sampling schedule was used for PK sample collection in in young children (< 6 years of age), the Applicant developed population PK and PK/PD model to

describe the kinetics of FiAg in children and the relationship between FiAg and FiAc in all age groups.

The FiAg and FiAc results from popPK and PK analysis for Trial 984 are summarized in the **Table 7** below.

Table7 Summary of Key FESILTY FiAg and FiAc Results by Age Group (based on popPK analysis)

		< 6 years N = 6	6 to < 12 years N = 3	12 to < 18 years N = 3	18 to 75 years N = 15
Fibrinogen Antigen					
C_{max} (g/L)	gMean	1.69	1.87	1.68	1.79
	gCV (%)	10.6	16.0	8.76	34.5
AUC_{0-∞} (g·h/L)	gMean	144	153	154	184
	gCV (%)	10.6	7.25	17.7	28.9
Fibrinogen Activity					
C_{max} (g/L)	gMean	1.15	1.30	1.03	1.23
	gCV (%)	10.7	22.0	18.1	44.9
AUC_{0-∞} (g·h/L)	gMean	86.4	93.3	82.9	110
	gCV (%)	8.99	13.2	26.2	35.3

Source: Summary of Clinical Pharmacology submitted by the Applicant

AUC_{0-∞} = area under the concentration-time curve extrapolated to infinity; C_{max} = maximum concentration; gCV = geometric coefficient of variation; gMean = geometric mean; N =number of subjects.

Reviewer Comment: The parameters in Table 1 originally submitted by the Applicant were estimated based on the popPK modeling and simulation results. An information request was sent to the Applicant to submit PK results based on NCA for all age groups that have extensive clinical PK sampling (e.g. 6 to <12 years, 12 to <18 years, and 18 years and older). These PK results were shown in **Table 8** below. Refer to Section 4.4.4 Pharmacometrics for the review team's evaluation of the Applicant's modeling method and results.

Table 8 Summary statistics of FiAc parameters based on observed data of all subjects who have extensive sampling (at least five observations) in Trial 984

FiAc parameters	Adults N=14	12 to <18 years N = 2	6 to < 12 years N = 1
$t_{1/2}$ [h]	53.8 ± 12.7 (32.6-80.1)	57.4 ± 25.7 (39.3-75.6)	63.1 ± 0.0 (63.1-63.1)
C_{max} [g/L]	1.49 ± 0.441 (0.800-2.22)	1.16 ± 0.474 (0.830-1.50)	1.74 ± 0.0 (1.74-1.74)
$AUC_{0-\infty}$ [g*h/L]	101 ± 40.1 (55.9-176)	79.4 ± 52.1 (42.5-116)	92.8 ± 0.0 (92.8-92.8)
$MRT_{0-\infty}$ [h]	79.1 ± 18.1 (48.6-116)	84.8 ± 39.3 (57.0-113)	88.6 ± 0.0 (88.6-88.6)
V_{dss} per kg [mL/kg]	59.2 ± 15.4 (32.9-102)	80.8 ± 18.5 (67.8-93.9)	66.8 ± 0.0 (66.8-66.8)
CL per kg (mL/[h*kg])	0.801 ± 0.307 (0.397-1.25)	1.13 ± 0.741 (0.602-1.65)	0.754 ± 0.0 (0.754-0.754)
IRobs (mg/dL per mg/kg dose)	2.13 ± 0.629 (1.14-3.17)	1.66 ± 0.672 (1.19-2.14)	2.49 ± 0.0 (2.49-2.49)

Source: Summary report of Non-Compartmental Analysis of the Observed FiAg and FiAc Concentrations in Trial 984, submitted by the Applicant on 9/24/2025
Values are presented as Mean ±SD (Min-Max). For each age group, the values are only from patients with extensive sampling.
 $MRT_{0-\infty}$ = mean residence time extrapolated to ∞ , V_{dss} = volume of distribution at presumed steady-state, CL= clearance, IRobs= incremental recovery based on observations

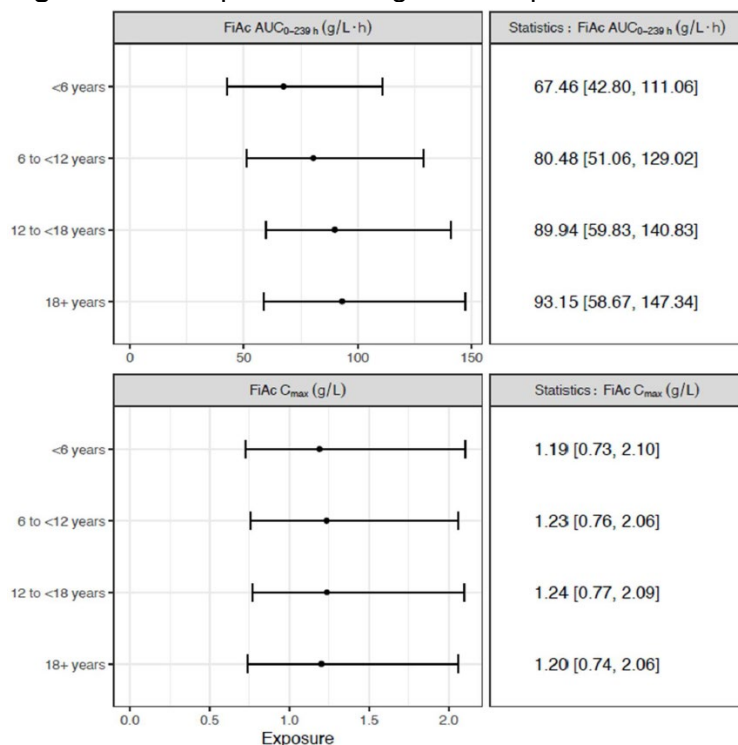
As shown in Table 7 and Table 8, pediatric subjects had lower exposure compared to adults. This is due to that clearance rate increases with decreasing body weight.

Reviewer comment: The C_{max} level was comparable across age groups, while the $AUC_{0-\infty}$ was lower in pediatric patients, especially for the age group of < 6 years (as shown in Table 7 above and Figure 1 below). The clinical efficacy outcome (overall hemostatic response [OHR]), was similar across different age groups (refer to Table 29 in Section 6.1.11). Therefore, the observed numerical difference in FiAc exposure is not considered clinically meaningful.

The review team sent an information request to ask the Applicant to perform exposure matching across the age groups in Trial 984. As a response, the Applicant conducted a modeling/simulation-based PK analysis to compare FiAc exposure across all age groups. As shown in the **Figure 1** below, the exposure comparison analysis supports that weight-based dosing with a fixed infusion duration achieves comparable FiAc

exposure across pediatric and adult populations. Refer details of modeling and simulation approach to the Section 4.4.4 Pharmacometrics.

Figure 1 Forest plot illustrating FiAc PK parameters



Source: Age Based Exposure Matching of FESILTY via Fibrinogen Antigen (FiAg) and Fibrinogen Note: Activity (FiAc) Population Pharmacokinetic Model, submitted by the Applicant on 9/24/2025. FiAc C_{max} and AUC from 0 to 239 hours after dose (AUC_{0-239h}) were stratified by age groups. Simulations (n=1000) were based on the population PK/PKPD model developed from both fibrinogen antigen (FiAg) and FiAc data. Closed dots represent the median of the predicted metric. The 90% prediction intervals associated with the medians are visualized by the error bars. Statistics of median and associated 90% prediction intervals are presented on the right.

In addition to the parameters listed in **Tables 1 and 2**, the estimated incremental recovery (IR) parameter based on modeling/simulation approach was also reported. Refer the IR parameter to Section 4.4.5, which is related to dosing justification.

4.4.3 Human Pharmacodynamics (PD)

The modeling-based approach was also used to evaluate the relationship between FiAc and maximum clot firmness (MCF), which is a secondary efficacy endpoint, and the relationship between MCF and overall hemostatic response (OHR). Refer to Section 6.1.11 (Efficacy Analyses) for MCF and OHR assessment. Refer to Section 4.4.4 Pharmacometrics for the corresponding analysis based on the modeling approach.

4.4.4 Pharmacometrics

A two-compartment popPK model was fit for integrated assessment of fibrinogen antigen (FiAg) and fibrinogen activity (FiAc) levels. The model adequately described the FiAg and FiAc levels across a wide age range (1 – 40 years). The popPK model-based

simulation predictions demonstrated 28% and 14% lower AUC for the <6 and 6-<12 year old age groups as compared to adults, respectively. Cmax was comparable across all age groups (**Figure 1**).

The popPK model was extended via a proportional slope model to describe maximum clot firmness (MCF) levels as the PD endpoint as a function of FiAc levels. The MCF to FiAc ratio was estimated to be 11.9 mm · L/g at FiAc levels of 1g/L, with slight decreases observed as FiAc increased, but was challenging to characterized due to limited MCF measurements and small sample size.

Overall, the popPK and the PK/PD analysis supports the approval of the 70mg/kg dose across the age ranges studied. Please refer to the pharmacometrics consult review for details.

4.4.5 Dose rationale

The Applicant proposed FESILTY dose when baseline fibrinogen level is known as following:

$$\text{Dose (mg/kg BW)} = \frac{\text{target fibrinogen levels (mg/dL)} - \text{fibrinogen baseline level (mg/dL)}}{1/(\text{incremental recovery of the specific product (mg/dL per mg/kg BW)})}$$

The IR parameter for FESILTY was estimated, as shown in **Table 9** below. Based on these data, the proposed IR to be used for the recommended dose calculation was 1.8

mg/dL per mg/kg dose for adults and pediatric patients aged ≥ 6 years, and 1.6 mg/dL per mg/kg dose for children aged < 6 years.

Table 9 Summary of FESILTY IR

Age group	N evaluated	Observed incremental recovery	
		mg/dL per mg/kg dose	CV (%), geometric mean
Overall	27	1.78	37.1
Adults aged ≥ 18 years	15	1.87	46.8
Adolescents aged 12 to < 18 years	3	1.54	30.7
Children aged 6 to < 12 years	3	2.00	23.9
Children aged < 6 years	6	1.59	12.2

Source: 2.7.3.A Summary of Clinical Efficacy– Congenital Fibrinogen Deficiency submitted by the Applicant

CV = coefficient of variation; N = number of subjects

The subject level raw values that were used to calculate the observed IR was provided, as shown in the **Table 10** below. The corresponding summary statistics stratified by age group is shown in **Table 11** below.

Table 10. Subject-level Values used to calculate Observed Incremental Recovery (IRobs) for Fibrinogen Activity

Subject	Age group	Dose (mg)	Body weight (kg)	C _{max} (0-4h) (g/L)	IRobs (mg/dL mg/kg dose)
(b) (6)	Children <6 years	815.5	11.6	1.04	1.48
		808.5	11.5	1.36	1.93
		1050.0	15.0	1.23	1.76
		720.0	10.3	1.07	1.53
		1029.0	14.7	0.930	1.33
		1260.0	18.0	1.06	1.51
	Children 6 to <12 years	3080.0	44.0	1.74	2.49
		2170.0	31.0	1.09	1.56
		1540.0	22.0	1.45	2.07
	Adolescents 12 to <18 years	3430.0	49.0	0.830	1.19
		3640.0	52.0	1.50	2.14
		2660.0	38.0	1.00	1.43
	Adults 18 to 75 years	5000.0	71.5	1.70	2.43
		5250.0	75.0	2.22	3.17
		4550.0	65.0	1.19	1.70
		3290.0	47.0	1.08	1.54
		6720.0	96.0	2.00	2.86
		5250.0	75.0	1.82	2.60
		4900.0	70.0	1.46	2.09
		4550.0	65.0	1.09	1.56
		6370.0	91.0	1.45	2.07
		4410.0	63.0	1.18	1.69
		4760.0	68.0	1.11	1.59
		3570.0	51.0	0.390	0.557
		4760.0	68.0	1.63	2.33
		5495.0	78.5	0.800	1.14
		6600.0	94.0	2.14	3.05

Source: Applicant's response to information request, submitted on 12/4/2025.

C_{max} (0-4h)= maximum concentration between 0 and 4 hours; IRobs, incremental recovery based on observations: the dose-adjusted maximum fibrinogen increase in plasma within 4 hours after the end of infusion (C_{max}(0-4h)).

*The IRobs value for Subject (b) (6) has been corrected to 1.33 (previously reported as 1.40) after identifying an oversight, where C_{max} was used instead of C_{max}(0-4h). The update is deemed minor since it has no impact on the overall interpretation of the findings.

Note: Pre-dose values for FiAc are not presented in Table 1, as they were 0 for all subjects. For the age group of 6 < years, the estimated Mean IR value based on popPK analysis is 1.65.

Table 11. Summary of Fibrinogen Activity (FiAc) Observed Incremental Recovery (IRobs) by Age Group based on Observed Data

Age Group (Years)	N	Mean IRobs (mg/dL mg/kg dose)	SD	CV (%)	gMean IRobs (mg/dL mg/kg dose)	gCV (%)
Children <6	6	1.59*	0.216*	13.6*	1.58*	13.4*
Children 6 to <12	3	2.04	0.466	22.8	2.00	23.9
Adolescents 12 to <18	3	1.59	0.494	31.1	1.54	30.7
Adults 18 to 75	15	2.03	0.729	36.0	1.87	46.8
Overall	27	1.88	0.613*	32.6*	1.78	37.3*

Source: Applicant's response to information request, submitted on 12/4/2025.

CV= coefficient of variation, gMean= geometric mean; IRobs= incremental recovery based on observations: the dose-adjusted maximum fibrinogen increase in plasma within 4 hours after the end of infusion (C_{max} (0-4h)), SD= standard deviation.

*As a result of the deviation identified in IRobs value for Subject (b) (6), minor discrepancies in decimal values are observed in the summary statistics when compared with previously reported figures. For the age group of children <6 years, the values are as follows: 1.59 vs. 1.60, 0.216 vs. 0.201, 13.6 vs. 12.5, 1.58 vs. 1.59, and 13.4 vs. 12.2; and for the overall age group: 0.613 vs. 0.610, 32.6 vs. 32.4, and 37.3 vs. 37.1. This revision is considered minor and does not affect the interpretation of the results or the conclusions presented in the dossier.

Reviewer Comment: The Applicant proposed dosing strategy was in agreement with that of FIBRYGA. The review team concurs that given the sample size for the age groups of 6 to <12 years and 12 to < 18 years was small, the observed IR values for these two age groups might not be reliable (although as shown in Table 10 and 11, the IR estimate for these two age groups combined is close to 1.8). Of note, the differences between the proposed IR value of 1.8 and the calculated IR values for these two age groups are approximately 10-12%. As described in Section 4.4.2, the exposure differences between adults and these two age groups were larger than 12% and were not considered clinically meaningful. Overall, based on the collective evidence from the PK evaluations, efficacy, and safety results from Trial 984, the Applicant proposed dosing regimens for different age groups are acceptable.

When baseline fibrinogen level is not known, the proposed FESILTY dose is 70 mg/kg BW for patients of all ages. This dosing strategy is in line with that of FIBRYGA and is acceptable.

4.5 Statistical

Please refer to the Statistical Review memo for further details. The primary objective of Study 984 was to evaluate the 14-day single-dose pharmacokinetics and pharmacodynamics and maximum clot firmness as a surrogate efficacy parameter in part I, and to evaluate efficacy by clinical endpoints such as overall hemostatic response. For continuous variables, descriptive statistics were given including mean, SD, median, quartiles, maximum and minimum. Categorical data is presented in frequency tables using counts and percentages.

4.6 Pharmacovigilance

The applicant presents a pharmacovigilance plan in module 1.16.1 of BLA 125833. No safety concerns have been identified that would require a risk evaluation and mitigation strategy or post-marketing requirement (PMR). The applicant's proposed intervention plan reports that Grifols plans to report, collect and assess suspected adverse event reports with Grifols products worldwide. The applicant reports that identified or potential risks include thromboembolic events, hypersensitivity, inhibitory antibodies and transmission of infective agents. Signal detection is performed by Grifols pharmacovigilance department to identify and monitor for potential safety signals. Routine pharmacovigilance activities have been considered sufficient by the applicant for post-authorization safety monitoring.

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

5.1 Review Strategy

The review focused on efficacy and safety data derived from Study 984.

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

The following materials from the BLA submission were reviewed:

Table 9. BLA Materials Reviewed For Submission

Module	Information
1.6	Meetings
1.14	Labeling
1.18	Proprietary names
5.2	List of Clinical Studies
5.3.1	Reports of biopharmaceutic studies
5.3.3	Reports of human pharmacokinetic studies
5.3.5	Reports of efficacy and safety studies
5.3.5.2	Study Reports of Uncontrolled Clinical Studies
5.4	Literature References

5.3 Table of Studies/Clinical Trials

Table 10 lists the clinical studies for FESILTY.

Table 10. Listing of Clinical Trials

Phase Status	Trial Identifier Location of CSR	Trial Period Region	Trial Design and Type of Control	Primary Efficacy Outcome	Test Product Dose Regimen, Administration	Trial Population	No. of Subjects (Treated)
Phase I/III Completed	Trial 984 (congenital fibrinogen deficiency) EudraCT No.: 2011- 004154-25 CT.gov ID: NCT02065882 Non-IND trial Module 5.3.5.2	2013-03-20 to 2020-05-18 (Bulgaria, Egypt, Germany, Lebanon, and Tunisia)	Prospective, single arm, open- label, uncontrolled, multicenter, multinational PK, PD, efficacy, and safety trial with 2 parts (part 1: PK/PD; part 2: efficacy and safety)	N/A (primary outcome was the PK profile evaluated in part 1); secondary efficacy endpoints included MCF and OHR	Part 1: BT524: single dose of 70 mg/kg BW Part 2: ODT or ODP (to prevent bleedings during, or after, specific surgical interventions); individually tailored dose Administration: IV infusion	Children, adolescents, and adults with congenital fibrinogen deficiency	Total: 45 Part 1: 27 Part 2: 36 ^a

Source: Table 5.2-1 Listing of Clinical Trials – FESILTY in module 5.2 Tabular Listing of Clinical Studies.

5.4 Consultations

No clinical consultations were requested or required during the review of this BLA.

5.4.1 Advisory Committee Meeting (if applicable)

An advisory committee was not convened for this product. The application did not raise significant safety or efficacy concerns that could not be addressed through information in label, consultative expertise was not required, and no public health concerns arose upon the review of this file.

5.4.2 External Consults/Collaborations

There were no external consults or collaborations sought for the clinical review of this BLA. There were external consultations from CMC regarding use of Nextaro device.

5.5 Literature Reviewed (if applicable)

Lasky J, Teitel J, Wang M, Dalton D, Schmidt DS, Brainsky A. Fibrinogen concentrate for bleeding in patients with congenital fibrinogen deficiency: Observational study of efficacy and safety for prophylaxis and treatment. *Res Pract Thromb Haemost*. 2020 Oct 11;4(8):1313-1323.

Mohsenian, S. et al. Congenital fibrinogen disorders: a retrospective clinical and genetic analysis of the Prospective Rare Bleeding Disorders Database. *Blood Adv* 2024; 8 (6): 1392–1404.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

Trial 984: A Prospective, Open-Label, Phase I/III Study Investigating Pharmacokinetic Properties Of FESILTY And Efficacy And Safety Of FESILTY In The Treatment And Prophylaxis Of Bleeding In Patients With Congenital Fibrinogen Deficiency

6.1.1 Objectives (Primary, Secondary, etc)

Primary objective:

- To investigate the 14-day single-dose pharmacokinetics (PK) of FESILTY following intravenous (IV) infusion in patients with congenital fibrinogen deficiency (afibrinogenemia or severe hypofibrinogenemia).

Secondary objectives:

- To investigate the 14-day single-dose pharmacodynamics (PD), the surrogate efficacy and safety of the single IV infusion of FESILTY.

6.1.2 Design Overview

Trial 984 is a prospective, open label, phase I/III multi-center, multi-national trial, with two parts: Part I – single intravenous (IV) infusion at 70mg/kg body weight to evaluate pharmacokinetics and pharmacodynamics and Part II is a single or repetitive IV infusion

of FESILTY for on-demand treatment (ODT) or on-demand prophylaxis (ODP) to evaluate clinical efficacy. In both parts, patients were evaluated for surrogate efficacy and safety.

Overall, there were 67 patients enrolled onto the study, with 45 total patients completing the study. In part I, there were 27 patients enrolled onto the trial with duration of treatment between one to two months. Patients were eligible to enroll onto part II after completing part I. Eighteen patients participated in parts I and II. In part II, there were 36 patients enrolled with duration of treatment lasting a minimum of 12 months. Seventeen subjects from part I enrolled onto part II. Please see below section 6.1.10.1.1 for further details of patient disposition.

6.1.3 Population

Key Inclusion Criteria included:

- Known congenital afibrinogenemia or severe congenital hypofibrinogenemia (known dysfibrinogenemia eligible for part II)
 - Age 6 to 75 years, with the first ten patients and patients with hypodysfibrinogenemia will be 18 years or older (Germany only)
 - Age 18 to 75 years (Tunisia only)
- Age 0-75 years
- Plasma fibrinogen activity ≤ 0.5 g/l and antigen ≤ 0.5 g/l (not applicable for patients with hypodysfibrinogenemia)

Key Exclusion Criteria included:

- Known congenital dysfibrinogenemia (not applicable for adult patients with hypodysfibrinogenemia in study part II)
- Known bleeding disorder other than congenital fibrinogen deficiency
- Known presence or history of venous/arterial thrombosis or thromboembolic event in the preceding 6 months (or family history of thrombophilia in adult patients with hypodysfibrinogenemia)
- History of esophageal variceal bleeding
- Known presence or history of fibrinogen inhibitory antibodies
- Known presence or history of hypersensitivity to human fibrinogen or human plasma proteins e.g., immunoglobulins, vaccines or hypersensitivity to any of the excipients
- Known positive serology for HIV-1 and HIV-2
- Treatment with any fibrinogen concentrate and/or fibrinogen-containing product within 2 weeks prior to infusion of FESILTY
- Concomitant medication interacting relevantly with the coagulation system (e.g., low molecular weight heparin, unfractionated heparin, factor Xa inhibitors, factor IIa inhibitors or PY12 inhibitors) within 2 weeks prior to infusion of FESILTY
- Recent vaccination within 3 weeks prior to infusion (only applicable for patients in PK part I)
- BW below 22 kg for patients ≥ 6 years (only applicable for patients in PK part I); BW below the 5th percentile of the normal range for children (refers to local standards*)

- Pregnant/ nursing woman, or woman of childbearing potential not using reliable/ effective contraceptive method(s) during the study and at least one month after the last administration of study drug (e.g., oral/ injectable/ implantable/ insertable/ topical hormonal contraceptives, intrauterine devices, female sterilization, partner's vasectomy or condoms) medical
- Any other condition that, in the investigator's judgment, could have an impact on patient's safety or study results (e.g. diabetes mellitus or liver function disorders in adult patients with hypodysfibrinogenemia)

Reviewer comment: Dyshypofibrinogenemia was allowed in a protocol amendment. However, no patients with dyshypofibrinogenemia were enrolled onto the study.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The study treatment given in this protocol for Study 984 was FESILTY (human fibrinogen), with active substance of fibrinogen concentrate from human plasma.

6.1.5 Directions for Use

The dose and mode of administration of FESILTY depended upon the severity, location and extent of bleeding and patient's clinical condition. Dosage was also based on individual body weight (BW) and individual fibrinogen level. Dosing was similar for patients ≤6 years of age, as for patients ≥6 to ≤75 years of age.

For part I (PK), the dose was 70mg/kg BW (IV) for a single dose.

For part II, the dose varied based on on-demand prophylaxis (ODP) or on-demand treatment (ODT). For bleeding events in part II, the dosing was variable and based on severity, location and extent of bleeding and patient's clinical condition.

- Part II – Surgical interventions
 - ODP: Variable dose (IV) with target fibrinogen level 1 g/L with number of doses to be determined by the investigator.
 - ODT: Variable dose (IV) with target fibrinogen level either 1g/L maintained until hemostasis is secure or >0.5g/L until wound healing is complete, with the number of doses to be determined by the investigator
- Part II – Spontaneous bleeding
 - ODT: Variable dose (IV) depending upon severity, location and extent of bleeding and patient's clinical condition. No target fibrinogen level was given.

6.1.6 Sites and Centers

Seven centers were initiated in this trial, with 6 active centers enrolling patients. One center in Lebanon did not enroll patients. The following table (**table 11**) includes the study sites for study 984:

Table 11. Study Sites for Trial 984

Site Identifier	Site Address
01	Beirut, Lebanon
11*	Cairo, Egypt
12	Tunis, Tunisia
14	Sousse, Tunisia

15	Sofia, Bulgaria
16	Frankfurt am Main, Germany

*Study site closed due to authority decision.

Reviewer comment: An information request was sent to the Applicant on March 7, 2025 to inquire on the closure of Site #11 due to “authority decision,” as noted in the Clinical Study Report. Study site #11 in Egypt was opened and approved on November 6, 2013 by the Egyptian Ministry of Health and National Organization for Research and Control of Biologicals (NORCB) on June 26, 2014. Following approval, there were 7 patients enrolled and dosed for part I before the site was closed by NORCB on November 28, 2017. According to the termination letter, NORCB stated that the *“Pharmacokinetics report of part I is not scientific enough to depend on to make phase III study”*. The Applicant noted that the interim pharmacokinetics data was given to NORCB to justify continuation of the study at the site. This interim report was non-formal and NORCB issued a termination letter on November 28, 2017. After termination, no further subject visits or trial procedures were conducted at this site. All 7 subjects that were enrolled and dosed had an end of trial visit per trial protocol. One patient (b) (6) participated in part I only, 3 patients (b) (6) participated in parts I and II, and three patients (b) (6) participated in part II. Three patients in part II had 1 bleeding event each and were dosed with FESILTY on (b) (6). The data for these subjects was included in the final efficacy and safety analysis of the trial. The FDA understands the inclusion of these 3 patients. If these patients were to be excluded from the final analysis, the overall conclusions in the efficacy and safety would not be affected.

6.1.7 Surveillance/Monitoring

The Data Monitoring Committee consisted of members with expertise in hematology and/or investigation and/or experience in the proper conduct of clinical studies, and/or statistical knowledge and who do not have any limiting conflicts of interest. The main aim of the DMC was to ensure the safety of study patients in particular to the inclusion of children and adolescents <18 years of age. Children and adolescents were not enrolled until after completion of dosing of the first 10 adult patients. The DMC also performed a secondary mandatory data review after the last patient finished the PK safety visit.

For part I of study 984, patients were followed for a maximum of 66+/-4 days (screening period 17 days, treatment period 49+/-4 days).

For part II, the minimum duration was 12 months of follow-up.

6.1.8 Endpoints and Criteria for Study Success

Primary Endpoints: Pharmacokinetics (PK) of FESILTY

Pharmacokinetics (PK) was assessed in part I of Study 984 with the following parameters: Terminal Elimination Half-life ($t_{1/2}$), Time to Maximum Concentration (t_{max}), Maximum Concentration (C_{max}), Area Under the Curve (AUC) calculated to the last measured concentration (AUC_{0-tz}), beyond last concentration (AUC_{extr}), and extrapolated to infinity ($AUC_{0-\infty}$), Area Under the first Moment Curve (AUMC)

calculated to the last concentration (AUMC_{0-tz}) and extrapolated to infinity (AUMC_{0-∞}), First-order terminal elimination rate constant (λ), Clearance (CL) and CL per kg BW, Mean Residence Time (MRT) extrapolated to infinity (MRT_{0-∞}), Volume of distribution at presumed steady-state (V_{dss}) and V_{dss} per kg BW, Incremental Recovery (IR), and Classical in vivo Recovery (CIR).

Secondary Endpoints: Pharmacodynamics (PD) of FESILTY

Single dose PD of FiAc was assessed by the same parameters as listed for the PK assessment of FiAg, including t_{1/2}, t_{max}, C_{max}, AUC_{0-tz}, AUC_{0-∞}, AUC_{extr}, AUMC_{0-tz}, AUMC_{0-∞}, λ , CL, CL per kg BW, MRT_{0-∞}, V_{dss}, V_{dss} per kg BW, IR, and CIR.

Efficacy Endpoints:

Surrogate Efficacy: Maximum clot firmness (MCF, mm) measured by rotational thromboelastometry was assessed as a surrogate efficacy parameter in study parts I and II.

Clinical Efficacy: The following efficacy endpoints were assessed in part II:

- Overall hemostatic response (OHR) to treatment with FESILTY for each surgical procedure and each treated bleed as assessed by the investigator according to a 4-point scale: "none", "moderate", "good" or "excellent".
- Total loss of blood (e.g., intra- and post-operatively, re-bleedings), if applicable.
- Units of other fibrinogen-containing products (FCP) infused besides FESILTY e.g., fresh frozen plasma (FFP) or cryoprecipitate.
- Units of transfusion products (TPs) infused e.g., allogenic or autologous blood (packed red blood cells (RBCs), fresh whole blood), platelets.
- Consumption of FESILTY (dose per kilogram BW required pre-, intra- or post-operatively for effective treatment).
- Quality of wound healing, if applicable.

Safety Endpoints:

- Adverse events
- Fibrinogen inhibitory antibodies
- Vital signs e.g., blood pressure, heart rate, body temperature
- Physical examination
- Electrocardiogram recordings
- Clinical laboratory assessments of hematology, clinical chemistry, and urine analysis
- Coagulation parameters: prothrombin time (PT) (international normalized ratio [INR]),
- activated partial thromboplastin time (aPTT), thrombin-antithrombin-III-complex (TAT),
- prothrombin fragment 1 and 2 (F1+2), D-dimer
- Ultrasonography
- Viral safety

6.1.9 Statistical Considerations & Statistical Analysis Plan

Please refer to statistical reviewer memo for further details.

For endpoints of pharmacokinetics and pharmacodynamics, descriptive summary statistics, including changes from baseline for the fibrinogen antigen (from part I), will be provided for each age group (based on SAF, FAS, PP, and PK population). PD parameters will be derived from concentration-time profiles using adapted methodology, non-compartmental analysis, compartment analysis, or population modelling, as required. For clinical endpoints in part II, efficacy parameters will be presented descriptively, including OHR. MCF will be evaluated pre-dose and 1 hour post infusion by means of non-confirmatory t-tests for comparison plus correlation between MCF and fibrinogen activity.

For safety, all analyses are based on the SAF with focus on TEAEs.

Statistical analyses were performed on the following analysis sets:

- **Pharmacokinetics analysis set (PK):** all patients with PK data in part I
- **All-patients enrolled set (APE I/II):** all patients with signed ICF for participation in part I/part II
- **Safety analysis set (SAF I/II):** all patients exposed to FESILTY in part I/part II
- **Full analysis set (FAS I/II):** all patients who received any portion of FESILTY and had at least one efficacy assessment in part I/part II
- **Per-protocol set (PP I/II):** all patients of the FAS I/II who had no major protocol deviations with potential to impact the results of the analysis in part I/part II.
- **Full bleeding event set (FBE):** all bleeding events treated with any portion of FESILTY and with at least one efficacy assessment during part II
- **Per-protocol bleeding event set (PPBE):** all bleeding events of the FBE that were compliant with study protocol, i.e. bleeding events in part II with no major protocol deviations that may impact the efficacy results of part II. Bleeding events documented for a patient with at least one major protocol deviation were excluded from PPBE.

6.1.10 Study Population and Disposition

The study was conducted in Lebanon, Egypt, Tunisia, Bulgaria, and Germany. In total, 7 study sites (2 in Tunisia, 2 in Lebanon, and 1 each in Egypt, Bulgaria and Germany) were approved and initiated to conduct the study. Of these, 6 sites (2 in Tunisia and 1 each in Lebanon, Egypt, Bulgaria and Germany) enrolled and treated patients. The majority of patients enrolled were from Lebanon (39 [58.2%]) of 67 patients overall. See **Table 12** for enrollment by site.

Table 12. Disposition and Percentages of Patients by Country – Part I and II

Country	Center ID	Part I N=35 n (%)	Part II N=59 n (%)	Overall N=67 n (%)
Total		35	59	67
Lebanon	01	21 (60)	38 (64.4)	39 (58.2)
Egypt	11	8 (22.9)	7 (11.9)	12 (17.9)
Tunisia	12	6 (17.1)	5 (8.5)	7 (10.4)
	14	0	6 (10.2)	6 (9.0)

Bulgaria	15	0	2 (3.4)	2 (3.0)
Germany	16	0	1 (1.7)	1 (1.5)

Abbreviations: n=number of patients; %=percentage

Source: Adapted from Table 14.1.1.2.1 from Clinical Study Report for Study 984

The study was divided into part I and II. Patients in part I who received treatment and completed the PK safety visit at day 49 were also to be enrolled into part II. There were 67 total patients enrolled and screened for the study, with 35 patients enrolled in part I and 59 patients enrolled in part II. Twenty-seven (27) patients who completed part I were also enrolled in part II. Enrollment by age group is noted in **table 13**.

Table 13. Demographics (Age)

Age	N=number, (%)
Adults (age >18)	31 (46.3%)
Adolescents (age 12-<18)	4 (6.0%)
Children (age 2-<12)	23 (34.3%)
Infants and toddlers (aged 28 days to 23 months)	4 (6.0%)
Total	67

The number of patients with congenital fibrinogen deficiency includes 53 patients with afibrinogenemia and 2 patients with hypofibrinogenemia, see **table 14**.

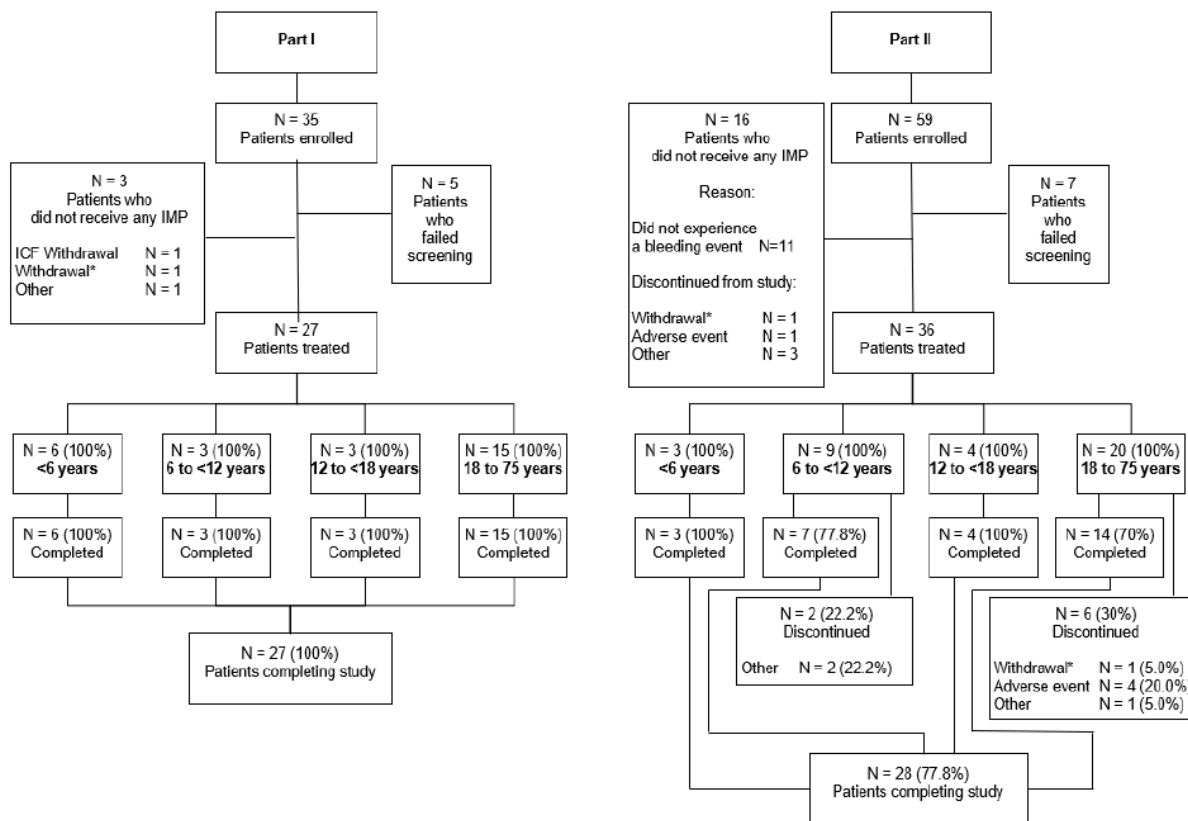
Table 14. Disease Under Study for FAS I and II

	Part I	Part II	Overall
Afibrinogenemia	27 (100%)	34 (94.4%)	53 (96.4%)
Hypofibrinogenemia	0	2 (5.6%)	2 (3.6%)
Overall	27	36	55

Source: ADSL Dataset

There were 27 patients treated in part I, with 27 patients completing part I of the study. In part II of the study, there were 36 patients treated, with 28 completing the study. Eight patients discontinued the study due to withdrawal (1), adverse event (4) and other (3). See **Figure 2** for more information.

Figure 2 Disposition of Patients in Protocol 984 (APE I/II, SAF I/II)



*Withdrawal by patient; Source: Table 14.1.1.2.4, Table 14.1.1.2.5, Table 14.1.1.2.6, and Table 14.1.1.2.7

ICF = informed consent form; IMP = investigational medicinal product; N = number of patients

Source: Clinical Study Report for Study 984, page 92.

6.1.10.1 Populations Enrolled/Analyzed

A total of 45 patients with congenital afibrinogenemia or severe congenital hypofibrinogenemia were treated in this study:

6.1.10.1.1 Demographics

The overall study population included 45 patients. There were 27 patients in part I and 36 patients in part II. There were 18 patients from part I that enrolled onto part II. The demographic characteristics of the overall study population were as follows: the median age was 14 (range 1-46), including 9 patients aged 0 to 6 years, 9 patients aged 6 to <12 years, and 6 patients aged 12 to 16 years and 21 patients >16 years. Out of 45 patients, 98% were white (n=44) and 2% (n=1) were black or African American. There were 43 patients with afibrinogenemia and 2 patients with severe hypofibrinogenemia. **Table 15** show age groupings for parts I and II and the overall study population. **Table 16** shows other demographics.

Study demographics for parts I, II and overall are in **tables 15-16**.

Table 15. Study Demographics - Age Groups

Study Demographics

Overall (n=45)					
	0 to <6 years % (n)	6 to <12 years % (n)	12 to 16 years % (n)	>16 years % (n)	Total
Part I (n=27)	22% (6)	11% (3)	11% (3)	56% (15)	27
Part II (n=36)	8% (3)	25% (9)	14% (5)	53% (19)	36
Overall (n=45)	13% (6)	27% (12)	13% (6)	47% (21)	45

Abbreviations: n = number of patients, % = percentage

Table 16. Study Demographics

	Part I % (n) Total 27 patients	Part II % (n) Total 36 patients	Overall % (n) Total 45 patients
Male	52% (14)	61% (22)	49% (22)
Female	48% (13)	39% (14)	51% (23)
White	96% (26)	100% (36)	98% (44)
Black or African American	4% (1)	0	2% (1)
Age (years), median (range)	18 (range 1-40)	18 (range 1-46)	14 (1-46)
Afibrinogenemia	100% (27)	94% (34)	96% (43)
Hypofibrinogenemia	0	6% (2)	4% (2)

Abbreviations: n = number of patients, % = percentage

Bleeding History

Prior to enrollment onto study 984, there were 582 total bleeding events for the 45 patients treated on study and 12.93 mean number of bleeds. The mean annualized bleeding rate (ABR) for the overall trial population was 2.30 (range 1-8 ABR) and the ABR for 36 subjects enrolled in Part II was 2.4 (range 1-8). There were 582 bleeding events prior to enrolling onto trial 984. The mean total number of bleeds was 12.93. For other bleeding history, see **table 17**.

Table 17. Bleeding History of Patients in Part I and II (SAF I and II)

Bleeding History Term	Part I N=27	Part II N=36
Mean number of bleeds (range)	14.3 (2-128)	14.5 (2-128)
Mean ABR, n (range)	1.9 (1-6)	2.4 (1-8)
Epistaxis, n (%)	14 (51.9)	18 (50.0)
Oral cavity bleeding, n (%)	20 (74.1)	26 (72.2)
Gastrointestinal bleeding, n (%)	5 (18.5)	8 (22.2)
Postpartum hemorrhage, n (%)	2 (7.4)	1 (2.8)
Umbilical cord bleeding, n (%)	24 (88.9)	24 (66.7)
Menorrhagia, n (%)	3 (11.1)	6 (16.7)
Muscle hematoma, n (%)	14 (51.9)	19 (52.8)
Hemarthrosis, n (%)	13 (48.1)	19 (52.8)
Intraperitoneal bleeding, n (%)	7 (25.9)	8 (22.2)
Intracranial bleeding, n (%)	5 (18.5)	8 (22.2)

Abbreviations: SAF=Safety Analysis Set; ABR = annualized bleeding rate; N=number of patients; n = number of events; % = percentage of patients

Overall, there were 36 patients with 175 total bleeding events. Of the 175 bleeding events, 65 (37.1%) were spontaneous bleeds, 54 (30.9%) were surgical bleeds (prophylaxis or treatment), 45 (25.7%) were post-traumatic bleeds and 11 (6.3%) “other” bleeds (included pleural effusion, prevention for splenectomy, muscular bleed, menorrhagia (2), chronic gingivitis and subcutaneous bleeds (2). See table 18.

Of the 175 bleeding events, 60 (34.3%) bleeding events treated as on-demand prophylaxis and 115 (65.7%) bleeding events treated as on-demand treatment. Bleeding events by type (spontaneous, surgical, post-traumatic and other) are listed in **table 18**.

Table 1. Type of Bleeding Events During Trial 984

Type of Bleeding Event	Number of Bleeds n (%)
Spontaneous	65 (37.1%)
Surgical	54 (30.9%)
Post-traumatic	45 (25.7%)
“Other” bleeds	11 (6.3%)

Abbreviations: n = number of patients, % = percentage. Other bleeds included pleural effusion, prevention for splenectomy, menorrhagia (2), chronic gingivitis and subcutaneous bleeds (2).

As stated above, there were 36 patients with a total of 175 bleeding events evaluable for the efficacy endpoint in part II of the trial. The mean age was 18 with a range of ages between 1 and 46. There were 3 (8.3%) subjects <6 years, 9 (25%) subjects aged 6 to <12 years, 4 (11.1%) subjects aged 12 to <18 years and 20 (55.6%) subjects aged 18 to 75 years.

There were 53 major and 122 minor bleeding events out of 175 total bleeding events.

The average number of infusions per bleeding event was 1.1 (range 1-6) for all patients, 1.2 infusions per ODP and 1.1 infusions for ODT. The number of infusions per adults and per children and adolescents can be seen in **table 19**.

Table 19. Mean Number of Infusions

	Children and Adolescents Total bleed events (n=84)	Adults Total bleed events (n=91)	Adults and Pediatrics (n=175)
Mean Number of Infusions per Bleeding Event (All Events)	1.1 (range 1-3)	1.2 (range 1-6)	1.1 (range 1-6)
Mean Number of Infusions per Bleeding Event for ODP	1.4 (range 1-2)	1.2 (range 1-6)	1.2 (range 1-6)
Mean Number of Infusions per Bleeding Event for ODT	1.03 (range 1-3)	1.2 (range 1-6)	1.1 (range 1-6)

Of note, there were 3 bleeding events in adults for which >3 infusions were given. Subject (b) (6) had two bleeding events with 5 and 6 infusions of FESILTY, respectively. There was one bleeding event of spontaneous bleeding from spleen rupture and hemoperitoneum. In an information request, the applicant reported that the patient received 1 infusion of FESILTY for the bleeding event and 4 additional infusions of FESILTY to promote wound healing per the protocol. The event was classified as moderate with excellent hemostatic response. There was one bleeding event of spontaneous intracerebral bleed with 6 infusions of FESILTY. The patient received 6 total infusions of FESILTY: 1 infusion of FESILTY for the bleeding event and 5 additional infusions to avoid re-bleed over the course of the proceeding 4 weeks. The cerebral bleed was classified as severe with excellent hemostatic response. Subject (b) (6) had on-demand prophylaxis for surgery of the left elbow (synovectomy). The patient received 6 infusions of FESILTY for this bleeding event. One infusion was given as ODP for the procedure, and 5 additional infusions of FESILTY were given to maintain fibrinogen levels above 0.5g/L until wound healing was complete. There was no re-bleeding documented. The bleeding event was classified as moderate with good hemostatic response and blood loss within the expected range.

The mean doses of FESILTY used for all bleeding events for adults was 70.1 mg/kg and 75.5mg/kg for children and adolescents ages 0-18, reported in **table 20**. For 54 perioperative bleeding events, there 49 events in adults and 5 events in pediatrics (age <18 years). The mean dose (mg/kg body weight) was 125.9 mg/kg for pediatrics (range 66.6-200 mg/kg BW) and 70.3 mg/kg (range 40-460.53 mg/kg).

Table 2. Mean Dose of FESILTY

	Children and Adolescents 0-18 years	Adults > 18 years
Mean Dose for All Bleeds	75.5 mg/kg	70.1 mg/kg
Mean Dose for ODP	102.1 mg/kg	74.8 mg/kg
Mean Dose for ODT	71.5 mg/kg	71.5 mg/kg

Source: FDA analysis, ADEX, ADSL dataset

A summary of exposure to FESILTY including baseline and target fibrinogen levels, total dose and number of infusions is noted in **table 21**. There were 87 bleeding events in the pediatric and adolescent populations.

Table 21. Exposure to FESILTY For All Bleeding Events

Variable	Statistic	Bleeding Events (Age 0 to 18 years) N=87	All Bleeding Events (Adults and Pediatrics) N=175
Target fibrinogen level (g/L)	Mean	1.1	1.16
	Median	1.2	1.2
Baseline fibrinogen level (g/L)	Mean	0.04	0.04
	Median	0	0
Total dose (mg)	Mean	2553.79	3879.5
	Median	2000	3000
Total dose (mg/kg BW)	Mean	75.5	72.7

	Median	66.67	62.6
Number of infusions per bleeding event	Mean	1.1	1.1
	Median	1.0	1.0

Abbreviations: BW = body weight, g = gram, L = liter, mg = milligram, kg = kilogram

Reviewer comment: The mean doses of FESILTY for bleeding events is similar between pediatric and adult patients. The dose of FESILTY is higher in pediatrics compared to adults, which is expected due to higher clearance of the treatment in the pediatric population.

There were 3 bleeding events in two adult patients who received >3 infusions of FESILTY. However, per information requests to the applicant, the patients received FESILTY during the bleeding events as initial ODT or ODP and additional FESILTY infusions to promote wound healing in one event, to prevent re-bleed after intracerebral bleed in another event and to maintain fibrinogen levels >0.5g/L until wound healing was completed in a third event. Per the protocol, the dosage and duration of FESILTY depend upon the severity, location and extent of bleeding. The explanations for additional doses of FESILTY are reasonable.

Comparison of Bleeds on Study versus Bleed History

There were 3 (8.3%) out of 36 patients in part II of study 984 with higher number of bleeds during the study compared to their bleeding history. All of these patients were receiving on-demand treatment (ODT) and/or on-demand prophylaxis (ODP). Two patients were in the pediatric population (age 6) and one patient was an adult (age 46). For patient (b) (6), they had history of 7 bleeds prior to the study and 11 bleeding events during the study. Of the 11 bleeding events, 10 bleeding events were classified as on-demand prophylaxis prior to surgeries and only 1 bleed was spontaneous. For patient (b) (6), they had history of 9 bleeds prior to the study and 18 bleeds during the study. All of these bleeds were spontaneous. For patient (b) (6), the patient had history of 3 bleeds prior to the study and 10 bleeding events during the study. One bleed was spontaneous, 7 bleeds were post-traumatic and 1 bleed was counted as "other." **Table 22** gives details on patients with increased bleeding events on study compared to bleeding history. **Figure 3** has comparison of number of bleeds on study for all patients in part II of study 984.

Table 22. Patients with Increased Number of Bleeding Events on Study Compared to Bleeding History (Part II of Study 984)

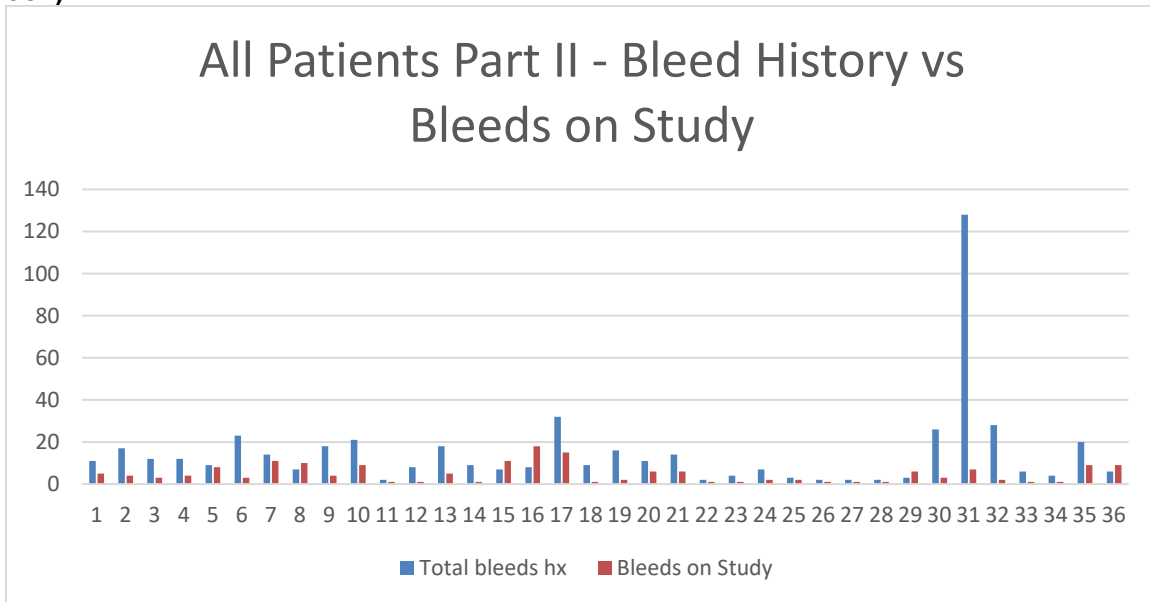
Subject Identifier	Age	Bleed History n	Bleeds on Study n	Time Frame of Study Participation	Details of Bleeds on Study n
(b) (6)	46	7	11	4 years	<ul style="list-style-type: none"> Surgical: 10¹ Spontaneous bleed: 1
(b) (6)	6	9	18	4 years	<ul style="list-style-type: none"> Spontaneous bleeds: 18 (17 were intramedullary bleeds 1 mucosal bleed)

(b) (6)	6	3	10	2 years	<ul style="list-style-type: none"> • Spontaneous bleed: 1 • Post-traumatic: 7 • Other: 1 (mouth bleed)
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¹FESILTY was given as on-demand prophylaxis in all 10 cases of surgical bleeding events.

Abbreviations: n=number of bleeds/bleeding events.

Figure 3. Bleed History Compared to Bleeding Events on Study (Part II of Study 984)



There were 4 (11.1%) subjects who received ODP who had more bleeds during the study compared to their bleeding history. Two patients (b) (6) were adults and the majority of the bleeding events were surgical. Two patients (b) (6) and (b) (6) were pediatric (age 13 and 6, respectively.) For patient (b) (6), age 13, they had 3 surgical bleeding events and 4 post-traumatic events. For patient (b) (6) they had 1 spontaneous bleed, 7 post-traumatic bleeds and 1 bleed classified as "other" (mouth). **Table 23** shows details of the 4 patients with higher bleeding events. **Figure 4** shows details of bleeding events and bleeding history for all 36 patients.

Table 23. Patients Receiving On-Demand Prophylaxis (ODP) with Higher Number of Bleeding Events on Study Compared to Bleeding History (Part II of Study 984)

Subject Identifier	Age	Bleed History n	Bleeds on Study n	Time Frame of Study Participation	Details of Bleeds on Study n
(b) (6)	34	7	10	3 years	<ul style="list-style-type: none"> • Surgery: 8¹ • Spontaneous: 1 • Post-traumatic: 1
(b) (6)	46	7	11	4 years	<ul style="list-style-type: none"> • Surgical: 10² • Spontaneous bleed: 1
(b) (6)	13	3	7	5 years	<ul style="list-style-type: none"> • Surgery: 3 • Post-traumatic: 4

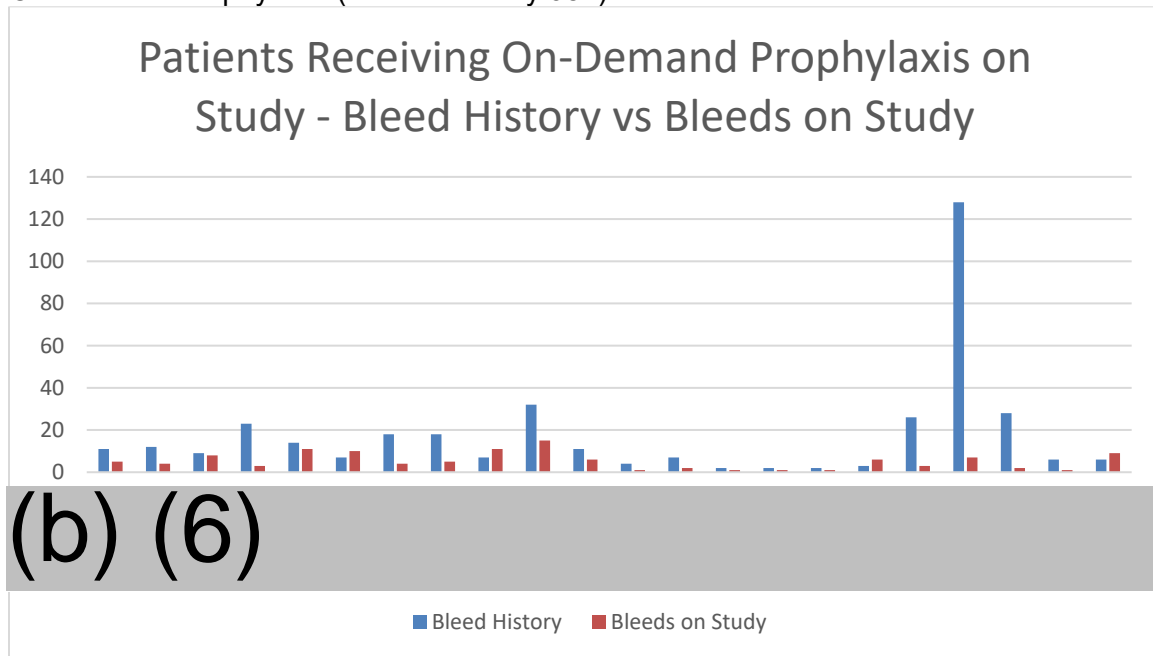
(b) (6)	6	3	10	2 years	<ul style="list-style-type: none"> • Spontaneous bleed: 1 • Post-traumatic: 7 • Other: 1 (mouth bleed)
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¹FESILTY was administered as ODP for 8 surgical bleeding events for patient (b) (6)

²FESILTY was administered as ODP for 10 surgical bleeding events for patient (b) (6)

Abbreviations: n=number of bleeds/bleeding events.

Figure 4. Bleed History Compared to Bleeding Events on Study for Patients Receiving On-Demand Prophylaxis (Part II of Study 984)



Reviewer comment: There were three patients in the overall population receiving ODP or ODT with higher number of bleeds on study compared to previous bleeding history. However, one adult patient had higher number of bleeds on study due to surgeries and only 1 spontaneous bleed. The other two patients were pediatric (age 6 for both patients). It is to be expected to report spontaneous or post-traumatic bleeds in this population due to their young age (eg, would expect more trauma in patients of younger age with congenital fibrinogen deficiency and due to length of time on the study).

There were 4 patients who received ODP who had higher number of bleeding events on study compared to their bleeding histories. For the adult patients, FESILTY was administered as ODP for surgical bleeding event. For the two pediatric patients, they had higher numbers of post-traumatic bleeds which can be expected due to their young age, length of time on study and potential for traumatic bleeding events in the pediatric population.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

There were 45 total subjects for trial 984 (part I and II). There were 43 (96%) patients with afibrinogenemia and 2 (4%) patients with hypofibrinogenemia. There were 582

bleeding events prior to enrolling onto trial 984. The mean total number of bleeds was 12.93. The majority of previous bleeding events prior to enrollment were oral cavity bleeding (31 events), umbilical cord bleeding (31 events), epistaxis (22 events), muscle hematoma (21 events), and hemarthrosis (20 events).

6.1.10.1.3 Subject Disposition

For trial 984, there were 27 patients who participated in part I, 36 patients who participated in part II with a total of 45 patients participating in the study overall. There were 18 patients who participated in both part I and II of trial 984 and 45 patients overall for parts I and II.

6.1.11 Efficacy Analyses

Primary Endpoints: Pharmacokinetics (PK) of FESILTY

Pharmacokinetics parameters were derived from time concentration profiles using adapted methodology (non-compartmental analysis (NCA), compartment analysis, or population modeling, as appropriate/ required).

Single-dose PK of FiAg was assessed in part I by the following parameters: Terminal Elimination Half-life ($t_{1/2}$), Time to Maximum Concentration (t_{max}), Maximum Concentration (C_{max}), Area Under the Curve (AUC) calculated to the last measured concentration (AUC_{0-tz}), beyond last concentration (AUC_{extr}), and extrapolated to infinity ($AUC_{0-\infty}$), Area Under the first Moment Curve (AUMC) calculated to the last concentration ($AUMC_{0-tz}$) and extrapolated to infinity ($AUMC_{0-\infty}$), First-order terminal elimination rate constant (λ), Clearance (CL) and CL per kg BW, Mean Residence Time (MRT) extrapolated to infinity ($MRT_{0-\infty}$), Volume of distribution at presumed steady-state (V_{dss}) and V_{dss} per kg BW, Incremental Recovery (IR), and Classical in vivo Recovery (CIR).

Secondary Endpoints: Pharmacodynamics (PD) of FESILTY

Single-dose PD of FiAc was assessed by the same parameters as listed for the PK assessment of FiAg, including $t_{1/2}$, t_{max} , C_{max} , AUC_{0-tz} , $AUC_{0-\infty}$, AUC_{extr} , $AUMC_{0-tz}$, $AUMC_{0-\infty}$, λ , CL, CL per kg BW, $MRT_{0-\infty}$, V_{dss} , V_{dss} per kg BW, IR, and CIR.

Efficacy Endpoints:

Surrogate Efficacy

- Maximum clot firmness (MCF, mm) measured by rotational thromboelastometry was assessed as a surrogate efficacy parameter in study parts I and II.

Clinical Efficacy: The following efficacy endpoints were assessed in part II:

- Overall hemostatic response (OHR) to treatment with FESILTY for each surgical procedure and each treated bleed as assessed by the investigator according to a 4-point scale: "none", "moderate", "good" or "excellent".
- Total loss of blood (e.g., intra- and post-operatively, re-bleedings), if applicable.
- Units of other fibrinogen-containing products (FCP) infused besides FESILTY e.g., fresh frozen plasma (FFP) or cryoprecipitate.
- Units of transfusion products (TPs) infused e.g., allogenic or autologous blood (packed red blood cells (RBCs), fresh whole blood), platelets.

- Consumption of FESILTY (dose per kilogram BW required pre-, intra- or post-operatively for effective treatment).
- Quality of wound healing, if applicable.

Safety Endpoints:

- Adverse events
- Fibrinogen inhibitory antibodies
- Vital signs e.g., blood pressure, heart rate, body temperature
- Physical examination
- Electrocardiogram recordings
- Clinical laboratory assessments of hematology, clinical chemistry, and urine analysis
- Coagulation parameters: prothrombin time (PT) (international normalized ratio [INR]), activated partial thromboplastin time (aPTT), thrombin-antithrombin-III-complex (TAT), prothrombin fragment 1 and 2 (F1+2), D-dimer
- Ultrasonography
- Viral safety

6.1.11.1 Analyses of Primary Endpoint(s)

The discussion of the primary endpoint of pharmacokinetics is reported in section 4.4.2 Pharmacokinetics.

6.1.11.2 Analyses of Secondary Endpoints

The discussion of secondary endpoint of pharmacodynamics (PD) is reported in sections 4.4.3 and 4.4.3.

There were 36 patients with a total of 175 bleeding events evaluable for the efficacy endpoint in part II of the trial. The mean age was 18 with a range of ages between 1 and 46. There were 3 (8.3%) subjects <6 years, 9 (25%) subjects aged 6 to <12 years, 4 (11.1%) subjects aged 12 to <18 years and 20 (55.6%) subjects aged 18 to 75 years.

Maximum Clot Firmness

Maximum Clot Firmness (MCF) was evaluated as a surrogate efficacy endpoint in part I and II. In Part I, MCF was measured pre-dose and at the following timepoints per age group: 1h and 8h after end of infusion (Eol) in patients ≥ 6 years; 1 h after Eol in children between 2 and < 6 years of age, and at Eol for children < 2 years. Descriptive statistics for MCF part I data also include changes from pre-dose baseline.

MCF values assessed as “not measurable” by the central laboratory were set to half the range below the detection limit (ie, value of 1mm).

Table 24 shows the MCF values for part I from the full analysis set (FAS I). Of note, there was 1 subject in each age group of 6-12 years and 12-18 years without a pre-dose MCF value. There were 3 subjects in age group 18 to 75 years without a pre-dose MCF value. Change at 1 hour values were not calculated for patients who did not have a pre-

dose value. Eol values were not obtained for patients aged ≥ 6 years. The change in MCF 1 hour after Eol ranged between 9.3 to 16.5mm in children and adolescents <18 years and 15 mm in adults ($p < 0.0001$). The change in MCF 8 hours after Eol ranged between 9-11.5mm in children and 11.3mm in adults ($p < 0.0001$). P values and 95%CI of pre-post changes of MCF could not be calculated in the pediatric populations due to small number of patients. For FAS part I, there are 3 subjects <6 years of age with values for 1 hour after Eol: (b) (6) with values 6, 16, and 7 with mean of 9.66. The change at 1 hr values are 5, 15 and 6 with mean of 8.66.

Table 24. Mean Maximum Clot Firmness (mm) and Changes from Pre-Dosing Values (Part I, FAS I)

	Statistic	<6 years, n=6	6-12 years, n=3	12-18 years, n=3	>18 years, n=15
Pre-dose	n	6	2	2	12
	mean (SD)	1.0 (0)	1.0 (0)	1.0 (0)	1.2 (0.58)
Eol	n	3	0	0	0
	mean (SD)	7 (5.29)	n/a	n/a	n/a
1 hr after Eol	n	3	3	3	15
	mean (SD)	10.3 (1.53)	16 (3.61)	10.7 (3.06)	13.1 (4.62)
8 hr after Eol	n	0	3	3	14
	mean (SD)	n/a	11.7 (2.08)	8.7 (2.52)	12.7 (4.68)
Change at Eol	n	3	0	0	0
	mean (SD)	6.0 (5.29)	0	0	0
Change 1 hour after Eol	n	3	2	2	12
	mean (SD)	9.33	16.5 (3.54)	11 (2.83)	11.1 (5.07)
	p value	n.e.	n.e	n.e	<0.0001
	95% CI				9.33; 14.47
Change 8 hr after Eol	n	0	2	2	11
	mean (SD)	n/a	11.5 (2.12)	9.0 (1.41)	11.3 (5.08)
	p value	n/a	n.e	n.e	<0.0001
	95% CI	n/a			8.83; 14.26

Abbreviations: FAS = full analysis set; n = number of patients; Eol = end of infusion; hr = hours; n.e = not evaluable; n/a = not applicable; CI = confidence interval.

Source: FDA analysis of ADLB, ADSL datasets; clinical study report of Study 984.

In part II, the mean overall change for in MCF in all age groups was 13.44 (range -17 to 70). One patient (ID# (b) (6)) had discrepancies in the MCF values, where the pre-dose value was listed as 18mm and the post-dose value was <2 mm. The applicant noted in the Clinical Study Report (11.1.3.1 Maximum Clot Firmness) assumed that the values were mixed up. See **table 25**.

Table 3. Mean Change in Maximum Clot Firmness (MCF) in Part II (FBE)

Change in MCF	Value (mm)
Mean change in MCF	10.76

Range	-17* to 27
-------	------------

Abbreviations: FBE = Full Bleeding Event set; mm = millimeters.

* There was one patient with pre-dose value of 18mm and post-dose value <2mm.

In part II, the MCF was measured pre-dose and 1 h after Eol, including repetitive infusions per bleeding event. Descriptive statistics for MCF in part II including changes from pre-dose (baseline) were provided per age group for FBE and PPBE. In table 34, Mean Maximum Clot Firmness (mm) and Pre-Post Changes for Bleeding Events in Part II (FBE) of the Clinical Study Report, there are missing pre-dose values for 1 subject <6 years of age, 4 subjects aged 6-12, 5 subjects aged 12-18, and 33 subjects aged >18 years. Per the statistical analysis plan, MCF as a surrogate efficacy will be evaluated by means of non-confirmatory t-test(s) pre/post comparison plus correlation between MCF and fibrinogen activity. A p-value was not calculated for age group <6 due to small number of subjects (4). The mean change at 1 hr after Eol was 3mm, 43mm (p <0.0001), 26mm (p <0.0001) and 56mm (p<0.0001) for age groups <6, 6-12 years, 12-18 years and >18 years respectively. See **table 26**.

Table 26. Mean Maximum Clot Firmness (mm) and Pre-Post Changes for Bleeding Events in Part II (FBE)

Time Point	Statistic	<6 years n=4	6-12 yrs n=47	12-18 yrs n=32	>18 years n=92
Pre-dose	N	3	43	27	59
	mean	1	1	1	2.1
1hr after Eol	N	4	47	31	82
	mean	10.8	11.7	11.3	12.7
Change at 1h after Eol	N	3	43	26	56
	mean	8.7	11.1	9.8	11.1
	p value	n.e	<0.0001	<0.0001	<0.0001
	95% CI		9.27, 12.09	8.27; 12.31	9.08; 12.25

Abbreviations: FBE = Full Bleeding Event set; mm = millimeters; hr = hour; Eol = end of infusion; n = number of patients; N = number of bleeding events; CI = confidence interval; n.e = not evaluable.

Subjects were evaluated for mean MCF pre and post changes in major and minor bleeding events treated with FESILTY for on-demand prophylaxis (ODP) and on-demand treatment (ODT). P-values were not calculated for subjects <18 years of age for ODP analysis due to small numbers of subjects. For adults treated with ODP, the mean change for major bleeds 1 hr after Eol was 17mm (p value <0.0001) and the mean change for minor bleeds 1 hr after Eol was 14 (p value 0.0002). **See table 27**.

Table 27. Mean Maximum Clot Firmness (mm) and Pre-Post Changes in Major and Minor Bleeding Events Treated with FESILTY for On-Demand Prophylaxis in Part II (FBE)

Event	Time Point	Statistic	<6 years n=2	6-12 yrs n=5	12-18 yrs n=1	>18 years n=52
Major Bleeds	Pre-dose	N	1	1	0	18
		Mean	1	1	n/a	1

	1 hr after Eol	N	1	1	0	26
		Mean	16	22	n/a	13.6
	Change at 1hr after Eol	N	1	1	0	17
		Mean	15	21	n/a	11.8
		p-value	n.e.	n.e.	n.e.	<0.0001
		95% CI				10.66; 14.49
Minor Bleeds	Pre-dose	N	1	4	1	14
		Mean	1	1	1	3.5
	1 hr after Eol	N	1	4	1	20
		Mean	7	13	16	13
	Change at 1hr after Eol	N	1	4	1	14
		Mean	6	12	15	9.6
		p-value	n.e.	n.e.	n.e.	0.0002
		95% CI				4.86; 14.04

Abbreviations: FBE = Full Bleeding Event set; mm = millimeters; hr = hour; Eol = end of infusion; n = number of patients; N = number of bleeding events; CI = confidence interval; n/a = not applicable.

For ODT, subjects <6 years and subjects age 6-12 for major bleeds were not evaluated with p-value due to small number of subjects (n=2 and n=2, respectively). The comparisons of pre-post MCF values for ODT showed p-values <0.0001 in adults and other age groups (except p-value of 0.0016 for age group 12-18 for major bleeds). See **table 28**.

Table 28. Mean Maximum Clot Firmness (mm) and Pre- Post Changes in Major and Minor Bleeding Events Treated with FESILTY for On-Demand Treatment

Event	Time Point	Statistic	<6 years n=2	6-12 yrs n=42	12-18 yrs n=31	>18 years N=40
Major Bleeds	Pre-dose	N	1	2	6	11
		Mean	1	1	1	1
	1 hr after Eol	N	1	2	5	12
		Mean	6	13.5	12.2	12.7
	Change at 1hr after Eol	N	1	2	5	10
		Mean	5	12.5	11.2	12
		p-value	n.e.	n.e.	0.0016	<0.0001

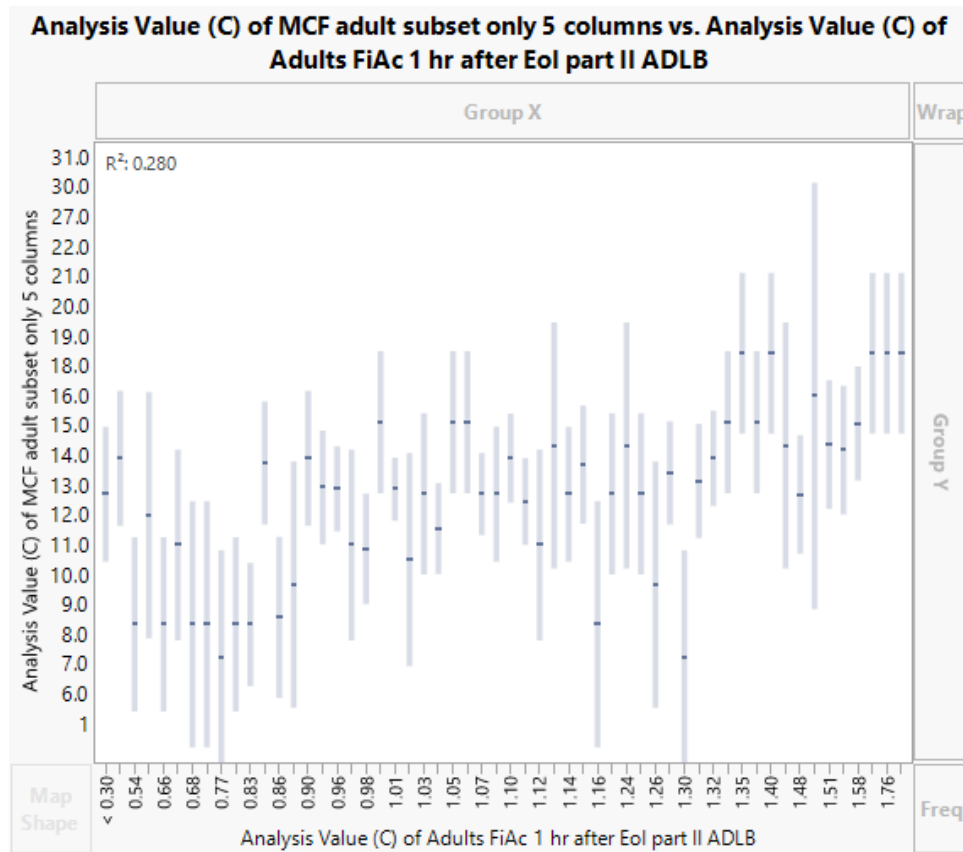
		95% CI			7.14; 15.26	9.36; 13.97
Minor Bleeds	Pre-dose	N	0	36	20	16
		Mean	n/a	1	1	2.7
	1 hr after Eol	N	1	40	25	24
		Mean	14	11.2	10.9	11.6
	Change at 1hr after Eol	N	0	36	20	15
		Mean	n/a	10.6	9.2	11.1
		p-value	n.e.	<0.0001	<0.0001	<0.0001
		95% CI		8.70; 11.70	7.48; 12.36	5.22; 12.65

Abbreviations: FBE = Full Bleeding Event set; mm = millimeters; hr = hour; Eol = end of infusion; n = number of patients; N = number of bleeding events; CI = confidence interval; n.e. = not evaluable; n/a = not applicable.

There were correlation analyses of MCF and FiAC levels at pre-dose and 1 hr after Eol of FESILTY in part II which showed positive correlation. See **figure 5**.

Furthermore, correlation analyses of MCF and FiAc levels at pre-dose and 1 h after Eol of FESILTY demonstrated a positive correlation of these parameters at both time points in part II (Pearson's correlation coefficients for FBE: 0.3395 at pre-dose and 0.4707 at 1 h after Eol for bleeding events in adults; and 0.2528 at pre-dose and 0.5551 at 1 h after Eol for all bleeding events in total), thus indicating a positive relationship between MCF and FiAc levels prior to and after dosing with FESILTY. Similar results were obtained for PPBE (Pearson's correlation coefficients for PPBE: 0.2798 at pre-dose and 0.4932 at 1 h after Eol for bleeding events in adults; and 0.2024 at pre-dose and 0.5748 at 1 h after Eol for all bleeding events in total.).

Figure 5. Correlation of MCF and Fibrinogen Activity



Reviewer comment: It is important to note that one patient (ID# (b) (6)) had discrepancies in the MCF values, where the pre-dose value was listed as 18mm and the post-dose value was <2mm. The applicant noted in the Clinical Study Report (11.1.3.1 Maximum Clot Firmness) assumed that the values were mixed up. However, they included the patient in the final analysis as they felt that this finding would not affect the overall result.

An information request was sent on April 11, 2025 to inquire on further information regarding central laboratory testing for trial 984. Local lab collection was only feasible for 2 of the 6 sites. MCF (b) (4) testing was otherwise performed centrally and these values were used in the final data analysis. (b) (4) /MCF testing was performed in a central lab in (b) (4). The timeframe between collection and availability of MCF results was around 2 months. Samples were prepared by being centrifuged at room temperature and then frozen shortly post-processing at -70 to -80 degrees Celsius. Frozen samples were shipped within 2 months of sample collection to Germany. The Applicant noted that this process was used in other clinical trials.

A formal method validation for (b) (4) /MCF analysis was conducted in 2013 at (b) (4). The validation was commissioned by Biotest specifically for the use of frozen citrated plasma samples analyzed centrally for this study. The MCF citrated plasma (b) (4) validation report is included in the information request. The

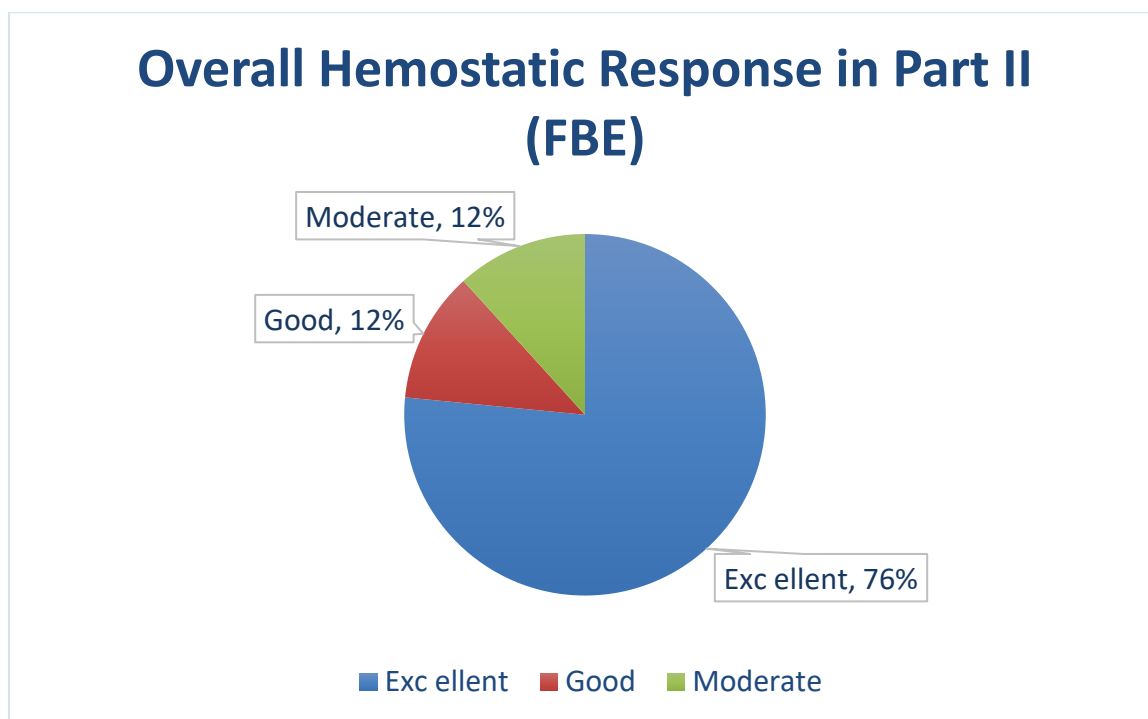
Applicant also noted that frozen samples were also utilized in Schoergenhofer, et al. Clin. Exp Med, 2017.

Overall Hemostatic Response

Overall hemostatic response to treatment with FESILTY per surgical procedure and treated bleeding event was rated on a 4-point scale ("none", "moderate", "good" or "excellent") and in addition for the sum of good and excellent ratings defined as "success" in the analysis.

Overall hemostatic response for the overall population (45 patients) in part II was assessed as excellent in 150 (85.71%) bleeding events, good in 23 (13.14%) bleeding events and moderate in 2 (1.14%) bleeding events, shown in **figure 6**.

Figure 6. Investigator's Assessments of Overall Hemostatic Response to All Bleeding Events in Part II (FBE)



Source: FDA analysis of ADBL, ADSL datasets. Abbreviation: FBE = Full Bleeding Event set.

OHR was assessed as excellent in 4 (100%) of bleeding events in patients <6 years, 40 (85.11%) of bleeding events in patients aged 6 to <12 years, 32 (100%) of bleeding events in patients aged 12 to <18 years and 74 (80.43%) bleeding events in patients >18 years, shown in **table 29**.

Table 4. Overall Hemostatic Response (OHR) for All Bleeding Events in Part II (FBE)

Investigator Assessment of OHR	<6 years n (%)	6 to <12 years n (%)	12 to <18 years n (%)	>18 years n (%)	Overall Population n=175

					n (%)
N	3	9	5	19	36
Excellent	4 (100.0)	40 (85.11)	32 (100.0)	74 (80.43)	150 (85.71)
Good	0	7 (14.89)	0	16 (17.39)	23 (13.14)
Moderate	0	0	0	2 (2.17)	2 (1.14)
None	0	0	0	0	0

Abbreviations: OHR = overall hemostatic response; FBE = Full Bleeding Event analysis; N=number of patients. n = number of bleeding events; % = percentage of bleeding events.

Administration of Other Fibrinogen Containing Products (FCPs)

There were no instances of fibrinogen containing products (FCPs) used at the day of FESILTY infusion or up to 1 day after FESILTY administration. Individuals who received other FCPs in part II outside of the time window from FESILTY administration to 1 day after infusion include 50 instances in 17 subjects of fibrinogen containing products given at other time periods including screening, or at least 1 day after FESILTY was given, see **table 30**.

Table 30. Administration of Fibrinogen Containing Products Given on Event Level - FBE

Fibrinogen Containing Product (FCP)	Number of Occurrences of FCPs Given
Haemocomplettan	45
Clotafact	1
Cryoprecipitate	1
Fresh frozen plasma	3

Abbreviations: FBE = Full Bleeding Event set.
Source: ADCM dataset for FBE

Transfusion of Other Blood Products

Units of other transfusion products (TPs) used for treatment of bleeding events at the day of FESILTY or up to 1 day after FESILTY administration were analyzed in the FBE and PPBE. The Clinical Study Report notes 2 (1.1%) occurrences of other blood products (red blood cells) being transfused in 2 subjects on the day of or within 1 day after FESILTY infusion. One subject aged 18-75 was given 1 unit of red blood cells (RBCs) post-operatively, and another subject aged 6-12 years was given 1 unit RBCs before splenectomy. Both of these occurrences were included in both the FBE and PPBE analysis. See **table 31**.

Table 5. Number of Other Transfusion Products Given – Full Bleeding Event Set (FBE)

	Age <6 years N=4 n (%)	6-<12 years N=47 n (%)	12-<18 years N=32 n (%)	18-75 years N=92 n (%)	Overall N=175 n (%)
Other TPs administered		1 (2.1)	0	0	2 (1.1)
Red blood cells	0	1 (2.1)	0	0	1 (0.6)
Red blood cells, concentrated	0	0	0	1 (1.1)	1 (0.6)

Abbreviations: FBE = Full Bleeding Event set; N=number of patients.

Source: Table 14.2.2.3.1 and table 14.2.2.3.3 of the Clinical Study Report for Study 984, Dataset ADCM, ADBL

FESILTY Consumption for Treated Surgeries

Descriptive analysis of FESILTY consumption for treatment of surgical bleeding events in part II was based on the total dose of FESILTY (mg/kg BW and mg/event) administered pre-operatively, post-operatively, and per surgical event in the FBE and PPBE.

For the overall population, there were 54 bleeding events, with the mean pre-operative value 60.09 mg/kg body weight (BW), mean post-operative value 118.60 mg/kg BW, mean value 75.47 mg/kg BW per surgery and 4996.48 mg per surgery.

There were three patients with dosing outside of the usual range. One patient (identifier (b) (6)) received 381.58mg/kg BW post-operatively and a total 35000.00 mg of FESILTY for the bleeding event on (b) (6) for left elbow synovectomy. Baseline weight was 78.50kg and BMI 24.78. Treatment was administered as on-demand prophylaxis with moderate bleeding and no re-bleeding. Total blood loss was 520ml and within expected range per the investigator. A second patient (b) (6) received FESILTY for on-demand prophylaxis for a surgical bleeding event for anal fissures on (b) (6). The baseline weight was 88kg and BMI 28.41. The bleeding was classified as severe, with excellent hemostatic response, and the investigator reported excellent wound healing. Total blood loss was listed as none. They received total dose of 12000mg. The third patient (b) (6) was treated with FESILTY for on-demand prophylaxis for splenectomy on (b) (6). The hemostatic response was excellent and total blood loss was 500ml and considered by the investigator as within expected range. See **table 32** for FESILTY consumption for treated surgeries in the overall population.

Table 32. Overall Population - Consumption of FESILTY for Treated Surgeries in Part II (FBE)

	Statistic	Overall (All Ages) n=21
Pre-operative (mg/kg BW)	N	54
	Mean	60.09
	Median	53.54
	Min	40.00
	Max	100.00
Post-operative (mg/kg BW)	N	7
	Mean	118.60
	Median	70.00
	Min	41.67
	Max	381.58
Per surgery (mg/kg BW)	N	54
	Mean	75.47
	Median	53.55
	Min	40.00
	Max	460.53
Per surgery	N	54

(mg)	Mean	4996.48
	Median	4000.00
	Min	1000.00
	Max	35000.00

Abbreviations: FBE = Full Bleeding Event set; n=number of patients; N=number of bleeding events; min=minimum value; max=maximum value; mg=milligrams; kg=kilograms; BW=body weight.

The number of surgical bleeding events was lower in the pediatric population compared to adults. Total doses of FESILTY for surgeries were higher for children and adolescents, which was expected due to low number of surgical bleeding events in that age group and variability in incremental recovery. See **table 33** for FESILTY consumption for treated surgeries in the overall population.

Table 33. Consumption of FESILTY for Treated Surgeries in Part II (FBE)

	Statistic	<6 years N=2	6 to <12 years N=2	12 to <18 years N=1	>18 years N=49
Pre-operative (mg/kg BW)	N	2	2	1	49
	Mean	83.33	75.71	71.43	58.28
	Median	83.33	75.71	71.43	53.19
	Min	66.67	71.43	71.43	40.00
	Max	100.00	80.00	71.43	97.66
Post-operative (mg/kg BW)	N	1	2	0	4
	Mean	100.00	69.88	-	147.61
	Median	100.00	69.88	-	83.59
	Min	100.00	69.77	-	41.67
	Max	100.00	70.00	-	381.58
Per surgery (mg/kg BW)	N	2	2	1	49
	Mean	133.33	145.60	71.43	70.33
	Median	133.33	145.60	71.43	53.19
	Min	66.67	141.60	71.43	48.39
	Max	200.00	150.00	71.43	70.00
Per surgery (mg)	N	2	2	1	49
	Mean	1500.000	3340.000	2000.00	5267.96
	Median	1500.000	3340.000	2000.00	4000.00
	Min	1000.000	3000.000	2000.00	3000.00
	Max	2000.000	3680.000	2000.00	35000.00

Abbreviations: FBE = Full Bleeding Event set; N=number of bleeding events; min=minimum value; max=maximum value; mg=milligrams; kg=kilograms; BW=body weight.

Reviewer comment: Information request was sent regarding discrepancies in the total number of surgical events in the dataset. There were 4 patients whose 5 bleeding events were classified in the ADEX dataset as being given FESILTY pre-operatively, but their category on the Bleeding Level dataset was classified as “other” and “post-traumatic.” These four patients (b) (6) had reported terms of pleural effusion (1), cutaneous wound (1), chronic gingivitis (1), and tooth extraction (2).

Wound Healing

Wound healing was assessed in part II by the investigator as none, moderate, good or excellent per bleeding event if applicable and were analyzed descriptively. For the overall population, there were 175 bleeding events in the Full Bleeding Event set (FBE). For the overall population, the majority of wound healing associated with bleeding events was classified as not applicable (77.7%), good (12%) or excellent (8.6%). There were no bleeding events with wound healing classified as “none,” and three events classified as moderate. For minor bleeds, the wound healing was classified as excellent or good (13.1-9%), though most bleeding events were not applicable (77.9%). For major events, the majority of bleeding events were not applicable (77.4%), good (9.4%) or excellent (7.5%). Assessments of wound healing from minor and major bleeding events are shown in **table 34**.

Table 34. Wound Healing (FBE)

	<6 years N=4 n (%)	6 to <12 years N=47 n (%)	12 to <18 years N=32 n (%)	>18 years N=92 n (%)	Overall N=175 n (%)
All Events (N)	4	47	32	92	175
None					
Moderate				3 (3.3)	3 (1.7)
Good	1 (25.0)	4 (8.5)	1 (3.1)	15 (16.3)	21 (12.0)
Excellent	2 (50.0)	5 (10.6)		8 (8.7)	15 (8.6)
Not applicable	1 (25.0)	38 (80.9)	31 (96.9)	66 (71.7)	136 (77.7)
Minor Events					
All Events (N)	2	44	26	50	122
None					
Moderate					
Good	1 (50.0)	4 (9.1)	1 (3.8)	10 (20.0)	16 (13.1)
Excellent	1 (50.0)	4 (9.1)			11 (9.0)
Not applicable		36 (81.8)	25 (96.2)	34 (68.0)	95 (77.9)
Major Events					
All Events (N)	2	3	6	42	53
None					
Moderate				3 (7.1)	3 (5.7)
Good				5 (11.9)	5 (9.4)
Excellent	1 (50.0)	3		2 (4.8)	4 (7.5)
Not applicable	1 (50.0)	2	6 (100.0)	32 (76.2)	41 (77.4)

Abbreviations: FBE=Full Bleeding Event set; N=Total number of bleeding events per category; n=number of bleeding events; %=percentage.

Wound healing was comparable for patients with on-demand treatment (ODT) or on-demand prophylaxis (ODP), noted in **table 35**. The majority of bleeding events did not have accessible wounds (not applicable). Wounds that were accessible for healing were mostly reported as excellent or good.

Table 6. Wound Healing in Part II (FBE)

Wound healing	On-demand prophylaxis	On-demand treatment
Total bleeding events, N	60	115
Moderate n (%)	3 (5.0)	0
Good	11 (18.3)	10 (8.7)
Excellent	11 (18.3)	4 (3.5)
Not applicable	35 (58.3)	101 (87.8)

Abbreviations: FBE=Full Bleeding Event set; N=Total number of bleeding events per category; n=number of bleeding events; %=percentage of total bleeding events.

Total Loss of Blood

Investigator's assessments of total loss of blood per surgical event were analyzed descriptively. Total loss of blood was described as "lower than expected," "within expected range," and "higher than expected." The majority of surgical bleeding events in the FBE subset had blood loss within the expected range (n=45, 83.3%), followed by 4 events with higher than expected blood loss (7.4%), and 3 (5.6%) events with lower than expected blood loss, noted in **table 36**. The four bleeding events with higher than expected blood loss were reported in 3 adult patients for dental (3) and gingival (1) surgeries. Three surgical bleeding events had excellent hemostatic response, and one event had good response. For the pediatric population, all surgical bleeding events in the FBE and PPBE subsets had total blood loss within expected ranges.

Table 36. Total Loss of Blood for Surgical Bleeding Events by Age (FBE)

	<6 years N=2 n (%)	6 to <12 years N=2	12 to <18 years	>18 years N=	Total Events n (%)
Lower than expected blood loss n (%)	0	0	0	3 (6.1)	3 (5.6)
Within expected blood loss n (%)	2 (100.0)	2 (100.0)	1 (100.0)	40 (81.6)	45 (83.3)
Higher than expected blood loss n (%)	0	0	0	4 (8.2)	4 (7.4)
Missing values n (%)	0	0	0	2 (4.1)	2 (3.7)

Abbreviations: FBE=Full Bleeding Event set; N=Total number of bleeding events per category; n=number of bleeding events; %=percentage of total bleeding events.

Reviewer comment: The numbers of bleeding events accessible for blood loss in pediatrics was low compared to adults. However, all pediatric patients had blood loss

within expected range. The majority of adults had blood loss within expected range (83.3%) during surgical bleeding events.

6.1.11.3 Subpopulation Analyses

For analyses, patients were assigned to the following age subgroups for all data listed in section 6.1.11.2 including: Adults (18 to 75 years), adolescents (12 to < 18 years), children (6 to < 12 years), and children < 6 years. No additional subpopulation analyses were performed.

6.1.11.4 Dropouts and/or Discontinuations

There were four (8.9%) out of 45 patients in parts I and II who discontinued the study prematurely due to adverse events (AEs). All patients were adults. One patient (3.7%) discontinued part I due to pain in the extremity four days after administration of FESILTY. This AE was considered severe. The patient had pain and coldness of the toes and had evaluation for thrombosis, which was non-revealing. The study medication was withdrawn and the AE was considered resolved 2.5 months later. Three (8.3%) patients in part II discontinued the study due to portal vein thrombosis, deep vein thrombosis and pregnancy. For patient (b) (6), portal vein thrombosis occurred 3 days after on-demand prophylactic FESILTY administration for splenectomy. For patient (b) (6), deep vein thrombosis occurred 9 days after FESILTY was given for prevention after spontaneous intracerebral hematoma. This was assessed by the investigator as possibly related to history of smoking, immobilization and afibrinogenemia. Patient (b) (6) reported pregnancy 11 months after FESILTY administration. The patient was withdrawn from the study and there were no reported complications from the pregnancy.

One patient died after diagnosis of extradural hematoma after an epileptic episode. They received a dose of FESILTY one month prior to the adverse event.

Reviewer comment: The number of patients who discontinued the study were 8.9% due to possible thrombotic event, two thrombotic events and pregnancy. Thrombosis is a known risk of fibrinogen administration. Other risk factors may have predisposed these patients to developing thrombosis as well.

6.1.11.5 Exploratory and Post Hoc Analyses

Not applicable.

6.1.12 Safety Analyses

6.1.12.1 Methods

AEs were coded with MedDRA version 23.0.

The analysis of adverse events (AEs) was focused on treatment emergent adverse events (TEAEs, defined as any AE that occurred or worsened on or after the first IMP administration and until the last study visit per study part) and was performed for both safety analysis set (SAF) I and SAF II. There were 45 patients in the safety analysis set.

All TEAE analyses were based on the SAF per study part. For part I, TEAEs were reported as occurring from the time of administration of single dose of FESILTY for assessment until day 49. For part II, TEAEs were reported between the time of FESILTY administration in a bleeding event until day 49. TEAEs reported outside of those time frames were only counted in the APE I and II and presented in the patient listings.

TEAE severity was reported as mild, moderate or severe.

6.1.12.2 Overview of Adverse Events

In the overall safety population including parts I and II of the study, there were 174 treatment emergent adverse events (TEAEs) in 33 patients (73.3%), with 9 (20%) of patients experiencing serious adverse events (SAEs). There was 1 (2.8%) patient with SAE of extradural hematoma leading to death. See **table 37** for details.

Table 37. Overview of Adverse Events

Type of Adverse Event		Part I N=27	Part II N=36	Overall N=45
TEAEs	N (%) n	15 (55.6) 31	27 (75.0) 143	33 (73.3) 174
SAEs	N (%) n	2 (7.4) 3	7 (19.4) 9	9 (20.0) 12
TEAEs leading to study discontinuation	N (%) n	1 (3.7) 1	3 (8.3) 3	4 (8.9) 4
AEs leading to death	N (%) n	0	1 (2.8) 1	1 (2.8) 1

Abbreviations: TEAE=treatment emergent adverse event; SAE=serious adverse event; AE=adverse event; N=number of patients; n=number of adverse events; %=percentage

Per the clinical reviewer assessment, most AEs were moderate (58%) or mild (53%), and only 29% of AEs were severe, see **table 38**.

Table 38. AEs by Severity for Study 984

Severity of AE	N=45 n (%)
Mild	24 (53)
Moderate	26 (58)
Severe	13 (29)
Unknown	1 (2)

Abbreviations: N=total number of patients in safety analysis; n=number of patients with AE; %=percentage.

Source: FDA analysis, ADAE dataset.

Per the applicant, TEAEs considered related to FESILTY included 3 events of pyrexia, fibrin D-dimer increased and pruritic.

Per the clinical reviewer assessment, the most related or possibly related common adverse reactions of all severities occurring in >2% of patients included pain in extremity, back pain, and swelling of the face (hypersensitivity), shown in **table 39**.

Table 397. Most Common Adverse Reactions (All Severities) Occurring in >2% of Patients in Study 984

Adverse Reaction	N=45 n (%)
Pain in extremity	3 (7)
Back pain	3 (7)
Hypersensitivity reactions ¹	3 (7)
Pyrexia	2 (4)
Thrombosis ²	2 (4)
Fibrin D dimer increased	2 (4)
Headache	2 (4)
Vomiting	2 (4)

¹Thrombosis includes portal vein thrombosis and deep vein thrombosis.

²Hypersensitivity reactions = all patients had adverse reactions of facial swelling.

Source: FDA analysis of ADAE, ADSL datasets.

Abbreviation: N=total number of patients; n = number of patients with at least 1 AE; % = percentage of patients.

Per the clinical reviewer assessment, the most common adverse reactions occurring in >2% of patients (moderate and severe events) which were considered related or possibly related included pain in extremity (7%), back pain (7%), and hypersensitivity reactions (7%), shown in **table 40**.

Table 40. Most Common Adverse Reactions (Moderate and Severe) Occurring in >2% of Patients in Study 984

Adverse Reaction	N=45 n (%)
Pain in extremity	3 (7)
Back pain	3 (7)
Hypersensitivity reactions ¹	3 (7)
Headache	2 (4)
Thrombosis ²	2 (4)
Vomiting	1 (2)
Extradural hematoma	1 (2)
Epilepsy	1 (2)

¹Thrombosis includes portal vein thrombosis and deep vein thrombosis.

²Hypersensitivity reactions = all patients had adverse reactions of facial swelling.

Abbreviations: n=number of patients with at least 1 adverse event; %=percentage.

Reviewer comment: The applicant proposed including adverse reactions of deep vein thrombosis, pruritic and pyrexia in the draft United States Prescribing Information (USPI). Per the clinical reviewer assessment, the most common adverse reactions and

common reactions (moderate and severe intensity) listed above in tables 39 and 40 include AEs that were thought to be related or possibly related based on FDA adjudication. Per the clinical reviewer assessment, AEs were assessed as related or possibly related to FESILTY based on both temporal relationship and biologic plausability. In general, the time window utilized was dependent upon the clinical event and usually within 30 days of FESILTY administration. AEs of all severities reported in >2% of patients were included in the USPI.

6.1.12.3 Deaths

One patient death was reported in this trial related to extradural hematoma. The patient had received FESILTY in part I for PK analysis and enrolled onto part II of the trial. The patient also received FESILTY in part II of the study as ODP for two surgical bleeding events (surgical synovectomy of left elbow and dental extraction). Four weeks after last FESILTY dose, the patient had an episode of epilepsy and diagnosed with extradural hematoma. The patient underwent emergency evacuation of the hematoma; however, the patient went into a coma and subsequently died 3 weeks after the event.

Reviewer comment: There was 1 death in the study. The patient was diagnosed with epileptic event and extradural hematoma 30 days after FESILTY administration. The patient was treated with surgery for extradural hematoma but was not administered FESILTY or other fibrinogen products.

6.1.12.4 Nonfatal Serious Adverse Events

The applicant reported 9 (20%) patients experiencing serious adverse events (SAEs), shown in **table 41**.

Per the clinical reviewer assessment, there were 5 SAEs in 4 (9%) out of 45 patients considered to be related or possibly related to FESILTY included pain in extremity (patient (b) (6)), portal vein thrombosis (patient (b) (6)), deep vein thrombosis (patient (b) (6)), epilepsy and extradural hematoma (patient (b) (6)).

In Part I, three TEAEs were considered severe and serious including pain in extremity, hypertensive encephalopathy and post-streptococcal glomerulonephritis. There were no AEs leading to death or discontinuation in part I. These events were assessed as not related to the study drug.

In part II, there were nine serious TEAEs in seven subjects, with six also classified as severe. Per the applicant's assessments, serious TEAEs were assessed as not related to FESILTY. These include portal vein thrombosis, deep vein thrombosis, muscle hematoma, pancreatitis, epilepsy, extradural hematoma, iron deficiency anemia, menorrhagia and traumatic hemorrhage. One serious TEAE did result in death due to extradural hematoma. Patient (b) (6) was treated with FESILTY in part I of the study, and received treatment during part II of the study. The patient received on-demand prophylaxis for surgical synovectomy and dental extraction. Four weeks after FESILTY administration, the patient had adverse event of epilepsy and extradural hematoma. The patient underwent surgery but did not receive additional fibrinogen products. The patient died due to extradural hematoma.

Per the clinical reviewer assessment, the SAEs of deep vein thrombosis, portal vein thrombosis and pain in extremity were classified as related or possibly related to FESILTY administration.

Table 41. Serious Adverse Events (SAE) Related to FESILTY in Study 984

Patient Identifier	Part of Study (I/II)	Serious Adverse Event (SAE)	Action Taken with Study Treatment	Other Actions Taken	Resulted in Death
(b) (6)	I	Pain in extremity ¹	Drug withdrawn	Workup for thrombosis, which was negative	No
	II	Portal vein thrombosis ¹	Drug withdrawn	Not applicable	No
	II	Deep vein thrombosis ¹	Dose not changed	N/A	No
	II	Muscle hematoma	Dose not changed	FESILTY given in multiple doses	No
	II	Pancreatitis	Dose not changed	Hospitalized in another facility, haemocomplettan given	No
	I	Hypertensive encephalopathy	Drug withdrawn	11 days after FESILTY in PK associated with post-strep GN	No
	I	Post-strep Glomerulonephritis	Drug withdrawn	11 days after FESILTY in PK	No
	II	Epilepsy ¹	Dose not changed	N/A	No
	II	Extradural hematoma ¹	Dose not changed	Surgical evacuation	Yes
	II	Iron deficiency anemia	Dose not changed	Hospitalization with red blood cell transfusion	No
	II	Menorrhagia	Dose not changed	Hospitalization with haemocomplettan given	No
	II	Traumatic hemorrhage / gingival bleeding	Dose not changed	Hospitalized, FESILTY given.	No

¹SAEs considered by the clinical reviewer to be related or possibly related to FESILTY. Abbreviations: N/A=not applicable.

Reviewer comment: Per clinical reviewer assessment, three SAEs were considered as related or possibly related to FESILTY administration: deep vein thrombosis, portal vein

thrombosis and pain in extremity. This adjudication was based on timing and known side effect profile of fibrinogen containing products. Patient (b) (6) experienced pain in extremity. In the patient narrative, the patient experienced this SAE 4 days after FESILTY administration of 70mg/kg BW during part I (PK) of the study. Clinically, the patient presented with acute pain of the first two toes of the left foot with coldness and blue discoloration. The patient had work-up for thrombosis including Doppler ultrasound, echography and NMR imaging. There was no evidence on imaging for thrombosis, though patient did receive clopidogrel and tinzaparin. This SAE led to drug withdrawal. Per the clinical reviewer assessment, this SAE was considered as a possible thrombotic event which is a known side effect of fibrinogen containing products. The investigator assessed the SAE as not related due to prior history of prior thrombosis with poor microvascularization and discontinuation of clopidogrel previously. Due to the SAE occurring in close proximity to FESILTY administration and possible thrombosis, the clinical reviewer assessment adjudicated this SAE as related or possibly related to FESILTY.

Patient (b) (6) experienced SAE of portal vein thrombosis 3 days after last administration of FESILTY. The patient was initially admitted with spleen necrosis, and FESILTY was administered as ODP prior to splenectomy. The patient received 1 additional dose of FESILTY 1 week after splenectomy. The patient had nausea along with elevated transaminases. Portal vein thrombosis was noted on Doppler 3 days after last dose of FESILTY. The patient was treated with tinzaparin and the study medication was withdrawn. The investigator assessed the event as not related, with explanation of recent splenectomy, high thrombocyte count and low INR as possible etiologies. However, thrombosis is a known possible side effect of fibrinogen containing products and this SAE occurred in close proximity to FESILTY administration. Per clinical reviewer assessment, this SAE is considered as related or possibly related to FESILTY.

Patient (b) (6) experienced SAE of deep vein thrombosis (DVT). The patient was diagnosed with spontaneous intracerebral hematoma 5 months after previous dose of FESILTY. Patient received 1 dose of FESILTY for the bleeding event, as well as 5 additional doses of FESILTY to prevent re-bleed with target level of fibrinogen 2g/L. On the last day of FESILTY administration, the patient complained of pain in the upper calf. Initial ultrasound was normal, but repeat after 9 days showed DVT. The study drug was withdrawn. Repeat doppler ultrasound did not show progression after 1 week and the DVT resolved within 3 months. The investigator assessed the SAE as not related and contributed other possible etiologies of DVT including afibrinogenemia, pro-inflammatory status due to underlying gastritis and hepatitis B infection, as well as positive smoking history. Per the clinical reviewer assessment, the timing of DVT in relation to FESILTY administration as well as thrombosis being a known side effect of fibrinogen containing products, this was assessed as related or possibly related to FESILTY.

6.1.12.5 Adverse Events of Special Interest (AESI)

Infusion-Related Adverse Events

Infusion related adverse events were defined as any TEAE that occurred during FESILTY infusion and within 24 hours after start of the infusion. The applicant reported for the overall population, there were 46 infusion-related AEs occurring in 16 (35.6%) of patients. Most events occurred in part II (40 events in 55% of patients). The most

common reactions were procedural pain (59%), followed by procedural hemorrhage (4%) and swelling of the face (4%).

The applicant reported that 2 infusion-related AEs in 1 patient in part II of the study were considered to be related to FESILTY: pyrexia and pruritis.

Per the clinical reviewer assessment, there were 7 infusion reactions considered related or possibly related to FESILTY administration which occurred in 6 (13%) of patients. All infusion reactions were considered mild except for one patient with AE of headache (severe.) Two infusion reactions of facial swelling were also considered to be hypersensitivity reactions. These reactions are shown in **table 42**.

Table 42. Infusion Reactions (Related or Possibly Related) to FESILTY Administration in Study 984

Infusion Related Adverse Event	N=45 n (%)
Swelling of the face	2 (4)
Headache	1 (2)
Nausea	1 (2)
Pruritus	1 (2)
Pyrexia	1 (2)
Vomiting	1 (2)

Abbreviations: n=number of patients with at least 1 adverse event; %=percentage.

Source: FDA analysis, ADAE, ADSL, ADBL datasets.

Hypersensitivity

There were 3 AEs in 3 (7%) adult patients of facial swelling that were considered to be hypersensitivity/anaphylaxis. All AEs were considered mild.

Thrombogenicity

There were two AEs of thrombosis in 2 (4%) patients, including portal vein thrombosis and deep vein thrombosis.

Fibrinogen Inhibitory Antibodies

The applicant considered 3 AEs in 3 (7%) of patients occurring as fibrinogen inhibitory antibodies. These AEs were reported as fibrin D-dimer increased in 2 patients and prothrombin time prolonged in 1 patient. However, per clinical reviewer assessment, there were no patients with fibrinogen inhibitory antibodies in the safety analysis set.

Transmission of Infective Agents

There were no reports of transmission of infectious agents in study 984.

Reviewer comment: The AESIs of infusion reactions, hypersensitivity/anaphylaxis, thrombogenicity and fibrinogen inhibitory antibodies were evaluated. The incidence of AESIs appears acceptable for this drug class. The applicant did report 3 patients with “fibrinogen inhibitory antibodies,” however, per the clinical reviewer assessment, no patients had fibrinogen antibodies on evaluation.

6.1.12.6 Clinical Test Results

The mean values of PT, PT/INR, and aPTT were generally elevated pre-dose prior to FESILTY and dropped after FESILTY administration and prior to discharge.

PT/INR

For the overall population (full bleeding event set), the mean pre-dose PT/INR was 3.58 and the mean post-dose PT/INR was 1.34.

aPTT (seconds)

For the overall population (full bleeding event set), the mean pre-dose aPTT (seconds) was 115.7 and the mean aPTT before discharge was 40.1.

Hematology

There were three patients in part I of study 984 with abnormal hematology labs. This included patient (b) (6) with low hemoglobin prior to FESILTY and was considered to have non-TEAE of anemia. A second patient (b) (6) had low hemoglobin/hematocrit on days 1, 2, 7 and 14 and was found to have TEAE of microcytic anemia. An additional patient (b) (6) had elevated white blood cell count found to be associated with TEAE of rhinitis.

There were five patients with abnormal hematology labs in part II. Excluding low values at pre-dose, there was one patient (b) (6) with drop in hemoglobin from pre-dose value (10.5g/dL) to 5g/dL which was attributed to splenic rupture. Hemoglobin improved to 10.5 prior to discharge.

Chemistry

There were no abnormal chemistry values observed after FESILTY administration. One patient (b) (6) had elevated AST at screening, days 1 and 2 which was attributed to pre-existing condition.

Coagulation

In part I of study 984, there was 1 patient with elevated D-dimer on days 2 and 4. In part II, there was 1 patient with elevated D-dimer 1 hour after FESILTY administration.

Vital Signs

There were no major concerns for vital signs after FESILTY administration.

Fibrinogen Inhibitory Antibodies

All 45 patients for the overall study had negative fibrinogen inhibitory antibodies. Immunoglobulin E results did not show abnormal results for hypersensitivity.

Viral Safety

There were no abnormal findings for viral tests in part I for hepatitis A, B, C or HIV.

Ultrasound

In part II of the study, there were two patients with confirmed thromboembolic events (TEE) and one with suspected TEE. For patient (b) (6), the patient was suspected to have TEE after complaining of left foot with coldness and blue color. Doppler ultrasound and NMR imaging was negative and the study medication was withdrawn. A second patient (b) (6) was confirmed to have portal vein thrombosis via portal echo

Doppler after splenectomy. A third patient (b) (6) was found to have deep vein thrombosis nine days after FESILTY administration for spontaneous intracerebral hematoma. The patient discontinued the study after the event.

6.1.12.7 Dropouts and/or Discontinuations

Four patients withdrew from the study after a treatment emergent adverse event. Patient 984-01005 withdrew after event of "pain in extremity" after FESILTY administration, which was a suspected TEE. Patient (b) (6) withdrew after diagnosis of portal vein thrombosis after FESILTY administration. Patient (b) (6) withdrew after diagnosis of deep vein thrombosis after FESILTY administration. Patient (b) (6) withdrew from the study after pregnancy.

6.1.13 Study Summary and Conclusions

Overall, study 984 demonstrated acceptable pharmacokinetics/pharmacodynamics, as well as efficacy and safety of FESILTY in patients with congenital fibrinogen deficiency. Efficacy was mostly based on the maximum clot firmness (MCF), and overall hemostatic response (OHR). The mean change in MCF 1 hour after FESILTY administration was 13.44 for the overall population. This finding was consistent across age groups and significant for all age groups except for age <6 years due to small number of patients. For 175 bleeding events (on-demand treatment and on-demand prophylaxis) in part II of study 984, 86% were considered to have excellent OHR, 13% good and 1% moderate.

The safety profile was acceptable. Please see section 6.1.12 for safety findings.

6.2 Trial #2 – Not applicable.

6.2.1 Objectives (Primary, Secondary, etc)

Not applicable.

6.2.2 Design Overview

6.2.3 Population

Not applicable.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Not applicable.

6.2.5 Directions for Use

Not applicable.

6.2.6 Sites and Centers

Not applicable.

6.2.7 Surveillance/Monitoring

Not applicable.

6.2.8 Endpoints and Criteria for Study Success

Not applicable.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Not applicable.

6.2.10 Study Population and Disposition

Not applicable.

6.2.10.1 Populations Enrolled/Analyzed

Not applicable.

6.2.10.1.1 Demographics

Not applicable.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Not applicable.

6.2.10.1.3 Subject Disposition

Not applicable.

6.2.11 Efficacy Analyses

Not applicable.

6.2.11.1 Analyses of Primary Endpoint(s)

Not applicable.

6.2.11.2 Analyses of Secondary Endpoints

Not applicable.

6.2.11.3 Subpopulation Analyses

Not applicable.

6.2.11.4 Dropouts and/or Discontinuations

Not applicable.

6.2.11.5 Exploratory and Post Hoc Analyses

Not applicable.

6.2.12 Safety Analyses

6.2.12.1 Methods

Not applicable.

6.2.12.2 Overview of Adverse Events

Not applicable.

6.2.12.3 Deaths

Not applicable.

6.2.12.4 Nonfatal Serious Adverse Events

Not applicable.

6.2.12.5 Adverse Events of Special Interest (AESI)

Not applicable.

6.2.12.6 Clinical Test Results

Not applicable.

6.2.12.7 Dropouts and/or Discontinuations

Not applicable.

6.2.13 Study Summary and Conclusions

Not applicable.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

Not applicable.

7.1.1 Methods of Integration

Not applicable.

7.1.2 Demographics and Baseline Characteristics

Not applicable.

7.1.3 Subject Disposition

Not applicable.

7.1.4 Analysis of Primary Endpoint(s)

Not applicable.

7.1.5 Analysis of Secondary Endpoint(s)

Not applicable.

7.1.6 Other Endpoints

Not applicable.

7.1.7 Subpopulations

Not applicable.

7.1.8 Persistence of Efficacy

Not applicable.

7.1.9 Product-Product Interactions

Not applicable.

7.1.10 Additional Efficacy Issues/Analyses

Not applicable.

7.1.11 Efficacy Conclusions

Not applicable.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Not applicable.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Not applicable.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Not applicable.

8.2.3 Categorization of Adverse Events

Not applicable.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

Not applicable.

8.4 Safety Results

8.4.1 Deaths

Not applicable.

8.4.2 Nonfatal Serious Adverse Events

Not applicable.

8.4.3 Study Dropouts/Discontinuations

Not applicable.

8.4.4 Common Adverse Events

Not applicable.

8.4.5 Clinical Test Results

Not applicable.

8.4.6 Systemic Adverse Events

Not applicable.

8.4.7 Local Reactogenicity

Not applicable.

8.4.8 Adverse Events of Special Interest

Not applicable.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

Not applicable.

8.5.2 Time Dependency for Adverse Events

Not applicable.

8.5.3 Product-Demographic Interactions

Not applicable.

8.5.4 Product-Disease Interactions

Not applicable.

8.5.5 Product-Product Interactions

Not applicable.

8.5.6 Human Carcinogenicity

Not applicable.

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

8.5.8 Immunogenicity (Safety)

Not applicable.

8.5.9 Person-to-Person Transmission, Shedding

Not applicable.

8.6 Safety Conclusions

Not applicable.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

Not applicable.

9.1.1 Human Reproduction and Pregnancy Data

No human data are available to indicate the presence or absence of a drug-associated risk. Animal reproduction studies have not been conducted with FESILTY. One patient in clinical trial 984 reported pregnancy 11 months after FESILTY. The patient withdrew from the study and there were no reports of complications during the pregnancy. It is not known whether FESILTY can cause fetal harm when administered to a pregnant woman or can affect fertility. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20% respectively.

9.1.2 Use During Lactation

In study 984, there were no reports of use of FESILTY in patients during lactation.

9.1.3 Pediatric Use and PREA Considerations

The safety and effectiveness of FESILTY have been established in pediatric patients in congenital fibrinogen deficiencies. Use of FESILTY in pediatric patients with congenital fibrinogen deficiency was supported by evidence from one single-arm study that enrolled 24 pediatric patients 1 to 16 years of age (6 patients aged 0-6 years, 17 patients aged 6 to less than 16). congenital fibrinogen deficiency.

A phase I pharmacokinetic (PK) clinical trial was performed in 27 patients with congenital fibrinogen deficiency, including 12 pediatric patients treated with FESILTY: 6 infants and children under 6 years, 3 children aged 6 to <12 years, and 3 adolescents aged 12 to <18 years. The phase III clinical trial in congenital deficiency included 16 pediatric patients treated with FESILTY for at least one bleeding event: 3 infants and children under 6 years, 9 children aged 6 to <12 years, and 4 adolescents aged 12 to <18 years. The overall safety profile did not differ between adults, adolescents, and children.

There were 6 patients aged 0 to less than 6 years and 17 patients aged 6 years to less than 16 years.

The FDA Pediatric Review Committee (PeRC) agreed with the applicant's request for pediatric assessment, including proposed extrapolation of effectiveness from the adult population to the pediatric population, as the number of patients <6 years was limited, and this is a rare disease.

9.1.4 Immunocompromised Patients

In study 984, there were no reports of use in of FESILTY in immunocompromised patients.

9.1.5 Geriatric Use

In clinical study 984 of FESILTY in congenital fibrinogen deficiency did not include patients aged 65 years and over to provide evidence as to whether or not they respond differently than younger patients.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

Not applicable.

10. Conclusions

The key efficacy endpoint was the overall hemostatic response (OHR) based on a 4-point scale assessed by the investigator as excellent, good, moderate or none. The other secondary endpoint was the mean change in maximum clot formation (MCF) at 1 hour after infusion. The OHR for 175 bleeding events in 36 patients was reported as excellent in 150 bleeding events (86%), good in 23 bleeding events (13%), and moderate in 2 bleeding events (1%). The mean change in MCF was 13.44 mm at 1 hour after FESILTY infusion.

The safety profile was consistent with the underlying disease and expected profile for human fibrinogen products, with 73.3% of patients experiencing treatment-emergent adverse events. The most common adverse reactions occurring in >2% of patients included pain in extremity (7%), back pain (7%), hypersensitivity reactions (7%), pyrexia (4%), thrombosis (4%), fibrin D-dimer increased (4%), headache (4%), and vomiting (4%). Serious adverse reactions included thrombosis in 2 subjects (portal vein thrombosis and deep vein thrombosis in one subject each), pain in extremity with suspected thrombosis in one patient, and one patient with epilepsy and extradural hematoma four weeks after FESILTY administration, which was fatal.

Considering the effect of FESILTY on bleeding events and the fact that the risks are mild and infrequent, the overall benefit-risk profile favors traditional approval of FESILTY for the treatment of acute bleeding episodes in pediatric and adult patients with congenital fibrinogen deficiency, including hypo- and afibrinogenemia.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

See **table 43**.

Table 43. Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> • Congenital afibrinogenemia and hypofibrinogenemia are rare diseases. • Inadequate functional fibrinogen can cause potentially fatal bleeding dyscrasias that start in infancy. 	<ul style="list-style-type: none"> • Afibrinogenemia and hypofibrinogenemia are hereditary disorders that present with life-threatening bleeding that may be spontaneous, traumatic and occur during surgical procedures.
Unmet Medical Need	<ul style="list-style-type: none"> • Currently, there are two fibrinogen concentrates approved for use in congenital afibrinogenemia and hypofibrinogenemia. 	<ul style="list-style-type: none"> • There is no unmet medical need with currently licensed products.
Clinical Benefit	<ul style="list-style-type: none"> • Efficacy was demonstrated for the treatment of 175 acute bleeds in adult and pediatric patients with congenital afibrinogenemia and hypofibrinogenemia, which was primarily based on overall hemostatic efficacy of bleeding events and maximum clot firmness. No new safety concerns were identified for this product. 	<ul style="list-style-type: none"> • There is evidence for clinical benefit for the treatment of acute bleeds.
Risk	<ul style="list-style-type: none"> • The most substantial risks of treatments are thrombosis, hypersensitivity reactions, fibrinogen inhibitory antibodies, and transmission of infective agents. There were two patients with thrombosis, 3 patients with hypersensitivity reactions. There were no reports of transmission of infective agents and there were no patients who developed antibodies. 	<ul style="list-style-type: none"> • The evidence of safety evaluation in FESILTY indicate risks that are expected for this class of plasma derived products.
Risk Management	<ul style="list-style-type: none"> • The most substantial risks of treatment are thrombosis, hypersensitivity reactions, fibrinogen inhibitory antibodies, and transmission of infective agents. • No other major safety signals were present. 	<ul style="list-style-type: none"> • Safety data was available for 45 patients in this single arm, open-label study. Routine post-marketing surveillance is appropriate to evaluate further risks of thromboembolism, immunogenicity and hypersensitivity.

11.2 Risk-Benefit Summary and Assessment

Study 984 has demonstrated efficacy with increase in maximum clot firmness (MCF) at 1 hour after infusion during bleeding events. The mean increase in MCF for the overall population was 10.76mm. The mean change in MCF 1 hour after FESILTY infusion was 8.7, 11.1 and 9.8 mm in patients <6 years, 6 to 12 years, and 12 to <18 years, respectively. The mean change in MCF was significant for all age groups, though due to small numbers of patients <6 years, a p-value was not able to be calculated. Additional clinical efficacy endpoint of overall hemostatic response (OHR) was rated by the investigator after FESILTY administration during a bleeding event on a 4-point scale (“none,” “moderate,” “good” or “excellent.”) For the overall population of adults and pediatric patients, the majority of bleeding events were reported as excellent (85.7%) or good (13.1%) OHR, with no notable differences between age groups or between major and minor bleeding events. The safety profile is acceptable and adverse reactions are consistent with other drug products derived from plasma. The benefit/risk profile is favorable.

11.3 Discussion of Regulatory Options

In support of the marketing application, the applicant submitted efficacy and safety data from clinical Study 984. Substantial evidence of effectiveness was established based on one adequate, single arm study supported by confirmatory evidence from preclinical studies. Efficacy is based on an improvement in maximum clot firmness (MCF) and a 4-point scale of overall hemostatic response with the majority of patients with bleeding events reported as excellent or good after FESILTY administration. These findings represent a clinically meaningful effect on hemostatic effect. The most common adverse events were pain in extremity, back pain, hypersensitivity reactions, headache, thrombosis and vomiting which is consistent with the drug class.

The available data support traditional approval for the indication of FESILTY in treatment of acute bleeding episodes in pediatric and adult patients with congenital fibrinogen deficiency including hypo- or afibrinogenemia.

11.4 Recommendations on Regulatory Actions

The review team recommends granting traditional approval for FESILTY for the treatment of acute bleeding episodes in pediatric and adult patients with congenital fibrinogen deficiency, including hypo- or afibrinogenemia based on substantial evidence of effectiveness demonstrated in study 984 which includes pharmacokinetics, pharmacodynamics and clinically meaningful endpoints of hemostasis and supported by preclinical studies.

11.5 Labeling Review and Recommendations

The applicant’s proposed indication of “for treatment and prophylaxis of pediatric and adult patients with congenital hypo- or afibrinogenemia with bleeding tendency” was considered unacceptable based on the review of the data.

The review team recommended the following revisions to the Applicant's proposed label summarized in Table 44 below:

Table 44: Summary of Significant Labeling Changes

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
Section 1: Indication and Usage	FESILTY is indicated for the treatment and prophylaxis in pediatric and adult patients with congenital hypo- or afibrinogenemia.	Indication was revised to "FESILTY is indicated for the treatment of acute bleeding episodes in pediatric and adult patients with congenital fibrinogen deficiency, including hypo- or afibrinogenemia." Limitations of Use on dysfibrinogenemia was added due to lack of data to support the safe and effective use in patients with a related but very different disorder of dysfibrinogenemia.
Section 2: Dosage and Administration	-	Revised for brevity, and to use active command language. Section 2.3 Administration was revised to include appropriate infusion rates for FESILTY infusion. Promotional links and QR codes were removed.
Section 4: Contraindications	FESILTY is contraindicated in patients who manifested severe immediate hypersensitivity reactions, including anaphylaxis, to FESILTY or its components.	Revised to "FESILTY is contraindicated in patients who have severe hypersensitivity reactions, including anaphylaxis, to FESILTY or its components (arginine hydrochloride, polysorbate 80, sodium citrate dihydrate, trehalose dihydrate)."
Section 6 Adverse Reactions	-	The information in this section was revised based on the current labeling practice to describe FESILTY exposure and safety database included in the USPI, for concise presentation of data and to remove redundant information. The list of serious adverse reactions was included. Table -2 was revised to include most common adverse reactions that occurred

		in ≥2% of patients in Study 984 based on clinical review teams' adjudication.
Section 8: Use in Specific Population	-	<p>Section 8.1 Pregnancy: Revised to include information on 1 patient who reported pregnancy after receiving FESILTY.</p> <p>Section 8.4 Pediatric Use: Revised to specify the data supporting the indication of FESILTY in pediatric population. Based on per 21 CFR 201.57(c)(9), the pediatric age group was revised to include patients 0 to 16 years of age.</p>
Section 12: Clinical Pharmacology.	-	Revised to remove promotional language and to describe MOA supported by data.
Section 14: Clinical Studies	-	<p>Section 14 was revised to describe the studies which provided the primary evidence of efficacy, intervention, population characteristics, and major efficacy results based on current labeling practice.</p> <p>Exploratory analyses were deleted as they are not part of substantial evidence and not considered informative.</p>
Section 17: Patient Counseling Information	-	This section was revised for clarity, use of command language, and to align with warning and precautions listed in section 5 of USPI.

Source: Created by FDA Clinical Reviewer and Acting Associate Director for Labeling

11.6 Recommendations on Postmarketing Actions

The applicant's planned pharmacovigilance plan is adequate. Based on the review of the BLA submission, the reviewer does not recommend any clinical PMR or PMC studies.

References

Mohsenian, S. et al. Congenital fibrinogen disorders: a retrospective clinical and genetic analysis of the Prospective Rare Bleeding Disorders Database. *Blood Adv* 2024; 8 (6): 1392–1404.