

**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Pharmacovigilance
Division of Pharmacovigilance**

Pharmacovigilance Review Memorandum

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Subject: Pharmacovigilance Plan Review

Sponsor: Grifols Therapeutics, LLC

Product: FESILTY (fibrinogen [Human])*

Proposed Indication: Treatment and prophylaxis in pediatric and adult patients with congenital hypo- or afibrinogenemia with bleeding tendency

Submission Type/Number: BLA 125833/0

Submission Date: December 27, 2024

Action Due Date: December 27, 2025

*This product is also referred to as BT524 throughout this memorandum.

1. OBJECTIVE

The purpose of this review is to assess the adequacy of the sponsor's pharmacovigilance plan (PVP) submitted under the original BLA 125833/0 based on the safety profile of Fesilty (Fibrinogen). Our review will determine whether any safety-related studies such as Postmarketing Requirements (PMRs) are warranted and/or if there will be agreed upon Post-Marketing Commitments (PMCs), or if Risk Evaluation and Mitigation Strategies (REMS) are required for Fesilty, should the indication for this product be approved.

2. BACKGROUND

Fibrinogen (coagulation factor I) is a soluble plasma glycoprotein synthesized by hepatic parenchymal cells. Fibrinogen plays a central role in maintaining hemostasis, specifically through clot formation and stabilization. In primary hemostasis, fibrinogen has an important role in mediating the binding among platelets (platelet aggregation) through the glycoprotein GP IIb-IIIa receptor. In secondary hemostasis, during the final step of the coagulation cascade, thrombin cleaves fibrinogen to fibrin. Fibrin molecules polymerize to form a 3D- network, and crosslinks introduced by factor XIII further stabilize the clot. Fibrinogen also plays an important role in wound healing and host defense against microbes. In case of fibrinogen deficiency, blood coagulation is impaired, potentially leading to severe hemorrhagic events. Rapid fibrinogen supplementation is critical to maintain hemostasis, normalize clot formation in bleeding patients, and restore fibrinogen levels as an important therapeutic target in bleeding.

3. PRODUCT INFORMATION

3.1 Product Description

Fesilty (fibrinogen [Human]) is a purified, sterile, non-pyrogenic, lyophilized powder of human fibrinogen for reconstitution for intravenous administration. Fesilty is prepared from pooled source plasma obtained from healthy volunteer donors. The manufacturing process for Fesilty employs several steps to remove/inactivate adventitious viruses to further increase the margins of safety.

Fesilty is supplied in a single-dose vial containing nominally 1 gram of fibrinogen. When reconstituted with 50 mL sterile water for injection Fesilty contains approximately 20 mg/mL protein, of which not less than 80% is fibrinogen.

3.2 Proposed Indication

Fesilty (fibrinogen [human]) is a human fibrinogen indicated:

- *for fibrinogen supplementation in patients with acquired fibrinogen deficiency.*
- *for treatment and prophylaxis in pediatric and adult patients with congenital hypo- or afibrinogenemia with bleeding tendency*

OBPV defers to product office on the final language for the indication statement. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon indication after FDA review.

4. PERTINENT REGULATORY HISTORY

The current submission is an original Biologics License Application (BLA) submission. The product has not been previously marketed.

5. MATERIALS REVIEWED

Materials reviewed in support of this assessment include the following:

5.1 Pertinent Sections of the Licensing Application

- Section 1.14 Proposed Labeling, BLA 125833/0
- Section 1.16 Risk Management Plan (RMP), BLA 125833/0.22
- Section 2.7.4 Summary of Clinical Safety, BLA 125833/0
- Section 1.11.3 Response to Clinical IR #20, BLA 125833/0.22

5.2 Input from the Clinical Reviewer

The clinical review team raised no new safety concerns that require additional post-marking studies or a risk evaluation and mitigation strategy for Fesilty.

6. DESCRIPTION OF FESILTY CLINICAL TRIAL SAFETY DATABASE

6.1 Clinical Studies

The clinical study safety data reviewed are from the Summary of Clinical Safety submitted to BLA125833/0. OBPV defers to the product office on final review of the clinical database, including safety and efficacy outcomes, which will inform the final language in the U.S. Package Insert (USPI). Below is our *focused* review of the sponsor data initially submitted to the BLA, to inform decisions pertaining to pharmacovigilance planning, should this BLA 125833/0 be approved. Please refer to the package insert for the final clinical safety data.

The safety data of Fesilty was based on two clinical trials (Trial 984 and Trial 995). A summary of each study and the pertinent safety issues is presented in Table 1.

Table 1: Overview of Clinical Studies Contributing to the Safety Assessment of Fesilty (Fibrinogen, BT524)

Study ID Study Phase	Study Design Type of Control	Objective(s) of the Study	Test Product(s)	Number of Patients	Trial Population	Study Status
Trial 984 Phase I/III 2013-03-20 to 2020-05-18	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)	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	Total: 45 Part 1: 27 Part 2: 36 ^a	Children, adolescents, and adults with congenital fibrinogen deficiency	Completed
Trial 995 Phase III 2018-02-12 to 2023-11-21	Prospective, partially blinded, active-controlled, multicenter, multinational; non-inferiority trial (efficacy, and safety) in 2 different settings Control: a) major spinal surgery: FFP b) abdominal surgery: Cryo	Total intraoperative blood loss (from time of decision to treat until end of surgery)	Spinal surgery: BT524: FIBTEM A10 guided; initial dose ≥ 2 g; maximum dose should not exceed 8 g FFP: per treatment guidelines/local standards; 15 mL/kg recommended Abdominal surgery: BT524: 4 g (fixed dose) Cryo: 10 units total (fixed dose) Administration: IV infusion	Total: 222 (BT524: 110 FFP/Cryo: 112) Spinal surgery: 124 (BT524: 62 FFP/Cryo: 62) Abdominal surgery: 98 (BT524: 48 FFP/Cryo: 50)	Adults with acquired fibrinogen deficiency a) undergoing major spinal surgery (EU or Switzerland) with an estimated intraoperative blood loss of approx. 1 L b) undergoing major abdominal surgery (cytoreductive PMP surgery; UK) with a predicted intraoperative blood loss of > 2 L	Completed

Abbreviations: AIO = clot amplitude obtained at 10 minutes (via FIB1EM); BW = body weight; Cryo = cryoprecipitate; CSR = clinical study report; CT.gov ID= ClinicalTrials.gov identifier; EU= European Union; EudraCT No. = European Union Drug Regulating Authorities Clinical Trials Database number; FFP = fresh frozen plasma; FIB1EM = fibrin-based thromboelastometry test; IND = Investigational New Drug; IV = intravenous; MCF = maximum clot firmness; NIA= not applicable; No.= number; ODP = on-demand prophylaxis; ODT = on-demand treatment; OHR= overall hemostatic response; PD= pharmacodynamics; PK = pharmacokinetics; PMP = pseudomyxoma peritonei; UK = United Kingdom.

^a Of the 36 subjects treated in part 2 of Trial 984, 18 subjects had already received single-dose BT524 treatment in part 1.

6.2 Adverse Events

The following topics were assessed as identified or potential risks for Fesilty: thromboembolic events (TEE), hypersensitivity, inhibitory antibodies, and transmission of infective agents.

6.2.1 Trial 984

6.2.1.1 Study design

Trial 984 was a prospective, open-label, multicenter, phase I/III clinical study investigating the efficacy and safety of BT524 in the treatment and prophylaxis of bleeding in patients with congenital fibrinogen deficiency. A total of 67 subjects were enrolled in Trial 984; of these, 45 received at least one dose of BT524 and were included in the safety analysis set (SAF) (27 subjects in part 1 [18 enrolled to part 2], and 18 new subjects in part 2). All 27 subjects dosed in part 1 received one 70 mg/kg BW dose of BT524. In part 2, a total of 36 subjects received BT524 for on-demand treatment (ODT) and/or on-demand prophylaxis (ODP) in case of bleeding events (i.e., surgical procedure, spontaneous or post-traumatic severe bleeding). Mean (standard deviation [SD]) total dose was 72.7 (48.42) mg/kg BW, with a median of 62.6 mg/kg BW.

6.2.1.2 Study results

The safety measures included treatment-emergent adverse events (TEAEs)¹, serious AEs (SAEs), death, and adverse events of special interest: thrombosis or TEE, hypersensitivity/anaphylactic reactions/anaphylactic shock, fibrinogen inhibitory antibodies, and suspicion of transmission of infective agents (viral safety).

TEAEs and SAEs

Overall, 73.3 % of subjects experienced at least one TEAE in part 1 or part 2 (Table A. Appendix). Four subjects discontinued Trial 984 prematurely due to a TEAE: one subject due to pain in extremity (part 1) and one each due to portal vein thrombosis, deep vein thrombosis, and pregnancy in part 2.

TEAEs reported for ≥ 10 % of subjects overall were procedural pain (20.0 % subjects), subcutaneous hematoma (15.6 %), back pain (13.3 %) and toothache and pain in extremity (11.1% subjects each).

The majority of TEAEs were mild or moderate in intensity. Overall, 14 subjects (31.1 %) experienced TEAEs of severe intensity; only severe procedural pain and pain in extremity (three subjects each) and back pain and menorrhagia (two subjects each) occurred in more than one subject.

Two subjects experienced TEAEs considered by the sponsor to be related to Investigational Medicinal Product (IMP). One subject in part 1 experienced increased fibrin D dimer and one subject in part 2 experienced pyrexia and pruritus. None of these events were serious.

¹ In Trial 984, a TEAE was defined as any AE during or after the first BT524 administration until the last trial visit of the respective bleeding event (day 49 \pm 4 days).

Serious TEAEs were reported for nine subjects (20.0 %) in total; no individual PT was reported as serious in more than one subject and none were considered related to BT524.

Overall, 16 subjects (35.6 %) experienced infusion-related TEAEs, most commonly procedural pain (9 subjects [20.0 %]), none of which were considered serious. None of the infusion-related TEAEs in children or adolescents were considered related to IMP in either Trial 984 part.

Death

One adult subject in part 2 of Trial 984 died due to an extradural hematoma 5 weeks after his final dose of BT524. This subject was first treated with BT524 in part 1 of the study and received on-demand treatment (ODT) for spontaneous hemarthrosis bleeding on the left elbow during part 2 of the study. Approximately 4 months after this BT524 treatment, the subject was diagnosed with an intracranial bleeding of severe intensity (PT: haemorrhage intracranial; not related serious AE (SAE) outside the 49-day follow-up period). For remedial therapy, the subject received Haemocomplettan P (human fibrinogen), followed by treatment with depakine (valproic acid) and tanganil (over-the-counter product containing acetyl-DL-leucine). The SAE was reported as recovered after 6 days. In part 2, the subject received BT524 on-demand prophylaxis (ODP) for two surgical bleeding events (surgical synovectomy of left elbow and dental extraction). Approximately 4 weeks after the last administration of BT524, the subject was hospitalized following an epileptic fit and was diagnosed with an extradural hematoma. The subject underwent emergency surgery for evacuation of the hematoma; however, subsequently remained in a coma, and died one week later. The serious TEAE of extradural hematoma was considered not related to BT524 by the investigator and the sponsor.

Adverse events of special interest (AESI)

Overall, the incidence of AESIs was low; no AESIs were noted in children and adolescents.

- In part 2, three adult subjects were reported with 'swelling face' in the AESI category of hypersensitivity/anaphylactic reactions/anaphylactic shock. The sponsor considered that all cases were mild, not related to IMP, confounded by a procedure, resolved without effect on the IMP dose, and were unlikely to be indicative of a true allergic reaction.
- In part 2, two adult subjects were reported with events in the AESI category of thrombogenicity (portal vein thrombosis [severe]; deep vein thrombosis [moderate]). None of the events were considered related to IMP by the investigator, deep vein thrombosis was however considered related to IMP by the sponsor. Both events were serious, resolved with sequelae, and led to discontinuation of the IMP.
- The broad search algorithm (SOC "Investigations") for fibrinogen inhibitory antibodies revealed no results on the presence of such antibodies. There were two TEAEs ('fibrin D dimer increased' and 'PT prolonged') reported in three adult

subjects (part 1: one subject; part 2: two subjects) based on this search criteria. These TEAEs were most likely a consequence of fibrinogen administration or underlying disease, respectively.

- There were no reports indicative of a potential transmission of infective agents during the study.

6.2.2 Trial 995

6.2.2.1 Study design

Trial 995 was a phase III, prospective, randomized, active-controlled, multicenter, non-inferiority trial in adult subjects (≥ 18 years) undergoing major spinal or abdominal surgery to demonstrate the efficacy and safety of intra-operative use of BT524 as a complementary therapy for the management of uncontrolled severe hemorrhage in acquired hypofibrinogenemia. Overall, 222 subjects were eligible and randomized into Trial 995; of these 110 received BT524 and 112 received FFP/Cryo (62 FFP, 50 Cryo). The median number of IMP administrations during surgery was comparable between treatment groups (1.0 for BT524 and 1.0 for FFP/Cryo). The mean planned and actual IMP volume administered for the BT524 group was identical. For the FFP/Cryo group, there was a small difference in the mean planned and actual IMP volume administered; this occurred because IMP infusion was interrupted in two subjects. The mean duration of first infusion and the mean time to start of first IMP infusion after decision to treat was lower for in the BT524 group (7.1 and 40.3 minutes, respectively) than in the FFP/Cryo group (33.1 and 69.0 minutes, respectively).

6.2.2.2 Study results

The safety measures included treatment-emergent adverse events (TEAEs)², serious AEs (SAEs), death, and adverse events of special interest: thrombosis or TEE, hypersensitivity/ anaphylactic reactions/anaphylactic shock, fibrinogen inhibitory antibodies, and suspicion of transmission of infective agents (viral safety).

TEAEs and SAEs

The overall incidence of TEAEs was similar for the BT524 (87.3 %) and FFP/Cryo (89.3 %) groups (Table B. Appendix). The majority of TEAEs in both treatment groups were non-serious, considered not related to IMP, and non-severe in intensity. No TEAEs leading to IMP or trial discontinuation were reported.

The most commonly reported TEAEs (MedDRA PT) were hallucination (24.8 %), hypotension (14.9 %), tachycardia (14.9 %), anaemia (11.7 %), hypertransaminasaemia (10.8 %), and anaemia postoperative (10.4 %); other TEAEs were reported for < 10 % of subjects overall.

In abdominal surgery, a higher incidence of TEAEs such as hallucination, tachycardia, and hypotension were observed in the BT524 group while a higher proportion of subjects in the Cryo group experienced pulmonary embolism, oxygen saturation decreased, and deep vein thrombosis. In spinal surgery, a higher incidence of post-

² In Trial 995, a TEAE was defined as any AE occurring from the administration of IMP until the subject's last study visit (day 36 [+35 days]).

operative anemia, hypotension, and nausea was observed in the BT524 group while urinary tract infections and blood loss anemia were experienced by a higher proportion of subjects in the FFP group. The sponsor considered these events were all surgery-related events and the difference in incidence was not clinically relevant.

TEAEs were predominantly mild or moderate for the majority of subjects; severe TEAEs were experienced by 15.8 % of subjects, with similar proportions in the BT524 group (15.5 %) and the FFP/Cryo group (16.1 %).

Overall, TEAEs causally related to the IMP (considered by the sponsor) were experienced by a low proportion of subjects (2.7%). In the BT524 group, causally related TEAEs (pulmonary embolism, thrombocytopaenia, and urticaria) were reported in 2 subjects (1.8 %). In the FFP/Cryo group, the causally related TEAE of pulmonary embolism was reported in 4 subjects (3.6 %).

The overall incidence of serious TEAEs was lower in the BT524 group (25.5 %) than in the FFP/Cryo group (36.6 %). The most commonly reported serious TEAE in both treatment groups was pulmonary embolism (BT524: 3 subjects [2.7 %]; FFP/Cryo: 7 subjects [6.3 %]); other serious TEAEs were reported for < 2 % of overall subjects.

Death

One subject in the FFP/Cryo group died due to a TEAE of respiratory failure approximately 6 weeks after undergoing surgery for pseudomyxoma peritonei (PMP). The TEAE was assessed as not related to IMP by the investigator. No subject in the BT524 group experienced a TEAE with a fatal outcome.

Adverse events of special interest

Overall, 47 subjects (21.2 %) were reported with AESIs. A similar proportion of subjects in the BT524 (22 subjects [20.0 %]) and FFP/Cryo (25 subjects [22.3 %]) groups had at least one AESI, but differences between surgeries were observed. A lower proportion of subjects who underwent abdominal surgery (BT524: 4 subjects [8.3 %]; FFP/Cryo: 11 subjects [22.0 %]) experienced AESIs than subjects who underwent spinal surgery (BT524: 18 subjects [29.0 %]; FFP/Cryo: 14 subjects [22.6 %]).

- The occurrence of TEAEs in the category hypersensitivity, anaphylactic reactions, and anaphylactic shock was generally low (3.6 % overall) with a higher frequency in subjects receiving BT524 (BT524 group: 6.4 %; FFP/Cryo group: 0.9 %). With the exception of one subject who experienced a causally related TEAE under the category hypersensitivity, anaphylactic reactions, and anaphylactic shock (PT: urticaria), no other causally related TEAEs were noted.
- There was a lower incidence of thrombosis or TEEs in the BT524 group (7.3 %) than in the FFP/Cryo group (11.6 %). The most commonly reported AESIs of thrombosis or TEE were pulmonary embolism (BT524: 3 subjects [2.7 %]; FFP/Cryo: 8 subjects [7.1 %]) and deep vein thrombosis (BT524: 1 subject [0.9 %]; FFP/Cryo: 5 subjects [4.5 %]). Causally related thrombosis or TEEs occurred in a lower proportion of subjects in the BT524 group (1 subject [0.9 %]) than in the FFP/Cryo group (4 subjects [3.6 %]).

- The incidence of relevant bleeding complications was similar in the BT524 group (14.5 %) and in the FFP/Cryo group (12.5 %). None of the relevant bleeding complications were related to the IMP.
- The incidence of bleeding related ischemic events was lower in the BT524 group (4.5 %) than in the FFP/Cryo group (12.5 %). Bleeding-related ischemic events considered causally related by the investigators were experienced by 1 subject (0.9 %) in the BT524 and 4 subjects (3.6 %) in the FFP/Cryo group.
- TEAEs of suspicion of transmission of infective agents were not experienced by any subjects.

Reviewer comment: *Data from these studies indicated that Fesilty had similar safety profile as human fibrinogen products and no new safety concerns were identified in the indicated patient population. All treatment-related AEs were well-known events following fibrinogen and are labeled in the proposed package insert.*

Note: when interpreting these findings, it should be noted that the sample size was relatively small (45 cases in Trial 984 and 110 cases in Trial 995) that is insufficient to detect the rare adverse events.

7. SUMMARY OF POSTMARKETING EXPERIENCE

The product has never been marketed, so there were no post-market adverse event analyses.

8. SPONSOR'S PHARMACOVIGILANCE PLAN

The sponsor Risk Management Plan (RMP version 2.0, dated July 31, 2024) includes the Pharmacovigilance Plan (PVP). The summary of identified risks, potential risks, and the important missing information is presented in Table 2:

Table 2: Summary of Safety Concerns as Proposed by the Sponsor

Important Identified risk(s)	<ul style="list-style-type: none"> • Thromboembolic events • Hypersensitivity
Important Potential risk(s)	<ul style="list-style-type: none"> • Inhibitory antibodies • Transmission of infective agents
Missing information	<ul style="list-style-type: none"> • Use in pregnancy and lactation

Reviewer comment: The initial RMP (version 1.0) did not include any safety concerns (no important identified or potential risks and no missing information). On June 12, 2025, we issued information request (IR) for asking the sponsor to include thrombosis and hypersensitivity as important identified risks, inhibitory antibodies and transmission of infective agents as important potential risks, and use in pregnancy and lactation as missing information. The sponsor agreed and revised the RMP (version 2.0) in an IR response submitted to STN125833/0.22 on July 1, 2025.

8.1 Analysis of Sponsor's PVP

8.1.1 Identified risk

Thromboembolic Events (TEEs)

TEEs are a well-known risk for the class of human fibrinogen products. Among all 146 subjects exposed to BT524 in the clinical trial program, only 2 patients (1.4%) experienced TEEs ("Deep vein thrombosis" and "Pulmonary embolism") considered related by either the investigator or the sponsor.

Other TEEs reported in the clinical trial program were pulmonary embolism (2 patients, 1.4%), paraparesis (2 patients, 1.4%), deep vein thrombosis, monoparesis, paraplegia and porta vein thrombosis (1 patient each, 0.7%). All these events were considered by the sponsor to be not related to BT524.

Thrombosis may occur spontaneously in patients with acquired or congenital fibrinogen deficiency with or without the use of fibrinogen replacement therapy. Patients given human fibrinogen should be observed closely for signs or symptoms of thrombosis. The recommended dose and infusion rate provided in the product information should be strictly followed.

Hypersensitivity

Hypersensitivity reactions including anaphylaxis are a class risk for all fibrinogen concentrates for human fibrinogen products, including Fesilty. Among all 146 subjects exposed to Fesilty in the clinical trial program, one subject (0.7%) experienced a related, non-serious AE of urticarial rash, mild in severity. The event was observed in a 58-year-old female approximately 15 minutes after administration of the last infusion of Fesilty. The urticarial rash resolved on the same day after treatment with hydrocortisone. Pyrexia and pruritus occurred in one adult male subject of 34 years and were considered mild in severity, non-serious and related to Fesilty. These infusion-related AEs lasted for approximately 30 minutes and were reported as resolved afterwards.

Other AEs indicative of hypersensitivity, including anaphylactic reaction observed in the clinical trial program were swelling face (3 subjects, 2.1%), anaphylactic reaction (2 patients, 1.4%), rash (2 patients, 1.4%), circulatory collapse, drug hypersensitivity and rash popular (1 patient each, 0.7%). All these events were considered by the sponsor to be not related to the trial medication.

Fesilty is contraindicated in patients who manifested severe immediate hypersensitivity reactions, including anaphylaxis, to Fesilty or its components. This risk is well known to physicians and can be managed adequately by treating physicians following instructions of the USPI and use of standard medical therapies.

8.1.2 Potential risks

Inhibitory Antibodies

Inhibitory antibodies are considered as a class effect of fibrinogen products. Administration of fibrinogen concentrates introduces donor-derived fibrinogen which may present structural epitopes that the patient's immune system perceives as "non-self". Repeat exposures raise the likelihood of generating high-affinity inhibitory antibodies. These might interfere directly with the fibrinogen function, leading to clinically significant inhibition and reduced fibrinogen levels. Immunogenicity of fibrinogen has been described for patients treated with cryoprecipitate and is an extremely rare event. The clinical development program with BT524 has not revealed any indication for the development of antibodies with clinically relevant inhibitory potential.

Transmission of Serious Infections

The possibility of transmitting infective agents cannot be excluded completely for any recipient of medicinal products prepared from human blood or plasma. This applies to unknown or emerging viruses and other pathogens. Therefore, transmission of infective agents is a potential risk for the class of human fibrinogen products. No case of suspected transmission of infective agents was reported during the development program. It is therefore strongly recommended that every time that Fesilty is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

8.1.3 Important missing information

There are no available data with Fesilty use in pregnant women. There are no available data with Fesilty in lactating women or information on the effects on the breastfed infant. Even though pregnant or lactating individuals were not included in the clinical trial program, they may receive treatment with Fesilty once it is approved. Additional data regarding pregnant and breastfeeding individuals exposed to Fesilty will be gathered for further understanding of the safety profile of Fesilty.

8.2 Analysis of Sponsor's PVP Activities

The sponsor proposed to use routine pharmacovigilance to monitor postmarketing safety of Fesilty. Routine pharmacovigilance activities include submission of Individual Case Safety Reports (ICSR), signal detection, literature review, and submission of sponsor summary of aggregate safety data in Periodic Adverse Experience Report (PAER).

Reviewer's assessment: *The sponsor's proposed post-marketing pharmacovigilance plan is adequate for all safety concerns noted in Table 2. No new safety signals have been identified that would justify further postmarketing study or a Risk Evaluation and Mitigation Strategy (REMS).*

9. DPV ASSESSMENT

Based on the review of the final results of two trials 984 and 955, we conclude that Fesilty has a similar safety profile to human fibrinogen products and no new safety concerns were identified in the indicated patient population. DPV concurs with the sponsor's proposed pharmacovigilance activities in the proposed RMP.

10. DPV RECOMMENDATIONS

Should Fesilty be approved, DPV agrees with routine pharmacovigilance for safety monitoring, as proposed by the sponsor in the RMP, with adverse event reporting as required under 21 CFR 600.80. The reviewed available safety data do not indicate a need for safety-related studies such as Postmarketing Requirements (PMRs) or a Risk Evaluation and Mitigation Strategy (REMS). There are no safety-related studies as agreed upon postmarketing commitments (PMCs). Please see the final version of the Package Insert submitted by the sponsor for the final agreed-upon language describing Fesilty.

Appendix

Table A. Overview of Adverse Events in Trial 984

Number of Subjects With	Part 1 N=27 n(%)m	Part2 N=36 n(%)m	Overall N=45 n(%)m
TEAEs	15 (55.6) 31	27 (75.0) 143	33 (73.3) 174
Related TEAEs	1 (3.7) 1	1 (2.8) 2	2 (4.4) 3
Severe TEAEs	2(7.4)5	12 (33.3) 24	14 (31.1) 29
Serious TEAEs	2 (7.4) 3	7 (19.4) 9	9 (20.0) 12
Related Serious TEAEs	0	0	0
TEAEs Leading to Discontinuation	1 (3.7) 1	3 (8.3) 3	4 (8.9) 4
AEs Leading to Death	0	1 (2.8) 1	1 (2.2) 1
Pregnancy	0	1 (2.8) 1	1 (2.2) 1

Source: Summary of Clinical Safety, BLA 125833/0/2, Table 2.7.4-3 in Page 12

AE = adverse event; m = total number of events; N = number of subjects in treatment group;
n = number of subjects with adverse event; TEAE = treatment-emergent adverse event.

Table B. Overview of Adverse Events in Trial 995

Adverse Event Category, [n (%) m]	BT524 (N=110)	FFP/Cryo (N=112)	Total (N=222)
Any AEs	98 (89.1) 431	101 (90.2) 394	199 (89.6) 825
Any Non-severe AEs	96 (87.3) 400	101 (90.2) 364	197 (88.7) 764
Any Treatment-emergent AEs	96 (87.3) 405	100 (89.3) 364	196 (88.3) 769
Any Non-treatment-emergent AEs	20 (18.2) 26	19 (17.0) 30	39 (17.6) 56
Any Non-serious Treatment-emergent AEs	92 (83.6) 361	93 (83.0) 305	185 (83.3) 666
Any Non-severe Treatment-emergent AEs	94 (85.5) 379	99 (88.4) 340	193 (86.9) 719
Any Treatment-emergent Treatment-related AEs	2 (1.8) 3	4 (3.6) 4	6 (2.7) 7
Any Severe AEs	20 (18.2) 31	22 (19.6) 30	42 (18.9) 61
Any Severe Treatment-emergent AEs	17 (15.5) 26	18 (16.1) 24	35 (15.8) 50
Any Severe Treatment-emergent Treatment-related AEs	0	2 (1.8) 2	2 (0.9) 2
Any Serious AEs	30 (27.3) 50	43 (38.4) 62	73 (32.9) 112
Any Serious Treatment-emergent AEs	28 (25.5) 44	41 (36.6) 59	69 (31.1) 103
Any Serious Treatment-emergent Treatment-related AEs	1 (0.9) 1	4 (3.6) 4	5 (2.3) 5
Any AEs Leading to Discontinuation from Trial	0	0	0
Any Treatment-emergent AEs Leading to Trial Discontinuation	0	0	0
Any Treatment-emergent Treatment-related AEs Leading to Discontinuation from Trial	0	0	0
Any AEs with Outcome of Death	0	1 (0.9) 1	1 (0.5) 1
Any Treatment-emergent AE with Outcome of Death	0	1 (0.9) 1	1 (0.5) 1
Any Treatment-emergent Treatment-related AEs with Outcome of Death	0	0	0
Any AEs of Special Interest	24 (21.8) 31	25 (22.3) 35	49 (22.1) 66
Any Treatment-emergent AE of Special Interest	22 (20.0) 28	25 (22.3) 35	47 (21.2) 63

Any Thrombosis or TEE	8 (7.3) 8	13 (11.6) 14	21 (9.5) 22
Any Suspicion of Transmission of Infective Agents	0	0	0
Any Relevant Bleeding Complication	16 (14.5) 20	14 (12.5) 21	30 (13.5) 41
Any Treatment-emergent Treatment-related AEs of Special Interest	1 (0.9) 1	4 (3.6) 4	5 (2.3) 5
Any Treatment-emergent AEs of Hypersensitivity/Anaphylactic Reactions/Anaphylactic Shock	7 (6.4) 8	1 (0.9) 1	8 (3.6) 9
Any Treatment-emergent AEs of Bleeding Related Ischemic Events	5 (4.5) 6	14 (12.5) 15	19 (8.6) 21

Data source: Summary of Clinical Safety, BLA 125833/0/2, Table 2.7.4-4 in Page 16

Note: For each category, subjects are included only once, even if they experienced multiple events in that category.

AE = adverse event; Cryo = cryoprecipitate; FFP = fresh frozen plasma; m = number of individual events; N = number of subjects in treatment group; n = number of subjects with adverse event; TEE = thromboembolic event.