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Applicant	Grifols Therapeutics LLC
Established Name	Fibrinogen (Human) (BT524)
(Proposed) Trade Name	FESILTY
Pharmacologic Class	Antihemorrhagics, human fibrinogen
Formulation(s), including Adjuvants, etc	Human fibrinogen concentrate
Dosage Form(s) and Route(s) of Administration	Lyophilized powder for reconstitution, for intravenous use
Dosing Regimen	Calculate the dose in mg fibrinogen per kg of BW for each patient individually. The target plasma fibrinogen level is 100 mg/dL for minor bleeding and 150 mg/dL for major bleeding.
Indication(s) and Intended Population(s)	Treatment of acute bleeding episodes and for perioperative management of bleeding in pediatric and adult patients with congenital fibrinogen deficiency, including hypo- or afibrinogenemia

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GLOSSARY

ANOVA	Analysis of Variance
AE	Adverse Event
BLA	Biologics License Application
BMI	Body Mass Index
CI	Confidence Interval
Cryo	Cryoprecipitate
EoI	End of Infusion
FAS	Full Analysis Set
FBE	Full Bleeding Event
FiAc	fibrinogen activity
FFP	Fresh Frozen Plasma
IMP	Investigational Medicinal Product
IV	Intravenous
MCF	Maximum Clot Firmness
ODP	On-demand Prophylaxis
ODT	On-demand Treatment
OHR	Overall Hemostatic Response
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per-protocol
SD	Standard Deviation
TP	Transfusion Product
RBC	Red Blood Cell

1. Executive Summary

This is an original biologics license application (BLA) 125833/0 for BT524, a lyophilized, heat-treated, virus- and prion-safe human fibrinogen manufactured from human plasma, indicated for treatment of acute bleeding episodes and perioperative management of bleeding in pediatric and adult patients with congenital fibrinogen deficiency, including hypo- or afibrinogenemia.

The primary evidence of efficacy and safety is based on the results from a Phase I/III, prospective, single-arm, open label study (Trial 984) conducted exclusively at non-US sites. The study was not conducted under a U.S. Investigational New Drug (IND) application. This study was designed with two parts: Part I assessed the pharmacokinetic and pharmacodynamic profile of BT524 following a single intravenous infusion of 70 mg/kg body weight; Part II evaluated efficacy and safety of single or repeated IV infusions of BT524 for on-demand treatment (ODT) or on-demand prophylaxis (ODP). In Part II, 36 patients treated with BT524 experienced a total of 175 bleeding events for ODP and/or ODT. BT524 was rated as successful (good or excellent hemostatic response) for 173 (98.9%; 95% CI: [95.9%, 99.9%]) of the 175 bleeding events.

The safety database consists of data from 45 patients in Trial 984. One adult patient in part II died due to an extradural hematoma. Treatment-emergent adverse events (TEAEs) occurred in 33 patients (73.3%), with a total of 174 events reported. Treatment-emergent serious adverse events (TESAEs) were observed in 9 patients (20.0%), comprising 12 total events.

In conclusion, no major statistical issues were identified in the review of this submission. The efficacy results were confirmed by independent analyses and support the proposed indication.

2. Clinical and Regulatory Background

This original BLA 125833/0 is for BT524, a lyophilized, heat-treated, virus- and prion-safe human fibrinogen manufactured from human plasma, proposed for treatment of acute bleeding episodes and perioperative management of bleeding in patients with congenital fibrinogen deficiency, including hypo- or afibrinogenemia.

2.1 Disease or Health-Related Condition(s) Studied

Congenital fibrinogen deficiency is a rare inherited coagulation disorder that can phenotypically manifest as afibrinogenemia, hypofibrinogenemia, or certain types of dysfibrinogenemia (dysfunctional fibrinogen, qualitative and quantitative abnormalities). The disorder is associated with bleeding symptoms ranging from mild to severe. Congenital hypo-, dys-, or afibrinogenemia are very rare diseases, with estimates of worldwide prevalence of afibrinogenemia of approximately 1 to 9 per million in the general population with similar proportions across reporting countries.

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

Conventional replacement therapy in fibrinogen deficiency consists of transfusion of allogenic blood products such as fresh frozen plasma (FFP) and cryoprecipitate (Cryo). However, both contain additional clotting factors, and the amount of fibrinogen varies, especially in FFP. In addition, the risks of plasma product transfusions (pathogen transmission) and limitations in handling (larger transfusion volumes requiring longer infusion times) led to the development of human fibrinogen concentrates as a further important therapeutic option. Human fibrinogen concentrate offers key advantages over conventional therapies: precise dosing of purified fibrinogen in small volumes (short infusion time), low pathogen transmission risk, and immediate administration without thawing or ABO compatibility testing.

Two human fibrinogen concentrates are currently licensed in the US for congenital fibrinogen deficiency (Haemocomplettan P/RiaSTAP and Fibryga).

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

Pre-Submission Regulatory Activities and Interactions:

- Type C, pre-IND meeting on 8 Sep 2022: To discuss the quality, nonclinical and clinical development of Fibrinogen Concentrate (BT524). FDA expressed concerns as the study was not conducted under IND, and asked the sponsor to provide justification on how the foreign data are applicable to the US population and US medical practice.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

This submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

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

5.1 Review Strategy

This review memo focuses on analyses of Trial 984.

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

The following documents in the BLA 125833/0 were reviewed:

- STN 125833/0 Module 1.2 Reviewers Guide
- STN 125833/0 Module 1.6 Meetings
- STN 125833/0 Module 1.14 Labeling
- STN 125833/0 Module 2.5 Clinical Overview
- STN 125833/0 Module 2.7 Clinical Summary
- STN 125833/0 Module 5.3.5.2 Clinical Study Report (CSR) for Trial 984 and supporting documents and datasets.

- STN 125833/0.3 Module 5.3.5.1 Additional SAS code
- STN 125833/0.28 Module 1.11.3 Response to Mid-Cycle Communication Meeting

5.3 Table of Studies/Clinical Trials

Key design features for Trial 984 are summarized in Table 1.

Table 1: Overview of Trial 984

Phase	I/III
Indication Studied	Congenital Fibrinogen Deficiency
Trial period, region	March 2013 to May 2020 2 sites in Tunisia, 1 each in Bulgaria, Egypt, Germany, and Lebanon
Therapeutic approach	Part I: single dose, 70 mg/kg BW by IV infusion Part II: <u>Surgical intervention:</u> Up to 100 mg/min for ODP to achieve and maintain target level of 1g/L. Up to 100 mg/min for ODT to maintain target level of 1 g/L until hemostasis is secure. Up to 100 mg/min for ODT to maintain target level > 0.5 g/L until wound healing is complete. <u>Spontaneous bleeding:</u> Up to 100 mg/min for ODT of bleeding events.
Trial design	Prospective, open-label, multicenter
Assessed	PK, PD, efficacy, safety
Trial population	Part I: 35 subjects enrolled, 27 treated (aged 0 to 75 years) Part II: 59 subjects enrolled, 36 treated (aged 0 to 75 years)
Primary outcome	PK parameters
Secondary efficacy outcomes	MCF (surrogate efficacy), overall hemostatic response, total loss of blood (intra- and post-operatively; re-bleedings), use of other fibrinogen containing products, use of transfusion products, consumption of BT524, and quality of wound healing
Safety outcomes	Adverse events, development of fibrinogen antibodies, vital signs, physical examination, ECG, clinical laboratory parameters, coagulation parameters ultrasonography, and viral safety

BW = body weight; ECG = electrocardiogram; IV = intravenous(ly); MCF = maximum clot firmness; ODP = on-demand prophylaxis; ODT = on-demand treatment; PD = pharmacodynamics; PK = pharmacokinetics.

Source: Adapted from BLA 125833/0; Clinical Overview, Table 2.5-1

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial 984

Trial 984 was titled “A prospective, open-label, phase I/III study investigating pharmacokinetic properties of BT524 and efficacy and safety of BT524 in the treatment and prophylaxis of bleeding in patients with congenital fibrinogen deficiency.” The study enrolled its first patient on March 20, 2013, and the last patient completed the study on

May 18, 2020. The study was initiated as a phase I/II trial investigating 14-day PK/PD profile in approximately 20 patients. In January 2015, the extension into a phase I/III trial, without changing the primary endpoint (PK/PD), was agreed upon with the PEI (Germany) within a Scientific Advice Meeting. Accordingly, the study was amended to a phase I/III trial, increasing the total number of patients to be treated in Part II from 20 to approximately 30.

6.1.1 Objectives

The primary objective of this study was to investigate the 14-day single-dose PK of BT524 following IV infusion in patients with congenital afibrinogenemia or severe congenital hypofibrinogenemia (Part I).

The secondary objectives included:

- To investigate the 14-day single-dose PD, the surrogate efficacy and safety of BT524 in Part I of the study.
- To investigate efficacy, surrogate efficacy and safety of single and/or repetitive IV infusions of BT524 for an on-demand prophylaxis (ODP) and/or on-demand treatment (ODT) of bleeding events (Part II).

This memo focuses on the efficacy objective and associated endpoints.

6.1.2 Design Overview

Trial 984 was a phase I/III, prospective, uncontrolled, open-label, multicenter study investigating the 14-day single-dose pharmacokinetic and pharmacodynamic properties, efficacy and safety of BT524 following intravenous administration in the treatment of acute bleeding episodes and perioperative management of bleeding in patients with congenital afibrinogenemia or severe congenital hypofibrinogenemia. The study was divided into two study parts (Part I and Part II) described below.

Part I

Part I was focused on the primary endpoint of the study, the 14-day single-dose PK, PD, and the evaluation of the maximum clot firmness (MCF) as a surrogate efficacy parameter. The enrollment target included twenty patients aged 6 to 75 years and at least three patients under 6 years. Individual follow-up (virus safety) was 49±4 days after the administration of BT524 for PK/PD assessment.

Part II

Part I was subsequently extended to Part II, which investigated the efficacy and safety of single and/or repetitive BT524 administrations for on-demand prophylaxis (ODP) and/or on-demand treatment (ODT) of bleeding events (e.g., elective surgical procedure, spontaneous or post-traumatic severe bleeding), if required. All patients from Part I without severe post-dosing complications ideally remained enrolled for ODP/ODT treatment in Part II. At least 10 additional patients ≥ 6 to ≤ 75 years and at least 3 additional patients < 6 years were planned for Part II (ODP/ODT) without PK/PD assessments (Part I). Individual study participation duration was variable, depending on

the timing of the last bleeding episode requiring study medication. For each bleeding event, individual follow-up was 49 ± 4 days after the last BT524 administration. For the last patient included, this comprised a minimum 12-month period for optional on-demand prophylaxis and/or treatment, including the safety visit 49 ± 4 days after the last BT524 administration.

6.1.3 Population

Diagnosis and main criteria for inclusion:

1. Known congenital afibrinogenemia or severe congenital hypofibrinogenemia.
2. Plasma fibrinogen activity (FiAc) ≤ 0.5 g/l and antigen (FiAg) ≤ 0.5 g/l.
3. Male or female.
4. Age 0 to 75 years, with the first ten patients will be 18 years or older.
5. Presumed to be compliant with the study procedures and to terminate the study as scheduled.
6. Willing and able to be hospitalized for 3 days for the PK assessment (if applicable).
7. Willing and able to be hospitalized - if required - in case of interventions (e.g., surgical procedures, major bleeds).
8. Written informed consent by the patient, his/her parents or by the patient's legal / authorized representative as applicable.

6.1.4 Study Treatments or Agents Mandated by the Protocol

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 >0.5 g/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

This 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.

6.1.7 Surveillance/Monitoring

Please refer to the clinical review regarding details of study monitoring.

6.1.8 Endpoints and Criteria for Study Success

The primary endpoints were PK parameters, which are not covered in this memo. This memo will assess the following efficacy endpoints.

Efficacy Endpoints:

- Surrogate Efficacy: Maximum clot firmness (MCF, mm) measured by rotational thromboelastometry was assessed as a surrogate efficacy parameter in study Part I and Part II.
- Clinical Efficacy (Part II):
 - Overall hemostatic response (OHR) to treatment with BT524 for each surgical procedure and each treated bleed as assessed by the investigator according to a 4-point scale: none, moderate, good or excellent. The overall assessment was to be performed on the day of hospital discharge (if applicable) or at the end of the treated bleeding event.
 - Total loss of blood (e.g., intra- and post-operatively, re-bleedings), if applicable.
 - Units of other fibrinogen-containing products (FCP) infused besides BT524 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 BT524 (dose per kilogram body weight [BW] required pre-, intra- or post-operatively for effective treatment).
 - Quality of wound healing, if applicable.

The only confirmatory testing was performed on the change of MCF 1h after end of infusion (EoI) compared to pre-dose values in Part I. A two-sided p-value less than 0.05 will then be considered statistically significant.

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

Sample Size Estimation

The primary endpoints of this study were PK parameters. For the PK parameters, no formal sample size calculation was carried out. As a general rule, approximately 20

patients in this single cohort were planned and should suffice to calculate PK parameters with the corresponding range of distribution.

A formal sample size calculation was performed for the surrogate (secondary) efficacy variable MCF using a t-test for dependent means (post minus pre-treatment difference; one sample). Mean MCF values (Fib-tem S of ROTEM) were assessed before and 1 hour after BT524 treatment. With 15 patients, assuming pre-treatment mean of 4 mm (SD 7 mm) and post-treatment mean of 10 mm (SD 8 mm), an effect size of 0.8 mm can be detected with 80% power at $\alpha = 5\%$ (2-sided).

Analysis Sets

- 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 BT524 in Part I/Part II
- Full analysis set (FAS I/II): all patients who received any portion of BT524 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 BT524 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.

For Part I analyses, the relevant framework for allocating patients to analysis sets was restricted to the time from enrollment in Part I to date of PK safety visit (Day 49 \pm 4) in Part I. For Part II analyses, the relevant framework for allocating patients to analysis sets was restricted to the time from enrollment in Part II to date of safety visit (Day 49 \pm 4) of the last patient's bleeding event treated in Part II. For patients who completed Part I and participated in Part II as well, time of enrollment in Part II was defined as the first day after the PK safety visit.

Efficacy Endpoints Analyses

- Maximum Cloth Firmness (MCF)
In Part I, MCF was to be measured pre-dose and at the following time points per age group: 1h and 8h after EoI for patients ≥ 6 years; 1h after EoI in children between 2 and < 6 years of age, and at EoI for children < 2 years. Descriptive statistics for MCF Part I data including changes from pre-dose (baseline) were to be provided per age group for SAF I, FAS I, and PP I.

MCF values assessed as “not measurable” (i.e., below the detection limit of 2 mm) by the central laboratory were to be set to half of the range below the detection limit (i.e., range is “0 to 2”, value used is “1 mm”) for the purpose of the planned descriptive statistical analyses.

Pre-post comparisons of MCF values in adults (patients aged ≥ 18 years) were to be assessed by means of one-sample t-test, with a two-sided type I error control at $\alpha = 0.05$:

$$H_0: \mu_{1,0} < 0 \quad v.s. \quad H_1: \mu_{1,0} > 0,$$

where $\mu_{1,0}$ is the mean difference between dependent measurements (1h post minus pre-treatment MCF). The analysis was considered confirmatory for the change in MCF 1h after EoI compared to pre-dose levels. Correlation between MCF and fibrinogen activity (FiAc) pre-dose and at 1- and 8-hours post-end of each IV infusion was to be assessed in patients ≥ 6 years.

Reviewer's comment: The above hypothesis was stated by applicant both in CSR and SAP, which created an incomplete parameter space by excluding the case where $\mu_{1,0} = 0$. Correct hypothesis for testing the superiority should be:

$$H_0: \mu_{1,0} \leq 0 \quad v.s. \quad H_1: \mu_{1,0} > 0.$$

In Part II, the MCF was to be measured pre-dose and 1h after EoI, including repetitive infusions per bleeding event. Pre-post comparisons of MCF values were to be summarized with two-sided 95% CIs based on the t-distribution. In addition, correlation between MCF and FiAc pre-dose and 1h after EoI were to be assessed by means of Pearson's correlation coefficient for the FBE and PPBE.

- Overall Hemostatic Response (OHR) and Treatment Success
Overall hemostatic response to treatment with BT524 per surgical procedure and treated bleeding event was to be rated on a 4-point scale ("none", "moderate", "good" or "excellent"). Treatment success was defined as a rating of either good or excellent. The overall assessment was to be performed at the day of hospital discharge (if applicable) or at the end of the treated bleeding event. Response rates and 95% CIs were to be calculated for each OHR assessment on event level and for treatment success.
- Other secondary efficacy analyses
 - Total Loss of Blood: Surgical bleeding was to be rated by investigators as "lower than expected," "within expected range," or "higher than expected." Ratings were to be analyzed descriptively (frequencies/percentages) for FBE and PPBE events.
 - Units of fibrinogen-containing products (such as FFP or cryoprecipitate), and units of transfusion products (such as allogenic or autologous blood [packed RBC, fresh whole blood]) used to treat bleeding and hemodynamic instability on the day of BT524 administration or next day were to be analyzed descriptively for FBE and PPBE events.
 - Consumption of BT524 (dose per kilogram body weight, dose per infusion and total dose) required pre-, intra- or post-operatively was to be analyzed descriptively for treated surgical bleeding events.

- Wound Healing: Descriptive statistics for quality of wound healing (none, moderate, good, excellent) was to be presented for ODT and ODP and overall by degree of bleeding event (minor, major) in the FBE and PPBE.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

6.1.10.1.1 Demographics

Demographic data for all subjects treated in Part I and Part II are summarized in Table 2. Median ages were 18 years for both parts of the study. All patients were white except for one patient who was black or African American in Part I. More male than female patients were treated in Part I (51.85% vs. 48.15%, SAF I) and Part II (61.11% vs 38.89%, SAF II).

Table 2: Demographics (SAF I, N=27; SAF II, N=36)

Category	Part I SAF I, N=27	Part II SAF II, N=36
Age (years)*		
Mean (SD)	17.6 (11.8)	19.6 (11.8)
Median (Min, Max)	18.0 (1.0, 40.0)	18.0 (1.0, 47.0)
Sex, N (%)		
Female	13 (48.1 %)	14 (38.9%)
Male	14 (51.9%)	22 (61.1%)
Race, N (%)		
Black or African American	1 (3.7%)	0
White	26 (96.3%)	36 (100.0%)
BMI (kg/m²)		
Mean (SD)	22.1 (5.8)	21.9 (5.7)
Median (Min, Max)	22.5 (14.7, 37.9)	21.8 (15.0, 37.9)
Age group, N (%)*		
<6 y	6 (22.2%)	3 (8.3%)
6 to <12 y	3 (11.1%)	9 (25.0%)
12 to <18 y	3 (11.1%)	4 (11.1%)
18 to 75 y	15 (55.6%)	20 (55.6%)

Abbreviations: BMI= body mass index; kg=kilogram; Max=maximum; Min=minimum; N = number of subjects; SD=standard deviation, y = years.

* For Part I, age at date of first BT524 treatment in Part I of the trial was used.

For Part II, age at date of first BT524 treatment in Part II of the trial was used.

Source: Adapted from BLA 125833/0; A Summary of Clinical Efficacy – Congenital Fibrinogen Deficiency, Table 2.7.3.A-5 and Table 2.7.3.A-6

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

All 27 patients in SAF I and 34 (94.4%) of the 36 patients in SAF II had afibrinogenemia at baseline. Severe hypofibrinogenemia was reported for 2 patients in SAF II, in the age group of children aged 6 to < 12 years.

A total of 385 and 521 previous bleeding events before the first IMP administration were reported for patients in Part I and Part II, respectively. The most common types of previous bleeding events in both parts were muscle haematoma (124 and 140 events, respectively), hemarthrosis (58 and 89 events, respectively), oral cavity bleeding (45 and 68 events, respectively), epistaxis (23 and 37 events, respectively), menorrhagia (28 and 34 events, respectively), and umbilical cord bleeding (24 and 25 events, respectively). The mean annualized bleeding rate during the 12 months prior to informed consent signature was 1.9 for Part I and 2.4 for Part II.

6.1.10.1.3 Subject Disposition

Overall, 67 patients were enrolled and screened in the study. Part I enrolled 35 patients, 27 of whom continued into Part II. Part II enrolled 32 additional patients, for a total of 59 patients enrolled in Part II.

In Part I, 5 of the 35 enrolled patients were not eligible (screening failures) and 3 of 30 eligible patients discontinued from study before receiving study treatment (withdrawal by patient: 1 patient; ICF withdrawal: 1 patient, other reason: 1 patient).

In Part II, 7 of the 59 enrolled patients were not eligible (screening failures), 5 of 52 eligible patients discontinued from the study before receiving IMP in Part II (withdrawal by patient: 1 patient; AE: 1 patient, other reason: 3 patients), and 11 of 52 eligible patients completed Part II without a bleeding event. A total of 36 patients in Part II received IMP treatment of which 18 patients were from Part I.

Table 3 and Table 4 provides the subject disposition and analysis population sets, respectively.

Table 3: Subject Disposition

	Part I, N	Part II, N
All Patients Enrolled	35	59
Screening Failures	5	7
Not Treated Reason		
Withdrawal by patient	1	1
ICF withdrawal	1	0
AE	0	1
Without a bleeding	-	11
Other reason	1	3
Treated Subjects	27	36
Patients Completed Study	27	28
Discontinuation Reason		
Withdrawal by patient	0	1
AE	0	4
Other	0	3

AE= adverse event; ICF = informed consent form; N = number of subjects.

Source: Adapted from BLA 125833/0; Clinical Report of Trial 984, Figure 2

Table 4: Analysis Population

	Part I	Part II
SAF, N	27	36
FAS, N	27	36
PP, N	24	33
FBE, n	NA	175
PPBE, n	NA	164

Abbreviations: FAS = full analysis set; FBE = full bleeding event; PPBE = per-protocol bleeding event; N = number of subjects; n = number of bleeding events; PP = per protocol set; SAF = safety analysis set.

Source: Adapted from BLA 125833/0; Clinical Report of Trial 984, page 3

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The primary endpoint of this study was PK parameters. Efficacy endpoints were secondary. Please refer to the clinical pharmacology reviewer's memo.

6.1.11.2 Analyses of Secondary Endpoints

MCF in Part I

Mean MCF values over time (pre-dose, and 1h and 8h after EoI) and changes from pre-dose to 1h and 8h after EoI in Part I of the study were summarized in Table 5. Of note, there were missing pre-dose MCF values for one subject each in the 6–<12 years and 12–<18 years cohorts, and for three subjects in the 18–75 years group. Additionally, one adult patient lacked an MCF value at 8 hours after EoI. These missing values were primarily due to insufficient material available for a valid control. Changes at 1 hour after EoI and changes at 8 hours after EoI were calculated for patients with both, pre-dose and post-dose MCF values.

Pre-dose MCF values were below the 2mm detection limit across all age groups, with the exception of one adult patient who had a value of 3mm. MCF values were considerably higher 1 hour after EoI, ranging from 10.3mm in children <6 years to 16.0mm in children aged 6 to <12 years. In adults, the mean difference between MCF levels at 1 hour after EoI and pre-dose was 11.1mm (95% CI: 7.9, 14.3; $p < 0.0001$).

Reviewer's comment: Table 33 of Clinical Report of Trial 984 shows that the mean difference between MCF levels at 1 hour after EoI and pre-dose was 11.1mm (95% CI: 9.33, 14.47; $p < 0.0001$). The 95% CI of (9.33, 14.47) was inappropriately calculated using a two-sample t-test approach. The correct approach, as the applicant's pre-specified, is to use one-sample t-test, which yielded a CI of (7.9, 14.3).

Table 5: Mean Maximum Clot Firmness (mm) and Changes from Pre-Dosing Values in Part I of the Study (FAS I, N=27)

Times	Statistics	<6 y (N=6)	6 to < 12 y (N=3)	12 to < 18 y (N=3)	18 to 75 y (N=15)
Pre-dose	n	6	2	2	12
	Mean (SD)	1.0 (0.0)	1.0 (0.0)	1.0 (0.0)	1.2 (0.6)
1h after EoI	n	3	3	3	15
	Mean (SD)	10.3 (1.5)	16.0 (3.6)	10.7 (3.1)	13.1 (4.6)
8h after EoI	n	-	3	3	14
	Mean (SD)	-	11.7 (2.1)	8.7 (2.5)	12.7 (4.7)
Change at 1h after EoI	n	3	2	2	12
	Mean (SD)	9.3 (1.5)	16.5 (3.5)	11.0 (2.8)	11.1 (5.1)
Change at 8h after EoI	n	-	2	2	11
	Mean (SD)	-	11.5 (2.1)	9.0 (1.4)	11.3 (5.1)

MCF levels at 8h after EoI were only measured in patients ≥ 6 years.

EoI = end of infusion; FAS = full analysis set; h = hours; N = number of patients in age group (based on patient's age at time of BT524 treatment in Part I); n = number of patients with assessments; SD = standard deviation; y = years

Source: Adapted from BLA 125833/0; Clinical Report of Trial 984, Table 33

MCF in Part II

In Part II of the study, MCF evaluations were based on bleeding events treated with BT524 and results were summarized in Table 6 per age group in the FBE. Missing pre-dose values were documented for 1 event in the <6 years group, 4 events in the 6–<12 years group, 5 events in the 12–<18 years group, and 33 events in the 18–75 years group. These missing values were primarily attributed to insufficient material available for valid control testing or non-reproducible results caused by unknown interfering substances. The secondary efficacy endpoint “change at 1 hour after EoI” was computed using only those subjects for whom both, pre-dose and a 1-hour post-EoI MCF measurement were available.

Table 6: Mean Maximum Clot Firmness (mm) and Pre-Post Changes for Bleeding Events in Part II (FBE, N=175)

Times	Statistics	<6 y (N=4)	6 to < 12 y (N=47)	12 to < 18 y (N=32)	18 to 75 y (N=92)
Pre-dose	n	3	43	27	59
	Mean (SD)	1.0 (0.0)	1.0 (0.0)	1.0 (0.0)	2.1 (4.0)
1h after EoI	n	4	48	31	82
	Mean (SD)	10.8 (5.0)	11.7 (4.8)	11.3 (5.5)	12.7 (5.5)
Change at 1h after EoI	n	3	43	26	56
	Mean (SD)	8.7 (5.5)	11.1 (4.6)	9.8 (5.3)	11.1 (5.5)

Age groups are based on patient's age at time of treatment of the specific bleeding event. One patient may contribute to bleeding events in different age groups.

EoI = end of infusion; FBE = full bleeding event set; h = hour; N = number of bleeding events in age group; n = number of bleeding events assessed; SD = standard deviation; y = years

Source: Adapted from BLA 125833/0; Clinical Report of Trial 984, Table 34

Overall Hemostatic Response (OHR)

The 36 subjects treated with BT524 in trial Part II experienced a total of 175 bleeding events. Out of 175 bleeding events, 45 were traumatic, 65 were spontaneous, 54 were surgical, and 11 bleeds were classified as other. Among them, 28 subjects were treated on-demand (ODT) with BT524 for 115 bleeding events, ranging from 1 to 18 events per subject. In addition, 22 subjects experienced 60 bleeding events during on-demand prophylaxis (ODP), with 1 to 10 events per subject. ODP was used in this trial to prevent bleedings during or after specific pre-planned surgeries or other treatments (BT524 administered prior to surgery or as peri- or post-operative infusion) rather than as routine prophylactic treatment over a longer time period. The classification of bleeding events into major and minor events was performed post-dose by the investigator. See Table 7 below for details:

Table 7: Summary of Bleeding Events by Age Group (FBE, n=175)

	< 6 y ^a N=3	6 to < 12 y ^a N=9	12 to < 18 y ^a N=5	18 to 75 y ^a N=20	Overall ^a N=36
Total, n (%)	4 (100.0)	47 (100.0)	32 (100.0)	92 (100.0)	175 (100.0)
By Severity, n (%)					
Major	2 (50.0)	3 (6.4)	6 (18.8)	42 (45.7)	53 (30.3)
Minor	2 (50.0)	44 (93.6)	26 (81.3)	50 (54.3)	122 (69.7)
By Type of Treatment, n (%)					
ODT	2 (50.0)	42 (89.4)	31 (96.9)	40 (43.5)	115 (65.7)
ODP ^b	2 (50.0)	5 (10.6)	1 (3.1)	52 (56.5)	60 (34.3)
Mean (SD) per subject	1.3 (0.6)	5.2 (5.9)	6.4 (5.9)	4.6 (3.3)	4.9 (4.33)

^a Bleeding events were assigned to the age group based on the subject's age at the start of BT524 treatment for the specific bleeding event, meaning that one subject could contribute bleeding events to different age groups. One subject aged 6 to < 12 years at the time of the first BT524 dose contributed an additional event to the 12 to < 18 year-age group; therefore, the number of adolescent subjects is N = 4 for subject-based analyses, but N = 5 for event-based analyses.

^b In Trial 984, ODP use generally refers to prophylactic use associated with a specific surgery or treatment rather than to routine prophylactic use.

Abbreviations: N = number of subjects per age group; n = number of bleeding events; ODP = on-demand prophylaxis; ODT = on-demand treatment; SD = standard deviation; y = years.

Source: Adapted from BLA 125833/0; Summary of Clinical Efficacy – Congenital Fibrinogen Deficiency, Table 2.7.3.A-8

For each bleeding event and surgical procedure, investigators rated the overall hemostatic response (OHR) as excellent, good, moderate, or none at hospital discharge or end of treatment. Treatment success was defined as combined good and excellent ratings. BT524 achieved a 98.9% success rate (173/175 events; 95% CI: 95.9-99.9%), with 150 (85.7%) excellent and 23 (13.1%) good ratings in FBE. Only two minor adult bleeding events (1.1%) received moderate ratings. The per-protocol bleeding events (PPBE) showed similar results with 98.8% success (162/164 events), comprising 88.4% excellent and 10.4% good ratings. There were no notable differences in OHR between bleeding

events treated with BT524 for ODP or ODT in the FBE (Table 8). PPBE results were comparable.

Table 8: Overall Hemostatic Response by Treatment Type (ODT or ODP) and by Event Type (Major or Minor) (FBE, N=175)

Event Category	Response category	Number of responses	Response rate, % (95 % CI)
On-demand treatment			
Total bleedings (N = 115)	Moderate	1	0.9 (0.0; 4.7)
	Good	16	13.9 (8.2; 21.6)
	Excellent	98	85.2 (77.4; 91.1)
	Success	114	99.1 (95.3; 100.0)
Major bleedings (N = 22)	Excellent	22	100.0 (84.6; 100.0)
	Success	22	100.0 (84.6; 100.0)
Minor bleedings (N = 93)	Moderate	1	1.1 (0.0; 5.8)
	Good	16	17.2 (10.2; 26.4)
	Excellent	76	81.7 (72.4; 89.0)
	Success	92	98.9 (94.2; 100.0)
On-demand prophylaxis^a			
Total bleedings (N = 60)	Moderate	1	1.7 (0.0; 8.9)
	Good	7	11.7 (4.8; 22.6)
	Excellent	52	86.7 (75.4; 94.1)
	Success	59	98.3 (91.1; 100.0)
Major bleedings (N = 31)	Good	2	6.5 (0.8; 21.4)
	Excellent	29	93.5 (78.6; 99.2)
	Success	31	100.0 (88.8; 100.0)
Minor bleedings (N = 29)	Moderate	1	3.4 (0.1; 17.8)
	Good	5	17.2 (5.8; 35.8)
	Excellent	23	79.3 (60.3; 92.0)
	Success	28	96.6 (82.2; 99.9)

Note: 95 % CIs were calculated using the Clopper-Pearson method.

^a In Trial 984, ODP use generally refers to prophylactic use associated with a specific surgery or treatment rather than to routine prophylactic use.

CI = confidence interval; CTR = Clinical Trial Report; N = number of bleeding events per category; ODP = on-demand prophylaxis; ODT = on-demand treatment.

Source: Adapted from BLA 125833/0; Summary of Clinical Efficacy – Congenital Fibrinogen Deficiency, Table 2.7.3.A-13

The overall treatment success rate for bleedings treated with BT524 in Trial 984 was 99.1% for ODT, well within the range of the published success rates of 80.0% to 100.0% observed for the three reference human fibrinogen concentrates (Haemocomplettan

P/RiaSTAP, Fibryga, and FibCLOT) in a total of six trials and observational studies. The overall treatment success rate of ODP surgery prophylaxis with BT524 was 98.3 %, again well within the range of 97.5 % to 100.0 % observed with the three reference human fibrinogen concentrates.

Administration of Other Fibrinogen-Containing Products (FCPs)

No other FCPs were used at the day of BT524 infusion or up to 1 day after BT524 administration for treatment of bleeding events.

Administration of Other Transfusion Products (TPs)

One pediatric patient aged 6 to <12 used 100 ml red blood cells (RBCs), and one adult patient used 300ml concentrated RBCs for treatment of 2 (1.1%) bleeding events at the day of BT524 infusion or up to 1 day after the infusion.

Consumption of BT524 for Surgical Bleeding Events

All 54 surgical bleeding events (100%) in 19 patients in the FBE received pre-operative administration of BT524. Post-operative administrations were reported for 7 (13.0%) surgical bleeding events. Intraoperative IMP administrations were reported for none of the study patients. A summary of BT524 consumption for treatment of 54 surgical events in the FBE is shown in Table 9.

Table 9: Consumption of BT524 for Treated Surgeries in Part II (FBE, N=175)

	Statistics	< 6 y N=2	6 to < 12 y N=2	12 to < 18 y N=1	18 to 75 y N=49
Preoperative [mg/kg BW]	n	2	2	1	49
	Mean (SD)	83.3 (23.6)	75.7 (6.1)	71.4	58.3 (13.1)
	Median (Q1-Q3)	83.3 (66.7-100.0)	75.7 (71.4-80.0)	71.4	53.2 (48.4-68.7)
Postoperative, [mg/kg BW]	n	1	2	0	4
	Mean (SD)	100.0	69.9 (0.2)	-	147.6 (158.7)
	Median (Q1-Q3)	100.0	69.9 (69.8-70.0)	-	83.6 (49.2-246.0)
Perioperative, [mg/kg BW]	n	2	2	1	49
	Mean (SD)	133.3 (94.3)	145.6 (6.2)	71.4	70.3 (61.9)
	Median (Q1-Q3)	133.3 (66.7-200)	145.6 (141.2-150.0)	71.4	53.2 (48.4-70.0)

Age groups are based on patient's age at time of treatment of the specific bleeding event. One patient may contribute to bleeding events in different age groups.

BW = body weight; FBE = full bleeding event set; N = number of surgical bleeding events in age group; n = number of surgical bleeding events assessed; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; y = years

Source: Adapted from BLA 125833/0; Clinical Report of Trial 984, Table 40

Wound Healing

Investigator assessments of wound healing (none, moderate, good, excellent) were analyzed descriptively for both FBE and PPBE. Of 39 evaluated bleeding events, 21 (53.8%) had good wound healing, 15 (38.5%) had excellent wound healing, and 3 (7.7%) had moderate wound healing. No events were rated as having no response to BT524 treatment. PPBE results were similar.

Total Loss of Blood

Investigator assessments of blood loss per surgical bleeding event ("lower than expected," "within the expected range," and "higher than expected") were analyzed descriptively for FBE and PPBE. Of 54 surgical events in the FBE, 45 (83.4%) had blood loss within the expected range, 4 (7.4%) had higher than expected loss, and 3 (5.6%) had lower than expected loss. PPBE results were similar.

6.1.11.3 Subpopulation Analyses

Because few enrolled patients were non-white, subgroup analysis by race would not provide clinically interpretable results and therefore was not performed. For the clinical efficacy endpoint OHR, subgroup analysis by type of treatment (ODP/ODT) was provided in Table 8.

Table 10 summarizes subgroup analyses results by age group and sex. There were no notable differences in OHR rates across the age groups or between sexes.

Table 10: Overall Hemostatic Response by Age Group and by Sex (FBE, N=175)

	Moderate, n (%)	Good, n (%)	Excellent, n (%)	Success, n (%)
Age Group				
<6 y (N=4)	0	0	4 (100%)	4 (100%)
6 to < 12 y (N=47)		7 (14.9%)	40 (85.1 %)	47 (100%)
12 to < 18 y (N=32)	0	0	32 (100%)	32 (100%)
18 to 75 y (N=92)	2 (2.2%)	16 (17.4%)	74 (80.4%)	90 (97.8%)
Sex, N (%)				
Female (N=62)	0	5 (8.1%)	57 (91.9%)	62 (100.0%)
Male (N=113)	2 (1.8%)	18 (15.9%)	93 (82.3%)	111 (98.2%)

Age groups are based on patient's age at time of treatment of the specific bleeding event. One patient may contribute to bleeding events in different age groups.

FBE = full bleeding event set; n = number of surgical bleeding events in each subgroup; y = years

Source: Adapted from BLA 125833/0; Clinical Report of Trial 984, Figure 7

6.1.11.4 Dropouts and/or Discontinuations

All 27 patients treated with IMP in Part I completed the study. In Part II, most of the 36 patients who received at least one dose of IMP (N = 28) also completed the study. Eight patients discontinued from Part II due to withdrawal by the patient (N = 1), adverse events (N = 4, including one death), or other reasons (N = 3). Part II analyses were based on bleeding events, and these 8 patients had 27 bleeding events in FBE before their discontinuation.

6.1.12 Safety Analyses

6.1.12.1 Methods

Please refer to the clinical reviewer's memo.

6.1.12.3 Deaths

One adult patient in Part II died due to an extradural hematoma. This patient was first treated with BT524 in Part I and received ODT for spontaneous hemarthrosis bleeding on the left elbow during Part II of the study. Approximately 4 months after this BT524 treatment, the patient experienced severe intracranial bleeding that resolved after 6 days. The patient subsequently received ODP for two surgical procedures (elbow synovectomy and dental extraction) in Part II. Approximately 4 weeks after the last BT524 administration (for dental extraction), the patient developed epilepsy and extradural hematoma. The patient died one week later from the extradural hematoma.

6.1.12.4 Nonfatal Serious Adverse Events

Overall, 174 TEAEs were reported in 33 (73.3%) of 45 patients in SAF I and SAF II (Table 11). TESAEs were reported in 9 (20.0%) patients overall, most of them (7 of 9) being reported in patients in Part II of the study.

Table 11: Overview of Adverse Events (SAF I, N=27; SAF II, N=36)

	Part I, (N=27)	Part I, (N=27)	Part II, (N=36)	Part II, (N=36)	Overall, (N=45)	Overall, (N=45)
	n1	n2 (%)	n1	n2 (%)	n1	n2 (%)
TEAEs	31	15 (55.6)	143	27 (75.0)	174	33 (73.3)
Related TEAEs	1	1 (3.7)	2	1 (2.8)	3	2 (4.4)
Severe TEAEs	5	2 (7.4)	24	12 (33.3)	29	14 (31.1)
TESAEs	3	2 (7.4)	9	7 (19.4)	12	9 (20.0)
TEAEs leading to study discontinuation	1*	1* (3.7)	3	3 (8.3)	4	4 (8.9)
AEs leading to death	0	0	1	1 (2.8)	1	1 (2.2)

*One patient completed Part I of the study but discontinued prematurely from Part II due to AE. AEs = adverse events; N = number of patients; n1 = number of adverse events; n2 = number of patients with at least one adverse event; SAF = safety analysis set; TESA = treatment-emergent serious adverse event; TEAE = treatment-emergent adverse event; % = percentage of patients with at least one event

Source: Adapted from BLA 125833/0; Clinical Report of Trial 984, Table 43

6.1.12.7 Dropouts and/or Discontinuations

One adult patient experienced an SAE (pain in extremity) approximately 4 days after the BT524 administration in Part I. This patient completed Part I of the study but discontinued prematurely from Part II. Three patients withdrew during Part II due to a portal vein thrombosis (SAE), a deep vein thrombosis (moderate AE), and pregnancy, respectively.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

The primary evidence of efficacy and safety is based on the results from a Phase I/III, prospective, single-arm, open label study (Trial 984) conducted exclusively at ex-US sites, which was not under a U.S. Investigational New Drug (IND) application. This study was designed with two parts: Part I assessed the pharmacokinetic and pharmacodynamic profile of BT524 following a single intravenous infusion of 70 mg/kg body weight; Part II evaluated efficacy and safety of single or repeated IV infusions of BT524 for on-demand treatment (ODT) or on-demand prophylaxis (ODP). In Part II, 36 patients treated with BT524 experienced a total of 175 bleeding events for ODP and/or ODT. BT524 was rated as successful (good or excellent hemostatic response) for 173 (98.9%; 95% CI: [95.9%, 99.9%]) of the 175 bleeding events.

The safety database consists of data from 45 patients in Trial 984. One adult patient in Part II died due to an extradural hematoma. Treatment-emergent adverse events (TEAEs) occurred in 33 patients (73.3%), with a total of 174 events reported. Treatment-emergent serious adverse events (TESAEs) were observed in 9 patients (20.0%), comprising 12 total events.

10.2 Conclusions and Recommendations

In conclusion, no major statistical issues were identified in the review of this submission. The efficacy results were confirmed by independent analyses and support the proposed indication.