



Our STN: BL 125833/0

**LATE-CYCLE  
MEETING MEMORANDUM**  
September 30, 2025

Grifols Therapeutics, LLC  
Attention: Sharleen Xiong, PhD, RAC  
Director, R&D Regulatory Strategy  
79 TW Alexander Drive  
4101 Research Commons  
Durham, NC 27709

Dear Dr. Xiong:

Attached is a copy of the memorandum summarizing your September 16, 2025, Late-Cycle Meeting teleconference with CBER. This memorandum constitutes the official record of the teleconference. If your understanding of the teleconference outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER in writing as soon as possible.

Please include a reference to the appropriate Submission Tracking Number (STN) in future submissions related to the subject product.

If you have any questions, please contact the Regulatory Project Manager, Candace Jarvis at (240) 402-8315 or by email at [Candace.Jarvis@fda.hhs.gov](mailto:Candace.Jarvis@fda.hhs.gov).

Sincerely,

Mara Miller, MA  
Director  
Division of Review Management and Regulatory Review 2  
Office of Review Management and Regulatory Review  
Office of Therapeutic Products  
Center for Biologics Evaluation and Research

### **Late-Cycle Meeting Summary**

**Meeting Date and Time:** September 16, 2025, 12:00-1:00PM ET  
**Meeting Location:** Virtual Face to Face

**Application Number:** 125833/0  
**Product Name:** Fibrinogen (Human) (BT524)  
**Indication:** -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

**Applicant Name:** Grifols Therapeutics, LLC

**Meeting Chair:** Sergey Akimov, PhD  
**Meeting Recorder:** Candace Jarvis

### **FDA ATTENDEES**

Sergey Akimov, PhD, CBER/OTP/OPPT  
Natalya Ananyeva, PhD, CBER/OTP/OPPT  
Kouassi Ayikoe, PhD, CBER/OCBQ/DBSQC  
Artur Belov, PhD, CBER/OBPV  
Colleen Caldwell, MS, MPH, CBER/OTP/ORMRR  
Jennifer Chan, PharmD, CBER/OCBQ/DIS  
Jennifer Dotson, DO, CBER/OTP/OCE/DCEH  
CDR Donald Ertel, MS, MT(ASCP), CBER/OCBQ/DMPQ  
Kori Francis, CBER/OCBQ/DBSQC  
Varsha Garnepudi, MS, RAC, CBER/OCBQ/DBSQC  
Lin Huo, PhD, CBER/OBPV/DB  
Candace Jarvis, CBER/OTP/ORMRR  
Xing Jing, PhD, CBER/OTP/OCE/DCEH  
Courtney W Johnson, MD, CBER/OTP/OCE/DCEO  
Alla Kachko, PhD, CBER/OCBQ/DMPQ  
George Kastanis, MS, CBER/OCBQ/DBSQC  
Megha Kaushal, MD, CBER/OTP/OCE/DCEH  
CDR Sadhna Khatri, PharmD, CBER/OCBQ/DCM/APLB  
Wei Liang, PhD, CBER/OTP  
Anthony Lorenzo, CBER/OCBQ/DMPQ  
Xiuju (Sue) Lu, PhD, CBER/OCBQ/DMPQ  
Mara Miller, MA, CBER/OTP/ORMRR  
Fadi Nossair, MD, CBER/OTP/OCE/DCEH  
Yen B. Phan, MLS(ASCP)CM, CBER/OCBQ/DBSQC/LMIVTS  
CDR Kenneth Phillips, CBER/OCBQ/DBSQC

Zuben Sauna, PhD, CBER/OTP/OPPT  
Yuyin Shi, PhD, CBER/OBPV/DB  
Lisa Stockbridge, PhD, CBER/OCBQ/DCM/APLB  
Hoda Thai, MS, CBER/OCBQ/DMPQ  
Shaokui Wei, MD, MPH, CBER/OBPV/DPV  
Kerry Welsh, CBER/OBPV/DPV  
Emily Wires, PhD, CBER/OTP/OPT  
Lihan Yan, PhD, CBER/OBPV/DB

## **APPLICANT ATTENDEES**

**Sharleen Xiong Director, R&D Regulatory Strategy, Grifols**

Neil Davie, Head Drug Development, Grifols

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Heike Böhm, Director, Clinical Strategy, Biotest  
Alexander Status, Senior Director, Biostatistics, Biotest  
Kim Hanna, Head Clinical Development, Grifols  
Peter Nelson, Senior Medical Director, Clinical Development, Grifols  
Miquel Barcelo Torns, Assoc Director Clinical Science, Clinical Development, Grifols  
Dermot Whymys, Head Biometry, Grifols  
Monika Richter, Head Regulatory Affairs, Grifols  
Joerg Schuettrumpf, CEO, Biotest & Chief Scientific Innovation, Grifols  
Clark Zervos, VP Quality, Grifols Therapeutics  
Christine Piasek, Senior Director, Regulatory Affairs, Biotest  
Christina Erb, Head Scientific Operations and Innovation, Biotest  
Josephine Buth Head, Regulatory Affairs, Biotest  
Sonia Amoros Reboredo, Senior Director, Biopharma Regulatory Affairs, Grifols  
Brittany Zick Senior Director, Global Program Leader, Grifols  
Christian Hüber, Senior Director, Program Leader Development Projects, Biotest  
Jodie Colvin, Senior Manager, R&D Regulatory Strategy, Grifols  
Johanna Hoffman, Medical Safety Advisor, Drug Safety, Biotest

## **BACKGROUND**

BLA 125833/0 was submitted on December 27, 2024, for Fibrinogen (Human) (BT524).

Proposed indication(s):	-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
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PDUFA goal date: December 27, 2025

In preparation for this meeting, FDA issued the Late-Cycle Meeting Materials on September 5, 2025.

## DISCUSSION

### 1. Discussion of Substantive Review Issues

After completing our review and analysis, the FDA review team has the following major review concerns:

- The difference in intra-operative eligibility criteria results in inclusion of an insufficiently severe patient population since all patients with abdominal PMP surgery did not have intra-operative bleeding prior to randomization and treatment.
- The difference in product administered in the control arm results in a control arm that is not fully comparable to BT524, in patients with spinal surgery, since FFP is a sub-optimal source of fibrinogen.
- There is a paucity of patients with protocol-defined pre-dose intra-operative hypofibrinogenemia (i.e., < 200 mg/dL) enrolled on the trial, resulting in an inappropriately small efficacy evaluable population of 4/98 (4%) patients with abdominal PMP surgery and 43/124 (35%) patients with spinal surgery.
- Inclusion of a covariate in the primary efficacy analysis, based on surgeon-determined bleeding prediction (without an objective protocol-based definition), was not appropriately justified. Removal of the covariate from the primary efficacy analysis in the full analysis set resulted in the trial not meeting its primary efficacy non-inferiority endpoint.

Based on these major review concerns, we are concerned regarding the approvability of BT524, as fibrinogen supplementation for patients with acquired fibrinogen deficiency.



#### **Meeting Discussion:**

The Applicant provided responses to the major review concerns stated above. They restated that patients with PMP are at high risk for bleeding due to hypofibrinogenemia and benefit from early fibrinogen supplementation. They also restated their position limiting the importance of laboratory-based hypofibrinogenemia in the surgical setting, despite pursuing an indication of fibrinogen supplementation. The Applicant provided further responses addressing the appropriateness of FFP, as a comparable control product to BT524, and the appropriateness of including intra-operative bleeding prediction, as a covariate in their primary efficacy analysis.

FDA acknowledged the Applicant's responses and provided responses to each of the Applicant's stated points, based on FDA review of the data provided and the proposed indication the Applicant is seeking. After the discussion, FDA restated that the points provided do not change the major

review concerns. FDA stated that based on FDA review of the submitted data, the submission does not provide substantial evidence of effectiveness, thus negatively impacts the approvability of BT524 as fibrinogen supplementation for patients with acquired fibrinogen deficiency. FDA recommended that the Applicant withdraw their pre-market request for approval of BT524 as fibrinogen supplementation for patients with acquired fibrinogen deficiency.

(b) (4)



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## 2. Additional Applicant Data

### **Meeting Discussion:**

The Applicant stated that they had planned to submit updated safety and clinical documentation by November 14, 2025, to include six previously underreported adverse events from Study 995 (acquired fibrinogen deficiency indication). This update represents a corrective action following a BIMO inspection of Site 51 in the Czech Republic. All identified adverse events are classified as non-serious and unrelated to treatment according to investigator assessments. While the Applicant initially sought confirmation that this submission would not constitute a Major Amendment due to the minor nature of the updates, they have indicated that this may become irrelevant as they are considering withdrawal of this indication based on FDA recommendations following substantive issues discussions.

## 3. Discussion of established Pharmacologic Class

Human blood coagulation factor. Final decision is pending.

**Meeting Discussion:**

There was no discussion during the meeting.

4. Information Requests

- a. Final responses to outstanding CMC Information Requests (combined response to CMC IRs ## 24 and 25 from June 27, 2025, and July 2, 2025, respectively) are pending. These include:
- Updated stability data from the four PPQ stability studies (end of September 2025)
  - Results of a forced degradation study with BT524 DP (by September 30, 2025)
  - (b) (4) spiking experiments with major known process-related impurities (by September 30, 2025).

Please provide updates on the status of these studies.

**Meeting Discussion:**

The Applicant is on track to provide responses to outstanding CMC Information Requests by September 30, 2025. Key ongoing activities include updating stability reports for four PPQ stability studies. Additionally, the (b) (4) study with BT524 drug product has been updated, with the report completed and response in preparation. (b) (4) spiking experiments with major known process-related impurities have been conducted, with the report finalized and response currently in preparation.

- b. IR#s 28/32 (Pharmacometrics) Final responses are due September 25, 2025
- *Exposure matching and model prediction error for populations with sparse sampling (<6 year old age group)*

**Meeting Discussion:**

The Applicant is on track to provide the pharmacometrics response to IR #28/#32 by the September 25, 2025, deadline. Current activities include ongoing non-compartmental analysis for relevant age groups and exposure matching across protocol-defined age groups.

- c. Information Request regarding Drug Product Specification is in preparation.

**Meeting Discussion:**

The Applicant is on track to provide the CMC response to IR #33 by the September 29, 2025, deadline. As part of this response, (b) (4) with acceptance criteria for fibrinogen monomer will be implemented for Identity testing in the drug product specification as a commitment. Additionally, the Applicant proposes aligning the limits for other specification parameters stated in IR #33 with stricter non-US standards.

FDA noted during the meeting that the review of the Nextaro v, 20/20 5 µm transfer device system is ongoing and there will be an additional IR to be submitted shortly.

5. Discussion of Upcoming Advisory Committee Meeting

An Advisory Committee meeting is not planned.

**Meeting Discussion:**

There was no discussion during the meeting.

6. Risk Management Actions (e.g., REMS, the ability of adverse event reporting and CBER's Sentinel Program to provide sufficient information about product risk)

We have not identified any issues related to risk management. We do not believe that a risk management action (e.g., REMS) is needed at this time.

**Meeting Discussion:**

There was no discussion during the meeting.

7. Postmarketing Requirements/Postmarketing Commitments

We have not identified any PMRs/PMCs at this time

**Meeting Discussion:**

There was no discussion during the meeting.

8. Major Labeling Issues

Review of the USPI and other labeling components is ongoing.

**Meeting Discussion:**

There was no discussion during the meeting

9. Review Plans

Review of the BLA is on-going. We will continue sending IRs as necessary to get clarification on any submitted information.

Milestones	Date
Communicate Anticipated PMRs	November 1, 2025
Communicate PMCs and Start Labeling Negotiations	November 27, 2025
PDUFA Date:	<b>December 27, 2025</b>

**Meeting Discussion:**

There was no discussion during the meeting.

10. Applicant Questions



**Meeting Discussion:**

The Applicant did not have any additional questions.

11. Wrap-up and Action Items

The Late Cycle Meeting Summary will be sent by October 15, 2025.

**Meeting Discussion:**

There was no discussion during the meeting.

This application has not yet been fully reviewed by the signatory authorities, Division Directors and Review Committee Chair and therefore, this meeting did not address the final regulatory decision for the application.