



Our STN: BLA 125833.0

**MID-CYCLE COMMUNICATION
SUMMARY**
July 1, 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 summary of your June 24, 2025, Mid-Cycle Communication 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 as soon as possible.

Please include a reference to STN BLA 125833 in your future submissions related to Fibrinogen (Human) (BT524).

If you have any questions, please contact Candace Jarvis at (240) 402-8315 or by email at 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

Mid-Cycle Communication Teleconference Summary

Application Type and Number: BLA 125833

Product Name: Fibrinogen (Human) (BT524)

Proposed Indication for Use: Treatment and prophylaxis of bleeding in pediatric and adult patients with congenital hypo- or afibrinogenemia with bleeding tendency.
Treatment as fibrinogen supplementation in patients with acquired fibrinogen deficiency.

Applicant: Grifols Therapeutics, LLC

Meeting Date & Time: June 24, 2025, 1:00PM-1:30PM ET

Committee Chair: Sergey Akimov

RPM: Candace Jarvis

FDA Attendees:

Sergey Akimov, PhD, CBER/OTP/OPPT
Colleen Caldwell, MS, MPH, CBER/OTP/ORMRR
Asha Das, MD, CBER/OTP/OCE/DCEO
Jennifer Dotson, DO, CBER/OTP/OCE/DCEH
Basil Golding, MD, CBER/OTP/OPPT
Lin Huo, PhD, CBER/OBPV/DB
Candace Jarvis, CBER/OTP/ORMRR
Beatrice Kallungal, MS, CBER/OTP/ORMRR
Megha Kaushal, MD, CBER/OTP/OCE/DCEH
Angelo Mao, PhD, CBER/OTP/OPT
Fadi Nossair, MD, CBER/OTP/OCE/DCEH
Zuben Sauna, PhD, CBER/OTP/OPPT
Yuyin Shi, PhD, CBER/OBPV/DB
Ramani Sista, PhD, CBER/OTP/ORMRR
Shaokui Wei, MD, MPH, CBER/OBPV/DPV
Lihan Yan, PhD, CBER/OBPV/DB

Applicant Attendees:

Sharleen Xiong, PhD, Director, R&D Regulatory Strategy, Grifols
Heike Böhm, Director, Clinical Strategy, Biotest
Alexander Staus, PhD, Senior Director, Biostatistics, Biotest
Jodie Colvin, Senior Manager, Regulatory Affairs, Grifols
Peter Nelson, MD, Senior Medical Director, Clinical Development, Grifols
Kim Hanna, VP, Clinical Development, Grifols
Dermot Whyms, Senior Director, Biometry, Grifols
Neil Davie, PhD, Senior VP and Head of Medicines Development and Evidence Generation, Grifols
Clark Zervos, VP, Quality, Grifols
Sonia Amoros Reboredo, Senior Director, Biopharma Regulatory Affairs, Grifols
Gabriel Saiki, Medical Pharmacovigilance, Grifols
Christine Piasek, Senior Director, Regulatory Affairs, Biotest
Jan Baltzer, PhD, Manager, Regulatory Affairs Clinical, Biotest
Snezana Subotic, Manager, Regulatory Affairs Clinical, Biotest

Volker Spehr, PhD, Senior Manager, Regulatory CMC, Biotest
Karen Erbguth, Manager, Regulatory CMC, Biotest
Stefanie Fas, Head of Quality Control, Biotest
Gerd Hanspach, Scientific Manager, Manufacturing Development, Biotest
Florian Zirkel, Senior Director, Pathogen Safety, Biotest
Marcus Gutscher, VP, Analytical Development and Validation, Biotest
Achim Hannappel, Head of Production 1, Biotest
Vera Ott, Head of Production 2, Biotest
Johannes Knoll, Head of VDMP, Production 3, Biotest
Johanna Hoffmann, Medical Safety Advisor, Drug Safety, Biotest
Silke Aigner, Head of Therapeutic Strategy, Medical Affairs, Biotest
Natascha Rippel, VP and Head of Drug Safety, Biotest
Christina Erb, Head of Scientific Operations and Innovation, Biotest
Matthias Germer, VP of Preclinical Research, Biotest
Christian Hüber, PhD, Senior Project Lead Dev. Projects, CPPM, Biotest

Agenda:

Discussion Summary:

1. Any significant issues/major deficiencies, categorized by discipline, identified by the Review Committee to date.
 - Based on our analysis, we noted that ~45% patients with spinal surgery, who received fresh frozen plasma (FFP), experienced an increase in fibrinogen levels, despite the limited amount of fibrinogen in FFP. Please provide an explanation for this observation and how it may impact the overall conclusions of the trial.

Meeting Discussion for Agenda item 1, point 1:

The Applicant noted possible factors that may explain the increased fibrinogen levels in the FFP arm:

- Patient-based variability in the timing of administration of FFP from the start of surgery and from when treatment was indicated after 1L blood loss was achieved.
- Site-based variability in FFP dosing resulting in variable dosing of fibrinogen and late administration; infusion of FFP may have occurred after cessation of bleeding

The Applicant stated that these factors did not affect the overall efficacy outcomes, although the results still reflected the limitations of FFP as a fibrinogen source.

FDA requested that the Applicant submit a formal written response, which should include additional analysis to support their explanation. Applicant response should be submitted within the next 2 weeks.

- Based on our analysis, we noted that patients with PMP abdominal surgery, who received cryoprecipitate, experienced a continuous decrease in fibrinogen levels from pre-dose levels until the end of surgery. This observation correlated with higher blood loss in this group, despite receiving a product with comparable fibrinogen content to the intervention arm. Please provide an explanation for these observations and how they may impact the overall conclusions of the trial.

Meeting Discussion for Agenda item 1, point 2:

The Applicant noted that the explanation for the decline in fibrinogen levels, despite cryoprecipitate treatment, was linked to longer preparation and infusion times for cryoprecipitate. BT524 allowed for faster hemostatic response and more consistent restoration of fibrinogen levels during surgery.

FDA asked if this delay could have been avoided by anticipating the need for cryoprecipitate treatment. The Applicant clarified that this was not possible since the decision to treat can only be done after 1 hour from initiation of surgery, based on the surgeon's assessment of predicted blood loss.

FDA asked if the predictive blood loss in PMP patients was based on standardized criteria and the Applicant mentioned that it was based on intraoperative observation only, without specific criteria. FDA asked the Applicant to submit literature and other supporting evidence to validate the use of this approach in prediction of blood loss in PMP.

FDA requested that the Applicant submit a formal written response, which should include additional analysis to support their explanation. Applicant response should be submitted within the next 2 weeks.

- You utilized predictive blood loss based on surgeon assessment, as a covariate, as per your protocol. Please indicate if this is correct or if there are objective criteria or definitions for predictive blood loss. In addition, please provide appropriate justification for using this variable as a covariate, as it only applies to the sub-population of patients with spinal surgery. We note that the NI margin is not met if the covariate is not utilized.

Meeting Discussion for Agenda item 1, point 3:

The Applicant stated that the predictive blood loss was a key covariate in the spinal surgery cohort. The basis for the surgeon assessment was clinical factors and was shown to be a strong prognostic indicator. For the

PMP patients, blood loss prediction was only established intraoperatively. The Applicant mentioned that NI was not met in full analysis set without covariate adjustment but was met per-protocol and modified analysis. The sensitivity analyses confirmed the robustness of results.

FDA asked the Applicant to submit literature and other supporting evidence to validate the use of this approach in prediction of blood loss in patients undergoing spinal surgery.

2. Information regarding major safety concerns.

- There are no safety concerns identified at this time.

Meeting Discussion for Agenda item 2:

There was no discussion of this question during the meeting.

3. Preliminary Review Committee thinking regarding a.) risk management, b) the potential need for any post-marketing requirement(s) (PMRs), and/or safety-related PMCs, and c.) the ability of adverse event reporting and CBER's Sentinel Program to provide sufficient information about product risk.

- Risk Evaluation and Mitigation Strategies (REMS) are not anticipated at this time.
- The review of the BLA is on-going. A PMR related to this submission is not anticipated at this time.
- We have not identified any PMCs at this time.

Meeting Discussion for Agenda item 3:

There was no discussion of this question during the meeting.

4. Any information requests sent, and responses not received.

- On 6/12/25, Information Request #20 (Pharmacovigilance) was issued. The original response due date was 6/20/25 and the sponsor requested an extension to 6/30/25. The IR was regarding the proposed Risk Management Plan.
- On 6/18/25, Information Request #22 (PT) was issued. The original response due date was 6/20/25 and the sponsor requested a 2-week extension to July 3, 2025.

Meeting Discussion for Agenda item 4:

There was no discussion of this question during the meeting.

5. Any new information requests to be communicated.

- As the review continues, new information requests will be conveyed as needed.
- The following CMC information requests are in preparation:
 - Regarding validation of analytical procedure (Identity and Quantity) for release testing of drug product
 - Regarding the safety evaluation of adventitious agents
 - Regarding stability of intermediates and drug product

Meeting Discussion for Agenda item 5:

There was no discussion of this question during the meeting.

6. Proposed date(s) for the Late-Cycle meeting (LCM).

- Late-Cycle Meeting between you and the review committee is scheduled on **September 16, 2025, from 12PM-1PM ET.**
- We intend to send the Late-Cycle Meeting Materials to you approximately 10 days in advance of the meeting.

Meeting Discussion for Agenda item 6:

There was no discussion of this question during the meeting.

7. Updates regarding plans for the AC meeting.

- There are currently no plans for an AC meeting.

Meeting Discussion for Agenda item 7:

There was no discussion of this question during the meeting.

8. Other projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates.

Milestones	Date
Communicate Anticipated PMRs	November 1, 2025
Communicate PMCs and Start Labeling Negotiations	November 27, 2025
PDUFA Date:	December 26, 2025 (Friday)

Meeting Discussion for Agenda item 8:

There was no discussion of this question during the meeting.

9. Discuss status of inspections (GMP, BiMo, GLP) including issues identified that could prevent approval. **Note:** Ensure notification of intent to inspect manufacturing facilities has been issued.
 - The inspections are ongoing or pending. We have no issues to report on the status of inspections at this time and any updates will be provided post inspections.

Meeting Discussion for Agenda item 9:

There was no discussion of this question during the meeting.