

**From:** [Janice Castillo](#)  
**To:** [Gildner, Jean](#)  
**Subject:** RE: BLA 125596 Information Request  
**Date:** Monday, January 29, 2018 10:58:30 AM  
**Attachments:** [image007.png](#)

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IR received.

Janice

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**From:** Gildner, Jean [mailto:Jean.Gildner@fda.hhs.gov]  
**Sent:** Monday, January 29, 2018 4:58 AM  
**To:** Janice Castillo  
**Subject:** BLA 125596 Information Request

Dear Janice,

Please see the following information request. This information request is in regards to the responses sent 1.19.18 (ADAE dataset) and the addendum to the CSR sent 12.29.17. Please acknowledge receipt of this email and the ability to respond as soon as possible.

- 1) For Subject (b) (6) and (b) (6), diagnosed with heparin induced thrombocytopenia (HIT) – the narratives provided in Section 7.1 of the Addendum to the CSR provided on 01.19.18 informs of a clinical diagnosis of heparin induced thrombocytopenia. The narratives do not provide information specifically laboratory tests to confirm diagnosis of HIT. Please provide information as to whether PF-4 antibody testing and/or platelet function assays were performed to confirm the diagnosis of HIT. In the absence of such testing, please clarify how a de-novo thrombotic event was excluded.**
- 2) Subject (b) (6) was listed as having DVT on Day 18 following andexanet infusion in Table 15 of the addendum to the CSR. The ADAE dataset and CRF do not report the DVT. Please provide a narrative of this subjects hospitalization, work up for DVT if any.**
- 3) Subject (b) (6) was noted to have elevated troponin lasting one day, and beginning 2 days following andexanet infusion. Please provide a narrative of this subject to include symptoms, clinical course and your rationale as to how myocardial infarction was excluded in the absence of appropriate work up.**
- 4) Subject (b) (6) experienced a V-tach 3 days following infusion, please provide a narrative of this event, specifically, the duration, cardiac enzymes and troponins, QT interval evaluations on ECG, and evaluation for cardiac ischemia and prior cardiac history.**
- 5) Subject (b) (6) narrative experienced sudden cardiac death, please provide a narrative.**
- 6) Subject (b) (6) experienced isolated respiratory failure, please provide a narrative, report of imaging or investigations conducted for the etiology of respiratory failure, including work up for pulmonary embolism.**

- 7) Subject (b) (6) was noted to have a possible subdural empyema. However, the narrative does not include for clinical signs of empyema. Please also provide MRI and CT reports.
- 8) Subject (b) (6) please provide a narrative of events leading to congestive heart failure
- 9) Subject (b) (6) was noted to have vtach lasting a day. Please provide a narrative specifically, the duration, cardiac enzymes and troponins, QT interval evaluations on ECG, and evaluation for cardiac ischemia and prior cardiac history..
- 10) Subject (b) (6) developed acute respiratory distress 2 days following andexanet administration. A differential diagnosis of pulmonary embolism was considered. A CT and ultrasound duplex imaging was planned but summary of the report was not provided. Please clarify whether a CT imaging and/or DVT work up was performed.
- 11) Subject (b) (6) experienced chest pain 4 days after the infusion. Please provide a narrative of the event, the work up for chest pain including cardiac enzymes, imaging and EKG findings.
- 12) Subject (b) (6) developed respiratory failure, please provide a narrative of this event, reports of imaging or investigations conducted for the etiology of respiratory failure, including work up for pulmonary embolism. Please provide AEENDY if available.
- 13) Subject I(b) (6) experienced chest pain lasting 1 day and occurring 21 days post andexanet infusion, please provide a narrative that includes work up to exclude cardiac or pulmonary (embolic) causes.
- 14) Subject (b) (6) appears to have numerous AEs that are unlisted in the ADAE dataset with AE start and end dates provided. Please update the ADAE data table. Please also provide the CT reports from 04/06/17 and 03/08/17
- 15) Subject (b) (6) – please provide a narrative and imaging reports of the new event of cerebrovascular event noted on (b) (6) (D15 following infusion). The fall was unwitnessed, therefore, it is unclear if the cerebrovascular event occurred following the fall or prior to the fall (resulting in the fall).
- 16) Subject (b) (6) died on (b) (6). Please provide a narrative of the hospitalization through death, including the work up for sepsis, events related to the renal failure and subsequent management of the subject.
- 17) The following subject deaths have not been listed in Table 16 of the addendum to the CSR: (b) (6). Please confirm that these subject deaths occurred.
- 18) In FDA's assessment of Adverse of Special Interest, we are including the following events as a) ischemic causes cannot be ruled out as contributory to the cardiogenic shock, CHF or acute respiratory failure or b) were related to thrombotic events were  
:

1) Cardiogenic shock and Congestive heart failure

- 2) *Acute respiratory failure (unexplained by pneumonia or other non-ischemic causes)*
- 3) *Cardiac thrombus (classified as thrombotic event)*
- 4) *Iliac artery occlusion (classified as thrombotic event)*

If you have any questions please feel free to contact me.

Sincerely, Jean

*Jean F. Gildner* MSHS, MT (ASCP)

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**Center for Biologics Evaluation and Research**  
**Office of Tissues and Advanced Therapies**  
**U.S. Food and Drug Administration**

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