

From: [Gildner, Jean](#)
To: ["Janice Castillo"](#)
Subject: RE: BLA 125586 Portola Label First round of edits - Excel spreadsheet attached.
Date: Wednesday, April 04, 2018 1:30:23 PM
Attachments: [Subset of Safety Analysis-FDAAESI-CMCAT.03.17.18\).xlsx](#)

Hi Janice,

Please see the following response to your request for clarification. If you have any additional questions please feel free to contact me. Also please acknowledge receipt of this email.

Below is the FDA assessment of the AESIs. We are not able to review any more additional data.

Based on the AEs that were included in the ADAE table and the most recent clarifications from Feb 26, 2018, the table below explains the list of subjects that were added based on FDA's analyses to the AESI list.

In addition, the excel table includes the list of AESI with subject IDs per our analysis. This includes the protocol specified AESI and the FDA assessment. Terms such as troponin increased are included as acute myocardial ischemia.

One subject (b) (6) inadvertently dropped from the previous excel spreadsheet has been added.

Subject ID	Event	Summary of Event	FDA comment	Safety Analysis Plan
(b) (6)	DVT per CSR, not reported in ADAE dataset	Erroneous reporting of DVT. Right lower extremity swelling was confirmed as hematoma and evacuated by surgical procedure. No DVT per duplex imaging (7 days post andexanet)	None. Duplex report reviewed	Agree with Applicant – no DVT. Subject will be excluded from the TEE/FDA AESI analyses.
(b) (6)	Troponin elevated for 24 hours	Elevated troponins were observed at three consecutive assessments over 24 hours, beginning 11 hours post infusion. EKG showed non-specific ST and T wave abnormalities unchanged from	Isolated but elevated troponin within 12 hours of andexanet is considered attributable to the andexanet and considered a cardiac ischemic	Subject will be included in the TEE/FDA AESI analyses.

		pre-treatment EKG. Cardiology consultant did not recommend any further work up	event. Subject had underlying CAD	
(b) (6)	Ventricular tachycardia (VT)	Telemetry noted 7 beat run of VT. Interrogation of the ICD did not confirm non-sustained VT but noted premature ventricular contractions (PVCs)	Agree with Applicant, and based on the ICD interrogation that VT is unlikely to have occurred.	Subject will be excluded from the TEE/FDA AESI analyses.
(b) (6)	Sudden Death	Unwitnessed, no further information is available.	The sudden death is considered attributable to andexanet.	Subject will be included in the TEE/FDA analyses.
(b) (6)	Respiratory failure	Underlying history of CAD, COPD, CKD. Readmitted 8 days following andexanet infusion, with acute shortness of breath and wheezing. D-dimer elevated (2.5 µg/mL), without troponin elevation, chest Xray suggestive of congestive heart failure. V/Q scan – low probability of pulmonary embolism, responded to nebulizer and diuretics and corticosteroids.	Agree with applicant, that based on the low probability V/Q scan, response to diuretics and COPD management. Elevated D-dimers could be explained by renal impairment.	Subject will be excluded from the TEE/FDA analyses.
(b) (6)	Subdural empyema	Subject presented with right occipital hemorrhage on CT. MRI imaging following andexanet	The MRI findings of acute frontal lobe cortical infarct is considered	This subject will be included in the TEE/FDA

		<p>infusion suggested that right occipital hemorrhage may represent hemorrhagic transformation of a prior infarct. However the MRI also noted acute infarct in the frontal cortex and right frontal subdural hematoma. Subsequent MRI noted that subdural collections were increasing in size and consistent with subdural empyema. Subject was also noted to have fever and leukocytosis.</p>	<p>attributable to andexanet as this event was first noted following andexanet infusion.</p>	<p>AESI analysis.</p>
(b) (6)	<p>Congestive heart failure</p>	<p>Subject was discharged 11 days post -andexanet and readmitted without response to diuresis and subsequently treated for pneumonia with antibiotics and recovered</p>	<p>Agree with the applicant that the likely cause of cardiac and respiratory decompensation were related to pneumonia</p>	<p>Exclude subject from TEE AESI analysis</p>
(b) (6)	<p>Ventricular tachycardia</p>	<p>Extensive cardiac history and dual chamber pacemaker which was interrogated and did not confirm the telemetry finding of Vtach</p>	<p>Agree with Applicant that Vtach was an unlikely event</p>	<p>Exclude subject from TEE/AESI analysis.</p>
(b) (6)	<p>Acute respiratory distress</p>	<p>Acute respiratory distress that occurred within 24 hours of andexanet infusion requiring</p>	<p>Unable to rule out cardiac ischemia contributed by andexanet as</p>	<p>Include subject in the TEE/AESI analysis</p>

		intubation. CT and ultrasound scans were negative for DVT/PE. Subject had a second episode of acute respiratory distress 13 days after infusion that required another intubation. No mention of work up for cardiac ischemic etiology.	possible etiology of the acute respiratory failure.	
(b) (6)	Chest pain	Transient chest pain 3 days post andexanet, without respiratory decompensation and without elevation of chest pain	Agree with Applicant, chest pain unlikely to be of cardiac etiology	Exclude subject from TEE/AESI analysis
(b) (6)	Respiratory failure	Bibasilar rales noted with rib fractures were noted within 24 hours of admission without respiratory decompensation, requirement for oxygen or other supportive measures	Agree that the event does not represent respiratory failure.	Exclude subject from TEE/AESI analysis.
(b) (6)	Chest pain	Chest pain associated with EKG changes, cardiac ischemia that occurred 21 days after andexanet infusion. Coronary angiography did not reveal an obstructive cause.	This event is considered an cardiac ischemic event. The Applicant's diagnosis of digitalis induced EKG changes is noted	Include in the TEE/AESI analysis as myocardial infarction.
(b) (6)	Cerebrovascular event	The subject experienced a fall 14 days after	Agree with the Applicant that the event is not	Exclude from TEE/AESI

		andexanet infusion and was noted to have decreasing hematoma (ICH being the index event for study eligibility). Initial CT and subsequent CT imaging did not confirm an infarct.	considered a ischemic stroke	analysis. Will be considered change in mental status following a fall.
(b) (6)	Death and multiorgan failure	Subject with ICH developed renal failure, pain in the shoulder (deemed septic joint) without supportive information approximately 2 weeks after andexanet infusion.	The event will be considered a death preceded by acute on chronic renal failure followed by multi-organ failure and death.	Not include in the TEE/AESI but in AE analysis.

Jean F. Gildner MSHS, MT (ASCP)

Regulatory Project Manager
Center for Biologics Evaluation and Research
Office of Tissues and Advanced Therapies
U.S. Food and Drug Administration
 Tel: 240-402-8296
jean.gildner@fda.hhs.gov

THIS MESSAGE IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify the sender by e-mail or phone.

From: Janice Castillo [<mailto:jcastillo@Portola.com>]
Sent: Tuesday, April 03, 2018 8:13 PM
To: Gildner, Jean <Jean.Gildner@fda.hhs.gov>
Cc: Patrick Yue <pyue1@Portola.com>
Subject: RE: BLA 125586 Portola Label First round of edits - Excel spreadsheet attached.

Jean,
Portola has the following request for clarification regarding the patients listed in the attached spreadsheet. Please acknowledge receipt of this request. Thank you.
Janice

For the following patients, please provide additional information (i.e., preferred term, date of event) regarding the specific event that FDA considers to be a sudden death, thrombotic event, or ischemic event. This will be necessary to determine time to event and re-anticoagulation status.

(b) (6)



From: Gildner, Jean [<mailto:Jean.Gildner@fda.hhs.gov>]
Sent: Tuesday, April 03, 2018 10:07 AM
To: Janice Castillo
Subject: RE: BLA 125586 Portola Label First round of edits - Excel spreadsheet attached.

Hi Janice,

Please see the excel spreadsheet that needs to be filled out as per instructions in a comment bubble associated with the label. Please acknowledge receipt of this email.

Thanks,
Jean

From: Janice Castillo [<mailto:jcastillo@Portola.com>]
Sent: Tuesday, April 03, 2018 12:44 PM
To: Gildner, Jean <Jean.Gildner@fda.hhs.gov>

Subject: Re: BLA 125586 Portola Label First round of edits

Draft label received.

Janice

Sent from my iPhone

On Apr 3, 2018, at 9:36 AM, Gildner, Jean <Jean.Gildner@fda.hhs.gov> wrote:

Hi Janice,

Can you acknowledge receipt of the label?

Thanks,

Jean

From: Gildner, Jean

Sent: Tuesday, April 03, 2018 7:50 AM

To: Janice Castillo (jcastillo@Portola.com) <jcastillo@Portola.com>

Subject: BLA 125586 Portola Label First round of edits

Dear Janice,

Please find attached the first round of edits from the FDA. Please provide your version of the label by Thursday April 4th at Noon EST. Please ensure that any comments from you are not anonymized so that we know it clearly from Portola (not specifically who they are just that it is an edit from you).

Please acknowledge receipt of this label and the ability to meet the requested deadline.

Sincerely, Jean

Jean F. Gildner MSHS, MT (ASCP)

Regulatory Project Manager

Center for Biologics Evaluation and Research

Office of Tissues and Advanced Therapies

U.S. Food and Drug Administration

Tel: 240-402-8296

jean.gildner@fda.hhs.gov

[<image001.png>](#)

[<image002.jpg>](#) [<image003.jpg>](#) [<image004.jpg>](#) [<image005.jpg>](#)

[<image006.jpg>](#)

THIS MESSAGE IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify the sender by e-mail or phone.

<BLA 125586_20180403_Label_FDAV2.docx>

This email message is for the sole use of the intended recipient(s) and may contain confidential and privileged information. Any unauthorized review, use, disclosure or distribution is prohibited. If you are not the intended recipient, please contact the sender by reply email and destroy all copies of the original message. If you are the intended recipient, please be advised that the content of this message is subject to access, review and disclosure by the sender's Email System Administrator.

This email message is for the sole use of the intended recipient(s) and may contain confidential and privileged information. Any unauthorized review, use, disclosure or distribution is prohibited. If you are not the intended recipient, please contact the sender by reply email and destroy all copies of the original message. If you are the intended recipient, please be advised that the content of this message is subject to access, review and disclosure by the sender's Email System Administrator.