

From: [Gildner, Jean](#)  
To: [Janice Castillo \(jcastillo@Portola.com\)](mailto:jcastillo@Portola.com)  
Subject: BLA125586 Comments Re: RCT study  
Date: Friday, April 13, 2018 9:21:49 AM  
Attachments: [image001.png](#)

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Dear Janice,

Please see the following comments from the clinical team in regards to the RCT. Please acknowledge receipt of this email. We seem to be having issues with our Outlook and I want to confirm receipt.

**1) Major deficiencies**

- a. With regard to use of concomitant medications: Per our prior request, you have defined re-bleeding that will trigger use of concomitant medications. Although the use of concomitant medications is discouraged, use of concomitant medications cannot be prevented. In cases where concomitant medications are used for hemostasis during the efficacy observation period, the effect of ANDEXXA may be challenging to interpret. Therefore, for primary efficacy assessment, please revise the adjudication criteria to state that efficacy outcome will be adjudicated as poor/none for patients in the ANDEXXA arm who experience re-bleeding or receive concomitant medications for treatment of bleeding within the primary efficacy observation period.***
- b. The balance between the two treatment arms for prognostic factors that affect hematoma expansion (for example time from symptom onset/bleeding event to screening) in ICH patients is an important consideration in the review of efficacy for regulatory decision making. We note that you do not plan to stratify for these factors at the time of randomization. In the absence of such plans, we request that you, please provide in your revised protocol, a list of these prognostic factors that will be evaluated at study entry. Please also ensure that the CRFs and the primary efficacy datasets include information regarding these prognostic factors.***

**2) Minor deficiencies**

- a. You propose clinical criteria that would trigger unscheduled imaging to evaluate for hematoma expansion. Please ensure that CRFs include information as to the criteria that were evaluated to decide whether additional brain imaging was or was not required. For example, CRFs at the 3 hour time point for NIHSS assessment should also include collection of data to verify whether new focal deficits emerged. Please also note that you have omitted to include in Appendix E a description of the NIHSS stroke scale. Please include these when you submit your revised protocol.***
- b. We agree in principle with the Guidance for Submission of Potential Thrombotic Events for Adjudication. However as written, there are instances where the absence of imaging criteria would permit a default conclusion that the safety event not having occurred (for example, occlusion of arterial embolism requires pathological or surgical verification or imaging, therefore in the absence of such***

*supportive studies, it appears that based on the guidelines, that the event will not be considered to be a TEE). Given the open label nature of the study, bias towards performing these procedures may occur. Imbalances in the use of imaging where it is required as a diagnostic criterion for a thromboembolic event maybe a review issue. Please ensure that the CRFs and narratives capture the reasons why an diagnostic imaging in such cases were omitted.*

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

Sincerely, Jean

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

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