

From: [Gildner, Jean](#)
To: [Janice Castillo \(jcastillo@Portola.com\)](mailto:jcastillo@Portola.com)
Subject: BLA 125586 Portola Comments Re: our RCT meeting
Date: Thursday, March 22, 2018 4:30:53 PM
Attachments: [125586 RCT study Clin-Stats comments V3_20180322.pdf](#)
[image001.png](#)

Dear Janice,

Please see the attached FDA comments in preparation for our meeting tomorrow. Please acknowledge receipt of this attachment. Please let me know if possible, the comments you wish to discuss in order of importance. If you have any questions please feel free to contact me.

Sincerely, Jean

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Comments for the RCT study of andexanet

A. Study design

1. You propose to stratify for randomization based solely on study sites. To minimize risk of imbalances between the treatment arms for prognostic factors related to ICH. Therefore, we recommend that you consider stratification for randomization based on key prognostic factors that are likely to influence hemostatic outcomes in ICH. (Major deficiency)
2. We acknowledge your concern that PCC (usual care) may be associated with a higher risk of thrombosis than andexanet. However, given the data for thrombotic and/or embolic risks associated with andexanet as noted in the ANNEXA 4 study, the justification based on excessive risk of thrombosis and/or embolism from usual care is not substantiated. Furthermore, since the thrombotic risks are generally manifested after the event, the management of the thrombotic event is anticipated to be similar in both arms. We do not agree with your justification, but note that it may not be feasible to blind investigators to the many therapeutic options available under the usual care treatment arm.
3. We acknowledge your plan to provide details of the blinding plan as a separate submission. Please ensure that such the blinding plan is provided for review and agreement by the Agency. (Major deficiency)

B. Study Duration

Anti-andexanet antibodies were observed in the ANNEXA 4 study. The persistence of these antibodies is unknown due to the limited duration of monitoring in this study. Please provide justification for the proposed 37 day follow up in the context of the presence and persistence of anti-andexanet antibodies. (Major deficiency)

C. Inclusion criteria

1. You have not provided information as to which of the oral FXa inhibitors treatments are to be included in the study. Please note that the highest dose explored in the edoxaban study in healthy volunteers may be insufficient to reduce the baseline anti-fXa levels substantially and therefore may not be sufficient to achieve a hemostatic response based on the purported mechanism of action. For these reasons, please exclude subjects who experience edoxaban related bleeding. (Major deficiency)
2. In Section 4.1 of the Protocol you state “To ensure that sufficient numbers of patients with various Factor Xa inhibitor therapies are enrolled, enrollment in certain subgroups may be increased or capped.” Please clarify whether the subgroups you are referring to are “intracerebral, subarachnoid and subdural”

bleeding events or whether you are referring to the different FXa inhibitors (apixaban, rivaroxaban, etc). (Major deficiency)

3. As a foot note to Table 3 which relates to the selection of high vs low dose, you propose to enroll subjects based on local laboratory reading of anti-fXa levels greater than 100 ng/mL. Harmonization of reagents may be necessary between the local laboratories for a local lab based anti-fXa assays to ensure results are consistent across local laboratories. Please clarify as to how the local lab readings represent “true” anti-fXa activity levels to permit enrollment to the study.
4. We agree in principle that local laboratory based anti-fXa activity levels may be considered for enrollment. However, in the absence of data to correlate consistency in the readings between central and laboratory assays we are unable to comment as to whether local laboratory readings may be substituted for central laboratory testing to support selection of patients who may be eligible to receive andexanet following a future approval of andexanet. (Major deficiency)

D. Schedule of visits and study procedures

1. You propose to record procedures and hemostatic treatments to record hemostatic efficacy and imaging procedures that are performed during the study interval from infusion to the 12 hour efficacy assessment time point. However, there is no protocol specified criteria that would trigger administration of the hemostatic agent or imaging based on clinical assessment. To ensure consistency across trial sites we recommend that you consider incorporating protocol specified criteria that would trigger diagnostic imaging or use of concomitant treatment to control bleeding. You may also include physician’s discretion as a trigger for those instances that are not covered by the protocol specified criteria. (Major deficiency)
2. The interval between the post infusion follow up at Day 3 and final visit at D30 does not include visits in between. Assessment of AEs noting that a substantial number of events in the ANNEXA 4 study occurred in the first 10 days, indicates the need for more frequent monitoring to capture all adverse events. Please include weekly visits to monitor for AEs. (Major deficiency)

E. Concomitant medications

1. In section 7.2.2 you state that 3 or 4 factor PCC, FFP, rFVIIa, whole blood and platelet transfusions may be administered. Furthermore, you imply that the administration of these products are permitted in the andexanet arm but is strongly discouraged. Please ensure that you revise the primary efficacy analyses, to state that use of these concomitant medications in the andexanet arm is considered a failure to achieve hemostatic response. (Major deficiency)

2. In Section 7.2.2 you state that systemic anti-fibrinolytic and local hemostatic agents may be administered in both arms. To minimize imbalances in the use of these agents between the two arms in an open-label study, we recommend that you pre-specify conditions where these agents may be used. Alternatively, at the very minimum use of systemic antifibrinolytic agents in the andexanet arm should be considered failure to achieve hemostatic response (Major deficiency)
3. You propose to allow therapeutic procedures for treatment of bleeding. Please provide details as to how subjects will be assessed for hemostatic efficacy when therapeutic procedures are used to control bleeding since these procedures are considered contributory to hemostatic control. (Major deficiency)
4. You propose to treat patients who experience re-bleeding with standard of care treatment. Please define re-bleeding in the context of the 12 hour period to assess efficacy of andexanet. For example, if a subject experiences re-bleeding within the 12 hour efficacy evaluable period, will this subject be considered to have a re-bleeding event? In addition, will re-bleeding events within this 12 hour period be considered failure of treatment. Will the use of rescue treatment be considered a failure of to achieve hemostatic response in the andexanet arm. (Major deficiency)
5. You state that investigators will be requested to consult the adjudication criteria for the diagnosis of the thrombotic events when considering whether an event should be submitted for adjudication. Please provide the referenced adjudication criteria for review. Please include in this AESI criteria, events that are suggestive of ischemic events, for example, sudden cardiac death, respiratory failure, cardiogenic shock, etc. in addition to the thrombotic and embolic events as proposed.

F. Statistical consideration

1. The efficacy analysis population is based on the modified ITT population (mITT). You have not provided a definition of mITT population which is necessary to evaluate whether efficacy analysis population is acceptable. (Major deficiency)
2. In the primary efficacy analyses population you intend to evaluate those subjects who did not receive study treatment according to the treatment received. We consider this approach as a per protocol analysis which may be subject to bias, especially in an open label study. Therefore, please revise your primary efficacy analysis population to only include the ITT population. (Major deficiency)
3. The hypothesis testing rests on an alternate hypothesis of demonstrating any improvement in hemostatic efficacy in the andexanet arm as compared to the

usual care arm. Please note that determination of effectiveness from a regulatory perspective is based on the achieving a clinically meaningful magnitude of benefit and a favorable risk benefit assessment which is review issue. Therefore, demonstrating any magnitude in improvement may not be sufficient to meet the regulatory requirements.

4. In your sample size calculation, you claim that 200 evaluable subjects each arm will have 90% power to detect a difference of 15%, assuming the hemostat efficacy rate is 80% and 65% for the treatment and control arms, respectively. Please note that based on the hypotheses, you are actually testing whether there is a statistically significant difference, rather than a 15% difference. Please modify your sample size calculation accordingly.
5. On page 57 of the protocol, you state that the inclusion/exclusion criteria may be changed during the study based on the accumulating data. You provide two examples of this change which is not sufficient. Please elaborate all possible changes. If this change is purely based on administrative reason (e.g., feasibility), please state so and provide a list of all possible changes to FDA. If the change is about adapting the population to achieve better power after reviewing the interim efficacy data, this would bias the analysis and potentially make the results uninterpretable, or jeopardize the generalization of the study finding. In that case, you need to prospectively plan this change and provide appropriate type I error rate control. If appropriate statistical approach is not available to handle this situation, you may not be able to pool the populations prior and after the change, and have to conduct separate analyses which may be underpowered. (Major deficiency)
6. Please provide an estimate of the proportion of missing data for the primary efficacy endpoint. If the amount of missing data is too excess, it would compromise the interpretation of the study results. Please try your best effort to minimize the amount of missing data. Please develop a comprehensive plan to handle missing data, including a method for the primary analysis and several methods for sensitivity analysis. The primary analysis could be multiple imputation, and the sensitivity analyses could include but not limit to worst scenario analysis (all the missing data are considered good hemostat efficacy outcome for the control arm and poor hemostat outcomes in the treatment arm), complete data analyses, tipping point analysis, etc.
7. For patients who are non-evaluable for administrative reasons, you plan to exclude them from the Efficacy Analysis Population. We recommend including them in the Efficacy Analysis Population and their hemostat efficacy outcome can be imputed assuming missing at random.

G. Efficacy Adjudication

1. The adjudication of the efficacy relies on criteria to be implemented in the adjudication charter to enable the EAC to determine hemostatic outcomes.

Therefore, the adjudication criteria is a critical component of the clinical and statistical review of this protocol. Please provide the adjudication criteria that will be utilized to adjudicate primary hemostatic efficacy outcomes. A few examples to illustrate critical issues to consider in the adjudication criteria are provided below. A tabular summary would expedite the review process when you submit such information. (Major deficiency)

- i. You propose to include subjects who may other additional sites of bleeding besides ICH. Please outline discrepant efficacy outcomes assessed at the two or more bleeding sites will be adjudicated.
- ii. You propose clinical neurological evaluations that may trigger imaging evaluations. Please outline how discrepant outcomes between clinical and imaging assessments will be adjudicated.
- iii. You propose to use NIHSS score of less than +7 points change from baseline and hemostatic rating based on imaging to assess effective hemostatic outcomes at the 12 hour timepoint. Please specify the procedures reconciling discrepant assessments between the NIHSS score and imaging.
- iv. You propose to evaluate for efficacy at the 12 hour time point, as well as based on clinically determined assessments between 0 and 12 hours. It is unclear as to how any ~~they~~ discrepant adjudicated assessments (as addressed in items c) and d) above) at timepoints between 0-12 hours and at 12 hours will be reconciled to determine the final efficacy outcome.
- v. You propose therapeutic interventions for control of bleeding from infusion to the 12 hour timepoint. How will the efficacy outcome be adjudicated if hemostatic efficacy was observed at the 12 hour time point?
- vi. You propose that use of concomitant hemostatic agents/ medication is permissible during the interval between infusion and the 12 hour efficacy assessment time point. Please outline the adjudication criteria for this scenario.
- vii. You propose to consider subjects non-evaluable for efficacy for clinical reasons but defer to the EAC for final adjudication. Please justify and outline how the definition of clinical deterioration and the reasons why these subjects should be excluded and not considered as failure to achieve hemostatic efficacy.