1. *In subjects anticoagulated with rivaroxaban, apixaban and edoxaban, andexanet caused a transient significant decline in anti-FXa activity during and shortly following a 2 hour infusion, which was followed by a return of anti-Xa levels to approximately 50% of initial levels with a subsequent decline as expected based upon the individual anticoagulant's half-life.*

   a) *Please comment on the adequacy of the observed duration of reversal in the treatment of intracranial hemorrhage (ICH) and to prevent further expansion of a subdural or parenchymal bleed.*

   Immediate and sustained reversal is essential in the setting of an ICH and to prevent expansion of a subdural or intraparenchymal bleed. Consequently, I would envision that the strategy in patients with an ICH would be an initial bolus followed by an infusion, or repeated doses, subsequently. I would continue the infusion for as long as one would expect circulating anticoagulant to be present, and then I would recheck anti-factor Xa levels as I decreased the dose of the andexanet.

The following questions refer to the proposed protocol for the Phase 3b/4 confirmatory study:

2. *In the Phase 3b/4 confirmatory study, two subjects with intraparenchymal bleeds on baseline CT were found to have intraventricular hemorrhage (IVH) on follow-up imaging, resulting in higher than baseline total bleed volumes. Please comment on whether the adjudication methods used in this study to assess hematoma expansion for those subjects who experienced IVH on follow-up imaging are appropriate.*

   The criteria for assessing response by brain imaging data are not provided in the document, so I'm not sure what was being used. From the text provided, it also appears that the adjudicators did not have criteria established prior to initiating the study, since they "…did not agree on whether the new IVH should be counted in the assessment of bleed volume".

   For a patient with an ICH that is adjacent to a ventricular, extension into the adjacent ventricle might occur as part of the natural extension of the initial bleed. I would recommend that intra-cranial bleeds be assessed by the following criteria: (i) initial size of ICH bleed; (ii) location of bleed, especially if adjacent to a ventricle or surface of the brain; (iii) follow-up size of ICH bleed; and (iv) follow-up notation of whether bleed is now present in new spaces, such as new extension into the ventricle, or new sites of bleeding.

3. *Please comment on the acceptability of the entry criteria (in terms of inclusion of an appropriate target population for whom immediate reversal of anticoagulation is necessary). Should there be specific criteria related to ICH (e.g., minimum volume/thickness of the lesion, imaging criteria that predict high-risk of hematoma expansion, specific symptoms)?*

   Several of the entry criteria can be better defined. For example, the following items need to be better defined: "…severe hypotension, poor skin perfusion, mental confusion, low urine output…". Defined values for hemoglobin level or drop are good.

   For the intracranial bleeding-related criteria, agree with 'symptomatic' and CT or MRI evidence of acute intracranial bleeding. I don't think that you need a minimum size or volume; in the patient on anticoagulant therapy, any symptomatic intracranial bleeding is not good.

4. *Following the start of andexanet treatment, subjects will be evaluated for the study efficacy endpoints, based on serial observations which include CT/MRI at baseline (defined as up to 4 hours prior to bolus), at 1 hour post infusion (defined as within 1 hour prior to and up to 3 hours following the end of the 2 hour andexanet infusion) and at 12 hours from the start of andexanet bolus with head CT and modified Rankin score (mRS) for ICH at 12 hours from the end of infusion.*

   a) *Please comment on the adequacy of the timing of the imaging and clinical evaluations in the assessment of treatment success or failure.*

      They may want an earlier follow-up imaging study for patients with intracranial bleeding if symptoms worsen or the patient deteriorates, prior to the 12 hr endpoint. If the patient is doing well clinically, follow-up imaging studies at 1 hr and 12 hr after the infusion should be fine.

   b) *Are the study design and proposed endpoints in the ongoing study adequate to assess efficacy of the study treatment in the ICH population?*

      I think that the study design should be more detailed concerning clinical assessment, including explicit descriptions of the clinical follow-up on these patients. There should also be some description of what symptoms/finds/changes in clinical status should prompt an earlier imaging study.

   c) *Are there other clinically relevant endpoints that should be considered for the current and future studies?*

      In addition to the anti-factor Xa activity, the investigators should provide a better description of how changes in the imaging studies will be evaluated. As written, it is very qualitative.

5. *Given the heterogeneity in the eligible population (with regard to location and size of the bleed), please comment on the relevance and feasibility of reduction in ICH-related morbidity and mortality as a primary endpoint for a confirmatory study intended to assess the hemostatic efficacy of a reversal agent for the three anticoagulants.*

   Given that intracranial bleeding will represent a subset of the total of ~250 subjects the study proposes to enroll, and out of the first 35 patients there were 13 patients with ICH, this would suggest that they would have ~90-95 patients with ICH. Of the 9 patients with ICH who had an anti-factor Xa level >75 ng/mL, 3 were intraparenchymal and 6 were subdural. I think that the heterogeneity of the eligible population will make it difficult to provide an assessment of the reduction in ICH-related morbidity and mortality that is more than qualitative.

   a) *Is there a relevant time-point to assess reduction in ICH-related mortality and morbidity (i.e., 30 days vs. a later time-point)?*

      Thirty days would probably be a reasonable timepoint to assess outcome. For the idarucizumab study, however, clinical outcomes were considered secondary, and, for ICH bleeding, they performed an assessment at 90 days (NEJM, 2015; 373: 511-20).

   b) *The applicant has proposed a "Usual Care Cohort study" designed to serve as a comparator group for the assessment of the efficacy of andexanet in a population that is similar to the ongoing Phase 3b/4 confirmatory study (ANNEX 4 study). The study is an observational study in which patients receive the usual standard of care at their institution. There is no restriction of what treatments a patient may receive. The primary objective of the study is to evaluate a cohort of patients with acute major bleeding (that includes subjects with ICH) while on a fXa inhibitor, receiving usual care, in order to determine the feasibility of using this cohort as a comparator group to assess the efficacy of andexanet. A blinded adjudication process is planned to assess efficacy between the ANNEX 4 study and the "Usual Cohort Study". Is such a cohort study an appropriate control to evaluate the efficacy of andexanet in the ICH sub-group? Please also comment on the feasibility of conducting a randomized controlled study in patients with ICH for this indication.*

I don’t think that this cohort would be an appropriate control to evaluate the efficacy of andexanet in the ICH sub-group. Most patients who don’t get andexanet at a participating site would meet exclusion criteria, which would not be an appropriate comparator group. Since none of the other treatment options for major bleeding on an anti-factor Xa agent are optimal (even protamine use in a patient receiving a low molecular weight heparin provides incomplete reversal, at best), it would not be appropriate to have a control arm, in my opinion. Similarly, I think that a randomized controlled study in patients with ICH for this indication would only be ethical if the data suggested that use of andexanet was of equivocal benefit for other types of bleeding events. If andexanet appears to provide benefit for other, non-ICH, bleeding events, some might consider it unethical to perform a randomized controlled trial with this agent in these patients.