

Questions for the Consultant (in regard to anticoagulant reversal in the face of intracerebral bleeding):

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 about 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.

Response: While it would be preferable to have a more prolonged deep decline in anti-FXa, the 2+ hour decline is probably adequate since most hematoma enlargement associated with neurologic deterioration occurs in the first few hours after bleeding onset. In the data described in the pilot studies to date, there is little evidence that bleeding has continued/recurred after the andexanet infusion, attesting to the adequacy of the observed decline. In the illustrative case, there was transient increase in SDH thickness at 10 hours post infusion which is difficult to understand. It could have been "blooming artifact", but if so it should also have been present and read the same way on the 12 hour scan, but in fact the thickness on the 12 hour scan was actually less than baseline. So I would not put too much weight on this one case. There were some cases in the material sent to me which did show enlargement, as will be described below, but these were SDH cases where measurements are more problematic.

However, this does bring up the issue of how the intracranial bleeding is read and adjudicated. I have reviewed all the protocols and amendments and don't see this spelled out. First, it is not clear how the volume of the parenchymal hematoma is measured. In the exclusion criteria, it is mentioned that the (b) (4) method will be used to be certain the hematoma is < 30 cc (< 60 cc after amendment 2), but I couldn't find what method would be used in the outcome measurements. Second, it is not mentioned in the protocol who will be doing the measurements. There is some subjectivity in this and since it is a critically important outcome measurement, it should be done using standard methodology preferably by a central qualified reader who uses the same method for all patients, and who is blinded to dose and other clinical data. This comment applies to your other queries as well.

This is even more important in measuring SDH thickness and volume. In general, SDH volume and thickness is much more difficult to measure than parenchymal ICH. Again, the criteria for measurement need to be spelled out and cases read by a single reader. Cases (b) (6) and possibly (b) (6) are the only cases in the material sent to me that showed convincing enlargement soon after andexanet infusion. (b) (6) showed an increase in volume but not thickness, and an increased shift meaning that the volume measurement was the one that was important and indicating that thickness alone is not sensitive.

Regarding the other illustrative cases:

(b) (6). Was the thickness on the 13 hour scan really 12 mm or is this a typo and should it be 1.2 mm similar to the previous reading. I suspect a typo since the volume as only slightly increased, and not significantly increased compared to baseline.

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.

Response: These cases also illustrate the need for a single centralized reader of the images rather than adjudication "by committee". The same criteria need to be applied to each case. I could not find a

description of the method of measuring IVH or who was doing the measuring in the protocols. In the two illustrative cases, it appears that the amount of increased volume is negligible. These were both very small bleeds (0.91 cc and 2.03 cc) and the increase to 2.34 cc in case (b) (6) would probably not be clinically important, yet hemostasis was graded as “poor”. If this increase was due to appearance of intraventricular blood, it should not have necessarily been calculated and weighted the same as if it had been an increase in parenchymal blood (though even if parenchymal it was probably within the realm of reader variability and unlikely to be clinically important). It is not unusual for some IVH to appear in the first few hours to days after an ICH, and it doesn’t necessarily mean continued interim bleeding. That would depend on the volume of IVH. A little “leakage” would be hard to measure in terms of volume and might simply represent rupture of ganglionic blood into an adjacent ventricle (and not further bleeding), whereas a ventricle that becomes filled with blood should be included and considered as further bleeding. There are published criteria on how to measure the volume of IVH which should be used.

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

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)?

Response: In patients with spontaneous ICH, the most important clinical variable that is related to further bleeding is time elapsed since onset of symptoms since hematoma enlargement occurs most in the first 3 hours. When evaluating a treatment intended to stop further bleeding in these patients, it would be much more likely to see a beneficial effect if it is given very early after bleeding onset, and failure to include such patients in trials of pro-coagulant drugs has been one explanation for their failure to translate to clinical benefit in trials to date.

This “time vs risk” relationship is probably longer in patients with coagulopathic ICH, and is probably related to the half-life of the anticoagulant on board. While having received a fXa inhibitor within the past 18 hours (current inclusion criteria) would put the patient at increased risk of further bleeding, that risk would be higher in a patient seen 3 hours after dosing than at 17 hours when presumably anti-fXa activity would be less. Anti-fXa levels will be measured at baseline, but elevated levels are not a criteria for inclusion. In the amended protocol, only patients with anti-fXa levels > 75ng will be included in the final analysis. Presumably these levels are not in the inclusion criteria because of the logistics of obtaining accurate levels on an emergent basis. Hence, it would seem to me that time from last dosing could be a surrogate for anti-fXa levels and should be considered in the statistical analysis of results, and should also be considered in the inclusion criteria beyond just saying < 18 hrs. It is harder to enroll patients early after onset of symptoms, so liberal criteria such as just saying < 18 hrs from last dose may not ensure inclusion of patients when anti-fXa levels are at their highest, patients are at their highest risk, and when andexanet may be most useful/effective. So a consideration would be some sort of enrolment stratification based on time from last dosing so that a percentage of patients are enrolled within the time frame when anti-fXa levels are highest.

Imaging features are also important in predicting further bleeding after spontaneous ICH and may also be important after fXa inhibitor therapy. The “spot” sign seen on CT scans after contrast is given for CT angiography, irregularity of the hematoma border, and variability in hematoma density have all been related to the risk of further bleeding. While CTA will not be done routinely in this study, and not enough is known about hematoma morphology to build into inclusion/exclusion criteria, it would be worth documenting hematoma border irregularity and density variability in the baseline scan (again arguing for a central reading) and explore the effect of andexanet in patients with and without these imaging features.

I think the current hematoma volume, GCS and other exclusion criteria are ok.

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.

Response: I think waiting 4 hours after baseline imaging to start bolus is too long for the reasons already mentioned pertaining to time. There may be considerable increase in hematoma volume during those 4 hours before dosing so that the “baseline” image may not reflect the true baseline at the time of dosing, thereby biasing results against the treatment. CT scans are easy to get and it should not take more than 60 minutes to consent and dose the patient. I recommend that dosing be within 60 minutes of last image, and that the baseline CT be repeated right before dosing if necessary. Other timing is ok.

The mRS is not useful for measuring clinical response to treatment in the early time period. It is used to measure disability. As such it is a useful and validated endpoint for final clinical outcome after stroke. But as a measure of disability, it requires assessment of patient’s gait, ability to participate in activities of daily living etc. These things cannot possibly be measured in the first days after a stroke. At the earliest they can be measured at hospital discharge. The best measure to determine neurological status and to detect change in neurological status is the NIH Stroke Scale score, and this is what should be measured at 12 hours along with imaging. Doing the mRS at 30 days is appropriate as planned.

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

Response: Yes if my comments in response to #s 1-4 above are taken into consideration especially enrollment of patients early after dosing, central adjudication of brain imaging using standard criteria for measuring hemorrhage volume, documenting hematoma morphology, and obtaining NIHSS at time of brain imaging. Also see response to #5d below regarding neurological deterioration associated with hematoma enlargement.

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

Response: see above

5. Please comment on the acceptability of the definition of hematoma expansion proposed in the rating scale for hemostatic efficacy.

a) Do these definitions correlate with expected neurologic and mortality outcomes?

b) Should the definition of hematoma expansion (cut-off values that define hematoma expansion) be specific for the type of ICH (e.g., cerebellar bleeds, subdural, intraparenchymal, etc.)?

c) For subdural bleeds, is it necessary to consider change in volume in lieu of thickness to assess hematoma expansion?

d) Should the definitions of each rating include changes in Glasgow Coma Scale (GCS) ratings and/or mRS? Please also comment on the appropriate time-points for GCS and mRS that should be included in the efficacy rating.

Response: the investigators define excellent as < 20% enlargement, good 21-35%, and poor as > 35%.

- a. These cutoffs are reasonable with regard to expected neurologic and mortality outcomes.
- b. yes—they need to be different for SDH and IVH as previously described
- c. yes—see case (b) (6)
- d. yes. However, as mentioned, use NIHSS instead of mRS. The GCS and NIHSS should be documented at the time of imaging. Many things besides hematoma volume change can effect the GCS and NIHSS. So for this study, the outcome should be hematoma enlargement (HE), but it would be worth subdividing into HE with or without neurological deterioration (i.e. 1-2 points lower on GCS or 2-4 points higher on NIHSS). I think the 1 and 12 hour post infusion time points for imaging are reasonable. It is possible that some further HE might occur between 12-24 hours, but the effect of the drug on reducing HE should be detectable by 12 hours.

6. Please comment on an acceptable approach to reduce variability in interpretations of radiographic images. Is it necessary to include an imaging protocol?

Response: Yes!! See response to # 1 and 2.

7. 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.

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)?

Response: There is a conundrum. Mortality and outcome after ICH is primarily related to hematoma volume and location. Excluding posterior fossa hematomas and exclusion of patients with hematoma volume > 60 cc means that mortality will not be high—probably in the order of 20% in the overall population. Furthermore, mortality will be more related to initial size of the hematoma than the amount of hematoma growth. For instance, growth of a hematoma from 10-20cc might worsen morbidity, but not mortality since very few patients with hematomas < 25 cc will die, whereas a hemorrhage of 80 cc will result in mortality whether or not it enlarges. So bottom line, given the size and location of hematomas likely to be enrolled, it is unlikely that andexanet will effect mortality alone without a very large sample size, but if it is effective in preventing hematoma growth, there should be an effect on the combined outcome of mortality and severe morbidity, probably a reduction in patients ending up in the mRS 4-6 categories. This endpoint (reducing mRS 4-6) is more important than reducing mortality (mRS = 6) alone, since patients rate a mRS of 5 (bed or chairbound) as being comparable or worse than death, so simply preventing death to keep patient alive as a mRS 4 or 5 is not making a difference in patient-centered outcome, whereas salvaging patients from a mRS 4-6 to <4 would be important and feasible.

Regarding timing, many patients with ICH have prolonged hospitalizations; they are often kept alive on a ventilator in the ICU and gradually weaned to go to a long term care setting, languish, and die of complications months later. On the other hand, others will recover substantial function but may require months of rehab. Therefore, to accurately assess mortality and outcome after ICH particularly in comparing two interventions, the final outcomes should not be assessed until at least 3 months and preferably 6 months after the stroke. In this study, patients will be followed only to 30 days. It is certainly worth measuring mortality and mRS, and the rates at 30 days will be strongly predictive of longer term outcome, but they will substantially underestimate both mortality and recovery.

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.

Response: A cohort control study has many weaknesses. It cannot enroll control patients at the same institutions participating in the intervention arm of the study because of the risk of “cherry picking” the best candidates for a treatment that looks promising like andexanet. Such a cohort study is certainly feasible but ensuring comparable patients would be difficult; it would be essential to select the “usual care” group using various predictive scores that match scores of patients in the treatment group. In addition, investigators would wind up comparing patients managed differently at different institutions. For instance, there would be variability in the speed and effectiveness of reversing the coagulopathy from center to center, as well as other differences in care such as blood pressure management, surgical intervention etc. Clear common guidelines for managing these patients would have to be adopted at each center, and center X outcome interaction would have to be considered in the data analysis.

I see no reason why a randomized controlled study could not be done, except for the obvious ethical issue. If it is possible to get the drug outside the trial, for a condition where there is no other treatment, and where preliminary studies indicate it is safe and has the desired biological effect, is it ethical to randomize the patient to a non-treatment arm, and is it feasible (i.e. will patients agree to randomization)? If the drug is not available outside a trial, then I think it would be feasible and ethical, but strict stopping rules and careful ongoing scrutiny of results by the DSMB would be needed to assure the study would not enroll more patients than needed to demonstrate efficacy.

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