



Meeting Summary

Application type and number: BLA 125586/0
Product name: Coagulation Factor Xa (Recombinant), Inactivated
Proposed indication: For patients treated with a direct or indirect fXa inhibitor when reversal of anticoagulation is needed in situations such as:

- Life-threatening or uncontrolled bleeding
- (b) (4)

Applicant: Portola Pharmaceuticals Inc. [Portola]
Meeting type: Other
Meeting category: BLA
Meeting date & time: July 27, 2016, 2 pm – 4 pm, ET
Meeting format: Face-to-face
Meeting Chair/Leader: Peter Marks, MD
Meeting Recorder: Sunday L. Kelly, MS, RAC, PMP

FDA Participants:

Howard Chazin, MD, MBA, Acting Director, Division of Hematology Clinical Review, OBRR/CBER
Jay S. Epstein, MD, Director, Office of Blood Research and Review, CBER
Basil Golding, MD, Director, Division of Hematology Research and Review, OBRR/CBER
Sunday L. Kelly, MS, RAC, PMP, Regulatory Project Manager, RPMS/OBRR
Sherry Lard-Whiteford, PhD, Ombudsman, CBER
Peter Marks, MD, Director, CBER
Mikhail Ovanesov, PhD, Research Biologist, LH/DHRR/OBRR

Portola Attendees:

Michele D. Bronson, PhD, Vice President, Program Management
Janice Castillo, Vice President, Regulatory Affairs and Quality Assurance
Stuart Connolly, MD, Director, Division of Cardiology, McMaster University
John T. Curnutte, MD, PhD, Executive Vice President, Research and Development
Alex Gold, MD, FACC Senior Vice President, Clinical Development
Bill Lis, Chief Executive Officer

By Phone:

Andrew Demchuk, MD FRCPC, University of Calgary, Director, Calgary Stroke Program,
Professor, Depts. of Clinical Neurosciences and Radiology

(b) (4)

Background and Objectives:

This meeting is the third in a series of meetings agreed upon by Portola and FDA during the April 28, 2016, teleconference with CBER's Director.

Portola submitted a slide deck related to product labeling via email on July 24, 2016. FDA received the email on the following business day, July 25, 2016. FDA indicated to Portola via email that the preference was to have a discussion during the meeting in lieu of going through the presentation to focus the time on ANNEXA-4 study.

Meeting Discussion:

Portola noted that the neurologist, Dr. Andrew Demchuk, is the head of core lab for the ANNEXA-4 study for scans of the brain and is a member of the adjudication committee providing advice on the issues related to adjudication of brain scans.

Portola said their goal for this meeting was to have a two-way conversation and gain agreement with FDA on how the BLA for ANDEXXA could be approved by the Action Due Date.

Portola summarized:

- This is a breakthrough therapy product indicated for the reversal of Factor Xa inhibitor activity; it acts as an antidote and is not a typical therapeutic protein.
- Portola considers they have met requirements for accelerated approval.
- Portola has an ongoing study that is half-way enrolled per the regulations for accelerated approval.
- ANDEXXA is an orphan drug. The unmet medical need continues to grow as the market share of the Factor Xa inhibitors continues to grow.

Portola understood from the June 22, 2016, meeting that FDA was in agreement with moving forward with the indication of short term duration of reversal of anti-FXa. Portola requested to discuss the issues FDA raised on the Usual Care Cohort and the ANNEXA-4 study during the first hour and reserve the second hour for discussion of the label.

FDA reiterated that they would listen to all that Portola wished to convey and there might be some clarifying questions only. FDA acknowledged Portola's remaining concerns and said that at this time, the primary objective of the review team is the completion of the BLA review. FDA informed Portola that for today's discussion, FDA would be in listening mode and was not in a position to deliberate further on any outstanding issues. Dr. Marks recounted that when Portola initially contacted him, they were concerned about the continuity of the review committee and the Advisory Committee Meeting. He stated that these issues have been fully addressed given that the review team has remained unchanged and the BLA was not taken to the advisory committee.

ANNEXA-4 Study:

Limitation of subjects to intracerebral hemorrhage (ICH):

Regarding Portola's July 25, 2016, response to FDA's July 18, 2016, information request regarding the ANNEXA-4 study amendment, Portola claimed that they agreed to almost all of the recommendations with the exception of limiting the study to ICH patients. Portola asked FDA what this limitation would mean for them going forward.

FDA stated that the basic concern is that ICH is the condition where there is the most uncertainty and the greatest need to help clinicians.

Portola stated that if FDA approved a narrow indication for the drug, it would be a disservice to the community as it would be used largely off label. Doctors will need to consider re-dosing and repeat infusion.

FDA said they want to assure there is a sufficient study in ICH, not to exclude other patient populations, but instead to have a more homogenous population to answer a highly important medical question.

Portola asserted that clinicians are interested not only in ICH, but in patients with all types of bleeding. ICH makes up about 10% of major bleeds in large trials and comprise 40% of the patient population in ANNEXA-4. Portola said they are reluctant to not enroll the other patients with other types of bleeds given that they have substantial medical issues related to their bleeds.

FDA acknowledged that any bleeding patient would need reversal; ICH is where there is greatest concern about depth and duration of reversal exists. It may be easier to monitor in clinical settings given that surgical and GI bleeds are different; ICH is the most difficult and where the efficacy of the drug should be evaluated. Success in ICH would generalize to other types of bleeds needing reversal.

Portola proposed enrolling a number of ICH patients to meet the minimum criteria. They projected that there would be around 110 ICH patients by the end of the study and offered to increase this to the number FDA would want to have confidence for ICH. Portola said they would perform a separate analysis of the ICH patients, split equally between subdural and intraparenchymal bleeds. They stated that it would be challenging to perform a separate study in ICH and asserted that the current metrics used for the study are optimal.

FDA stated that there could be a future discussion on the required number of ICH patients. FDA provided assurance that Portola's proposal provided a path forward that might work if they can reach enrollment in ICH. FDA stated that the intent was not to be prohibitive, but to recommend the clearest path to closure. FDA cautioned that of the 57 ICH patients of a total of 134 have already enrolled, the data might not have been prospectively collected with the proper protocol criteria in place and as a result the outcomes in those patients may be uninterpretable.

Regarding the radiographic endpoints, Dr. Demchuk, who runs the core lab, reviewed the FDA responses related to ICH that were sent to Portola via email on July 18, 2016, under IND 15089. Portola summarized:

- They are already implementing many of the features as requested by FDA.
- They agree with the radiographic assessment; and are already adjudicating the scans as FDA requested.
- They are not using ABC/2 but a quantitative method to measure the volume and thickness of bleeds. The ABC/2 is used as a rough estimate for eligibility. There is a cut-off of 60 cc for the size of the initial bleed.
- The core lab has a protocol and Quality Control.
- The same radiologists read the scans from beginning to end. The scans are reviewed with a standard method to evaluate the size of the hemorrhage.
- Portola will apply the radiographic assessment retrospectively to the first 57 patients.

Primary endpoint - hemostasis endpoint versus clinical endpoint

Portola recapped that this product is being developed as a hemostatic agent that takes away the anticoagulant and allows hemostasis to occur. The goal of the ANNEXA-4 study was to validate that the biomarker correlates in all clinical cohorts with a hematologic outcome, namely cessation of bleeding. Portola said they have followed all the types of clinical conditions with bleeding outcomes based on a hemostatic assessment. The goal of the study is to stop bleeding as early as possible; all of the efficacy endpoints are to ensure there are rigorous and precise measurements on hematoma size which is a measure of bleeding. Portola said they measured the thickness on the scans based on the approval of Kcentra which they consider the benchmark for hemostatic endpoint criteria. Portola asserted that there is objectivity in the independent reading of the scans that give a stronger sense of the outcome compared to short term clinical assessment. Portola said they wish to keep comparison of scans and hemostatic assessment of cessation of bleeding via CT scan as the primary outcome measure for intracranial hemorrhages.

FDA agreed with Portola about the value of the scans, but stated that the main issue is the timing of ANDEXXA administration related to the onset of clinical symptoms, as reflected in time to CT and time from CT to bolus. Variability in these areas presents itself as a major confounder. For example, earlier intervention is more likely to have an observable effect. Conversely, bleeding will stop because of increased intracranial pressure around the hemorrhage in the absence of anticoagulant reversal. One cannot dissociate this from the issue of the timing of the last dose of anticoagulant, the initial bleed and clinical symptoms, the initial screening CT scan, the initial bolus and infusion, and the follow up CT scan. It is critical to collect and examine a distribution of timing of these major events.

Portola (Dr. Demchuk) said there is a difference in the natural pattern of an anticoagulant induced bleed compared to a non-anticoagulant induced bleed. Portola has observed a number of patients at different times past the anticoagulant bleed with differing levels of anticoagulants. In a non-anticoagulant bleed, the primary hemorrhage expansion occurs early and settles down after a few hours. Alternatively, in warfarin-related bleed, bleeding can continue for as long as 12-24 hours. For NOACs, the bleeding timeframe is somewhere in the middle of these two types of

bleeds, perhaps maximizing at 6 hours, indicating a need for late scans. Most patients have three to four CT scans across a spectrum of timeframes. There are large numbers of patients who have scans after 12 hours. For direct anticoagulant related bleeding, you want two or three time points to account for late bleeding events.

Portola said their goal is to shorten the time of administration of ANDEXXA to less than 1.5 hours from CT scan to bolus because the progression of the hematoma is working against the efficacy assessment of ANDEXXA. In the clinical setting, there are Emergency Department (ED) doctors dealing with intracranial hemorrhage and time is of the essence, but there is not much that can be done to speed up the consenting of subjects and reconstitution of the currently being used smaller vials. The time from arrival in the ED to CT scan is about 4.5 hours and the mean time from the CT scan to the ANDEXXA bolus is about 1.5 hours. Portola suggested that post-marketing efforts would reduce the time from arrival at the ER to infusion, similar to the development of tissue plasminogen activator (tPA) products for stroke.

FDA agreed with the real world limitations in the ED and stressed that to gain understanding of the treatment effects, Portola needs to optimize the timing of arrival to consent and to treatment; and agreed that any delays confound the efficacy analysis. Additionally, FDA requested that Portola evaluate the distribution of timing of the bolus of ANDEXXA and to stratify the data related to timing of the administration of ANDEXXA to help with the interpretability of the outcomes.

Portola summarized the current state of the ANNEXA-4 trial:

- In the first 57 patients, 84% of them have an anti-Factor Xa activity level greater than 75ng/mL. The anticoagulant stays around and contributes to the pathology. Portola intends to add a series of exploratory clinical endpoints.
- For all ICH, 22 are intracranial, 11 are subdural hematomas, 0/11 of the subdural bleeds have required neurosurgery; this will be part of the secondary efficacy outcome data presented to the FDA.
- Portola is monitoring number of days in ICU, rebleeding events in the first 12 hours, any bleeding during the subsequent 30 days, days to discharge, and survival status as additional secondary/exploratory efficacy endpoints.
- Portola said that the NIH stroke scale (NIHSS) would be a nice addition to this suite of assessments as a secondary, exploratory endpoint. FDA agreed that some clinical validation would be important. The NIHSS is a way to monitor neurological deterioration in the short term and relates to clinical efficacy. However, Portola reiterated that the primary endpoint for the ANNEXA-4 study should remain as a hemostatic endpoint, i.e., the change in the volume of the hematoma.

FDA reiterated that change in the volume of the hematoma is a surrogate marker; in the study, under Accelerated Approval, Portola has to demonstrate that the surrogate marker directly relates to clinical outcomes. Modified Rankin Scale is a later measure of clinical outcome; the NIHSS is an early measure.

Portola responded that their drug helps achieve hemostasis by removing the anticoagulant. There are multiple patient-dependent covariates and co-morbidities that will affect clinical outcomes. Given the track record in stroke development, it is hard to achieve a direct effect on clinical endpoints. Portola said they cannot have a primary endpoint as improvement in stroke because mechanistically, ANDEXXA was not designed to directly improve stroke outcomes and therefore affect the NIHSS. In order to do this, Portola said they would have to enroll many more patients and stratify different strokes to power the study appropriately and perform any assessment with a change in primary endpoint and that this would be onerous. Short of this, Portola noted that stroke volume is a strong correlate of clinical outcome.

Portola asserted that for the question of hemostatic efficacy, volumetric assessment for hematoma is a better outcome measure than the clinical assessment. Portola also noted that location of the hematoma could be a major modifier to clinical outcome which supports that volume itself is a clinically important endpoint.

Another Portola representative reasserted that out of 11 subdural bleeds, none of the patients required surgery. Further, the location could be a major modifier to the outcome; therefore, the hematoma volume is a more important clinical measurement because it drives interventions and next steps in therapy. Small hematomas will almost never have a clinical impact on the NIHSS. Portola said that by using the volumetric measure, the drug is being put to a tougher test.

FDA responded that in trauma studies, in terms of bleeding, FDA has always insisted that studies measure outcomes that are clinically meaningful (e.g. survival), not just cessation of bleeding. In response, Portola recalled that both parties discussed the clinical meaningful endpoint at the EOP2 meeting in August 2012 and agreement was reached on hemostasis, i.e. cessation of bleeding as a clinically meaningful endpoint. Portola asserted that they guided their development program based on Kcentra correlated outcomes and FDA feedback. Portola said they hoped to meet FDA expectations by collecting the additional NIHSS.

FDA recapped that they understood Portola's appeal to consider the radiologic endpoint as primary and they would consider it. FDA reminded Portola that AA regulations require demonstration of clinical benefit. No agreement was reached on the use of hematoma volume alone as a primary clinical endpoint, but FDA would consider a hemostatic endpoint with positive trends in secondary clinical endpoints and would continue these discussions with Portola at a later date.

Usual Care Cohort (UCC) Study:

Portola acknowledged receipt of feedback from FDA related to the UCC and has not yet sent in their written responses. Portola noted that it was ready to do the UCC but wanted to discuss and develop a mutual understanding as to what it will deliver. Portola agreed that the UCC would generate useful information, but did not agree that the UCC itself could be a definitive comparator arm to ANNEXA-4. This is because there are too many covariates to consider and also that this is not a definitive control study arm. Portola reiterated the previous agreement with

FDA in February 2016 whereby FDA would consider the totality of the data including the ANNEXA-4 study, the (b) (4) and the UCC in reaching any final determinations.

(b) (4) :

FDA informed that the (b) (4) ; it should not be rolled into the ANNEXA-4 study at this time. FDA advised that Portola needs approval for the current iteration and then would submit a BLA supplement (b) (4) . Portola could submit a separate protocol to the IND at any time; however, at this stage in the Accelerated Approval pathway review, Portola should modify the current ANNEXA-4 protocol by (b) (4) .

Portola indicated that they would withdraw the amendment for the (b) (4) , but sought clarification on “totality of the evidence” as the review standard. They said they had not added the ICH NIHSS in the most recent IND amendment.

FDA said it understood Portola’s concerns about biases with the Usual Care Cohort and assured that as always, FDA would consider the totality of the data submitted.

Regarding the UCC, Portola agreed to:

- Complete enrollment of the UCC without an interim analysis.
- The sample size of the UCC will be the same as the evaluable patient population, 162 evaluable patients for 80-90% power if ANNEXA-4 is running at 84%.
- Not do the propensity score matching, but utilize the propensity score stratification as suggested by FDA
- Utilize the data from the rapidly moving ANNEXA-4 study to help shape the composition of the UCC to optimize matching of the cohorts.
- Perform data analysis by the type of bleed and by anticoagulant – given that these are the major covariates that introduce issues.
- Ensure that the time measurements are now properly matched between both the ANNEXA- 4 and the UCC.
- Utilize the methodology for the prospective propensity score stratification to adjust for the differences between the two cohorts.
- Portola suggested having supplemental multi-variate analyses to correct for not having enough patients in one group or another.

Portola suggested a separate, parallel study between the UCC and the ANNEXA patients not as a strict, definitive comparator, but to understand the ANNEXA-4 data. Portola reminded FDA that this cohort comparison would never replace a randomized controlled trial (RCT). There are confounders that cannot be account for, but a RCT is not feasible or ethical. Portola stated their intention to keep the UCC study separate from the ANNEXA study with an attempt to have the two groups as well matched as possible in terms of hospitals, inclusion criteria and bleeding type.

FDA acknowledged the challenges with this type of comparative cohort study. Portola acknowledged that they would have to evaluate the results and statistically determine how to interpret the data.

FDA said that there is no issue with this study plan conceptually, but it is unclear if there is a true benchmark with Kcentra. This topic has been discussed several times in the past with Portola. FDA noted that Portola will attempt to measure the degree of matching with the propensity score stratification. Portola will complete the ANNEXA-4 study without the (b) (4) subpopulation and compare that to the benchmark derived from the Kcentra study. FDA said they did not expressly agree to the benchmark but would exercise judgment both with regard to efficacy as measured against the benchmark and the statistical comparison of outcomes in ANNEXA-4 versus the UCC. . FDA said Portola has an outstanding request from June to submit the Statistical Analysis Plan (SAP) for review.

FDA expressed concern about Portola's commitment to perform the study after approval because doctors will want to use ANDEXXA once it is available.

Portola assured that they are committed to performing the UCC study and carry it through post-approval and that they already have some sites ready. Portola said they would submit a revised protocol to address FDA's comments and submit the updated UCC protocol including the SAP addressing the comparison to the ANNEXA-4 study.

FDA said that the parties would need to agree on the study design and Portola would need to show evidence of good faith to perform the study.

Labeling:

Portola went through the labeling portion of the slide presentation received by the FDA on July 22, 2016. FDA informed Portola that they had not reviewed the labeling at this time because the focus has been review of other issues within the BLA.

Slide 5:

- The italicized wording on this slide represent items that Portola wanted to discuss further.

Slide 6:

- Portola withdrew the (b) (4) indication per FDA's email response of July 18, 2016.
- Three anticoagulants/inhibitors are listed (apixaban, rivaroxaban, and edoxaban) with an added a limitation of use qualifier.

Slide 7:

- Concordance between the model and what was observed in patients on Rivaroxaban.

Slide 8:

- Demonstrates the robustness of the model for Apixiban by comparing the predicted % reversal to the observed % reversal 95% confidence interval. Portola noted that the “noise gets high” as the time progresses making it more over predicted after 8 hours.

Slide 9:

- All three anticoagulants behave remarkably similar. Portola did not have edoxaban in the phase 3 trial.
- Consistent behavior based on thrombin generation in phase 2 (rivaroxaban and edoxaban) studies and phase 3 (rivaroxaban) studies. There were no edoxaban phase 3 studies.

FDA noted that the graph of a correlation between anti-FXa activity and thrombin generation on Slide 9 is in apparent contradiction with the phase 3 data presented on Slide 26. FDA noted that peak thrombin generation levels were closer to 2000 thrombin units on Slide 26 which is substantially higher than the peak thrombin generation of 1400 thrombin units as shown on Slide 9.

Portola explained that data from a placebo arm of phase 3 study are shown on the right side of Slide 9. However, averaged data from both the ANDEXXA arm and the placebo arm of the phase 2 study are shown on the left side of the graph. Portola explained that this graph was also presented at the pre-BLA meeting to show the class affect.

Slide 10:

- Portola suggests that apixiban, rivaroxaban and edoxaban are similar. FDA does not agree and noted that the Andexanet affinity by (b) (4) for edoxaban is higher with a larger standard deviation. FDA noted that they have not completely reviewed this data or made the same conclusions regarding edoxaban.

Slide 11:

- This is a combination of the phase 2 data with the PK/PD model to show that this should have an effect on bleeding similar to apixaban and rivaroxaban.
- In bleeding patients, the model will be able to predict that the 800 mg bolus +8 mg/min one hour infusion will achieve reversal.
- Portola recalled that FDA said there were not enough patients in ANNEXA-4 so this is now detailed in the label. Portola said they could just exclude it, but practitioners in the clinic will not know how to dose a patient on edoxaban. Portola suggested that it might be better to provide the data to practitioners with the explanation that this is based on robust modeling with a clear limitation on use.

Edoxaban:

Regarding edoxaban, Portola noted robust modeling to support their claims, but FDA told Portola that they would take this under advisement. FDA reminded Portola of the regulatory legal issues in that Accelerated Approval focuses on the surrogate of reversal and the depth of reversal here is different. FDA related that one could argue that modeling is another surrogate or

a surrogate validating a surrogate. The open question is whether or not the depth and extent of reversal is good enough.

Portola asserted that they have shown statistical difference over the placebo and that the required depth of reversal is unknown. Portola further claimed that, based on some of the modeling, there is a good likelihood that reversing by 75% is enough. In the rabbit model, with edoxaban, they showed a 75% drop in anti-Factor Xa activity correlated with a response in the lacerated liver rabbit model. In the ANNEXA-4 study, 75% reversal of anti-FXa activity yielded good to excellent hemostasis.

Portola asked what would be required to include edoxaban in the label, data from ANNEXA-4 or additional dosing work? FDA said there could possibly be a future discussion of options for including edoxaban in the label, but FDA cannot allow it to be included as a claim if the data are not sufficient and it would imply an intended use claim.

FDA reiterated the continuing concern about the percent reversal of edoxaban by ANDEXXA and in the healthy volunteer study and whether patients would be left therapeutically anticoagulated after treatment. This makes it problematic to accept this surrogate for edoxaban and there are no edoxaban treated patients in ANNEXA-4. FDA encouraged Portola to explore further dose ranges of edoxaban to improve depth of reversal. No agreement was reached on the inclusion of the limitations of the available edoxaban data in the labeling.

Enoxaparin:

Slide 13:

- There are 9 patients on enoxaparin in the ANNEXA-4 study to date; 6 were in the original submission and another 3 since then, including patients treated at the higher dose bolus and infusion.
- Portola is gaining experience and has the PK/PD data not in patients, but in human blood samples spiked with enoxaparin. These spiked samples show reversal of anti-FII activity.

FDA discussed that they had received Portola's submission regarding (b) (4) but had not had completed its review. FDA reiterated its concern for the dual mechanism of action and again related that placing such data in the labeling would imply an intended use. Portola related it was FDA's decision and they understood but are willing to understand what data is still necessary.

TFPI Inhibition:

Slide 22:

- Portola measured TFPI in the rabbit liver laceration model with rivaroxaban and noted the 5 mg dose had no effect on bleeding in animals
- High homology in the critical function domain.
- Demonstrates that ANDEXXA will fully block TFPI activity with no effect on hemostasis.

- Portola proposed to state in the label that the reversal of anti-Factor Xa activity is the predominant mechanism of action and the contribution of TFPI inhibition is minimal.

Slide 23:

- 75mg of ANDEXXA fully blocks TFPI activity without affecting hemostasis (9g of blood loss in non-anticoagulated rabbits and 10g of blood loss in anticoagulated rabbits.)

Slide 24:

- High homology between the rabbit and human TFPI sequences and Kunitz-2 domain.

Slide 26:

- Predominant action of ANDEXXA is not TFPI mediated.
- Portola noted that 2/3 of the thrombin generation overshoot is related to TFPI inhibition and 1/3 is independent of TFPI.
- The thrombin generation does not spiral down into the anti-coagulated range. It remains in the normal range, same as placebo. Minor TFPI inhibition maintains the thrombin generation for 22 hours. The effect is small but you still see it. Portola said they would send more data.

Agreements:

Portola noted that they would send in the ANNEXA-4 protocol amendment and the UCC study protocol and statistical analysis plan to the IND 15089 within the next week.

Post Meeting Notes:

1. FDA is concerned about the potential bias of adjudication of CT scans in ICH subjects by having Dr. Andrew Demchuk participate in both roles, one as the head of core lab for the ANNEXA-4 study CT scans and also as a member of the adjudication committee providing advice on the issues related to adjudication of CT scans. Dr. Demchuk should not be in both roles as this presents potential bias in evaluating the brain scans independently.
2. In a follow-up review of the minutes of the August 2012 meeting, FDA ascertained that there was no discussion of primary end-points for a phase-4 study of ANDEXXA.

Attachments/Handouts:

1. Portola's Slides – received via email on July 22, 2016

END