



Meeting Summary

Application type and number: BLA, BL 125586/0
Product name: Coagulation Factor Xa (Recombinant), Inactivated [ANDEXXA]
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 – Escalation Series [BLA Review]
Meeting category: BLA
Meeting date & time: May 20, 2016, 11:30 am – 1:00 pm, ET
Meeting format: Face-to-face
Meeting Chair/Leader: Jay Epstein, MD
Meeting Recorder: Thomas J. Maruna, MSc, MLS(ASCP), CPH

FDA Participants:

Howard Chazin, MD, MBA, Acting Director, CBER/OBRR/DHCR
Jay S. Epstein, MD, Director, CBER/OBRR
Bindu George, MD, Chief, CBER/OBRR/DHCR/CRB
Sherry Lard, PhD, Ombudsman, CBER
Peter Marks, MD, Director, CBER
LT Thomas J. Maruna, USPHS, MSc, Senior Regulatory Management Officer, CBER/OBRR
Mikhail Ovanosov, PhD, Research Biologist, CBER/OBRR/DHRR
Nicole Verdun, MD, Acting Deputy Director, CBER/OBRR

Portola Attendees:

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

Background and Objectives:

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

FDA set the scope of this meeting as follows:

1. FDA will provide the status of ongoing review for BLA 125586/0.
2. FDA will communicate key issues requiring immediate attention and resolution.
3. FDA will communicate what additional information is required at this stage of review.

Discussion:

1. Status of Review

FDA noted the following:

- a. All information submitted to date, including all amendments have been reviewed. Additional information requests (IRs) will be sent; specifically concerning the pharmacodynamics due to ANDEXXA inhibition of TFPI activity as it relates to (1) the procoagulant effect inferred from the thrombin generation test (TGT) assay and (2) the overall assessment of ANDEXXA's safety and efficacy.
- b. A separate CMC teleconference has been scheduled for Monday, May 23, 2016, to discuss the comparability protocol submitted on December 17, 2015. A second IR will be sent following this teleconference.
- c. FDA has requested consultations from several external subject matter experts (e.g. from CDER); further noting that FDA will not respond to Portola's email dated May 6, 2016, (attached) until the consultants have provided their input, which FDA has determined to be essential.

2. Key Issues Requiring Resolution

- a. FDA reiterated its position that the depth and duration of reversal of anti FXa activity levels remain the principle concerns. Further, FDA specifically addressed (b) (4) :
 - i. (b) (4) FDA noted that the dataset to support adequate reversal of this inhibitor is weakest and that the depth of reversal (less than (b) (4)) is significantly less than that compared to the other inhibitors (i.e., apixaban and rivaroxaban); and in addition FDA notes that very few patients on (b) (4) are included in the studies, all suggesting that consideration of a class-effect may not be appropriate. FDA suggested stratification among inhibitors and narrowing the indication and that Portola provide any additional information related to (b) (4)
 - ii. (b) (4) FDA notes a paucity of subjects in ANNEXA-4 and lack of clarity concerning the mechanisms in relation to the surrogate including reversal of anti-FIIa activity.

FDA noted it is stratifying its review and considering the anticoagulants separately.

- b. ICH is another chief concern.
 - i. FDA stated that it is not opposed to the surgical study with extended infusion; however, concern was expressed about the timing of data submission in relation to the current review cycle (i.e. it would not be feasible to collect, process and submit the additional data in time for a substantive review within this review cycle).
 - ii. FDA noted concerns with the adjudication of clinical outcomes, specifically with respect to the ANNEXA-4 study.
 - iii. FDA questioned whether the 2 hour duration of reversal would be sufficient in these (i.e. ICH) patients.
 - iv. FDA questioned whether normal-healthy volunteers provided any meaningful data with respect to this patient population.
 - v. FDA noted its preference for an extended infusion leading to complete and maintained reversal of anticoagulation and that extended dosing of ANDEXXA either through additional bolus or extended infusion needs to be understood both from efficacy and safety standpoints.
- c. FDA stated that discussion of strengthening of the ANNEXA-4 trial will have to be revisited pending an agreement on accelerated approval; that it would not be possible to finalize the trial design until other concerns have been resolved.

3. Additional Information Required

- a. FDA noted that it does not accept a short period of reversal as adequate prima facie; FDA requires data to support this claim as it represents a paradigm shift from what has been done in the past (i.e. complete and sustained reversal with warfarin, heparin and monoclonal antibody).
 - i. Portola noted that current therapy does not rely on complete reversal of anti-FXa activity.

FDA accepted Portola's point, stating that this was the basis for breakthrough designation and FDA agreed on the unmet medical need. However, FDA noted that it is obligated to establish safety and efficacy and we have to be convinced of, "reasonably likely" to approve the product based on a surrogate marker.

- b. FDA noted that the depth and duration of TFPI inhibition by ANDEXXA was not sufficiently investigated nor described adequately in the BLA to allow for a meaningful review. Specifically:
 - i. Because the reversal of anti-FXa activity is so transient and TFPI inhibition is potentially thrombogenic, the accurate assessment of the two observed mechanisms of action of ANDEXXA (anti-FXa activity reversal and TFPI inhibition) is necessary.
 - ii. The transient nature of the reversal of anti-FXa activity suggests that it may not contribute directly to the sustained procoagulant effect as inferred from the sustained increase in TGT assay in healthy volunteer studies.
 - iii. The new data obtained with a (b) (4) TGT assay indicate that the effect of inhibition of TFPI activity is more significant than it was previously thought.
 - iv. The *Clinical Study Reports* need to be updated with all results available to Portola so that FDA can consider all of the evidence. Specifically, the results of the assay for the inhibition of TFPI activity was not provided in the phase 2 and phase 3 reports
 - v. FDA noted that in relation to TFPI inhibition effect, the results obtained with the TGT assay methods are not congruent between the preclinical and clinical studies.
 - 1. For example, TFPI inhibition had no procoagulant effect on the TGT assay in preclinical spiking studies. In contrast, there was increased TGT in excess of baseline in clinical studies. This discrepancy indicates that the assays used in the phase 3 studies were not properly qualified to study the anti-FXa reversal action of ANDEXXA. FDA stated that the evaluation of retained samples using (b) (4) TGT assay and TFPI activity assays would be helpful to explain the sustained procoagulant effect observed by the tissue factor-activated TGT assay in phase 3 studies.
 - 2. TFPI activity inhibition should be monitored carefully under any additional bolus administration or extended infusions.

All items noted above concerning the inhibition of TFPI activity by ANDEXXA will be communicated to Portola via an IR describing the deficiencies and FDA's concerns in detail along with potential paths to resolving them.

4. Additional Discussion Items

- a. Portola discussed studies that have been conducted concerning TFPI and additional data planned to be submitted in the BLA in their responses to the forthcoming IRs.
 - i. Portola stated that measurements of plasma TFPI activity and TFPI antigen had been taken following bolus infusion in phase 1 and phase 2 studies but not phase 3 studies.
 - ii. Portola stated that TFPI binding and TFPI activity data demonstrated that (a) ANDEXXA binds to TFPI and (b) TFPI sequestration is maintained for a period of time exceeding 24 hours.
 1. Portola stated that TFPI is present in plasma and on the surface of endothelial cells. Portola does not have a method for measuring TFPI bound to endothelial cells. FDA requested that Portola submit their data and concerns regarding endothelial cell TFPI in writing.
 - iii. Portola stated that they started using a (b) (4) TGT assay following advice they received from the Agency in September of 2015. They also studied plasma levels of prothrombin fragment F1+2 and D-dimer, the interplay between TFPI activity, increased thrombin generation and the response of the fibrinolytic system.
 1. Portola will provide all data including (b) (4) TGT assay and from other studies they have accumulated for the last 3 – 4 months.
 2. Portola stated that they have performed studies of TFPI inhibition using the TGT assays activated by the extrinsic (tissue factor) and intrinsic (b) (4) coagulation pathways. Portola stated that TFPI inhibition has no bearing on the TGT assay activated by the intrinsic pathway.
 3. Portola noted that it is their interpretation that when TGT is activated with (b) (4) ANDEXXA is not a prothrombotic agent and has an indirect effect on TFPI.
 - iv. Portola stated that use of retained samples for future TFPI analysis may be difficult because it was not part of their original phase 3 protocol and informed consent forms. Portola noted some IRB resistance to retesting stored samples. It may take several months to obtain permission for use of retained samples. Portola noted to FDA that dosing was done and optimized during phase 2 as that was when dose ranging was evaluated.

- b. In response to Portola's statement regarding TFPI activity testing in the phase 2 studies, FDA noted that the TFPI activity data were only reported for the phase 1 study. However, a comparative analysis of the results between TFPI *activity* and TFPI *antigen* results (observed in phase 1 studies) indicated that a 50% decrease in the TFPI antigen assay (observed in phase 2 studies) corresponds to a nearly 100% complete inhibition of TFPI in anticoagulated patients 24 hours after ANDEXXA administration. Portola agreed with the assessment and explained that this is because the concentration of TFPI in blood (3 nM) is very low in comparison to the pharmacological concentration of ANDEXXA (b) (4).
- c. In reference to the new data obtained with a (b) (4) TGT, FDA requested Portola to provide assay qualification data on all TGT assay variants used in all clinical trials and to provide all TFPI-related data they have not yet reported in the BLA. FDA explained that the primary goal of the TFPI requests is to obtain a complete picture on the depth and duration of TFPI inhibition and its relation to the observed elevation in TG. FDA related their safety concerns about a potential prothrombotic effect of TFPI inhibition in general and, specifically, the possibility that this prothrombotic effect may be prolonged under the conditions of discussed extended infusions (longer than 2 hour infusions studied in phase 2 and 3 studies).
- d. FDA reiterated that the depth and duration of the anti FXa activity reversal are of principal concern and that FDA needs to understand all of the mechanisms of action of ANDEXXA.
- e. Portola noted that in the (b) (4) only (b) (4) of (b) (4) domains is blocked by ANDEXXA and therefore complete inhibition will not be observed. Testing of TFPI in bleeding patients would be hopelessly confounded due the complexity of coagulation cascade activation in bleeding patients, which is why a normal healthy volunteer study was so important.
 - i. FDA questioned the ethics of a normal healthy volunteer study if there is a significant risk of thrombosis in extended infusion studies. And although bleeding patients would be more complicated, the benefit to risk ratio in bleeding patients might be better and the data would be more useful.
 - ii. Portola stated that the submission of the discussed data may be delayed and asked how the delay will affect the ongoing review.
 - 1. FDA stated that it may not be feasible to review the data within the current review cycle which may result in a *Major Amendment* designation and clock extension; however this will be a review issue and a final determination cannot be made until the data have been submitted and evaluated. If the clock needs to stop for necessary data, then it happens.
- f. Portola stated that it will commit to providing the data and analysis of all major issues noted above in a "timely manner."

5. ICH and adjudication of cases

- a. FDA expressed concerns about the adjudication of ICH cases, specifically as it concerns efficacy in relation to the surrogate, and requested that Portola provide an overview. Further FDA noted that the TFPI studies would be supportive.
 - i. Portola provided a concise overview of the adjudication process: each type of bleed has specific rules/criteria for good, excellent or poor; ICH cases are mostly based on imaging whereas GI bleeds are based on corrected hemoglobin and not based on a visual assessment. Portola stated that independent adjudicators are responsible for applying the criteria to each case and Portola does not have interaction with these independent adjudicators. Portola noted that two independent hematologist reviewers evaluate the patient data and apply the adjudication rules. In the beginning there was a training period with 4-5 reviewers doing adjudication. The adjudication committee meets and has a general discussion regarding the decisions made, after the first few cases there was a less rigorous approach. Now there are three adjudicators per case, if two of three agree, there is no further discussion. Some cases are difficult but eventually are headed to a consensus group discussion where consensus is usually reached.
 1. Portola will provide a written overview of the adjudication process, specifically highlighting individual cases, in their IR response.
 2. Portola stated that the specific criteria were based upon the criteria of the Kcentra study as discussed and agreed upon with FDA.
 - a. FDA did not dispute the criteria; FDA's concern was about the process and thus reproducibility and consistency and to determine how the adjudicators come to their own conclusions. FDA noted that its own reviewers, as part of their own clinical review, do independent adjudications of each of these cases and in doing so some questions were raised.
 - i. Portola maintained that FDA will begin to see consistency once additional adjudicated cases are submitted. Portola plans to enroll 250 patients and noted that they have 56 adjudicated cases that will be submitted after the day 180 study update.
 - ii. They noted that by the second DSMB meeting on May 4, 2016, and they evaluated 87 patients, found no safety signal and allowed the study to proceed.

- b. Concerning the depth and duration of reversal, Portola noted that the limits pertaining to warfarin reversal are still unknown after several decades. For example, an INR of 1.5 to 1.7 may be safe in surgery, but still demonstrates anticoagulation. Portola asked FDA what would be considered a “safe” level and noted that ANDEXXA will not be able to reduce the anti-FXa activity level to zero.
 - i. FDA stated that there is not a predetermined threshold for adequacy of reversal.
 - ii. Portola maintained that they can achieve sufficient hemostasis even without complete reversal consistent with targeting of 50% factor replacement to reverse bleeding in hemophilia.
 - 1. FDA agreed, but could not determine the risk:benefit relationship for ANDEXXA. FDA believes that an extended infusion study is necessary because providers will likely use ANDEXXA this way in practice, and this should be addressed at the time of approval, if approved.
 - 2. Portola maintained that an adequate clinical response is observed following the first infusion and whether a better clinical response is observed following a longer infusion is a secondary question. Portola noted that even though the infusion lasts 2 hours, the TGT assay elevation goes beyond that and that they already have a good clinical response with the two hour infusion.
 - a. FDA stated that it cannot agree that efficacy has been shown until the adjudication process questions have been resolved.
 - 3. Portola noted that they were very supportive of the protocol and Kcentra criteria and is following this as close as possible. They noted that adjudicators rated 90% of 10 intraparenchymal and 80% of 10 subdural bleeds as excellent or good.
- c. Portola felt that the stabilization of the hematoma is shown by a “failure to progress” and that they are getting a good glimpse at this in their ICH data. Portola considers they are on the right track and that the shorter duration of reversal of anticoagulation leads to clinically meaningful hemostasis and this is supported by the kinetics of clotting (fibrin generation and formation of hemostatic plugs) and as shown in animal studies.

Portola noted that their CT scans are done by a “core lab review” and that the adjudication committee gets this from the core labs.

- d. FDA asked about the stabilization rate with NOAC ICH bleeding. FDA reiterated its need to be convinced that anti FXa levels were a reasonably likely surrogate, the relationship between the surrogate and clinical outcome, the need for a control arm in the confirmatory trial, the final design of Annexa-4 and any additional data.
- e. FDA reiterated the scientific aspect of INR and warfarin and acknowledged that surgeons do procedures at an increased INR and that liver failure related increased INR was different. FDA also relayed that increased INR relates to factor levels. FDA related that the problem that remains scientifically uncertain is that anti FXa levels in healthy volunteers ranged by the 100s in ng/mL and in patient with renal failure, the anti FXa levels will vary much more, exceeding the levels studied in phase 1, 2 and 3 studies. The open ended question regarding reversal is therefore whether or not ANDEXXA causes a relevant drop in anti-FXa levels or is there some target level that a patient should be below? Dropping anti-FXa down to 50%, 70%, 80% is relative and not related to warfarin.

6. Remaining issues and agreements

- a. FDA suggested and Portola agreed to postpone the next meeting until the week of June 13, 2016, to allow FDA to consider feedback provided by requested external consults.
- b. Portola stated that a response to the clinical IR, dated May 13, 2016, will be submitted by May 27, 2016, and a response to the IR related to TFPI can be submitted within one week of receipt.

Post-meeting notes:

- 1. On May 31, 2016, a CMC IR was sent to Portola concerning the items discussed during the May 23, 2016, teleconference.
- 2. On June 1, 2016, a CMC IR was sent to Portola concerning the TFPI and TGT assay concerns noted above.

END