



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 category: BLA Review
Meeting date & time: June 22, 2016, 11 a.m. to 12:30 p.m. ET
Meeting format: Face-to-face
Meeting Chair/Leader: Peter Marks, MD
Meeting Recorder: Edward Thompson

FDA Participants:

Howard Chazin, MD, MBA, Acting Director, Division of Hematology Clinical Review (DHCR)/OBRR
Jay Epstein, MD, Director, Office of Blood Research and Review
Bindu George, MD, Chief, Clinical Review Branch, DHCR/OBRR
Basil Golding, MD, Director, Division of Hematology Research and Review (DHRR), OBRR
Sherry Lard, Ombudsman, Center for Biologics Evaluation and Research
Mark Levi, PhD, Regulatory Project Manager, RPMS/OBRR
Peter Marks, MD, Director, Center for Biologics Evaluation and Research
Mikhail Ovanosov, PhD, Research Biologist, DHRR/OBRR
Edward Thompson, Regulatory Project Manager, RPMS/OBRR
Iliana Valencia, MS, MCPM, Chief, Regulatory Project Management Staff, OBRR
Nicole Verdun, MD, Acting Deputy Director, Office of Blood Research and Review

Portola Attendees:

Michele Bronson, PhD, Vice President, Program Management
Janice Castillo, Senior Vice President, Regulatory Affairs and Quality Assurance
Pamela Conley, PhD, Vice President Biology
John Curnutte, MD, PhD, Executive Vice President, Research and Development
Alex Gold, MD, FACC, Senior Vice President, Clinical Development (By Phone)
Bill Lis, CEO
Genmin Lu, PhD, Senior Scientist II, Biology

Clinical Consultants

Richard C. Becker, MD, Chief, Division of Cardiovascular Health and Disease, University of Cincinnati College of Medicine

Jeffrey Weitz, MD, Professor of Medicine and Biochemistry, McMaster University

Stuart Connolly, MD, Director, Division of Cardiology, McMaster University

Background and Objectives:

Ongoing meeting with Portola and CBER concerning relevant scientific issues that remain unresolved for this BLA review; the agenda below was submitted to the FDA on June 21, 2016:

1. Review TFPI responses to FDA RFI dated June 1, 2016, and address Agency questions; includes safety and efficacy update on ANNEXA-4 (Day 180 BLA update).
2. Confirm adequacy of Portola responses to FDA regarding adjudication process.
3. Portola requests FDA to provide feedback from their consultants' review of data.

Portola submitted a slide presentation via email on June 22, 2016. FDA did not have an opportunity to review the slide deck before the meeting with Portola.

Meeting Discussion:**Opening Remarks**

In the opening remarks, FDA summarized the review efforts to date. FDA noted that all issues would not be able to be resolved at today's meeting, including the issue of the *relative importance* of TFPI inhibition. FDA explained that it was more important to agree that TFPI inhibition is real because of FDA's concerns with the procoagulant nature of the TFPI inhibition. FDA stated ongoing concerns for the data submitted to support reversal of all oral FXa inhibitors as a class, and noted that there were uncertainties with regard to the unmet need for reversal of bleeding related to enoxaparin given the availability of protamine and the limited data available to date in the healthy volunteers for edoxaban and enoxaparin.

FDA noted that the necessary external and internal consultations were complete. FDA noted that there is a general agreement that the reversal of anti-FXa activity immediately following ANDEXXA administration in healthy volunteer subjects who received apixaban and rivaroxaban was compelling. FDA reaffirmed that despite the depth of reversal, FDA remains concerned about the transient nature of reversal specifically with regard to control of bleeding and prevention of re-bleeding in subjects with intracranial hemorrhage (ICH) where the anticipated need is for sustained reversal of anti-FXa activity. To address the concerns with the transient nature of the reversal, FDA advised Portola to consider re-dosing and/or extended infusions specifically in clinical indications where extended duration of reversal is advised. To this end, FDA recommended that Portola revise their ongoing ANNEXA-4 study to selectively enroll subjects with ICH with consideration of morbidity outcomes (for example, 30 day modified Rankin score) as the primary efficacy outcome. FDA reiterated that evaluation of efficacy in the

surgical study could be a standalone study under the existing IND because the primary role of such a study would be supportive to the ongoing confirmatory study.

FDA appreciated the response to the information request related to ICH and gastrointestinal bleeding and noted that Portola's responses were taken into consideration before FDA's current recommendation to revise the ANNEXA-4 study to selectively enroll subjects with ICH.

FDA has not completed its review of the 180 day update but anticipated that the safety review of the 180 day update would be completed shortly.

Portola agreed that data was lacking to support approval for the (b) (4), and understood FDA's position that data was lacking to support a labelling claim with regard to reversal of bleeding following both edoxaban and enoxaparin therapy. Portola agreed to deliberate further regarding revisions to the ANNEXA-4 protocol, a study in subjects undergoing surgery and their clinical development plans with regard to edoxaban and enoxaparin.

Briefing Slides – TFPI Inhibition

The briefing slides were discussed. Portola noted that overall there is a 4 hour treatment window over which an anti-FXa activity reversal effect is observed. Portola stated that the slide presentation supports their claim that TFPI is not a predominant mechanism of action of ANDEXXA. Portola noted that TFPI inhibition is an expected effect of ANDEXXA because only a very small amount of ANDEXXA is sufficient to saturate all TFPI. Only 175 nanomoles of TFPI is available in a human body, of which 170 nanomoles are bound to endothelial cells and about 5 nanomoles exist in plasma. The TFPI plasma concentration is 2 nM (nanomoles per liter) of which only 0.4 nM is in a free "active" form. Additional evidence was provided by PK modeling which demonstrated a saturable, high-affinity, low capacity tissue compartment of ANDEXXA of (b) (4) nanomoles similar to the total TFPI (175 nanomoles).

Portola noted that they could not do a human study so they focused their efforts on evaluating their animal studies. FDA noted that one critical question would be whether or not the rabbit TFPI would bind to ANDEXXA. Portola responded by saying that they did not know this and that they hoped that the human and rabbit TFPI proteins will have similar binding sites because of their (b) (4) sequence homology.

Portola noted on their slides that there was no independent procoagulant effect of low doses of ANDEXXA on blood loss in three species. In addition, there was no prothrombotic effect including thrombosis models in the (b) (4) monkeys. Portola reiterated their rat liver laceration model.

Portola noted that it was not possible to measure TFPI in the presence of FXa inhibitors and that the (b) (4) method to detect antigen concentration of Free TFPI can be a direct measure of TFPI activity.

FDA reiterated their request to see data that FXa inhibitors interfere with the TFPI activity assay. Portola noted that they do not have the assay validation data with the inhibitors in the plasma and

have not performed the interference tests on retained samples from phase 2. FDA noted that the TFPI activity assay validation data including any data on the interference with FXa inhibitors have not been submitted to the BLA.

FDA reiterated the discussion from the May 20, 2016, meeting whereby FDA needed information to address the depth and duration of TFPI inhibition. FDA related to Portola that TFPI inhibition does happen and that the remaining issue was the exact depth and duration with each clinical trial.

Portola noted that in phase 1 studies that there was no FXa inhibitor; therefore no assay interference studies were needed. In phase 2 studies, there was increased concentration of FXa inhibitor therefore the assay will show some inhibition and interference. Portola reiterated that they chose the free TFPI (b) (4) as the readout and that they have additional interference information. FDA noted that Portola chose to switch their activity assay to the (b) (4) assay and that this was not described in the BLA. For example, this information is missing from the Clinical Study Reports. FDA considers this an important technical clarification.

FDA noted that their review focus was to address the potential for a claim for short term reversal but that the TFPI issue will be more important to understand the safety of extended dosing.

Portola continued its presentation of the slides noting the use of the free TFPI as a surrogate of TFPI activity in phase 2 studies using apixiban. Portola noted that with bolus and bolus plus infusion that there was a prolonged blockade of TFPI with the lowest dose bolus blocking free TFPI for 8 hours and with the 420 mg bolus plus infusion, a blockade of 21 hours.

FDA reiterated their concern about the duration of TFPI inhibition. Portola noted that they do not know when TFPI returns to the pre-treatment baseline.

FDA was concerned regarding the error bars in the presentation noting the possibility of outliers. FDA analysis of phase 1 data identified one subject with very high free TFPI levels. Portola agreed that additional analysis may be needed. Portola expressed a need for an additional smaller meeting with Mikhail Ovanesov and other reviewers to discuss this issue further as the meeting was running low on time.

Portola noted that free TFPI remains low and suppressed and therefore has a minimal effect on thrombin generation. FDA reiterated its opinion that ANDEXXA is likely inducing thrombin generation by binding TFPI.

With reference to animal models in which low doses of ANDEXXA failed to normalize bleeding, FDA inquired whether Portola performed testing of TFPI activity in animal plasma to confirm that ANDEXXA blocked TFPI activity in animals. FDA also inquired whether control experiments were performed with anti-TFPI antibodies to demonstrate that Portola's animal models of bleeding are sensitive to TFPI inhibition. FDA noted several publications in which inhibition of TFPI activity was associated with normalization of bleeding in rabbits and mice. Portola explained that they are aware of these publications. At this time Portola does not have any data on TFPI activity in animals and does not know if their animal models are sensitive to

TFPI inhibition by anti-TFPI antibodies. Portola proposed that the difference in results between their studies and those reported in publications may be related to the unique mechanism of ANDEXXA action on TFPI but Portola has no experimental data at this time.

Summary

1. Portola will follow up with Mikhail Ovanesov regarding data on the assays as needed.
2. Portola will follow up on RFIs.
3. Portola and FDA will continue discussions regarding the ANNEXA-4 protocol.

Attachments/Handouts:

1. Slide Presentation FDA TFPI 062216

END