DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Meeting Summary

Meeting ID #:	CRMTS #10265
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:	Type A
Meeting category:	BLA
Meeting date & time:	April 20, 2016, 12:30 pm – 2 pm, ET
Meeting format:	Face-to-face
Meeting Chair/Leader:	Peter Marks, MD
Meeting Recorder:	Thomas J. Maruna, MSc, MLS(ASCP), CPH

FDA Participants:
Howard Chazin, MD, MBA, Acting Director, Division of Hematology Clinical Review, CBER/OBRR
LCDR Bryan Emery, USPHS, Program Management Officer, CBER/OM/DSAC
Jay Epstein, MD, Director, Office of Blood Research and Review, CBER
Anne T. Farrell, MD, Director, CDER/OND/OHOP/DHP
Vanita Hill, Executive Assistant to Dr. Marks, CBER
Christopher Joneckis, PhD, Associate Director for Review Management, CBER
Sherry Lard, Ombudsman, CBER
Diane Maloney, Associate Director for Policy, CBER
Peter Marks, MD, Director, CBER
LT Thomas J. Maruna, USPHS, MSc, Senior Regulatory Management Officer, 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
Alejandro A. Rabinstein, MD, Department of Neurology, Mayo Clinic

Background and Objectives:
Portola submitted a meeting request via direct email to the CBER Director, and as an amendment to the BLA on April 15, 2016, to discuss ongoing disputes between Portola and CBER concerning relevant scientific issues that remain unresolved; specifically the following unresolved issues were noted:

1. Use of anti fXa activity as the biomarker endpoint for accelerated approval.

2. Dose and dosing regimen for the ongoing phase 3b/4 ANNEXA-4 bleeding patient study.

3. FDA's requested Prospective Usual Care Cohort Study design - a comparator to the ongoing ANNEXA-4 bleeding patient study.

4. Lack of continuity of review team.

5. The review division's decision to present Portola's application to the Blood Products Advisory Committee (BPAC) Meeting on June 20 and 21, 2016.

The CBER Director confirmed the meeting via email on April 16, 2016. A formal confirmation letter was not dispatched to the applicant.

Portola submitted a slide deck via email on April 20, 2016. FDA did not have an opportunity to review the slide deck before the meeting with Portola.

Meeting Discussion:

FDA acknowledged to Portola that ANDEXXA is an important product and that the overall goal of interactions with Portola is to establish a process towards resolution with collaboration between CDER and CBER.

FDA acknowledged Portola's concerns regarding the continuity of review staff as a result of high personnel turnover and assured Portola that CBER will continue to do everything possible to maintain consistency with assigned reviewers on this BLA file.

Portola acknowledged CBER's scientific concerns as reasonable and noted they were similar to questions and concerns previously discussed with CDER. Portola reminded those attending the meeting of the preceding years of collaboration with CBER (2009-2015) leading up to FDA's formal communication dated August 3, 2015. Portola felt that before that time they were aligned with FDA. Portola reiterated it is committed to collaboration going forward.

From their briefing slides (attached) Portola asserted that since August 2015, following changes in reviewers and management, there have been alignment and then misalignment in both the process and agreements on the issues leading to the reversal of prior agreements that led to design and conduct of the phase 2, phase 3, and phase 3b/4 studies. Portola hopes to restore what they view as prior agreements to achieve scientific consensus obviating the need for a BPAC meeting.

Portola stated that over 2,200 man-hours have been allocated to resolving CBER's scientific concerns since August 2015, causing delay in submitting the surgical cohort and the TFPI studies and they stressed that holding the BPAC will cause further disruption to their operations. Portola asserted that every step taken to date was fully adjudicated through FDA in advance of any action.

Portola identified the following six questions/issues for discussion (refer to Portola slide 4):

1. *Is a 15-30 minute bolus plus 2 hour infusion a clinically effective duration for reversal of anti-fXa activity?*

2. *Is the level of PD reversal by andexanet variable or consistent for each Factor Xa inhibitor and does it impact FDA's ability to assess efficacy?*

3. *In the setting of intracerebral hemorrhage, is complete reversal of anticoagulation desirable throughout the period while a patient is stabilized? Address clinical scenario posed by FDA.*

4. *Are thrombin generation levels seen in healthy volunteer studies during andexanet infusion elevated or within the normal range?*

5. *Is TFPI binding problematic in prothrombotic patients, particularly if the infusion of andexanet were extended? What data are reassuring?*

6. *Is E*CT a more validated PD marker for idarucizimab than anti-fXa activity is for Factor Xa inhibitors?

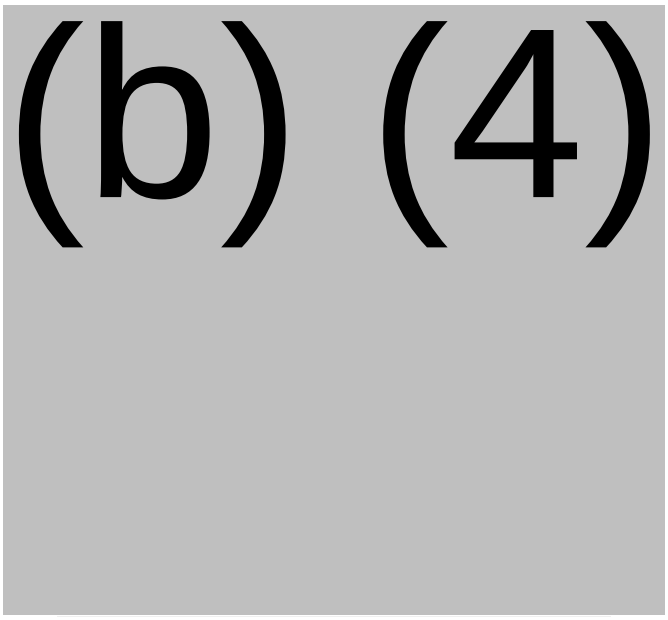
FDA agreed to discuss Portola's proposed agenda items, and reserve comments until the end of the presentation, but emphasized that there were additional issues that could not be discussed due to time constraints (e.g. renal impairment concerns). Portola acknowledged and stated that a separate renal study was to be performed in the near future.

Item 1: Is a 15-30 minute bolus plus 2 hour infusion a clinically effective duration for reversal of anti-fXa activity?

Portola highlighted their central question in slide 5 of their presentation, i.e. *how long (duration) and how deep does the reversal need to be to achieve hemostasis?*

Portola stated that the answer is currently unknown to them, but highlighted some of their ANDEXXA data to support their conclusion; those included:

a. Kinetics: Portola stated that a hemostatic plug formed very rapidly (i.e. within seconds to upwards of two minutes). The following kinetic diagram was presented as a visual (slide 16):



b. With respect to their animal models, Portola stated that a single bolus of andexanet results in rapid and near-complete hemostasis.

c. *Andexanet phase 3 data – A single bolus of andexanet (+/- an infusion) results in a durable correction of thrombin generation that remains in the normal range for > 20 hours*

d. *Andexanet phase 3 data – A single bolus of andexanet (+/- an infusion) results in a durable correction of thrombin generation that remains in the normal range for > 20 hours*

Portola stated that the data show no expansion of hematoma or re-bleeding in the first 35 of 49 evaluable patients (of approximately 89 enrolled to date) from the ANNEXA-4 study and therefore a 2-hour infusion *may* be adequate to maintain hemostasis.

Item 2: Is the level of PD reversal by andexanet variable or consistent for each Factor Xa inhibitor and does it impact FDA's ability to assess efficacy?

Portola stated that rivaroxaban, apixaban, and (b) (4) all bind to Factor Xa and andexanet with identical stoichiometry, consistent with a single PK/PD model, i.e. that it correlates 1:1 with the plasma concentrations of rivaroxaban, apixaban, and (b) (4) for example, 100 ng/mL of plasma apixaban = 100 ng/mL anti-fXa activity of apixaban). Portola also stated that these anticoagulants each have nearly identical binding affinities.

Further, Portola asserted that rivaroxaban, apixaban, and (b) (4) all show identical correlation between anti-fXa activity and thrombin generation, as well between anti-fXa activity and plasma concentration. Portola maintained that this allowed them to select the correct PK-PD model for all three anticoagulants based on the apparent "class-effect" observed.

Concerning the depth of reversal, Portola asserts that *full restoration of coagulation does not appear to be required for hemostasis* and highlighted the following four points from slide 6 of their presentation:

- *Hemophilia treatment – Recombinant Factor VIII or IX treatment of major bleeds in hemophilia patients requires only 50-60% restoration of normal levels (per label).*

- *Animal models –* (b) (4) *-anticoagulated animals showed near-complete reversal of bleeding with just a 50% decrease in anti-fXa activity to a level (~2.5 IU/mL) that was still a supra-therapeutic level.*

- *ANNEXA-4 data – The magnitude and speed of the anti-fXa reversal appears important, not just the depth. 6 patients presented with supra-therapeutic levels of apixaban (487-950 ng/mL) or rivaroxaban (362-862 ng/mL) and partial, but steep, reversal. 5/6 were adjudicated with excellent hemostasis.*

- *Consistent with warfarin reversal* [of vitamin K-dependent factors] *with FFP (factor replenishment to 50-60% normalizes the INR)*

Portola concluded that the *minimum depth of reversal was defined as the level of reversal needed to restore thrombin generation back to the normal range*.

FDA inquired how Portola determined the number of subjects needed for their ANNEXA-4 bleeding patient study considering that 90 subjects in phase 3 validated Praxbind making the cohort of ANNEXA-4 patients studied small by comparison. Portola stated that the agreement to include 10 – 20 patients for preliminary assessment was reached through collaboration between Portola and FDA during the pre-BLA meeting (i.e. referencing the September 4, 2015 meeting designated CRMTS 9914).

Portola admitted that to be statistically relevant, they would require data from over 250 subjects using strict adjudication against the same criteria in the Kcentra study to demonstrate efficacy, and that as a compromise, FDA agreed to review data from 10 – 20 subjects to provide preliminary evidence of efficacy and that Portola would provide additional efficacy and safety data as it became available. Portola noted that enrollment has been good and they expected to have 140 patients enrolled by summer 2016. Portola noted that ANDEXXA was developed independent of Praxbind whereby a large volunteer study focused primarily on PK/PD.

Item 3: In the setting of intracerebral hemorrhage, is complete reversal of anticoagulation desirable throughout the period while a patient is stabilized?

Portola presented their ANNEXA-4 ICH data from slide 7:

- *In the first 35 ANNEXA-4 patients, there were 13 ICHs:*
  - *5 intraparenchymal bleeds ranging from 0.27 cc to 38 cc at presentation. 4/5 had excellent/good hemostasis (lack of hematoma expansion). 1/5 had poor/none hemostasis.*

- *8 subdural bleeds ranging from 2-31 mm (8-181 cc). The Adjudication Committee determined that 6/8 had an excellent/good hemostatic response (including patients with 12.8 and 31 mm SDH, both with midline shifts of 2.8 and 6.5 mm, respectively).*

- *All patients had persistent, normal levels of Thrombin Generation for at least 14 hours.*

Portola also addressed FDA's hypothetical question concerning a repeat bolus infusion, stating that a repeat bolus *may* be useful citing data from their (b) (4) monkey GLP toxicology study, which included a repeat bolus exposure over a 2-week period (two boluses 4 hours apart every third day x 2 weeks) in which no thrombosis were seen. Portola also noted that in a phase 2 study of apixaban reversal, a repeat bolus was observed to be safe as well as effective.

Discussion with Dr. Alejandro Rabinstein:

Dr. Rabinstein, Portola's Neurologist expert from Mayo Clinic joined the meeting by phone and discussed certain issues related to ICH. He noted that there was limited treatment for ICH and that most patients who were anticoagulated and had an ICH had a worse prognosis. He noted that even if reversed, some hematomas expand especially subdurals (SDH) for lack of tamponnade. Some patients worsen despite reversal. He noted that the 13 cases (in ANNEXA-4) were encouraging, with some patients destined to continue bleeding. Dr. Rabinstein noted that 20-30 out of 100 patients with coagulopathy will have expansion, even more in SDH, usually within the first 6 hours; mostly in the first hour. He noted that the time since onset of bleed to imaging is important in the analysis and was unrelated to the drug effect.

In terms of how long the duration of infusion for ICH should be, Dr. Rabinstein noted that the majority of ICH expansion occurs in the first few hours, perhaps 6-8 hours. Once hemostasis has been obtained, risk of expansion is much lower and especially after 20 or more hours.

FDA pointed out that there is a very rapid loss of the drug effect of ANDEXXA within 2 hours of cessation of infusion.

Dr. Rabinstein noted that from a neurological perspective, control is needed for several hours and noted how important the ANNEXA-4 data are to assessing ICH in the 13 patients. Portola noted that the current protocol has a one hour delay to administer the infusion because of the need for a prior CT. This allows time for risk of expansion.

Dr. Rabinstein noted that it is a pragmatic issue and that he favors an accelerated approval because direct reversal agents have the best hope of helping patients for whom the outcomes are poor. The data for any other reversal agent for FXa inhibitors is poor and noted again that 20-25 percent of ICH patients who are not anticoagulated will worsen.

FDA pointed out that the lack of correlation between the surrogate biomarker with clinical benefit is concerning.

Portola reiterated that it would require a very large number of subjects to validate the surrogate; some of whom will not respond; while others will respond regardless of dosage, duration or intervention. Portola asserts that even with the 30 – 40 subjects studied, "a hint at correlation exists." Therefore, a "general correlation" between anti-factor Xa levels and bleeding risk can be assumed. Portola noted that the ANNEXA-4 study will establish the correlation.

Item 4: Are thrombin generation levels seen in healthy volunteer studies during andexanet infusion elevated or within the normal range?

Portola summarized the bullet points outlined on slide 8 of their presentation:

- *The thrombin generation (TG) assay – Normal human plasma on its own does not generate thrombin unless the coagulation cascade is activated via the extrinsic pathway (using Tissue Factor) or the intrinsic pathway (using* (b) (4) *The level of TG is dependent upon the degree of activation which is, in turn, dependent upon the amount of Tissue Factor or* (b) (4) *added to the assay.*

- *Effect of Factor Xa inhibitors and andexanet on TG – TG is restored to normal by andexanet predominantly due to its ability to bind and sequester the Xa inhibitors. Andexanet also binds to TFPI and therefore removes this "Tissue Factor Pathway Inhibitor" from the patient plasma in the TG assay. The Tissue Factor reagent* (b) (4) *" - this is entirely due to the sequestration of TFPI by andexanet in the assay mixture. This "* (b) (4) *is not seen in the* (b) (4) *TG assay. These assays demonstrate that andexanet on its own has no prothrombotic activity as measured by enhanced thrombin generation.*

- *Magnitude of the andexanet-TFPI "* (b) (4) *in the Tissue Factor version of the TG assay – In the Phase 3 healthy volunteer studies with andexanet, the "* (b) (4) *was on average* (b) (4) *above the normal range, was transient, and returned to normal within* (b) (4) *minutes after the infusion.*

- *ANNEXA-4 TG data – The TG data from the first 35 patients do not show this "* (b) (4) *or any TG overshoot. Interestingly, many of the bleeding patients present with "normal" TG - we hypothesize that this is due to Tissue Factor in the plasma released as part of the physiologic response to bleeding.*

Portola concludes the following: "*The mechanism for the "* (b) (4) *in TG in the Tissue Factor TG assay is well-understood – TFPI in the plasma is bound to andexanet, resulting in a decreased inhibition of Factor Xa by TFPI-Tissue Factor, leading to higher Factor Xa activity and increased TG. There is no evidence that andexanet on its own increases Factor Xa activity or increases TG."*

Item 5: Is TFPI binding problematic in prothrombotic patients, particularly if the infusion of andexanet were extended? What data are reassuring?

Portola stated that they have not studied a prolonged infusion, but plan do so as part of their surgical cohort.

Portola highlighted the following bullets from slide 9 of their presentation:

- *Thrombotic events were not observed in Phase 1, 2, 3 studies in healthy volunteers.*
- *The rises in F1+2, TAT, and D-dimer were transient (over 1-3 days) in these subjects*
- (b) (4) *GLP toxicology studies with 2-week repeated dose showed no evidence of clot, thrombosis, or fibrin. TAT and DD were elevated as in humans.*
- *Thus far in ANNEXA-4, we do not have evidence for early, unexplained thrombotic events*
- *The further data from ANNEXA-4 is designed to explore this matter.*

Item 6: Is ECT a more validated PD marker for idarucizimab than anti-fXa activity is for Factor Xa inhibitors?

Due to time constraints this item was not discussed during the meeting.

Additional Discussion:

Concerning the benchmark control for ANNEXA-4, Portola restated their original position that the initial "agreement" with the FDA was to use the Kcentra pivotal study to provide the most reliable and controlled historical benchmark for a "clinically meaningful level of acceptable hemostatic control" for an anticoagulant reversal agent. However, Portola has agreed to FDA's request for a controlled study in phase 4.

FDA acknowledged the public health importance of ANDEXXA and the urgent need for a reversal agent for anti-FXa, especially in ICH. FDA noted that persistent elevated anti FXa levels in a patient with an expanding ICH would be problematic and a legal concern. GI bleeding could be easier to assess, but there exists the role of confounding of other treatments.

Concerning ICH cases, FDA noted that the first 24 hours following ICH were critical and persistent anti-FXa levels would demand immediate action noting that the current established paradigm was to achieve complete reversal and maintain it for a prolonged duration. Portola pointed to slide 15 of their presentation, specifically noting that two units of fresh frozen plasma was the standard of care used; and as noted on the slide, would not immediately, or for a prolonged period, correct the warfarin effect. Additionally, Portola stated that if ANDEXXA is not approved, "what would we do?" given that PCCs are ineffective and prothrombotic and would do nothing for addressing anti-FXa levels. Portola remarked that they thought agreement had been reached on FDA acceptance of anti-FXa levels as a reasonably likely surrogate or they would not have proceeded with the ANNEXA-4 study.

FDA requested justification for Portola's 12-hour evaluation endpoint instead of an earlier time point, specifically pointing out that patients tend to re-bleed sooner. Portola stated that the original protocol included a 24-hour evaluation, but FDA suggested, in a previous communication, a 12-hour evaluation endpoint as an alternative.

FDA asked if anti-FXa levels are tested in real time in hospitals. Portola agreed that this was a highly variable practice. Dr. Rubenstein noted that in a patient who re-bleeds, a level could be obtained, but that this was usually after the fact after empirical use of a PCC and reiterated again that some patients will do poorly despite a reversal. Dr. Rubenstein noted that, "in the absence of alternatives, we should not blame the drug and that the surgeon won't be sued if reversal is not maintained." Dr. Rubenstein supported continued evaluation of the patients in ANNEXA-4 rather than a consideration of a study with a different dosing regimen. FDA noted that there needs to be time for a deeper "dive" into the data sets.

FDA acknowledged Portola's concerns that the BPAC may be a distraction, but that a decision could not be made during this meeting; instead a teleconference would be scheduled for the week of April 25, 2016, to discuss the BPAC and other currently unresolved scientific issues after an in-depth review of the file. FDA committed to holding a series of future teleconferences if necessary. Portola agreed and reiterated their commitment to the science and is willing to have the CBER Center Director meet with their experts.

Post Meeting Notes:

1. FDA held a follow-up teleconference with Portola on April 28, 2016. The summary for this teleconference were transmitted by Dr. Peter Marks from FDA to Portola via email on May 3, 2016.

Attachments/Handouts:

1. Slide Deck: *Portola - FDA ANDEXXA™ (Andexanet Alfa) Type A Meeting April 20, 2016*
2. E-mail dated April 24, 2016, from John Curnutte to Peter Marks and Jay Epstein
3. April 28, 2016 Teleconference Summary (Sent via email May 3, 2016)
4. John Curnutte's Email dated April 24, 2016
5. Excerpts from past meetings

END