



Our Reference: BLA 125586/o

November 16, 2016

Portola Pharmaceuticals Inc.

ATTENTION: Ms. Janice Castillo

270 East Grand Avenue
South San Francisco, CA 94080

Dear Ms. Castillo:

Attached is a copy of the memorandum summarizing your October 17, 2016 Type-A Biologics License Application (BLA) meeting with CBER. This memorandum constitutes the official record of the meeting. If your understanding of the meeting outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER as soon as possible.

Please include a reference to BLA 125586 in your future submissions related to the subject product.

If you have any questions, please contact me at thomas.maruna@fda.hhs.gov.

Sincerely,

Thomas J. Maruna, MSc, MLS(ASCP), CPH
Lieutenant Commander, USPHS
Senior Regulatory Management Officer
Division of Regulatory Project Management
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research

Enclosures: Meeting summary, Sponsor slides & Communication Plan

Meeting Summary

Meeting ID #: CRMTS 10471
Application: BLA 125586/o
Product name: Coagulation Factor Xa (Recombinant), Inactivated
Proposed indication: For patients treated with a direct or indirect Factor Xa inhibitor when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.
Applicant: Portola Pharmaceuticals Inc.
Meeting type: Type A
Meeting category: BLA
Meeting date & time: October 17, 2016, 2:30 pm – 4:30 pm, ET
Meeting format: Face-to-face
Meeting Chair/Leader: Stephanie Simek, PhD
Meeting Recorder: Thomas J. Maruna, MSc, MLS(ASCP), CPH

Preliminary Responses sent October 12, 2016

FDA Participants:

John Eltermann, Director, CBER/OCBQ/DMOQ
Mahmood Farshid, PhD, Deputy Director, CBER/OTAT/DPPT
Basil Golding, MD, Director, CBER/OTAT/DPPT
Christine Harman, PhD, Chemist, CBER/OCBQ/DMPQ/BI
Larissa Lapteva, MD, Medical Officer, CBER/OTAT/DHT
Tim Lee, PhD, Acting Branch Chief, CBER/OTAT/DPPT/HB
Mark Levi, PhD, Regulatory Manager, CBER/OTAT/DRPM/BII
Thomas J. Maruna, MSc, Senior Regulatory Manager, CBER/OTAT/DRPM/BII
Mikhail Ovanesov, PhD, Biologist, CBER/OTAT/DPPT/HB
Carolyn Renshaw, Chief, CBER/OCBQ/DMOQ/BI
Patrick Riggins, PhD, Chief, CBER/OTAT/DRPM/BII
Stephanie Simek, PhD, Director, CBER/OTAT
Deborah Trout, Team Lead, CBER/OCBQ/DMOQ/BI

Applicant Attendees:

John T. Curnutte, MD, PhD	Evangelia Raptis-Zarou, MS
Andrew Ramelmeier, PhD	Annie Sturgess, PhD
Ms. Janice Castillo	Dominick Vacante, PhD
Michele D. Bronson, PhD	Clarice Hutchens, PhD
Lee Mermelstein, PhD	Scott Greenfeder, PhD
Pamela Conley, PhD	Carol Zoltowski, VMD
Debby Feder, PhD	Genmin Lu, PhD
Mark Karbarz, PhD	Aditya Wakankar, PhD

(b) (4)

Background and Objectives:

Portola submitted a meeting request on September 26, 2016, to discuss the Lifecycle Strategy for ANDEXXA Commercial Supply, submit Portola's response strategy to FDA's CMC and bioassay CRL feedback, obtain clarification where indicated, and to reach agreement with the Agency on the data that will support resubmission and approval of the BLA and a target resubmission date. The pre-meeting materials were submitted on September 26, 2016.

FDA provided its proposed responses to Portola's questions on October 12, 2016. After reviewing the proposed responses, Portola notified FDA on October 17, 2016, of its decision to limit the meeting to discuss only question numbers 1, 2, 3, 9, 13 and 15.

Post meeting note – Communication Plan:

Portola and FDA discussed the benefits of drafting a communication plan during the October 17th, Type A meeting. Portola should construct\propose a communication plan addressing each deficiency outlined in the CR letter dated August 17, 2016.

In your communication plan, please include details on Portola's approach to address each deficiency – including details of planned\ongoing studies with a date of completion and an outline of the planned data in support of your response to each deficiency. A sample communication plan is enclosed as guidance to draft Portola's plan. Please note, the enclosed communication plan is an example with just a cross section of information from the CR letter. Portola's document should be a considerably detailed plan covering each deficiency.

General Discussion:

Given the recent internal reorganization at CBER, and transfer of BLA 125586/o to the Office of Tissues and Advanced Therapies (OTAT), Portola was reassured that the principal review committee members will remain on the BLA file and no changes are planned at this time. FDA reaffirms its commitment to move this product forward with Portola.

For future communications and meetings, FDA will send Portola a "Communication Plan" that will present in tabular form upcoming items and deliverables, based upon FDA's understanding of Portola's plan in addressing the August 17, 2016 Complete Response Letter (CRL), and for Portola to assign reasonable completion dates for the studies needed to provide a complete response to the CRL. FDA will not grant future meetings with Portola until prerequisite milestones have been met and deliverables completed. FDA stated that it will remain flexible with informal communication for clarification purposes only. FDA reiterated its position that it will not review a "piecemeal" submission; the responses to the CRL must be complete and submitted as a single submission for FDA to review. FDA affirmed that it is Portola's responsibility to ensure completeness of the submission. FDA and Portola must come to an agreement on the contents of the communication plan before future meetings are granted.

FDA informed Portola that continued face-to-face meetings may not be feasible with every request, given a limitation of resources and reviewer's schedules; therefore,

teleconferences will be the principal form of communication. Further, future meetings will be limited to one hour and will be based upon the milestones identified in the communication plan. Future meetings must be preceded by the submission of a brief (no more than 1-2 pages) background/summary document; FDA will not review voluminous amounts of data outside of the formal BLA resubmission.

FDA strongly reiterated that all future communication must be channeled through the Regulatory Project Manager (RPM) assigned to the file, including those communications intended for CBER's Director.

Portola stated that receipt of the CRL was unexpected. Portola acknowledged that the CRL listed many gaps which have been identified in previous communications with the Agency and Portola anticipated that those gaps would be covered under Post-Marketing Commitments (PMCs). Portola also noted that they were unaware of some of the problems which were identified by the FDA reviewers.

Portola stated that their mission of bringing this Breakthrough Therapy (BT) to patients as soon as possible resulted in a clinical development that was moving faster than the CMC program was moving. Portola's management acknowledged that they perhaps were carried away by unrealistic expectations from the BT designation, and they underestimated the significance of the manufacturing deficiencies which they encountered. At the time of BLA submission, Portola was hoping that any remaining gaps in manufacturing knowledge would be addressed during the BLA review cycle or post-licensure through the ongoing process development and characterization studies.

Portola stated that the ANDEXXA program is in jeopardy, and that the FDA's help is critical to getting the program back on track. Portola committed to working in partnership with the Agency and providing whatever data/information is necessary to approve ANDEXXA, and to provide the assurance that their commitments will be executed in a quality manner.

FDA noted that all items in the CRL must be addressed prior to approval and FDA does not automatically grant approval based upon BT designation alone. Further, FDA noted BT designation is common during the pre-licensing phase and only allows for increased communication with the Agency to facilitate development; Portola is still responsible for demonstrating that the product is safe and effective.

Applicant Question 1a:

Portola acknowledges the request for supplementary validation studies to establish impurity clearance and confirms that this study will be performed and the data included in the resubmission. Portola does not believe the current data set supports that there is a (b) (4) impurity in the (b) (4) that is generating the (b) (4). Clearance of potential (b) (4) impurities will be demonstrated by evaluation of the levels of the (b) (4) by (b) (4) (as (b) (4) methods) and (b) (4) by the Process-specific assay in the (b) (4) and in in-process streams of the downstream process for (b) (4) representative (b) (4) batches. The study will be designed to demonstrate no increase in (b) (4) levels across the purification process when the

samples are (b) (4) through a combination of (b) (4). In addition, as described in the following response strategies, validation data from the (b) (4) control (Comments 1c & 1d) and hold time stability (Comment 1e.) studies will provide further evidence that (b) (4) impurities are cleared through the downstream process. Furthermore, a root cause analysis will be provided for previous findings on “failed” hold time studies (Comment 1e.). Finally, to support a lack of protease activity in the (b) (4) levels will be trended on stability with robust and orthogonal methods (Comment 1d). All validation protocols and reports will be reviewed and approved by the Portola Quality Assurance unit.

Does FDA concur that documenting the removal of (b) (4) and control of the (b) (4) will be sufficient to complete the Validation studies to demonstrate clearance & control of impurities?

FDA Response to Question 1a:

No, the scope of your proposed studies is not sufficient to demonstrate control over the manufacturing process. In addition to the proposed evaluation of the levels of the (b) (4), please characterize the identity and biochemical properties of the impurities, including those with (b) (4), and demonstrate clearance of the impurities on the basis of their observed characteristics. For example, you had described some of the ongoing impurity identity studies in the July 17, 2016, amendment to the BLA. We agree that it would be helpful to demonstrate no increase in (b) (4) levels across the purification process when the samples are (b) (4) through a combination of (b) (4).

Additional Discussion:

Portola agreed to include a study report on the validation of impurity clearance in the resubmission. Portola noted that the validation study is currently underway, and the report will include characterization based on a number of orthogonal methods. FDA noted that its principal concern was the evidence of (b) (4) impurities in the Final Drug Product (FDP) that have the potential to affect product purity and stability. FDA also noted that, in addition to the proposed impurity clearance studies, Portola should characterize the identity and biochemical properties of the impurities. FDA referred to exploratory studies, which Portola acknowledged in the July 17, 2016 response to the Agency’s information request. At that time, Portola was unable to provide information on the identity of the (b) (4) impurities but described their attempts to explore it. Portola agreed to include this information in their complete response to the CRL. Portola requested the Agency’s opinion on the overall sufficiency of the proposed studies. FDA noted that the scope of the described studies is reasonable and therefore it may be sufficient to address the concerns about (b) (4) impurities, and that FDA will make that determination upon review of the data in the resubmission.

Applicant Question 1b:

Portola acknowledges the request to demonstrate that the apparent trends in the purity and stability attributes of the (b) (4) Final Drug Product (FDP) for (b) (4) do not adversely affect the quality, safety, purity, or potency of the product as they relate to its safety and effectiveness.

Portola confirms that it will provide in the resubmission an analysis and discussion of any purity and stability data, generated by testing with the new and revised assays, which demonstrates trends that may adversely affect the quality, safety, purity, or potency of the product. In addition to a thorough assessment of the current (b) (4) data, and data from an (b) (4) method ((b) (4)) for (b) (4) levels will be included in the assessment. Trending of data from side-by-side batch analysis release data, and purity and potency evaluation including samples that are (b) (4) in the (b) (4) product-related substance will also be assessed.

Does FDA agree with this approach?

FDA Response to Question 1b:

Yes, we agree with your approach and acknowledge your commitment to provide analysis and discussion of all purity and stability data, generated by testing with the new and revised assays, which demonstrate trends that may adversely affect the quality, safety, purity, or potency of the product. We also agree that it would be helpful to trend data from side-by-side batch analyses and purity and potency evaluations, and inclusion of samples that are (b) (4) in the (b) (4) product-related substances.

Additional Discussion:

This question was not discussed during this meeting.

Applicant Question 1b(i):

Portola acknowledges the request to address the apparent increase in both the levels of the (b) (4) and batch-to-batch variability in the (b) (4) when (b) (4) was replaced with (b) (4).

It should be noted that data in Figure 5b of the Investigation Report for DEV-1632 was not generated in a side by side manner and only includes (b) (4) batches. Therefore, Portola proposes to provide in the resubmission a more comprehensive data set (all available (b) (4) and (b) (4) lots manufactured to date) generated in a side-by-side manner by the validated (b) (4) and (b) (4) methods. This will provide more informative evidence of the capacity of (b) (4) to produce levels of the (b) (4) consistent with those seen in (b) (4). The side-by-side data will be statistically analyzed for trends in beta form levels and the comparability of (b) (4) and (b) (4).

Does FDA agree with this approach to addressing the (b) (4) levels between (b) (4) and (b) (4) as well as the batch-to-batch variability within a Process?

FDA Response to Question 1b(i):

Yes, we agree with your plan to conduct a comparative study by performing side-by-side testing of all available (b) (4) and (b) (4) lots using the validated (b) (4) and (b) (4) methods. However, in your report, please also explain how the variability of the analytical methods was responsible for the apparent (b) (4)

in both the levels of the (b) (4) and batch-to-batch variability in the (b) (4) when (b) (4) was replaced with (b) (4).

Additional Discussion:

This question was not discussed during this meeting.

Applicant Question 1b(ii):

Portola commits to statistically evaluate (b) (4) and (b) (4) data from all accelerated stability studies for an (b) (4) in rate of (b) (4) formation in (b) (4) batches. It should be noted that the (b) (4) is a characterization method that does not accurately discriminate between the (b) (4) as some (b) (4) as part of the (b) (4). In addition, Portola will provide data supporting that (b) (4) variants, which are generated under accelerated conditions of (b) (4), confounding the (b) (4) data with respect to (b) (4) of the (b) (4). Furthermore, reassessment of the (b) (4) data from the (b) (4) Comparability study, in conjunction with preliminary stability data from the new (b) (4) assay, indicate that there are no adverse trends in (b) (4) levels beyond assay variability. Given limitations of the (b) (4) and the (b) (4) assays, Portola will provide (b) (4) data as the definitive evidence of (b) (4) level control and comparability in the submission.

Does FDA agree with using the totality ((b) (4)) of the data to examine the apparent adverse stability trends seen for (b) (4)?

FDA Response to Question 1b(ii):

Yes, we agree with your plan to statistically evaluate (b) (4) data from all accelerated stability studies, and supplement it with (b) (4) data to demonstrate control of the (b) (4). With reference to your hypothesis that an apparent (b) (4) in the (b) (4) was caused by the interference of the (b) (4) variants in the detection of the (b) (4) by (b) (4), please assess the effects of (b) (4) on the purity and potency of andexanet alfa.

Additional Discussion:

This question was not discussed during this meeting.

Applicant Question 1b(iii):

Portola acknowledges that the 6 month data submitted in the BLA for batch (b) (4) suggested an apparent adverse stability trend. However, the 9 and 12 month stability points have now been completed and the additional data show that there is no adverse stability trend beyond expected analytical variability of the (b) (4) method. These data will be provided in the resubmission.

Does FDA agree with this approach?

FDA Response to Question 1b(iii):

Yes. In addition, please evaluate the root cause for the adverse stability trends observed in the early stages of the real-time stability studies.

Additional Discussion:

This question was not discussed during this meeting.

Applicant Question 1c:

Portola acknowledges the request to demonstrate the effectiveness of the control strategy for the newly established critical process parameter (b) (4) - in assuring the consistency of (b) (4) performance and (b) (4) quality.

Portola commits to conduct a prospective supplementary validation study to specifically demonstrate the effectiveness of the control strategy for (b) (4), which is a critical process parameter for the (b) (4) step, for (b) (4) representative batches of (b) (4). Consistency of (b) (4) performance will be demonstrated by successfully meeting the IPL acceptance criteria for the (b) (4) step. (b) (4) quality will be confirmed by complete release testing, including all of the new or revised assays. Portola intends to conduct the validation studies for the control of (b) (4) prior to implementation of the point of use (b) (4). Once the (b) (4) is installed and an IQ/OQ is performed, a PQ will be performed to demonstrate (b) (4) control under the validated manufacturing conditions. Portola will include the (b) (4) -control validation report as well as the PQ report for the (b) (4) in the resubmission. In addition, Portola commits to including in the resubmission an addendum to the existing PPQ report that demonstrates the effectiveness of the control strategy for critical process parameters and key operating parameters established since submission of the BLA.

Does the Agency agree with the staged approach, first validating the (b) (4) control parameters for the (b) (4) step, followed by the implementation and qualification of the (b) (4) to control (b) (4) within validated ranges?

FDA Response to Question 1c:

We are unable to agree with the described proposal because you did not provide a rationale for conducting the validation studies for the control of (b) (4) before implementation of the point of use (b) (4). Our understanding is that if the (b) (4) is being added to the process to provide control of the (b) (4) of the (b) (4) during the (b) (4) step, then the (b) (4) should be installed and qualified before the process validation of the (b) (4) step.

Additional Discussion:

Portola acknowledged that insufficient information was submitted to explain their rationale for conducting validation studies prior to implementation of the point of use (b) (4). Portola explained that including the (b) (4) at this time is not necessary because they have already implemented several manufacturing changes which they consider sufficiently effective to manually control the (b) (4). Portola

stated their intention to provide validation of the (b) (4) as a post-approval supplement. Portola believes that the current manual controls will support process validation activities. Furthermore, including the (b) (4) would result in significant schedule delay of their March 2017 target resubmission date.

FDA noted that Portola is responsible for setting realistic deadlines. If Portola expects that more time is needed to demonstrate control of the manufacturing process, FDA recommends delaying the submission of the CRL complete response. Portola stated that they are willing to submit the CRL response without the (b) (4), and asked if this would be acceptable to the FDA. FDA responded that Portola has not provided sufficient information for the FDA to agree or disagree with Portola's proposal. FDA noted that Portola's claim that the process can be controlled in the absence of the (b) (4) may be acceptable from the product perspective, but reiterated that this strategy could be risky. Portola is at its own risk to submit the CRL response without the implementation of the (b) (4). FDA will carefully review the totality of evidence submitted in the CRL response; and any identified deficiencies with the proposed control strategy will likely result in a negative impact on the outcome of the BLA review. FDA reminded Portola that their past decision to submit the BLA in December of 2015 prior to the completion of the process performance qualification (PPQ) studies was premature when evidence of poor control over the (b) (4) in their new (b) (4) was linked to the concerns over comparability between (b) (4) and many other issues described in the CRL.

Portola agreed that ultimately it would be its decision to move forward without the (b) (4). FDA also noted that the proposal for a PMC to implement a new control strategy, including any requirement for equipment qualification and re-inspection of CMC Facilities, would have to be discussed separately. Portola agreed to provide all supporting information in the CRL complete response to justify its proposals.

Applicant Question 1d:

Portola did not provide a question for 1d.

Applicant Question 1e:

Portola did not provide a question for 1e.

Applicant Question 1f(i):

Does the Agency agree that the description of the decisions and timing behind using (b) (4) lot (b) (4) for the FDP PPQ support the inclusion of this batch in the PPQ series? Does the Agency agree with Portola's approach on determining the disposition of this batch?

FDA Response to Question 1f(i):

No, we do not agree with the inclusion of the out-of-specification (OOS) (b) (4) batch (b) (4) in the FDP PPQ series and Portola's approach on determining the disposition of this batch.

Please provide, for our review, all supporting documentation regarding the use of the OOS (b) (4) batch in FDP production, and the decisions that led to the disposition of the affected (b) (4) and FDP batches. In your response, please provide a list of all the deviation investigations regarding the use of the OOS batch, which were opened at (b) (4) [REDACTED] Portola, and related CAPAs, and explain why this information was not provided in Portola's BLA and (b) (4) FDP PPQ report. Specifically, please describe the measures that were put in place to prevent the recurrence of these deviations. Please support your conclusions with references to the relevant Quality Agreements and Quality Assurance SOPs at Portola, (b) (4) [REDACTED], as well as at (b) (4) [REDACTED].

Additional Discussion:

Portola acknowledged the Agency's concerns as described above and agreed to provide the requested information. Portola recognized that the deviations were not adequately documented in the BLA. The company is in the process of updating procedures to ensure such deviations are appropriately documented in the future and to prevent their recurrence. Portola will provide that information in the resubmission as requested. Portola stated its desire to exclude the affected PPQ batch from the series and move forward with the remaining batches in the existing PPQ series to avoid further delays and proposed to provide data on (b) (4) additional continued process verification (CPV) "confirmatory" batches. FDA stated that there is insufficient information, particularly with respect to the documentation surrounding the use of Lot (b) (4) [REDACTED] in the FDP PPQ series, to make a decision and the issue cannot be resolved at this meeting. FDA requested specific information, as a part of the response to this meeting request as noted above, concerning the quality systems at Portola (b) (4) [REDACTED]. FDA suggests providing this information in advance of the formal resubmission. FDA stated its principal concern is the controls that are in place to prevent this cGMP nonconformance from happening again. Additionally, Portola should provide evidence detailing how similar deviations were managed; this data must convince the Agency that the cGMP nonconformance was an isolated incident. Portola agreed to provide the information on their quality systems. Portola understands that they made a mistake which reflected negatively on their credibility as a cGMP compliant company. FDA stated that a separate discussion with Portola on this subject with full participation of DMPQ can be arranged. An agreement on the timeline for data submission and a detailed Briefing Document will be needed.

Applicant Question 1f(i & ii):

Does the Agency agree that the totality of the FDP data, as outlined in Table 4, support the consistency and validation of the FDP process?

FDA Response to Question 1f(i & ii):

No. Please refer to FDA Response to Question 1f(i).

Additional Discussion:

This question was not discussed during this meeting.

Applicant Question 2a:

Portola did not provide a question for 2a.

Applicant Question 2b(i):

Portola acknowledges the request to validate a (b) (4) assay as an identity test for andexanet alfa, and to validate the methods for determining the (b) (4) content.

As described in the 20 April, 08 July, and 29 July 2016 responses, Portola will provide in the resubmission validation reports for the (b) (4) assay, the (b) (4) method for determining the (b) (4) content assay, and justifications for proposed specifications

Does FDA agree with this approach?

FDA Response to Question 2b(i):

Yes.

Additional Discussion:

This question was not discussed during this meeting.

Applicant Question 2b(ii), Parts 1 & 2:

As described in the IR response of 08 July 2016 (SN0055), Portola will provide in the resubmission analytical methods for the mannitol, sucrose, and Polysorbate 80 FDP assays. All available released lots of (b) (4) andexanet alfa FDP will be tested by the validated assays to establish commercial specifications. Portola will provide validation reports and justifications for the proposed specifications.

Portola will provide summaries of the compendial method verifications performed for the analytical methods used for release of raw materials intended for the FDP formulation.

Does FDA agree with this approach?

FDA Response to Question 2b(ii), Parts 1 & 2:

Yes.

Additional Discussion:

This question was not discussed during this meeting.

Applicant Question 2b(iii):

Portola acknowledges the request to develop and validate potency units for andexanet alfa to replace the current unit of “percent of a reference standard.”

Portola commits to validate potency units to andexanet alfa reference standard for direct and indirect assays by January 2017. (Please refer to response in 3d.)

Does FDA agree with this approach?

FDA Response to Question 2b(iii):

Yes. However, in addition to validating the potency units of the reference standards, please also establish a correlation between the existing and new potency units such that the results of the previous stability studies and batch analyses expressed in the old potency units could be made relevant to the specification limits expressed in the new potency units.

Additional Discussion:

This question was not discussed during this meeting.

Applicant Question 2c:

Does FDA agree that the totality of andexanet alfa variants can be controlled with this matrix approach?

FDA Response to Question 2c:

Yes, your proposal to demonstrate control over all product-related variants by using a matrix approach appears reasonable. However, in your response, please provide trending graphs for all the (b) (4), including those for which quantitative acceptance criteria will not be developed.

Additional Discussion:

This question was not discussed during this meeting.

Applicant Question 2d:

Portola acknowledges the request to eliminate the “(b) (4)” from the (b) (4) specification. It is acknowledged that (b) (4) could be indicative of protein solubility and stability issues. Therefore, Portola agrees to revise the specification for (b) (4) to “(b) (4)” This specification for (b) (4) provides control for, and is consistent with, drug product requirements in (b) (4) - Foreign and Particulate Matter in that the inspection process shall be designed and qualified to ensure that every lot of parenteral preparations is essentially free from visible particulates.

In regards to the request to revise the FDP specification at lot release, Portola believes the FDP specification provided to FDA, “essentially free...” complies with (b) (4) compendial requirements as well as ICH Q6B, Particulate matter: Parenteral products should have appropriate acceptance criteria for particulate matter. This will normally include acceptance criteria for visible particulates and /or clarity of solution, as well as for sub-visible particulates as appropriate. Lastly, Portola feels the FDP specification as provided is consistent with industry standards and global regulatory expectations.

Does FDA agree with this approach?

FDA Response to Question 2d:

Yes, we agree with the proposed specification for the release of (b) (4) reconstituted FDP expressed as “Clear, colorless to slightly yellow solution, essentially free of visible particulates.”

Additional Discussion:

This question was not discussed during this meeting.

Applicant Question 2e:

As stated in our IR response of 15 June 2016 (SN0039), Portola is developing a potency assay and release specifications to measure the inhibition of TFPI activity by AndexXa FDP. Portola proposes to modify the format of the current direct potency release assay for this purpose, (b) (4)

. The units of the assay will be defined using the new units to be incorporated into the direct fXa inhibitor potency assay, to be traceable to the international reference preparations distributed by the (b) (4)

In addition, Portola will use the CAT Thrombin Generation assay used in clinical studies to characterize the TFPI interaction by ETP, peak thrombin and lag-time parameters as part of the characterization and validation of the new TFPI potency assay.

Does the agency agree with this proposal for development and validation of a release assay to measure the inhibition of TFPI activity by AndexXa FDP?

FDA Response to Question 2e:

No. Your current direct potency release assay is not suitable for the evaluation of the inhibition of TFPI activity by andexanet alfa because this assay does not measure the interaction of TFPI with its biological target, Tissue Factor/Coagulation Factor VIIa complex, nor does it measure the reversal of the inhibition of Factor X activation by this complex.

Additional Discussion:

Portola acknowledged FDA’s request for a potency assay that measures the interaction of TFPI with its biological target, Tissue Factor/Coagulation Factor VIIa (TF/FVIIa) complex and the reversal of the inhibition of Factor X activation by this complex.

Portola proposed the following:

- *Purified Proteins in a (b) (4) System-that would include a fixed composition of TF:FVIIa complex and TFPI, which would allow the assessment of the interaction of TFPI with its biologic target.*

- Utilize a (b) (4) assay that would measure the conversion of FX to FXa, and could be read in a (b) (4) l format. This is a variation of the assay that was included in the IND, which is a robust and sensitive assay.
- A range of andexanet concentrations would be added in to the assay to demonstrate reversal of inhibition, via binding of andexanet to TFPI.
- An EC50 would be measured against the reference standard, and the EC50 will be converted to the new activity units that will be defined in a similar manner and calibrated to the (b) (4) FXa standard (either (b) (4), whichever is currently available).
- For example, (b) (4).

FDA stated that Portola's response covers one of the principal concerns (i.e., clinical relevancy); however, further review is necessary. FDA reiterated that the assay must be traceable to what is used in the clinical trials (i.e., TG assay and/or TFPI activity assay). In addition, assay validation should also demonstrate its sensitivity to detect product degradation by testing (b) (4) materials. FDA stated that further clarification would be provided in the post-meeting notes below.

Post-Meeting Comments:

The proposed approach appears acceptable in general. Please also consider the following advice:

1. Because no international reference standards for TFPI activity and mass are available at this time, the proposed definition of anti-TFPI activity unit, (b) (4), will not be traceable to any external biological reference standards. We, therefore, recommend that the anti-TFPI activity of the first andexanet alfa reference standard is assigned to match the potency value determined by the assays for the reversal of either the direct or indirect anti-FXa activity. In this scenario, all future andexanet alfa standards will have assigned to it three potency values calibrated against the first reference standard for andexanet alfa, but the first reference standard is assigned by only two assays.
2. Because you plan to use a purified TFPI protein as the source of TFPI activity, the proposed potency assay will be different from the clinical assay in which patient plasma was the source of TFPI activity. In your complete response to the CRL, please provide analytical data to show the correlation between the potencies determined by the validated anti-TFPI activity assay and the TFPI-sensitive methods used in clinical trials. Specifically, please show the decrease in TFPI activity and antigen and the increase in thrombin generation parameters as a function of andexanet alfa activity expressed in units of anti-TFPI activity by testing normal plasma spiked with andexanet alfa of known potency (in the

presence or absence of FXa inhibitors if needed) in the dynamic range of the TFPI activity, TFPI (b) (4) and thrombin generation test assays.

3. With reference to your original proposal to test anti-TFPI activity of andexanet alfa in the presence of FXa and absence of TF and FVIIa, please comment on the role of TFPI inhibition in andexanet alfa-dependent elevation of the contact-activated thrombin generation in clinical trials because thrombin generation may be sensitive to the inhibition of FXa by TFPI even in the absence of TF and FVIIa.

Applicant Question 2f:

Portola did not provide a question for 2f.

Applicant Question 2g:

As discussed with FDA at the October 2014 Type C meeting as well as at the pre-BLA CMC meeting in July 2015, Portola has initiated development of a process-specific (b) (4) method. We have generated a process-specific (b) (4) preparation using (b) (4)

(b) (4). Adequate coverage of the anti-(b) (4) antibodies for the CHO-derived impurities will be established. A combination of the process-specific (b) (4) preparation and the (b) (4) antibodies will be used to develop and validate an (b) (4) method that can be used for release testing of the commercial material. A bridging study will be performed to compare (b) (4) results from the new process specific assay to that of the (b) (4) commercially available (b) (4) assay currently used for release testing. This data will be provided in the BLA resubmission. Portola will develop specifications for the new (b) (4) assay which will be justified statistically by manufacturing lot history and clinical experience.

Does FDA agree with the proposed bridging approach?

FDA Response to Question 2g:

Yes. In addition, please use samples of representative process intermediates to demonstrate that the new process-specific (b) (4) assay is at least as sensitive as the currently used commercially available (b) (4) assay (b) (4).

Additional Discussion:

This question was not discussed during this meeting.

Applicant Question 2h & 2h(i):

Portola acknowledges the request to develop new specifications for the (b) (4) and provide complete reports for the investigations into the root causes behind the observed changes in product quality attributes after the introduction of (b) (4). See sections 1b, 1c, 1d, 1e. for Portola's commitments in regards to these requests.

As discussed in the Introduction Section, Portola will provide a risk-assessment of the (b) (4) and the (b) (4) impurities and their impact on the purity, quality, potency, and stability of the product.

Does FDA agree with this approach?

FDA Response to Question 2h & 2h(i):

Yes.

Additional Discussion:

This question was not discussed during this meeting.

Applicant Question 2h(ii):

Portola will use the current (b) (4) method and the new (b) (4) method, once validated, for the measurement of the (b) (4) to compare the (b) (4) and (b) (4) batches, and to monitor the (b) (4) in stability studies for the (b) (4) FDP. This approach is more fully described in the response to Question 2c. Specifically, all available (b) (4) and (b) (4) and FDP batches will be tested side-by-side and the data analyzed by the appropriate statistical methods. (b) (4) is currently used for stability studies, and the (b) (4) method, once validated, will be added to the stability protocol as an addendum and used as the orthogonal method for monitoring the (b) (4) in stability studies for the (b) (4) FDP going forward.

Does FDA agree with the use of (b) (4) to as the (b) (4) method?

FDA Response to Question 2h(ii):

We agree that the use of improved and (b) (4) methods is essential in demonstrating control over the (b) (4) at release and in stability studies. However, without reviewing the assay qualification data, we are unable to comment on the suitability of the (b) (4) assay for this purpose.

Additional Discussion:

This question was not discussed during this meeting.

Applicant Question 2h(iii):

Portola acknowledges the request to explain how the available clinical data support the beta forms specifications, and to use (b) (4) methods to detect the ranges of levels for each (b) (4) in all batches used in the completed clinical trials and address the possible effect of the (b) (4) on the AndexXa circulatory half-life. Portola will analyze the available (b) (4) batches, side-by-side, by the (b) (4) method and the validated (b) (4) (proposed (b) (4) method) method in order to establish the ranges of levels for the (b) (4) in all released batches, including those used in the completed clinical trials. This will provide a more statistically significant sampling than used previously. As described in the Portola IR response of 13 July 2016 (SN0059), Portola anticipates the precision of the (b) (4) based (b) (4) method to be superior to that of the (b) (4) method, allowing for a revised specification for (b) (4). Furthermore, the analysis of all available batches of (b) (4), compared to the limited batches that were used to derive the (b) (4) specification is anticipated to more accurately reflect the capabilities of the manufacturing process and align the specification with the (b) (4) levels observed in the clinical batches. This side-by-side (b) (4) data will be

used to justify how the available clinical data supports the (b) (4) specification, and discussed in the Justification of Specifications.

Does FDA agree with this approach to developing new specifications for the (b) (4) and explaining how the available clinical data supports the (b) (4) specifications?

FDA Response to Question 2h(iii):

Yes.

Additional Discussion:

This question was not discussed during this meeting.

Applicant Question 2h(iv):

Portola acknowledges the request to use orthogonal methods to compare the specific potencies of the (b) (4) with the other product-related molecular forms of AndexXa, and the suggestion to use a biomarker assay, e.g., TF-activated TGT, in addition to validated potency method.

Portola is developing biochemical methods to generate a test sample that is a mixture of AndexXa (b) (4) for the (b) (4), but that will still be a mixture of all the (b) (4). This test sample will be used to evaluate the (b) (4) in (b) (4) studies (see question 6b below) and other functional assays. This (b) (4) mixture will be compared in the (b) (4) assay to the lot of AndexXa (b) (4) from which it was derived, as well as all the direct, indirect, and the new TFPI potency assays. In addition, the (b) (4) sample will also be analyzed in the TF-activated TG assay to compare against the (b) (4) starting material, using ETP, peak thrombin and lag-time parameters. Portola will also analyze data from prior studies where (b) (4) was used in the (b) (4) method to isolate (b) (4) and identify (b) (4) present in each (b) (4). The (b) (4) data will be further analyzed to identify the (b) (4) which contain various (b) (4), and the potency of these (b) (4)-containing (b) (4) will be compared to that of (b) (4) containing (b) (4).

Does FDA agree with this approach?

FDA Response to Question 2h(iv):

Yes. In addition, please demonstrate parallelism between the dose-response curve of the (b) (4) material and that of the ordinary (b) (4) batch in the proposed potency assays and TF-activated TG assay. Furthermore, because the (b) (4) of andexanet alfa may be produced by (b) (4) by Factor Xa and because high amounts of human Factor Xa are used as a reagent in your potency assay, please evaluate the effect of this Factor Xa on the generation of (b) (4) in the potency assay.

Additional Discussion:

This question was not discussed during this meeting.

Applicant Question 2i:

Portola did not provide a question for 2i.

Applicant Question 2j:

Portola acknowledges the request that the justifications for specifications should explain how the finalized specifications and validated release methods will demonstrate the consistent performance of the manufacturing process to produce drug product with the appropriate identity, quality, safety, purity, and potency attributes.

Portola will provide a complete justification of the specifications, using appropriate statistical methodology for defining both release and end of shelf life specifications, taking manufacturing process consistency and data obtained from lots used in clinical studies into consideration. The justification will include how the additional release methods will further demonstrate consistent performance of our manufacturing process.

Does FDA agree with this approach?

FDA Response to Question 2j:

Yes. In your response, please also provide the raw data and the results of your statistical analyses.

Additional Discussion:

This question was not discussed during this meeting.

Applicant Question 3a:

Portola's current reference standard Lot (b) (4) was qualified against an approved specification document. Portola will calibrate this standard with the (b) (4) reagents (refer to question 2b (iii)). Portola will use this reference standard until a new PRS is manufactured and qualified for use. (Refer to question 3b.)

Does the agency agree that PTLA can continue to use the existing RS, standardized against the (b) (4), while developing the PRS in parallel.

FDA Response to Question 3a:

No. Please develop a primary reference standard (PRS) and a qualification protocol for the preparation of subsequent RS, which will ensure consistency of the characteristics of all RS, including its potency unit, throughout the life-cycle of the product. With reference to the proposed use of the existing RS Lot (b) (4), please describe the measures you have in place that can ensure the continuity and comparability of the quality and characteristics of previous, current, and future RS, such as evaluation of stability and process development investigations.

Additional Discussion:

FDA reiterated the importance of the availability of a PRS in demonstrating the consistency, comparability, and stability through various studies over time. FDA became especially concerned after Portola acknowledged in July of 2016 that the reference standard described in the BLA is no longer available, and a new standard is introduced less than a year after the previous standard. In the BLA resubmission,

Portola should address the possible impact of frequent changes in the reference standard on both the completed and ongoing stability and comparability studies. FDA also noted that stability excursions for the reference standard were observed during the PLI but they were not reported in the BLA. In the complete response to the CRL, Portola should address all known adverse trends with its reference standards.

Portola agreed to develop a PRS and qualification protocol for the preparation of subsequent PRS. Portola stated that its current strategy would be to convert the current reference standard to a PRS through a process of requalification against the international standard.

FDA noted that Portola should be attentive to the availability of sufficient number of the existing standard in stock as Portola may have to replace the RS sooner than expected, which could have an impact on the stability and comparability studies; Portola stated that its current inventory appears adequate. FDA requested that Portola include in its protocol a description of the process for replacing the PRS and to develop a plan for the development of working reference standards that can be linked to all reference standards that have been used.

Applicant Question 3b:

Portola did not provide a question for 3b.

Applicant Question 3c:

Portola did not provide a question for 3c.

Applicant Question 3d:

Portola will assign potency to the PRS. The detailed information on the method and reagents used in the assignment of potency to the PRS and secondary standards, studies to monitor the stability of the reference standards will be provided in the resubmission.

Primary and Working reference standards will be calibrated against (b) (4) reagents. (b) (4) in the Direct Potency Assay and (b) (4) in the Indirect Potency Assay. The IC50s of (b) (4) determinations will be averaged to determine a mean IC50 for each assay. For Direct Potency the IC50 value will represent (b) (4) AndexXa Direct Potency Units and will be described as (b) (4)

(b) (4). For Indirect Potency, the IC50 value will represent (b) (4) AndexXa Indirect Potency Units and will be described as (b) (4)

Portola will provide the requested protocol for the replenishment of these reference standards in the resubmissions.

Does the agency agree with this approach?

FDA Response to Question 3d:

Yes. Please note that (b) (4) is finalizing the development of a new standard for human Factor Xa activity. We recommend using this new standard in place of, or in addition to, the (b) (4).

Additional Discussion:

This question was not discussed during this meeting.

Applicant Question 3e:

Portola did not provide a question for 3e.

Applicant Question 3f:

Portola did not provide a question for 3f.

Applicant Question 4a:

Portola will retest all available (b) (4) batches using the new validated release methods to demonstrate that the old batches meet shelf-life specifications, and proposed comparable stability profiles. Portola plans to evaluate the comparability of (b) (4) to (b) (4) and if demonstrated will evaluate the (b) (4) stability data to propose a shelf-life for (b) (4) product.

Does FDA agree that, if comparability is demonstrated, the retest data will be sufficient to establish a proposed shelf-life for commercial (b) (4) drug product?

FDA Response to Question 4a:

Yes, we agree that, if comparability between (b) (4) and (b) (4) batches is demonstrated, (b) (4) data can be used to support a proposed shelf-life for the commercial (b) (4) drug product.

Additional Discussion:

This question was not discussed during this meeting.

Applicant Question 4b:

Portola did not provide a question for 4b.

Applicant Question 4c:

Portola did not provide a question for 4c.

Applicant Question 4d:

Portola did not provide a question for 4d.

Applicant Question 5a:

Portola acknowledges the request to include (b) (4) testing as a critical process parameter for the (b) (4) step. Portola will revise the status of the (b) (4) test of the (b) (4) to a Critical Process Parameter.

Does FDA agree with this approach to revision of the (b) (4) parameter designation?

FDA Response to Question 5a:

Yes.

Additional Discussion:

This question was not discussed during this meeting.

Applicant Question 5b:

Portola did not provide a question for 5b.

Applicant Question 5c(i to v):

Portola proposes that if comparability between first generation (GEN1) (b) (4) manufactured at (b) (4) and second generation (GEN2) product, manufactured at Lonza (Porriño, Spain) is demonstrated with analytical and PK/PD and safety data, approval of GEN2 can be achieved by a Prior-approval Supplement (PAS).

Does the Agency agree?

FDA Response to Question 5c(i to v):

This question is outside the scope of the CR Letter and will be discussed in a separate meeting for the GEN 2 process. Moreover, it is premature to discuss the regulatory pathway for the GEN2 process before we resolve all the deficiencies in the current process. In general, FDA and Portola would need to agree on the extent of the comparative studies and the criteria for establishing comparability between the (b) (4) manufactured at (b) (4) and the GEN2 preparations manufactured at Lonza in Spain. The GEN2 process introduces several manufacturing changes that are considered significant; for example, (b) (4) step may change the profiles of process- and product-related impurities and/or the distribution of the (b) (4) variants that are found in the current (b) (4) andexanet alfa product. These changes may affect the quality, purity or potency of the product.

Additional Discussion:

This question was not discussed during this meeting.

Applicant Question 6a:

Portola will evaluate the suitability of the (b) (4) method for assessing interactions of TFPI and andexanet alfa (b) (4). As we mentioned in the IR response dated 15 June 2016, Portola has not performed (b) (4) experiments to examine protein:protein interactions with andexanet alfa. All previous (b) (4) studies with andexanet alfa have measured the interaction with small-molecule inhibitors. Since the method may not be readily suitable for measuring the high-affinity interactions between andexanet alfa and TFPI, method development may be required. If the assay performance is suitable for the requested parameters (n and ΔH), Portola will proceed with characterization studies to compare (b) (4) (b) (4) batches) and (b) (4) (b) (4) batches) using this (b) (4) method.

Does FDA agree with this approach?

FDA Response to Question 6a:

Yes.

Additional Discussion:

This question was not discussed during this meeting.

Applicant Question 6b:

Portola did not provide a question for 6b.

Applicant Question 6c:

Portola acknowledges the request to investigate the sensitivity of the (b) (4) method to evaluate the (b) (4) of AndexXa and to consider including the (b) (4) assay in the (b) (4) release specifications.

Portola agrees to investigate the sensitivity of the (b) (4) method to evaluate the (b) (4) of AndexXa and to consider including the (b) (4) assay in the (b) (4) release specification focusing on the (b) (4) parameters of ΔH and n. However, Portola has not been able to identify a contract lab that has this instrumentation available to run under GMP conditions, therefore we will not be able to incorporate (b) (4) into testing as a release assay. All (b) (4) studies to date have been run at Portola as characterization assays in a non-GMP environment. In addition, the currently proposed potency assays for release (including the new TFPI potency assay described in question 2 e above) are considered sufficient to address all mechanisms of action of andexanet.

Does FDA agree with the proposed plan to address the questions raised in 6 a, b, and c?

What samples are to be tested to address the question raised in 6c above?

FDA Response to Question 6c:

Yes, we agree with the proposed plan to address the questions raised in Questions 6a, 6b, and 6c. With reference to Question 6c, we recommend using (b) (4) samples to investigate the sensitivity of the (b) (4) method to evaluate the (b) (4) of ANDEXXA.

Additional Discussion:

This question was not discussed during this meeting.

Applicant Question 7:

Portola acknowledges the request to identify the proteins in the (b) (4) identified by FDA using a (b) (4)

Portola has observed similar (b) (4) resolution when using (b) (4) and has identified the (b) (4) to comprise primarily of the intact and (b) (4) forms, which are controlled by the (b) (4) method. Portola developed and validated the (b) (4) method with (b) (4) as a method intended to monitor and control the levels of (b) (4). See response to question 2(c) for a more complete discussion of the (b) (4) method.

Does FDA agree this adequately explains the (b) (4) observation made by FDA using the alternate (b) (4) ?

FDA Response to Question 7:

Yes. However, please also demonstrate that the intact and (b) (4) forms are properly controlled by the remaining release assays.

Additional Discussion:

This question was not discussed during this meeting.

Applicant Question 8:

Portola did not provide a question for #8.

Applicant Question 9:

Does the provided justification clarify how the lab-scale studies support the lyophilization parameter ranges at commercial scale?

FDA Response to Question 9:

We acknowledge that extensive studies have been performed by (b) (4) including comparability and scalability studies that were used to set and support the design space. However, we have not had the opportunity to review these studies, thus we cannot adequately assess the justification provided. Based on this, we recommend the following be provided in the BLA resubmission:

- a. All comparative and scalability studies performed that were used to determine the design space and to explore parameters in the lab-scale lyophilizer and that are indicated to support the comparability of the small and commercial scale lyophilizers for setting the parameter ranges for the commercial scale lyophilizer.
- b. Indicate how the NORs and PARs are acceptable considering the comparison of the dryer load and capacity of the lab scale lyophilizer vs. the commercial scale lyophilizer.
- c. A plan to perform and submit results of at least (b) (4) commercial runs at the high and low ends of the PARs to verify the PARs at the commercial scale.

Additional Discussion:

Portola indicated that they will provide the information to address items (a) and (b) which included providing all studies used to determine design space and demonstrate comparability of the lab scale and commercial lyophilizers. In regards to item (c), recommending to provide (b) (4) commercial runs at the high and low ends of the PARs, Portola asked why runs at commercial scale to support the NORs and PARs ranges were necessary as from their understanding and in collaboration with colleagues at (b) (4) that challenging the large-scale process at extremes of the NORs and PARs is not a standard industry practice or expectation for validation. FDA indicated that the NORs and PARs that will be used at commercial scale are very broad and that there was minimal information provided in the BLA to support that these ranges were acceptable at the commercial scale. The information provided in the BLA did provide some results of (b) (4) developmental runs that were used to established the NOR and PAR ranges; however these runs were performed using a lab-scale lyophilizer and there was no information provided in the BLA that demonstrated comparability of the lab-scale to the commercial scale; nor was there any justification for why the ranges established using the lab scale lyophilizer would also be supported in the commercial scale lyophilizer. FDA did acknowledge that it appears extensive studies were performed by (b) (4) to determine the design space and show comparability between the lab scale and commercial scale; however, FDA has not had the opportunity to review these studies during the BLA review nor as part of the review of the meeting package. Since FDA cannot adequately assess the robustness of the studies conducted at the lab scale, confirmatory runs at commercial scale are needed to support the extremes of the NOR and PAR ranges if these ranges are to be used in commercial production.

As follow up to this discussion, during another meeting held with Portola Oct 27, 2016 in regards to the GEN 2 process, the issue relating to lyophilization was re-visited. Portola asked FDA, if tightening the limits of the NOR and PAR would address the FDA concerns with the small scale data not demonstrating sufficient robustness to support the process at commercial scale. The FDA agreed that the ranges could be tightened and that the tightened ranges should be supported by the parameters used for the validation runs performed at commercial scale that was provided in the BLA. If an NOR range is exceeded a deviation should be initiated. The investigation associated with the deviation would evaluate product impact, and additional testing or monitoring required. Developmental studies could be leveraged to support release of the lot, provided the investigation's conclusions support this outcome.

Applicant Question 10:

Portola asks that FDA confirms a “point of failure” control is a positive control for a container/closure defect.

FDA Response to Question 10:

Please provide detailed information of the “control” that is used to demonstrate the sensitivity of the test in detecting a critical defect in the container closure. The point of failure sample should be positive in the testing. Please note, as indicated in past communications, to support sensitivity of the container closure integrity testing, we recommend that the defect diameter be as small as reasonably possible.

Additional Discussion:

This question was not discussed during this meeting.

Applicant Question 11:

Portola acknowledges the request for details, SOPs, a description of course 04-01-C001 etc. in reference to the qualification of the operators that perform (b) (4) for the CCIT method performed at (b) (4). Portola will provide in the resubmission of the BLA the description of course 04-01-C001, that was used for the qualification of operators as noted in our response to IR item 5 in Amendment 50, and a copy of Course 04-01-C001.

Does FDA agree with this approach?

FDA Response to Question 11:

Yes, we agree with the approach to providing the course description of qualifying operators for (b) (4) for CCIT. Additionally, please also provide in the BLA resubmission, relevant SOPs used for performing (b) (4) for CCIT and indicate the acceptance criteria used.

Additional Discussion:

This question was not discussed during this meeting.

Applicant Question 12a & 12b:

Portola did not provide a question for 12a & 12b.

Applicant Question 13a:

Portola did not provide a question for 13a.

Applicant Question 13b:

Portola is developing an (b) (4) assay and will use it to test for neutralizing antibodies against endogenous factors X/Xa. This assay was not developed previously, as we have routinely screened for antibodies against native fX or fXa in all our clinical studies to date, and have yet to identify a sample that was positive for antibodies against fX or fXa.

Does FDA agree with this approach?

FDA Response to Question 13b:

Yes. Please also cross-validate the existing (b) (4) assay for binding antibodies against endogenous Factors X and Xa with (1) the proposed (b) (4) test for neutralizing antibodies, and (2) the (b) (4) assay for antibodies against endogenous Factors X or Xa in human plasma in the phase 1 clinical studies.

Additional Discussion:

This question was not discussed during this meeting.

Applicant Question 13c:

In order to use the limited plasma samples retained from the completed clinical studies, Portola proposes to split the retained samples for (b) (4) antibody and anti-FX/Xa neutralizing antibody tests. For the (b) (4) antibody assay, Portola proposes to use the retained plasma samples in the Phase 2 study (Study 12-502) with the highest andexanet doses with apixaban (module 1, cohort 6) and rivaroxaban (module 2, cohort 5). Does the agency agree with this proposed testing approach?

FDA Response to Question 13c:

No, your sample testing plan is not sufficiently detailed and justified. Please provide an immunogenicity testing plan to include, but not be limited to the following:

- 1) The evaluation of retained samples positive for anti-andexanet alfa antibodies;
- 2) The availability of the samples at time-points at sufficient time intervals following andexanet alfa dosing at which antibody development would be expected to occur, e.g., 14, 21, or 28 days post-dose;
- 3) The availability of samples from sufficient numbers of subjects or patients at these later time-points for the antibody results to be meaningful;
- 4) The additional data from the ongoing confirmatory study (ANNEXA-4);
- 5) The clarification on how the samples will be split.

Additional Discussion:

Portola requested clarification concerning the use of retained clinical samples in the two new assays (i.e., (b) (4) antibody assay and anti-FX/Xa neutralizing antibody assay); specifically, Portola requested FDA to provide clarification concerning which assay would be prioritized in the event that there is insufficient sample volume to run both assays.

FDA responded that the Agency could not address Portola's question at this meeting as it is a cross-disciplinary issue requiring primary input from the clinical and pharmacology/toxicology teams. FDA acknowledged that retained samples are in short supply and testing every retained sample by all immunogenicity assays may not be needed, for example, preference should be given to samples that are taken at time points when the immune response is likely to be detected. FDA reiterated the importance of testing samples which were confirmed positive for anti-andexanet alfa binding antibodies. FDA suggested this dialogue become a part of the communication plan and requested that Portola submit an immunogenicity testing plan to facilitate these discussions.

Portola asked the Agency to explain its request to measure (b) (4). FDA explained that the request to analyze (b) (4) antibodies was supported by the presented evidence that links (b) (4) proteolytic activity with the adverse stability trends in the levels of the (b) (4), which were seen in several (b) (4) FDP

stability studies. FDA acknowledged that the risk of (b) (4) antibody production may be low if a product is administered only once in the patient's life time, however, FDA reiterated its position that the presence of poorly characterized (b) (4) activity in the FDP should be addressed by assessing the immunogenicity of these (b) (4).

Applicant Question 13d(i):

Portola is assessing possible interference by antibodies to fX or fXa, using a surrogate anti-human fX/fXa neutralizing antibody, in the following PD assays: anti-fXa and thrombin generation, as well as the (b) (4). We are also assessing the possible interference of antibodies in the assay used to determine andexanet PK.

Does the Agency agree with this testing approach?

FDA Response to Question 13d(i):

Yes.

Additional Discussion:

This question was not discussed during this meeting.

Applicant Question 13d(ii):

Please refer to our response to Question 13c) for the (b) (4) antibody assay. Portola proposes to test the retained plasma samples from the Phase 2 study (Study 12-502) with the highest andexanet doses with apixaban (module 1, cohort 6) and rivaroxaban (module 2, cohort 5).

For anti-fX/fXa neutralizing antibody tests, Portola proposes to test the following retained clinical samples from the Phase 3 studies: Although there may be limited availability of the retained samples from Part 2 of Phase 3 studies that have already been used for non-TF initiated thrombin generation, we propose to test any remaining samples from Part 2 of the Phase 3 studies (Study 14-503 and 14-504) with apixaban and rivaroxaban for potential presence of anti-fX/fXa neutralizing antibody activities, as these cohorts represent the highest andexanet doses tested in the Phase 3 studies.

Overall timeline for generating data to address these responses is dependent upon how long it takes to develop and validate the new assay being requested, and on how many samples FDA wants tested in the assays.

Do the responses provided to question 13 d, parts i and ii, satisfy the requested requirements?

Does the agency agree with the proposed testing schema of retained clinical samples?

Additional Discussion:

This question was not discussed during this meeting.

FDA Response to Question 13d(ii):

No, please refer to FDA Response to Question 13c.

Additional Discussion:

This question was not discussed during this meeting.

Applicant Question 14a:

Portola did not provide a question for 14a.

Applicant Question 14b:

We have addressed this question in our previous IR response, dated 19 July 2016 (Response to Question 2), and agree with your assessment. We will include this explanation again in the BLA resubmission. In addition, Portola will provide anti-fXa activity versus TGT comparison separately for each of the fXa inhibitors (apixaban, rivaroxaban, edoxaban) as part of the resubmission.

Please confirm that the above anti-fXa vs TGT comparisons are for each fXa inhibitor (apixaban, rivaroxaban, edoxaban) in the Phase 2 and Phase 3 clinical studies, similar to Table A1-5 referenced-above, to compare the relative changes from pre-andexanet time point to 2 min post-andexanet bolus, for anti-fXa and TGT, respectively.

FDA Response to Question 14b:

We are unable to confirm the receipt of your response to Question 14b. Please provide a reference to the document from your July 19, 2016, submission in which the explanation of the differences in TGT assay results in phase 1 and 2 versus phase 3 studies can be found.

With reference to the requested anti-FXa vs. TGT comparison, in addition to the Day 1 Pre-dose, pre-andexanet alfa, and 2 min post-andexanet bolus time-points described in Table A1-5, please provide the correlation between the anti-FXa and TGT data obtained during the first 3 hours after andexanet alfa bolus and plot these correlations as graphs referenced in the CR letter question 14a.

Additional Discussion:

This question was not discussed during this meeting.

Applicant Question 14c:

Portola did not provide a question for 14c.

Applicant Question 15a:

Portola did not provide a question for 15a.

Applicant Question 15b(i & ii):

Portola did not provide a question for 15b(i & ii).

Applicant Question 15b(iii):

Portola has previously provided a subset of the requested data set in our submission for the 19 July 2016 meeting. We will supply the complete data set using all available samples from Part 2 of the 14-503 and 14-504 studies as part of the BLA resubmission. Portola will also provide a side-by-side comparison for the time course between TF- and (b) (4) -initiated thrombin generation.

Does the FDA agree with this approach?

FDA Response to Question 15b(iii):

Yes. In addition to the time courses, please also provide your interpretation of the contributions of the anti-FXa reversal and TFPI inhibition actions of ANDEXXA to TGT elevation, and full method qualification reports for all TGT methods used in these studies.

Additional Discussion:

This question was not discussed during this meeting.

Applicant Question 15b(iv):

Portola did not provide a question for 15b(iv).

Applicant Question 15b(v) 1 & 2:

Portola did not provide a question for 15b(v) 1 & 2.

Applicant Question 15b(vi) in reference to Question 1.b.iv:

In our 19 July 2016 (SN0060) response, Portola provided additional TFPI activity data from the Phase 1 study. As previously committed, we will provide all the TFPI data from Phase 1 and 2, including total and free TFPI antigen levels, as well as the correlation between TFPI activity and the “free” TFPI levels determined using the (b) (4) assay from the Phase 1 study. In addition, we will include graphs of the “free” and total TFPI from all Phase 2 studies to show the time course of TFPI levels.

Would this approach to the data requested satisfy the above request for the resubmission?

FDA Response to Question 15b(vi) in reference to Question 1.b.iv:

No, your proposed response does not directly address the magnitude of the inhibition of TFPI activity and the timing of the resumption of TFPI activity to either the pre-andexanet treatment baseline or the normal range. We agree that the re-analysis of the levels of TFPI activity and TFPI antigen in retained samples may be helpful. However, you also need to demonstrate that the available data-points are sufficient to describe the effect of the andexanet dose (bolus and bolus plus infusion) on the timing of the changes in TFPI activity in anticoagulated and non-anticoagulated subjects. In addition, you need to demonstrate the equivalency of the TFPI activity assay used in the Phase 1 studies and the TFPI antigen assay(s) used in the Phase 2 and 3 studies.

Additional Discussion:

Portola asked if the data from the phase 1 and phase 2 studies would be sufficient to address the Agency's concern regarding the magnitude of the inhibition of TFPI activity and the timing of the resumption of TFPI activity to either the pre-andexanet alfa treatment baseline or the normal range (i.e., depth and duration).

FDA stated that the answer to this question requires input from the clinical team, but reiterated that it had not been provided with sufficient information to assess the adequacy of the time-points of collection and the graph submitted by Portola was not sufficient. FDA noted poor correlation between the TFPI activity and TFPI (b) (4) values, and advised Portola to address within-assay, assay-to-assay and patient-to-patient variability by plotting the time-courses of the TFPI assay data individually for each patient. Portola must show FDA how the different andexanet alfa dosing scenarios would affect TFPI activity over time, e.g., the magnitude and duration of the inhibition of TFPI activity, and the time when TFPI activity returns to the normal range and pre-treatment value, which is the purpose of the studies requested in the CRL.

With reference to a Portola claim that the TFPI activity assay is not suitable for use to test the plasma from patients who are on FXa inhibitors, FDA reiterated its concern that Portola has not validated this method, and did not provide any information on the interference of the TFPI assay by FXa inhibitors despite repeated requests from the FDA to do so. FDA stated that the data to evaluate assay interference are important for the assessment of the sensitivity of all three assays, TFPI activity, TFPI_{total} (b) (4) and TFPI_{free} (b) (4), to anti-TFPI action of andexanet alfa in the clinical trials.

Portola explained that TFPI activity assay validation has recently been finalized and can be submitted for review, and inquired about FDA's preference for the TFPI (b) (4) assay to be used for TFPI activity evaluation in the phase 3 and 4 studies. FDA explained that it is Portola's responsibility to decide whether it is best to use the TFPI_{free} assay or the TFPI_{total} assay for the evaluation of the inhibition of TFPI activity by andexanet alfa, and provide a rationale for the decision. FDA requested Portola to submit the validation reports for the TFPI activity assays in the IND, as it is relevant to the review of the phase 4 clinical study protocols, as soon as possible.

Applicant Question 15b(vi) in reference to Question 1 c.xii:

Portola is performing the requested studies using (b) (4) cells, repeating the prior work described in the Study # NC-15-0662-R0001, with all four inhibitors, in the presence and absence of plasma proteins. These additional data and updated report will be available by December 2016 and included in the BLA resubmission.

Portola has carefully considered the extent of the work being required by the Agency and the time needed to complete the work. The company has also taken into consideration the unmet medical need that is addressed by AndexXa, a Breakthrough product, i.e., there is no approved reversal agent for the fXa inhibitors, and the safety profile of the product thus far, including the bleeding patient data from the ongoing ANNEXA-4 study. We believe that the majority of the deficiencies in the control strategy for the AndexXa manufacturing process that were identified by the Agency

could be addressed in a March 2016 resubmission of the BLA for (b) (4) . The remaining items, beyond March, which would be in progress at the time of resubmission, would be completed as Post-Approval Commitments (refer to table, page 13). Furthermore, we believe this proposal meets the spirit and intent of PDUFA V and the Guidelines for Expedited Programs.

Does the Agency agree that the proposed data package as outlined in the response strategies is sufficient to support a March 2017 resubmission?

FDA Response to Question 15b(vi) in reference to Question 1 c.xii:

With reference to Questions 1.c.xi and 1.c.xii from the June 1, 2016, request for information, please note that you were to justify statements regarding the properties of andexanet alfa with experimental data that were not presented, e.g., that rivaroxaban blocks the interaction of TFPI and andexanet alfa. If you do not have evidence to confirm the validity of the referenced statements, you may choose to withdraw them from the BLA.

Additional Discussion:

This question was not discussed during this meeting.

Additional FDA Questions/Comments:

1. With reference to the table of on page 13 of your September 22, 2016, briefing document in which you described the timing of deliverables, we cannot agree to your proposal to submit some of the items as postmarketing commitments because these items are essential in bridging the study results from different phases of product development, specifically:
 - a. The development of a PRS (Primary Reference Standard) and link back to all RS and clinical lots (May 2017);
 - b. The development of bioassays for (b) (4) antibodies (June 2017) and TFPI activity and TFPI antigen (March 2017).

Additional Discussion:

This question was not discussed during this meeting.

Decisions made and/or agreements reached:

1. FDA and Portola will improve communication through implementation of the following changes:
 - a. All communication between Portola and FDA, including CBER management, should go via the RPM.

- b. A Communication Plan will outline critical development goals and associated communications, as needed. FDA will not grant future meetings with Portola until prerequisite milestones have been met and deliverables completed.
 - c. FDA will remain flexible with informal communication for clarification purposes only.
2. The outlined studies to address CMC deficiencies identified in the CRL may be acceptable; however, FDA would need to review the data to confirm if the studies are successful in addressing the concerns.
3. If the FDA does not receive the information that is requested in its entirety, the CRL response will not be accepted for review.
4. FDA acknowledged Portola's decision to demonstrate control over (b) (4) [REDACTED] without the (b) (4) [REDACTED] installed, and include the (b) (4) [REDACTED] installation as a post-approval supplement, but it is at Portola's risk to assume that manual controls alone are sufficient to ensure robust control over the manufacturing process.
5. The anti-TFPI activity potency assay may be acceptable but must be correlated to other assays used in the clinical studies and sensitive enough to assess product quality.
6. A primary reference standard can be generated by requalifying the present reference standard, and a protocol should be in place to describe how the primary reference standard will be replaced. In addition, continuity of reference standards (and studies which relied on those standards) should be demonstrated in the complete response to the CRL.

Issues requiring further discussion:

1. Portola's proposal to use the existing FDP PPQ data along with the (b) (4) [REDACTED] CPV batches is not acceptable at this time. Portola should provide all deviations related to the use of OOS batch (b) (4) [REDACTED] as well as others related to the quality system and manufacturing, and the relevant SOPs that show how a similar incident will not occur again, so FDA can evaluate the robustness of Portola's quality system and assure that this will not recur. FDA will arrange a separate discussion with Portola on this subject with full participation of DMPQ.
2. Regarding lyophilization, (b) (4) [REDACTED] will provide a bridging report that links present activities to small-scale studies.
3. Portola will submit an immunogenicity testing plan for interdisciplinary review.
4. Regarding the studies needed to assess the anti-TFPI activity action of andexanet in the clinical trials, it is Portola's responsibility to find the assay suitable for this purpose. To assist in the review of Clinical Study Protocols, Portola should submit

relevant information in the IND, e.g., the validation of TFPI activity assay used in the clinical trials.

Action items:

1. FDA will provide the Communication Plan as soon as possible. Portola should fill in the plan with timelines.

Attachments/Handouts:

1. Slide Deck, submitted by Portola October 17, 2016
2. Communication Plan.

END