



From Grainne Tobin, DBSQC/OCBQ

To STN 125586/o

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Product Coagulation Factor Xa (Recombinant), Inactivated, ANDEXXA

Sponsor Portola Pharmaceuticals, Inc.

Subject Review Memo for the Response to the CR Letter for the Reference Standard Qualification and (b) (4) Tissue Factor Pathway Inhibitor Assay for the (b) (4) Drug Product for ANDEXXA

Recommendation Approvable

Summary

A new Biological License Application (BLA) for ANDEXXA was submitted by Portola Pharmaceuticals in April 2012. Due to significant deficiencies, a Complete Response (CR) letter was issued on 17 August 2016. Deficiencies include inadequate Reference Standard qualification for the Direct and Indirect Potency assays, and lack of a (b) (4) assay to measure ANDEXXA inhibition of endogenous Tissue Factor Pathway Inhibitor (TFPI). The sponsor submitted their response in Amendment 76, received on 4 August 2017. This memo constitutes the review of the Amendment for the qualification of the Reference Standard and Working Standard, and review of the Potency by TFPI inhibition assay and its validation for lot-release testing.

Background

Portola Pharmaceuticals submitted an original BLA for ANDEXXA in April 2012. ANDEXXA is a modified human FXa which has no coagulation activity but can bind to FXa inhibitors such as (b) (4) (direct inhibition) and enoxaparin (indirect inhibition). It also inhibits the endogenous FXa inhibitor Tissue Factor Pathway Inhibitor (TFPI), which reverses the inhibition of FVIIa-TF by TFPI. The drug product is proposed for patients administered with rivaroxaban or apixaban, when urgent reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. ANDEXXA is a recombinant protein expressed in Chinese Hamster Ovary cells. It retains the ability to bind and reverse the effect of direct and indirect FXa inhibitors.

At the time of the Action Due Date, several deficiencies still had not been sufficiently addressed; specifically, qualification of the Reference Standard and development and validation of a (b) (4) assay to measure the inhibition of endogenous TFPI by ANDEXXA. A CR letter was issued on 17 August 2016. Portola submitted a response to the CR letter on 4 August 2017 as Amendment 76.

Documents submitted:

This is an electronic submission. Documents submitted and reviewed include:

-125586/0.76 – 1.2 Cover Letters

- Cover Letter 20170803 - Complete Response to Complete Response Letter
- Reviewer's Guide

-125586/0.76 – 3.2.S.5 Reference Standards or Materials

- 3.2.S.5 Reference Standard or Materials
- TP.002/o: Protocol for the Qualification of ANDEXXA Working Reference Standards
- TR.014 / o: Protocol for the Qualification of ANDEXXA Primary Reference Standard RM-K-0030

-125586/0.76 – 3.2.P.5.1 Specifications

-125586/0.76 - 3.2.P.5.2 Analytical Procedures

- 3.2.P.5.2.17: (b) (4) by TFPI Inhibition

-125586/0.76 – 3.2.P.5.3 Validation of Analytical Proc.

- 3.2.P.5.3.1.11 (b) (4) by TFPI Inhibition

-125586/0.76 – 3.2.R Regional Information

- 3.2.R.2 MVR-0013, TME-0632 (b) (4) – (b) (4) TFPI Inhibition Assay Validation Report

-125586/0.78 – 1.11 Information Amendment: Information Not Covered Under Modules 2 to 5

- 1.11.1 Quality Information Amendment

-125586/0.78 – 3.2.S.4.2 Analytical Procedures

- TME-0632: (b) (4) – (b) (4) TFPI Inhibition Assay

-125586/0.86 – 1.11.1 Quality Information Amendment

- 1.11.1 Quality Information Amendment – DBSQC Information Request (received 02 November 2017)

1. Qualification of Reference Standard for the Direct and Indirect Potency Assays

The Direct and Indirect Potency assays are (b) (4) assays which measure the ability of ANDEXXA to reverse the inhibition of FXa by the direct inhibitor, (b) (4), or the indirect inhibitor, enoxaparin. The assays were validated adequately and an in-

house reference standard was developed; however, insufficient information was provided as to how the standard was qualified. A CR letter, including a request for information on qualification of the Reference Standard, was submitted to the sponsor on 17 August 2016. A response to the CR letter was received on 4 August 2017 as Amendment 76. The IR, the response of the sponsor and the review of the response are discussed below:

Question 3:

In reference to our IR about ANDEXXA potency standards dated 12 February 2016 and your 22 February, 20 April, 18 May, 06 June, 21 June, 27 June, 06 July, 08 July, 13 July and 29 July 2016 responses which are incomplete, please note that a Primary Reference Standard (PRS) is required to control and preserve the existing and new unitages of the potency of ANDEXXA. A secondary standard is needed for routine control of the manufacturing process and control of product quality. The PRS is critical in maintaining a consistent potency unit and allows "like vs like" comparisons when changes are made in assay reagents or methodologies, and manufacturing process. To demonstrate control over potency unitage, please:

- a. Provide your reference standard qualification protocol for review.

Review of Response: The sponsor provided protocol TR.014/O, Protocol for the Qualification of ANDEXXA PRS RM-K-0030, and protocol TP.002/O, Protocol for the Qualification of ANDEXXA Working Reference Standards, as well as a detailed description of the PRS development in Section 3.2.S.5. Review of the protocols and report demonstrated that the qualification of the standards was conducted as described in the protocols. This is adequate.

- b. Qualify and establish one lot of ANDEXXA as the Primary Reference Standard and ensure that your Working Reference Standards are qualified against this Primary standard over the product life-cycle. Your Primary reference standard should be established in such a way as to link to your clinical and safety outcomes as a surrogate. In addition, you should perform adequate number of replicate analyses to qualify reference standards so that the potency can be assigned with sufficient statistical power.

Review of Response: In the report in section 3.2.S.5, Reference Standards or Materials, the sponsor provided information on development of the PRS, how it was to be qualified against the International Standard, and the establishment of potency units in Units/mg. (b) (4) replicate measurements each of the PRS and Working Reference Standards (WRS) were performed to establish their potencies, allowing the potency to be assigned with sufficient statistical power. This is acceptable. A detailed review of the qualification report of the reference standard is included below.

- c. Qualify the reference standards independently for both the Direct and the Indirect potency assays.

Review of Response: The sponsor indicated that the PRS and WRS used for the Direct and Indirect potency assays were qualified for use in both assays independently. However, since there is no International Standard for TFPI, it was not possible to qualify the (b) (4) of the PRS and WRS using the (b) (4) TFPI inhibition assay test. Hence, the potency value of the PRS in the Direct Potency assay is assigned for the (b) (4) TFPI inhibition assay. This is acceptable.

Qualification of Reference Standard

In response to the CR letter, the sponsor provided details on the production of a PRS, the qualification of this standard against the International Standard for the Direct and Indirect Potency assays, the assigning of potency units relative to the potency of the International Standard, and qualification of a WRS, in Amendment 76.

In 3.2.S.5, Reference Standard Materials, the sponsor reported how a PRS lot had been produced using the current drug substance manufacturing process, (b) (4), and defined the potency units for the Direct and Indirect potency assays. As detailed in Table 3.2.S.5.-1, for the Direct Potency assay, the potency units are defined as: (b) (4)

(b) (4). The potency units for the Indirect potency assay are defined as: (b) (4)

(b) (4). The PRS was qualified in the Direct Potency assay by replacing human FXa with (b) (4) FXa from (b) (4), which had been qualified against the (b) (4) FXa (b) (4). The PRS for the Indirect Potency assay was qualified by substituting the human FXa with the (b) (4) FXa from (b) (4), and the (b) (4), for the indirect inhibitor enoxaparin, a low molecular weight heparin.

Since there is no WHO IS for TFPI, the potency value assigned for the Direct Potency assay was also assigned for the (b) (4) TFPI inhibition assay.

(b) (4) replicates of the PRS were measured against the (b) (4) FXa for the Direct Potency assay and (b) (4) FXa and the (b) (4) in the Indirect Potency assay. The relative potency of the PRS to the IS was (b) (4) in the Direct Potency assay and (b) (4) in the Indirect Potency assay. The EC₅₀ ((b) (4)), the effective concentration at 50% inhibition point in the dose-response curve, and the concentration of each component in the assay was used to calculate the potency of the PRS in the Direct Potency and Indirect Potency assays. Thus:

One Direct Potency unit = (b) (4)

One Indirect Potency unit = (b) (4)

From this, the (b) (4) was calculated:

(b) (4)

The potency value of the PRS, (b) (4), in the Direct Potency assay and the (b) (4) TFPI inhibition assay is (b) (4), while the potency value in the Indirect Potency assay is (b) (4). It was not apparent how the equations were derived based on the definition of the potency units. An IR was sent to the sponsor for clarification (see IR i. below).

(b) (4) WRS were developed, (b) (4) manufacturing process, and (b) (4) manufacturing process. (b) (4) of the WRS were consumed, leaving (b) (4) WRS remaining, (b) (4) for future use. To link the potency of the current PRS to previous reference standards, (b) (4) measurements of the percentage relative potency of each WRS relative to the PRS were performed and the potency of the WRS in (b) (4) calculated using the following equation:

WRS Potency ((b) (4)) = (b) (4)

In the Direct Potency assay, (b) (4). In the Indirect Potency assay, (b) (4)

. This demonstrates that there was no shift in potency of the reference standards over the course of the drug development. The PRS was examined using all lot-release specific tests to ensure the PRS gave results which are within the acceptance criteria.

In addition to assigning the potency values for the Direct Potency, Indirect Potency and (b) (4) TFPI Inhibition assays to the WRS, lot-release testing was performed on the WRS and the results evaluated to ensure that they are within the acceptance criteria for all of the tests.

The proposed specifications were updated in section 3.2.P.5.1 to include the (b) (4)

(b) (4) for each test as well as the specifications for the (b) (4) TFPI Inhibition assay. The proposed specifications for the Direct Potency assay are:

(b) (4). The proposed

specifications for the Indirect Potency assay are: (b) (4)

First Information Request and Review

The following IR was submitted to the sponsor on 29 March 2018. The response was received on 6 April 2018 as Amendment 118. The IR question, the response of the sponsor and review of the response are discussed below:

- i. We have reviewed your response to the CR letter submitted as STN 125586/o.76, and received on 4 August 2017 in, and have the following Information Requests for your Direct and Indirect Potency assays.

In 3.2.S.5, you provided the following equations:

(a) One Direct Potency unit = (b) (4)

(b) One Indirect Potency unit = (b) (4)

, and

(c) (b) (4)

We could not understand how you arrived at these equations based on the definitions of potency units for the Direct and Indirect Potency assays: for the Direct Potency assay “One direct potency unit of ANDEXXA activity is (b) (4)

” and for the Indirect Potency assay “One indirect potency unit of ANDEXXA is (b) (4)

Please provide detailed step by step explanations how you derived equations (a), (b) and (c), and provide one example each of the calculation of (b) (4) for the Direct and Indirect Potency assays based on your results.

Review of Response: The sponsor provided detailed explanations as to how the three equations were derived:

(a) For the derivation of the Direct Potency unit, (b) (4)

(b) For the derivation of the Indirect Potency unit, (b) (4)

(b) (4)
(b) (4)
(b) (4)
(b) (4).

(c) (b) (4)
(b) (4)

(b) (4) (b) (4)
(b) (4)

The (b) (4) for the Reference Standard in the Direct Potency assay was calculated as (b) (4), while in the Indirect Potency assay, it was calculated as (b) (4).

The sponsor has demonstrated that they have developed potency units for their Reference Standard which are traceable to an International Standard; FXa, for the Direct Potency assay and FXa and Low Molecular Weight Heparin, for the Indirect Potency assay. They have provided examples of how these calculations were performed and how the potency units were used to determine a (b) (4) value for the Reference Standard in the Direct and Indirect potency assays. This is adequate.

Conclusion

The protocols and results demonstrate that the PRS has been adequately qualified against the WHO IS, and that the WRS are adequately qualified relative to the PRS. The assigned potencies of the PRS and WRS may be used to assign potency of test sample measured for lot-release testing.

2. (b) (4) TFPI Inhibition Assay

ANDEXXA is a modified human FXa which has no coagulation activity but can bind to FXa inhibitors, such as (b) (4) and enoxaparin, with high affinity. ANDEXXA also inhibits the endogenous FXa inhibitor, TFPI, which reverses the inhibition of FVIIa-TF by TFPI. The sponsor had not developed an assay to measure the (b) (4) of ANDEXXA by inhibition of TFPI, nor validated the method. A CR letter, including a request to develop and validate a (b) (4) assay to measure the inhibition of TFPI activity by ANDEXXA, was issued to the sponsor on 17 August 2016. The response from the sponsor, received on 4 August 2017 as Amendment 76, and the review of the response are discussed below:

Question 2:

- e. In reference to our IR dated 01 June 2016 and your 15 June and 19 July 2016 responses which are incomplete, develop a (b) (4) assay and associated release

specifications to measure the inhibition of Tissue Factor Pathway Inhibitor (TFPI) activity by ANDEXXA FDP. Please base your assay for TFPI inhibition activity on (b) (4) used as a biomarker in Phase 3 clinical studies.

Review of Response: The sponsor provided a description of the (b) (4) TFPI Inhibition assay as well as a validation report. The specifications for the test were established using (b) (4) drug product lots. The review of these documents is provided below:

Review Narrative

This (b) (4) method measures the ability of ANDEXXA (b) (4) drug product to bind to TFPI, thus reversing the inhibition of Factor VIIa-Tissue Factor (FVIIa-TF) complex by TFPI. The proposed specification for the drug product are:

(b) (4)

██████████. The SOP was not provided in the response to the CR letter in amendment 76, and was requested in an IR (see IR 1.i. below).

Method

The (b) (4) TFPI inhibition assay measures the ability of ANDEXXA (b) (4) drug product to bind to endogenous TFPI to reverse the inhibition of FVIIa-TF complex by TFPI. The FVIIa-TF then activates FX to FXa, which is measured by (b) (4)

A horizontal bar chart consisting of 20 bars of varying lengths, all rendered in a solid gray color. The bars are arranged in a single column, with the longest bar in the middle and the shortest bars at the top and bottom. The lengths of the bars vary significantly, creating a dynamic visual pattern. The bars are separated by small gaps, and the overall layout is clean and minimalist.

(b) (4)

Method Validation

This is a quantitative method. The characteristics examined in the validation report were: (b) (4)

(b) (4) [Redacted]
[Redacted]

[Redacted]
[Redacted]
[Redacted]

[Redacted]
[Redacted]
[Redacted]
[Redacted]
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First Information Request and Review

The following IR was submitted to the sponsor on 6 September 2017. The response was received on 12 September 2017 as Amendment 78. The IR question, the response of the sponsor and review of the response are discussed below:

- 1.i. Please provide a representative copy of your SOP, TME-o632 (b) (4)–(b) (4) [Redacted]
TFPI Inhibition Assay

Review of Response: The sponsor provided the standard operating procedure. It was clearly written and contained sufficient details. This is adequate.

Second Information Request and Review

The following IRs were submitted to the sponsor on 1 November 2017. The response was received on 17 November 2017 as Amendment 86. The IR questions, the response of the sponsor and review of the responses are provided below:

- 2.i. Please explain why the composition of the (b) (4) described in Table 1 of the Validation Report, MVR-0013 differ from the composition of (b) (4) described in Table 3.2.P.2.2.1 of section 3.2.P.2.2 Drug Product?

Review of Response: The sponsor clarified that the (b) (4) used in the DP (b) (4) is the same as the (b) (4) used for the validation study. This (b) (4) is currently used to produce the (b) (4) the drug product, the results from which are included in the BLA. The (b) (4) used in the Generation 2 (b) (4), denoted as (b) (4) in the validation study, was used in the original IND 015089, for preparation of the (b) (4), and differs from (b) (4) in having a (b) (4). Since this (b) (4) is no longer used in the manufacture of ANDEXXA, (b) (4) is not relevant to this validation study and the results were removed from the table in section 3.2.P.5.3-6. Sufficient specificity data was provided relevant to drug product in formulation (b) (4). This response is therefore adequate.

- 2.ii. Please describe how the stressed test sample is prepared.

Review of Response: The sponsor stated that (b) (4) test samples were prepared by (b) (4). This is adequate.

- 2.iii. The (b) (4) test sample gave a mean relative potency of (b) (4), while the controls and test samples ranged from (b) (4). Since the relative potency of the stressed test sample are very similar to the control and test sample results, please explain how these results indicate the method may be used to indicate stability?

Review of Response: The sponsor stated that the (b) (4) used to make the (b) (4) test samples were (b) (4) to give a (b) (4) in (b) (4) in the TFPI inhibition assay. Alternatively, (b) (4) produced a (b) (4) in (b) (4) which was (b) (4) the drug product. The relative (b) (4), as measured by TFPI inhibition, had (b) (4) to (b) (4), indicating that the test was stability indicating. This is satisfactory.

Conclusion

The SOP and validation studies indicate that this method is suitable for use for lot-release testing.