

From: Maruna, Thomas
Sent: Friday, May 13, 2016 11:17 AM
To: 'Janice Castillo'
Cc: Faulcon, Lisa
Subject: 13-May-2016 Information Request - BLA 125586.0 - Response
Required
by 27-May-2016

Importance: High

Portola Pharmaceuticals Inc.
Attention: Ms. Janice Castillo
May 13, 2016
Sent by email

Dear Ms. Castillo:

We are reviewing your December 17, 2015 biologics license application (BLA) for the following:

STN	Name of Biological Products
125586/0 Inactivated	Coagulation Factor Xa (Recombinant),

We have determined that the following information is necessary to continue our review:

GIB

We have the following request for information based on the review of subjects who experienced Gastrointestinal Bleeding (GIB) in study 14-505 (ongoing ANNEXA-4 study)

In your response to the items below, please reference the data that is used to provide the response or supporting justification. If the data you reference are available in the Case Report Form (CRF), please document the specific CRF page or form that is being referenced. If the referenced data is not included in the CRF, please provide source documents with reference to the page or location of the data within the source document.

For the majority of these comments below, we are requesting additional justification or information to understand the adjudication process. During our review of the adjudication forms both for study entry and efficacy assessment, it appears that some adjudicators utilize multiple parameters for decision making and in other instances, adjudicators seem to rely on a one to two

parameters. In the comments below, we have provided detailed reports of some or all of the parameters from the CRFs that are generally considered to be relevant to assessment of overt bleeding or major bleeding (for example bleeding at the site, transfusion, hemoglobin parameters pre-baseline and screening, etc.) and hemostasis to better understand your perspective as whether these parameters were incorporated in the adjudication process.

1. Subject ID (b) (6): This subject had baseline anti-fXa levels of 227.8 ng/ml, experienced bright red bleeding per rectum (PR) without hemodynamic compromise (3 hours pre-bolus Blood pressure (BP): 115/66 Heart Rate (HR): 90, 15 minutes (min) prior to infusion: BP 122/76 HR: 79), and hemoglobin (Hb) > 8g/dL, without a >2g/dL drop in Hb. The subject had a prior history of stroke and the "mental confusion" noted at study entry was attributed to prior stroke by one adjudicator. Two of five adjudicators considered this subject ineligible for study entry, yet 3/5 adjudicators felt that the subject had life-threatening bleeding.

a. Please justify why this subject is considered to have acute major or life-threatening bleeding given the hemodynamic stability and baseline hemoglobin levels.

b. The subject had a screening endoscopy 30 minutes prior to the bolus and a GI bleed scan 1 hour post-infusion. Please provide the endoscopy report.

2. Subject ID (b) (6): Please provide the report of the procedure performed on (b) (6) at 15:00 hours (approximately 10 hours post-infusion).

3. Subject ID (b) (6):

a. Regarding study entry: Hb dropped from 13.3 to 8.2 g/dL over 11 days prior to study entry, at 3 hours prior to bolus (of andexanet) the BP was 91/56 and HR 87, 15 minutes before the bolus the BP was 104/68 and HR 86, and at 12 hours post-infusion BP was 87/63 and HR 92. Based on these observations Please justify why this subject met the entry criteria for acute major/life threatening bleeding based on hemoglobin, stable BP parameters and lack of other symptoms of acute bleeding.

b. Regarding hemostasis assessment

Melena noted at screening was not present at pre-bolus or thereafter.

Shortness of

breath was the only "other sign" of bleeding noted at 4 hours post-infusion, but

was not noted thereafter. Please explain how the attribution of the efficacy

adjudicated as "Good" is attributable to andexanet given that melena was absent

pre-bolus and during the entire 12 hour post-infusion observation period.

c. Please also provide a report of the colonoscopy and endoscopy performed on the

2nd day following the andexanet infusion.

4. Subject ID (b) (6): Subject had baseline Hb value of 13.5 g/dL, which was unchanged

from the pre-baseline Hb value of 12.7 g/dL which was done 5 days prior, stable (BP 3

hours pre-bolus was 85/59 HR 68, 12 hour post-infusion BP was 81/42 and HR 63) albeit

low BP possibly accounted for by the subject's low Ejection Fraction, over the pre-bolus

and the 12 hour evaluation period. No PRBCs were infused and 12 hours post-infusion

the Hb was 12.6 g/dL (with crystalloid/colloid administration). Based on these

observations, please justify how this subject met the study entry for acute life threatening

or major bleeding.

5. Subject ID (b) (6): The subject presented with hematemesis, but no hematemesis was

present at pre bolus through the 12 hour observation period. Please justify why the

hemostasis is attributable to study treatment.

6. Subject ID (b) (6) Please provide the report of the procedure performed on (b) (6),

approximately 14 hours post-infusion.

7. Subject ID (b) (6): The "8 hour assessment CRF" notes that a procedure was

performed. However, CRF form #049 does not report the procedure performed in this

CRF, but documents a procedure approximately 15 hours post-infusion, an IVC filter

placement 2 days following the infusion, and a liver biopsy 3 days following the infusion

Please provide a report of the procedures performed at 8 hours and 15 hours post-

infusion to clarify the discrepancy noted in the 8 hour assessment and the 15 hour post

infusion records.

8. Subject ID (b) (6) :

a. Subject met entry criteria based on Hb <5.5 g/dL and shortness of breath without documentation of bleeding or hemodynamic compromise. Based on these observations please explain why the subject met the criteria for acute major/life threatening GI bleeding.

b. Please provide copies of the endoscopy and colonoscopy reports for the procedures performed on (b) (6) (16 hrs post-infusion) and (b) (6) respectively.

9. Subject ID (b) (6) :

a. Subject met entry criteria based on an observation of Upper GI bleed and hemodynamic compromise (based solely on BP of 101/56 and cold clammy skin). The subject did not qualify for study entry based on Hb of 11.6 g/dL at baseline (pre-baseline Hb before 12 days prior was 12.1), however study entry was based on the opinion of the investigator that the Hb would have fallen to <8g/dL. Based on these observed pre-baseline and baseline Hb values and the clinical status of the subject, please justify how it was predicted that the subject would experience a drop of in Hb of >2g/dL.

b. Subject received 1 unit PRBC 1.5 hours prior to bolus. Please provide Hb parameters that triggered the PRBC transfusion on (b) (6) at 00:22 hours.

c. Microscopic hematuria was noted at screening and at 8 hours. Was a follow up urinalysis obtained at 12 hours?

d. Please provide the report of the CT scans performed at screening.

10. Subject ID (b) (6) :

a. Please provide the Hb levels that resulted in the PRBC transfusion on (b) (6) at 18:00 hrs.

b. Please provide the reports of the Abdominal CT scan performed at screening and the Ultrasound performed on (b) (6) at 9:23 hrs.

c. The CRF, form #120, describes gastric bleeding, however CRF #042 reports melena per rectum at screening. Please explain the discrepancy.

d. Please justify the attribution of hemostasis to the study product given that no melena or gastric bleeding were noted pre-bolus through the 12 hour evaluation period.

ICH

We have the following request for information to further evaluate the clinical significance of the post-baseline PR and QTc prolongation that were observed in the phase 3 trials of andexanet (study 14-503 and 14-504):

1. Since common mechanisms underlying PR prolongation include calcium channel-blockade and increase in vagal tone, we request that you explore whether there are other findings to suggest calcium channel blockade (e.g., bradycardia, constipation, worsened reflux) or vagal tone (e.g., bradycardia). Please submit your results of these analyses.

2. For both QTc and PR effects, we request that you explore the placebo-subtracted mean change from baseline ("double delta") at the time of maximal exposure to andexanet (and any relevant metabolites). Please submit your results of these analyses.

To further evaluate if andexanet has a clinically significant effect on PR or QT intervals, please:

3. Revise the protocol of study 14-505 (ongoing ANNEXA-4 study) to include cardiac monitoring using standard 12-lead ECG at pre-specified time-points and specify whether the ECG will be read locally by the Investigator.

The following request for information is based on the review of subjects who experienced intracranial hemorrhage (ICH) and retroperitoneal bleeding in the ongoing ANNEXA-4 study. In your response to the items below, please reference the data that is used to provide the response or supporting justification. If the data you reference are available in the Case Report Form (CRF), please document the specific CRF page or form that is being referenced. If the referenced data is

not included in the CRF, please provide source documents with reference to the page or location of the data within the source document. For the majority of these comments below, we are requesting additional justification or information to understand the adjudication process.

4. Regarding the efficacy rating scale for ICH:

a. Please revise the definition for the category of "good" hemostatic efficacy to specify a requirement of "no plasma or blood products (excluding PRBCs) and/or coagulation factor products required through 12 hours after initial treatment with Andexanet." This revised rating definition reduces any confounding in the efficacy assessment.

b. Please revise the definitions of each rating to include assessments in changes in clinical status using either the Glasgow Coma Scale and/or modified Rankin score.

5. Clarify your adjudication methods and procedures. Page 6/39 of the Endpoint Adjudication Committee (EAC) Charter states: "Cases after the first 5-10 will be assessed by two adjudicators. If the two adjudicators agree there will be no further review of the case and the case is considered complete and the result entered in the database. If the adjudicators disagree, the case will be reviewed by a convened Committee at the next meeting and decided by consensus (or by majority vote if consensus cannot be achieved after all reasonable efforts). This process will be used for adjudication of eligibility, hemostatic efficacy, thrombotic events and all deaths."

a. Explain why three adjudicators were used to determine which subjects met the entry criteria and for the adjudication of hemostatic efficacy.

b. It is unclear from the documentation submitted how disagreements in adjudication were resolved. For example, for cases where there is disagreement regarding whether they met the entry criteria (e.g., (b) (6)) or achieved hemostatic efficacy (e.g., (b) (6)) there is no documentation that the case was reviewed by a convened Committee.

6. For subject (b) (6) :

a. Page 33/83 of the patient narratives states that the subject was noted to have a subdural hematoma (SDH) and mild subarachnoid hemorrhage (SAH). However, baseline and follow-up CT scans and comments from the adjudicators only mention the SDH. Please clarify the discrepancy.

b. The subject began their infusion of andexanet prior to receiving a baseline

CT. Clarify why this bleeding event was considered evaluable and how a rating

of excellent was given in the absence of a baseline CT.

c. One adjudicator references an "outside" hospital's CT scan from 10 hours earlier

that showed no change in subdural hematoma size compared to the one hour post

bolus CT, suggesting the subdural was not actively bleeding at time of enrollment.

Please clarify if the CT findings from the "outside" hospital were made available

to all adjudicators.

d. Please comment on the follow-up status of the subject's mental confusion that

was described at the time of study enrollment.

e. A repeat CT was done at 14:51 on (b) (6) (25 minutes after the 12 hour

CT scan) which showed an increase in the volume and thickness from a volume of

18.72 cc to 29.25 cc and a thickness of 1.22 mm to 12 mm. Please confirm the

timing and recorded dimension. Please also provide an explanation for the

additional CT scan and reported findings.

f. Please clarify if the patient was re-anticoagulated post-treatment.

7. For subject (b) (6) :

a. Page 41/83 states that the andexanet infusion was completed on (b) (6) at

1:50 AM. However, the follow-up CT was done at 15:58 of the same day.

Please

clarify how a rating of excellent was determined in the absence of both a 1- and

12-hour post-infusion assessment.

b. Page 42/83 states that on study day 2 the subject experienced "moderate

worsening of neurological status." Please specify the specific time frame of the change in status with regard to the completion of the andexanet infusion.

8. For subject (b) (6), the final adjudication rating was poor/none; however, 2 out of the 3 adjudicators gave ratings of excellent. Please clarify the discrepancy.

9. For subject (b) (6), the scan done at 11 am on (b) (6) shows a significant increase in thickness from 12.44 mm to 37.02 mm 2 hours and 40 minutes following the prior CT evaluation. A follow-up CT 2 hours later shows reduced thickness to 11.5 mm. Please confirm the timing and recorded dimension of each of the aforementioned CT reports.

10. For subject (b) (6) :

a. Please clarify what symptoms were used to justify the inclusion of this subject under the "acute symptomatic bleeding" entry criterion and where the reviewer can find the documentation.

b. One adjudicator noted a discrepancy between the (b) (4) volumetric report of increased size and the radiology interpretation of stable for the end of the infusion CT scan. Please clarify how the (b) (4) analysis is weighed against radiology interpretation.

11. For Subject (b) (6) :

a. The patient profile documents two platelet transfusions within 3 hours of completing the andexanet infusion; however, the hemostatic efficacy for this bleeding event was "excellent." The platelet contribution to the hemostatic process confounds the assessment of efficacy in this case. Please see our comment 4a above for our request on how to revise the rating scale. Please consider excluding these subjects from the efficacy analysis. Please also state why the subject received the platelet transfusions.

b. The baseline CT scan reports both ICH and IVH (total hemorrhage 58.66); however not all of the adjudicators reference this higher volume. Furthermore, the patient narrative does not discuss the additional report of ICH. Please clarify.

12. For subject (b) (6)

a. Provide the reports from the first CT and clarify why that CT was not considered the baseline CT.

b. Clarify how the interim development of IVH was considered during the adjudication process.

13. For subject (b) (6), the Patient Scoring Forms report a rating of "Good" from two adjudicators and one rating of "Non-evaluable". However, the reported adjudicated outcome was "Poor/None." Please clarify the discrepancy.

14. For subject (b) (6):
The patient narrative states that the subject received "1 unit PRBCs before and 1 unit PRBCs and normal saline after the infusion." However, the patient summary lists transfusions on Study Day 1, 2 and 3. Please clarify the discrepancy.

a. There is no reported hemoglobin/hematocrit measurement at the 12 hour assessment; however, the reported adjudicated outcome was "Excellent." Please clarify how an assessment of excellent was made without a 12 hour measurement.

The review of this submission is on-going and issues may be added, expanded upon, or modified as we continue to review this submission.

You are required to submit your responses as an amendment to this file by close-of-business, Friday, May 27, 2016.

The action due date for these files is August 17, 2016.

If you have any questions, please contact me.

Respectfully,

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