

From: Thompson, Edward
Sent: Tuesday, June 09, 2015 1:41 PM
To: 'Kevin Darryl (KD) White (Kevin.White@cslbehring.com)'
Cc: Monica.Richardson@cslbehring.com
Subject: Information Request for BL 125582/0

Contacts: Kevin Darryl (KD) White - CSL Behring

Dear Mr. White:

We are reviewing your December 5, 2014 biologics license application (BLA) for Coagulation Factor IX (Recombinant), Albumin Fusion Protein. We are providing the following comments and request for additional information to continue our review:

Study 3003 subject (b) (6)

The (interim) clinical study report states:

(p. 176) The estimated actual blood loss was 50 mL, which was within the range predicted by the Investigator/surgeon (30 to 100 mL), with no additional hemostatic interventions as planned. The actual transfusion requirement of 280 mL of packed red blood cells was less than the predicted value of 500 mL prior to surgery.

(p. 177) Following surgery, no surgical wound hematomas were observed, no surgical evacuation was required, and no postoperative bleeding through surgical drains or late rebleeding episodes were detected within 72 hours.

The subject's vital signs and hematology were monitored before, during, and after the surgery. There were no clinically significant abnormal values. Preoperatively and intraoperatively, the subject's hemoglobin was low, but not considered clinically significant by the Investigator; values were within normal range by the end of the surgery substudy

1. There are inconsistencies in these statements. The statements: "actual blood loss was 50 mL"; "no postoperative bleeding through surgical drains or late rebleeding episodes were detected within 72 hours", and "Preoperatively and intraoperatively, the subject's hemoglobin was low, but not considered clinically significant by the Investigator" all indicate intraoperative and postoperative bleeding that was limited to 50 ml and an amount of blood loss that did not require intervention. These statements are not consistent with the reported transfusion of 280 ml PRBC. Please review this report and provide additional information that may reconcile the discrepancy between the reported blood loss and PRBC transfusion.

In your laboratory dataset titled (b) (4), analysis values for urine protein are reported as trace, positive, negative, or given a numerical value. Your response to our May 26 information request indicates that urinalysis was performed by the local laboratory and that local laboratory results

were recorded in the eCRF. Hence, as we understand, you aren't reporting the results in a standardized fashion in your dataset.

2. Your dataset contains the information shown below for Subject (b) (6) (i.e., a negative screening value for urine protein and positive values at weeks 12, 28 and EOS). In your response, you state that the subject had "...fluctuations in urine protein as measured by urine dipstick. Positive trace urine protein (document range: positive or negative) was measured at Week 12, 28 and EoS ..." We are trying to reconcile the information in your dataset with the information provided in your response. Please clarify your use of the terms "trace", since all results were "positive" and "fluctuations", when this subject's results during the study were invariant.

Unique Subject Identifier (C)	Analysis Visit	Analysis Value
CSL654_3001-(b) (6)	SCR	Negative
CSL654_3001-(b) (6)	WK12	Positive
CSL654_3001-(b) (6)	WK28	Positive
CSL654_3001-(b) (6)	EOS	Positive



125821_001...

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

Please submit your response to this information request as an amendment to this file by June 17, 2015 referencing the date of this request. If you anticipate you will not be able to respond by this date, please contact the Agency immediately so a new response date can be identified.

If we determine that your response to this information request constitutes a major amendment, we will notify you in writing.

The action due date for this file is December 5, 2015.

Please send an acknowledgement for receipt of this request.

If you have any questions, please contact me at (240) 402-8443.

Sincerely,
Edward Thompson
Regulatory Project Manager
FDA/CBER/OBRR/RPMS



Our Reference: BL 125582/0

CSL Behring Recombinant Facility AG
Attention: Mr. Kevin D White
June 9, 2015
Sent by email

Dear Mr. White:

We are reviewing your December 5, 2014 biologics license application (BLA) for Coagulation Factor IX (Recombinant), Albumin Fusion Protein. We are providing the following comments and request for additional information to continue our review:

Study 3003 subject (b) (6)

The (interim) clinical study report states:

(p. 176) The estimated actual blood loss was 50 mL, which was within the range predicted by the Investigator/surgeon (30 to 100 mL), with no additional hemostatic interventions as planned. The actual transfusion requirement of 280 mL of packed red blood cells was less than the predicted value of 500 mL prior to surgery.

(p. 177) Following surgery, no surgical wound hematomas were observed, no surgical evacuation was required, and no postoperative bleeding through surgical drains or late rebleeding episodes were detected within 72 hours.

The subject's vital signs and hematology were monitored before, during, and after the surgery. There were no clinically significant abnormal values. Preoperatively and intraoperatively, the subject's hemoglobin was low, but not considered clinically significant by the Investigator; values were within normal range by the end of the surgery substudy

1. There are inconsistencies in these statements. The statements: "actual blood loss was 50 mL"; "no postoperative bleeding through surgical drains or late rebleeding episodes were detected within 72 hours", and "Preoperatively and intraoperatively, the subject's hemoglobin was low, but not considered clinically significant by the Investigator" all indicate intraoperative and postoperative bleeding that was limited to 50 ml and an amount of blood loss that did not require intervention. These statements are not consistent with the reported transfusion of 280 ml PRBC. Please review this report and provide additional information that may reconcile the discrepancy between the reported blood loss and PRBC transfusion.

In your laboratory dataset titled (b) (4), analysis values for urine protein are reported as trace, positive, negative, or given a numerical value. Your response to our May 26 information request indicates that urinalysis was performed by the local laboratory and that local laboratory results were recorded in the eCRF. Hence, as we understand, you aren't reporting the results in a standardized fashion in your dataset.

2. Your dataset contains the information shown below for Subject (b) (6) (i.e., a negative screening value for urine protein and positive values at weeks 12, 28 and EOS). In your response, you state that the subject had "...fluctuations in urine protein as measured by urine dipstick. Positive trace urine protein (document range: positive or negative) was measured at Week 12, 28 and EoS ..." We are trying to reconcile the information in your dataset with the information provided in your response. Please clarify your use of the terms "trace", since all results were "positive" and "fluctuations", when this subject's results during the study were invariant.

Unique Subject Identifier (C)	Analysis Visit	Analysis Value
CSL654_3001-(b) (6)	SCR	Negative
CSL654_3001-(b) (6)	WK12	Positive
CSL654_3001-(b) (6)	WK28	Positive
CSL654_3001-(b) (6)	EOS	Positive

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

Please submit your response to this information request as an amendment to this file by June 17, 2015 referencing the date of this request. If you anticipate you will not be able to respond by this date, please contact the Agency immediately so a new response date can be identified.

If we determine that your response to this information request constitutes a major amendment, we will notify you in writing.

The action due date for this file is December 5, 2015.

Please send an acknowledgement for receipt of this request.

If you have any questions, please contact me at (240) 402-8443.

Sincerely,
Edward Thompson
Regulatory Project Manager
FDA/CBER/OBRR/RPMS