

**From:** Thompson, Edward  
**Sent:** Wednesday, April 08, 2015 3:39 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 determined that the following information is necessary to continue our review:

CSL654 3001 Clinical Study Report (CSR)

1. Please reference pages 149 (and p. 120) please clarify the term, prespecified success criterion, in the sentences: Of these, 353 bleeding episodes (98.6%) [95% CI 96.2% to 99.5%] were treated successfully with 1 or 2 infusions. The lower bound of this 95% CI exceeds the prespecified success criterion.

2. Please reference page 120:

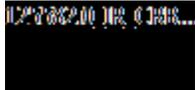
A total 358 bleeding episodes required treatment. Of these, 353 bleeding episodes (98.6%) [95% CI 96.2% to 99.5%] were treated successfully with 1 or 2 infusions (Table 11–15). The lower bound of this 95% CI exceeds the prespecified success criterion.

3. If the term, prespecified success criterion, refers to the statement on p. 58:

To be considered clinically relevant, one would expect to observe that 85% of bleeding episodes were treated with 1 or 2 infusions (Windyga et al., 2013). As an acceptance criterion, the lower limit of the 2-sided CI should exceed 80%, and to similar statements in the Clinical Study Protocol (p. 90), then please cite specific data from this reference which support this statement. If there is another source for the “prespecified success criterion”, then please provide it.

4. Please provide the location in the BLA of:

- a. Statements that the IRBs met requirements in 21 CFR 312.3
- b. Summaries of IRBs’ decisions to approve or modify the trials.
- c. Country or institution specific compensation information (costs as a direct result of participation or payment for participation in PK studies) for subjects.
- d. Reports of audit findings for data integrity



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 April 13, 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/CPMS

\

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone and return it to us at the above address by mail. Thank you.



Our Reference: 125582/0

CSL Behring Recombinant Facility AG  
Attention: Mr. Kevin D White  
April 8, 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 determined that the following information is necessary to continue our review:

CSL654 3001 Clinical Study Report (CSR)

1. Please reference pages 149 (and p. 120) please clarify the term, prespecified success criterion, in the sentences: Of these, 353 bleeding episodes (98.6%) [95% CI 96.2% to 99.5%] were treated successfully with 1 or 2 infusions. The lower bound of this 95% CI exceeds the prespecified success criterion.
2. Please reference page 120:  
A total 358 bleeding episodes required treatment. Of these, 353 bleeding episodes (98.6%) [95% CI 96.2% to 99.5%] were treated successfully with 1 or 2 infusions (Table 11–15). The lower bound of this 95% CI exceeds the prespecified success criterion.
3. If the term, prespecified success criterion, refers to the statement on p. 58:  
  
To be considered clinically relevant, one would expect to observe that 85% of bleeding episodes were treated with 1 or 2 infusions (Windyga et al., 2013). As an acceptance criterion, the lower limit of the 2-sided CI should exceed 80%, and to similar statements in the Clinical Study Protocol (p. 90), then please cite specific data from this reference which support this statement. If there is another source for the “prespecified success criterion”, then please provide it.
4. Please provide the location in the BLA of:
  - a. Statements that the IRBs met requirements in 21 CFR 312.3
  - b. Summaries of IRBs’ decisions to approve or modify the trials.

- c. Country or institution specific compensation information (costs as a direct result of participation or payment for participation in PK studies) for subjects.
- d. Reports of audit findings for data integrity

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 April 13, 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

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail.

Thank you.