

From: Thompson, Edward
Sent: Monday, June 10, 2013 7:51 AM
To: 'Jennifer Spinella (jspinella@raretx.com)'
Cc: Lin, Xue (Mary); Kennedy, Michael
Subject: Information Request for BL 125488/0

Contacts: Jennifer Spinella

Dear Ms. Spinella:

We are reviewing your March 16, 2013 biologics license application (BLA) for Crotalidae (pit viper) Immune F(ab')₂ (Equine) Injection. We are providing the following comments and request for additional information to continue our review:

1. Patients who were randomized and received study treatment but did not have any follow-up data were excluded from your "ITT" analysis. These patients should be included in the ITT analysis. Please use the multiple imputation method to impute the missing values for those patients as the primary ITT analysis and conduct several sensitivity analyses to assess the robustness of the study results due to missing data handling.
2. We noticed that your study has high proportion of missing data. Out of the 121 subjects who were randomized and received study treatment, 8 subjects did not have any Fibrinogen or platelet measurement data on either Day 5 or Day 8 and 11 subjects had at least one measurement missing. This amounts to missing data (complete missing or partial missing) in about 16% of all subjects. The missing data issue is especially prominent in the Anavip/Anavip and CroFab/CroFab groups, as each had about 20% of subjects with missing data. Please investigate and address why the proportion of missing data is so high in the Anavip/Anavip and CroFab/CroFab groups.

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 21, 2013 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 March 18, 2014.

Please send an email message acknowledging receipt of this request.

If you have any questions, please contact me at (301) 827-9167.

Sincerely,

Edward Thompson
Regulatory Project Manager
FDA/CBER/OBRR/DBA/RPMB

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