



Teleconference Memo

From: Pratibha Rana, MS, Regulatory Project Manager, RPMS/OBRR

RE: STN 125574/0, Antihemophilic Factor (Recombinant)

Through: Megha Kaushal, MD, Medical Officer, DHCR, OBRR

Date of teleconference: March 2, 2015

FDA Attendees:

Megha Kaushal, Bindu George, Natalya Ananyeva, Howard Chazin, Deepa Arya, Marthe Bryant, Christopher Jankosky, Craig Zinderman, Pratibha Rana

Bayer Attendees:

Olubunmi Afonja, MD, Director, Medical Affairs, Hematology
Vicki Chen, MS, Associate Director, Global Regulatory Affairs - Hematology
Chi Li, PhD, MBA, Senior Director, Head of Hematology Group, Global Regulatory Affairs
Monika Maas Enriquez, MD, Global Clinical Leader, Global Clinical Development
Lisa Michaels, MD, Vice President, Head of Hematology, Global Clinical Development
Gerhard Schlueter, PhD, Vice President, Head of Specialty Medicine, Global Regulatory Affairs

Background:

In response to the information request sent on February 29, 2016, the sponsor requested a teleconference regarding the FDA's comment on inhibitor information of previously untreated patients (PUPs).

The applicant also provided the following question:

In the labeling comments dated February 29, 2016, FDA stated "Based on discussion with our Office level, we recommend to include the 4-month Safety Update Report results of the ongoing PUPs study submitted 4/15/2015. Please include the rate of inhibitor development with the confidence intervals around the point estimates for the 14 subjects." Bayer would like to clearly understand and discuss the Agency's perspective on this recommendation during the teleconference scheduled for March 2, 2016.

Leopold Kids Part B study in PUPs is ongoing, and the number of subjects treated has increased to 18. As the study remains open to enrollment, the observed inhibitor rate continues to change over time. At this time, the incidence of clinical relevant inhibitors falls in the expected range, based on the small number of patients currently studied. Due to the small sample size, addition of only a small number of subjects is expected to change the observed inhibitor rate. Thus, a fair reflection of the safety of the product in the targeted patient population cannot be obtained until the study is completed. Until its completion, Bayer plans to continue updating the Agency about the study through PBRER and BLA annual report post-approval.

Bayer stated they have reviewed the US package insert (USPI) of the recently approved rFVIII drugs and none of the USPI's contains inhibitor related information from ongoing studies in PUPs. Bayer suggests that consistency should be applied across the rFVIII products in this regard.

We called the applicant and conveyed the following:

FDA emphasized the need to include the results of the ongoing PUPs study in the labeling, as this safety information should be known to the prescribing physician. FDA noted the applicant's information that 18 subjects were enrolled, however the duration of exposure for these subjects was limited and therefore could not be considered robust. Thus, FDA considers the information in the 4 month Safety Update Report with 14 enrolled subjects as sufficiently up to date for the purpose of safety. An agreement was made to include the inhibitor rate of 6/14 PUPs and to add the 95% confidence intervals to show the upper and lower bound with the small sample size. This information would be included in the Immunogenicity section of the label and provide a descriptive statement of those subjects with high and low titer inhibitors. In addition, the warnings section would also include a reference to this finding. FDA also recommended that the sponsor report the one subject (pediatric PTP) in Study 3 who developed a positive inhibitor titer.

The applicant agreed to add this information in the labeling and submit the revised PI to the BLA as an amendment for review.

END.