

From: Do, Yu  
Sent: Thursday, October 01, 2015 11:59 AM  
To: Erik.Bjornson@baxalta.com  
Cc: tung.koh@baxalta.com; Thompson, Edward  
Subject: Information Request: Protocol 261203, Response Due by THURSDAY, October 08, 2015 - Original BLA, BL 125566/0, Anti hemophilic Factor (Recombinant), PEGylated [ADYNOVATE]

Importance: High

Dear Mr. Bjornson:

We are reviewing your original November 25, 2014 submission to BLA 125566/0 for Anti hemophilic Factor (Recombinant), PEGylated. We are providing the following comments and request additional information to continue our review:

Protocol 261203

1. Please revise the inclusion criteria to specify that only subjects who develop a positive high titer inhibitor ( $\geq 5.00$  Bethesda Units [BU]) or those who develop a positive low titer inhibitor ( $\geq 0.60$  and  $< 5.00$  BU/mL) with poorly controlled bleeding despite increased BAX855 doses or requiring bypassing agents to treat bleeding with the product will be (b) (4).

2. Page 60, section 12.7.1 Immunogenicity, of the protocol states that "any positive titers should be confirmed with a second repeat sample." Please specify the time-frame for which the second sample must be drawn.

3. FDA acknowledges that there is no standardized protocol for (b) (4). However, we have the following comments about your plan to describe the (b) (4):

a. Please clarify if your intent (b) (4).

b. Please clarify (b) (4).

c. Please specify if (b) (4).

d. Per the US guidelines for (b) (4) in patients with hemophilia (b) (4), (b) (4).

Please clarify if (b) (4).

e. Please specify how (b) (4).

f. Please define the (b) (4).

(b) (4)

g. Please revise the definition of partial success to indicate that two of the following criteria must be met:

(b) (4)

h. Page 52, section 11.4 (b) (4) (Part B), states that (b) (4)

Please specify what criteria will be used to determine an adequate clinical response.

i. Please specify (b) (4)

j. Please specify a plan for how subjects will be (b) (4)

k. Please plan to conduct separate analyses of data from subjects dosed with the two dosing regimens of 50 IU/kg 3x weekly and (b) (4)

4. Page 65, section 13.3 Handling of Missing, Unused, and Spurious Data, states that "If the date of onset for an AE is missing completely then it will be imputed with the date of the first study drug ap." Please clarify the date that will be imputed.

The review of this submission is ongoing and issues may be added, expanded upon, or modified as we continue to review this submission. Please submit your response as an amendment to this file by October 08, 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 November 25, 2015.

Please acknowledge receipt of this request and contact me at (240) 402-8343 or Yu.Do@fda.hhs.gov if you have any questions.

Sincerely,

Yu Do, M.S.  
Regulatory Project Manager  
FDA/OMPT/CBER/OBRR/IOD/RPMS

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yu.do@fda.hhs.gov

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