

Valencia, Iliana

From: Valencia, Iliana
Sent: Monday, January 26, 2015 11:57 AM
To: Allison Kennedy (akennedy@ebsi.com)
Subject: STN125562 Anthrax Immune Globulin Intravenous (Human): Information Request (IR)

Our Reference: BL125562

Cangene Corporation
Attention: Allison Kennedy
January 26, 2015
Sent by EMAIL

Dear Ms. Kennedy:

We are reviewing your July 25, 2014 biologics license application (BLA) for Anthrax Immune Globulin Intravenous (Human). We request are requesting the following information:

1. Whether the protocol AX-003B would be exempt from IND regulations may require further discussion following submission of the full protocol.
2. Your proposal to submit the final protocol by October 2015, which is seven months following the action due date (ADD), is acceptable. However, we request you submit a draft protocol prior to the ADD.
3. Please provide the date by which you expect to submit the case report form (CRF) for this PMR.
4. Please revise your milestones for AX-003A such that you target data collection to be completed within 6 to 9 months of enrollment of the last patient in the study and final study report submission to FDA by 6 months following completion of data collection (12 to 15 months following enrollment of the final patient in the study). For study AX-003B, please revise your milestone for submission of the final study report to be within 9 to 10 years of final protocol approval, rather than 5 years.
5. Please include in the protocol for AX-003A plans for analysis of survival as well as major morbidity (organ system failure) by the size of the initial dose, by whether single or repeated doses were administered, and by total cumulative dose. Please conduct these same analyses for study AX-003B to the extent that the data permit such analyses.
6. We note that, in cases where it may be possible to collect data outside of the USA, you have indicated you will explore these situations as they arise. For PMR studies AX-003A and AX-003B please include overseas cases of administration of the product where feasible. Please modify the protocol accordingly.
7. If sufficient pediatric subjects are treated under this PMR, the protocols should include plans to analyze PK data for each pediatric age stratum, not just for the overall pediatric population.
8. Your proposal to use the secondary endpoint of time to death from symptom onset, with the analysis limited to patients who die despite therapy, in comparison to the historical control reference of 5.2 days from symptom onset until death to support the verification of clinical benefit is not acceptable in that this interval is not clearly related to clinical benefit. In addition, it is not clear how the relationship between mortality through day 14 and mortality through day 30 would relate to efficacy of AIGIV. You state that

it is not meaningful to compare the mortality rate in patients administered AIGIV to an historical control rate, due to missing data, including the known duration of follow-up. We agree that this is likely true for the pre-2001 cases, but we regard a comparison to the mortality rate among the 2001 U.S. inhalational anthrax attack cases to be appropriate and potentially informative, provided the demographics, time between onset of symptoms and initiation of treatment with (a) antibiotics and (b) AIGIV, and whether the above treatments are initiated in the prodromal stage or in the fulminant stage in the patients in the two datasets are examined and taken into account in the analysis. Please modify your analysis plan accordingly.

9. Please analyze primary and secondary endpoints by body weight (in addition to body mass index).
10. Regarding testing of patients pre- and post- AIGIV administration for lethal factor/lethal toxin, we understand that the assay using mass spectrometry developed at the CDC would be suitable in this regard. It is our understanding that universal precautions are deemed adequate for handling clinical specimens from anthrax-infected patients. Please see http://www.cdc.gov/anthrax/labs/recommended_specimen.html and <http://www.cdc.gov/anthrax/labs/cdcspecimens.html>.
11. For the secondary endpoint in AX-003A and AX-003B, incidence of serious suspected adverse reactions (SSARS), please combine this with the incidence of serious adverse reactions (SARs).
12. For studies AX-003A and AX-003B, please record the volume(s) and dates of pleural and ascitic fluid removal.
13. For studies AX-003A and AX-003B, you state you plan to collect the date of discharge from the ICU and/or hospital. Please collect both the date of discharge from the ICU as well as the date of hospital discharge.
14. We understand that you and the CDC do not currently have the hospital discharge dates for injectational anthrax cases patients (b) (6) Please endeavor to obtain the hospital discharge *status* of these patients. If these data cannot be obtained, FDA will consider the survival status of these patients unknown and the draft package insert will require revision accordingly

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

The action due date for this file is March 25, 2015.

Please submit a response as an amendment to the file by February 9, 2015.

If you have any questions, please contact me.

Sincerely,

Iliana Valencia, MS
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FDA/CBER/OBRR/IOD
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