FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Antimicrobial Drugs Advisory Committee (AMDAC) Meeting
Tommy Douglas Conference Center
10000 New Hampshire Avenue, Silver Spring, Maryland
April 25, 2019

QUESTIONS

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1. **DISCUSSION: Information Needed to Support Trials in Rabies-Exposed Individuals**
   Please discuss any recommendations concerning the data required prior to evaluating a monoclonal antibody (mAb) cocktail in place of rabies immune globulin (RIG) in clinical trials in rabies-exposed subjects.

2. **VOTE:** Would clinical trials of an investigational mAb cocktail product as part of post exposure prophylaxis (PEP) in rabies virus-exposed subjects be acceptable if the data package available to support trial initiation included the following elements?

   a. Cell culture data demonstrating breadth of coverage,
   b. Animal challenge studies demonstrating a survival benefit, and
   c. Clinical studies in healthy volunteers (not rabies virus-exposed) demonstrating a similar half-life, comparable early rabies virus neutralizing antibody (RVNA) levels, and comparable vaccine interference of the mAb cocktail versus human rabies immune globulin (HRIG)

   If no, what additional data elements would be needed?

3. **DISCUSSION**: **Information Needed to Support Submission of a biologic license application (BLA)**
   In addition to the cell culture, animal challenge, and healthy volunteer clinical data, please discuss the type and amount of clinical data in rabies-exposed individuals needed to support submission of a U.S. BLA for a rabies mAb cocktail as part of PEP.

QUESTIONS (cont.)

4. **VOTE:** Would a data package containing the following additional information be sufficient to support submission of a U.S. BLA?

    a. Comparable early RVNA levels and vaccine interference with the mAb cocktail versus HRIG in a clinical trial of rabies-exposed subjects,
    b. A comparable safety profile of the mAb cocktail versus HRIG in at least 1000 subjects who receive the mAb cocktail, and
    c. Lack of mortality in ≥750 subjects with World Health Organization (WHO) category III exposures in rabies endemic countries randomized to the mAb cocktail arm (indicating >99.5% survival with PEP including the mAb cocktail in place of RIG)

    If yes, would the described data package support a first-line indication for use as part of PEP or a second-line indication (such as when HRIG is not available)?

    If no, what additional data elements would be needed?

5. **DISCUSSION**: **Post-Marketing Studies**
    Please discuss the types and amount of data that should be collected post-approval.

    a. Would a post-marketing study that demonstrated >99.9% survival with PEP including the mAb cocktail, which would require 6000 rabies-exposed subjects, be appropriate?
    b. Do you have alternative recommendations for assuring the efficacy of the mAb cocktail as part of PEP?
    c. Do you have recommendations on design elements that might increase the feasibility of post-marketing studies?

    Please consider the sample size calculations in your discussion.