Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Antimicrobial Drugs Advisory Committee Meeting
April 25, 2019

Location: Tommy Douglas Conference Center 10000 New Hampshire Ave. Silver Spring, Maryland

Topic: The committee discussed one or more possible pathways for approval of rabies virus monoclonal antibodies for use as the passive-immunization component of post-exposure prophylaxis (PEP).

These summary minutes for the April 25, 2019 meeting of the Antimicrobial Drugs Advisory Committee of the Food and Drug Administration were approved on May 31, 2019**.**

I certify that I attended the April 25, 2019 meeting of the Antimicrobial Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/S/
Lauren Tesh Hotaki, PharmD, BCPS
Designated Federal Officer
Antimicrobial Drugs Advisory Committee

/S/
Lindsey R. Baden, MD
Chairperson
Antimicrobial Drugs Advisory Committee

Final Summary Minutes of the Antimicrobial Drug Advisory Committee Meeting
April 25, 2019

The Antimicrobial Drug Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on April 25, 2019, at the Tommy Douglas Conference Center 10000 New Hampshire Ave. Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA. The meeting was called to order by Lindsey R. Baden, MD (Chairperson). The conflict of interest statement was read into the record by Lauren Tesh Hotaki, PharmD, BCPS (Designated Federal Officer). There were approximately 120 people in attendance. There were no Open Public Hearing speaker presentations.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda: The committee discussed one or more possible pathways for approval of rabies virus monoclonal antibodies for use as the passive-immunization component of post-exposure prophylaxis (PEP).

Attendance:
Antimicrobial Drug Advisory Committee Members Present (Voting): Lindsey R. Baden, MD (Chairperson); CAPT Timothy H. Burgess, MD, MPH, FACP; Nina M. Clark, MD; Dean A. Follmann, PhD; Michael Green, MD, MPH; Barbara M. Gripshover, MD; Ighovwerha Ofotokun, MD, MSc; George K. Siberry, MD, MPH; Sankar Swaminathan, MD; Peter Joseph Weina, PhD, MD

Antimicrobial Drug Advisory Committee Members Not Present (Voting): Jennifer Le, PharmD, MAS; Joanna M. Schaenman, MD, PhD; Roblena E. Walker, PhD (Consumer Representative)

Antimicrobial Drug Advisory Committee Member Present (Non-Voting): Nicholas A. Kartsonis, MD (Industry Representative)

Temporary Members (Voting): Judith Baker, DrPH, MHSA (Acting Consumer Representative); Catherine M. Brown, DVM, MSc, MPH; James A. Ellison, PhD (Speaker and Temporary Member); Alexia Harrist, MD, PhD; Susan M. Moore, PhD, MS, HCLD(ABB), MT(ASCP)SBB; Laura D. Porter, MD (Patient Representative)

FDA Participants (Non-Voting): John Farley, MD, MPH; Debra Birnkrant, MD; Jeffrey Murray, MD, MPH; Stephanie Troy, MD; Tanvir Bell, MD, FACP, FIDSA; Damon Deming, PhD

Designated Federal Officer (Non-Voting): Lauren Tesh Hotaki, PharmD, BCPS

Open Public Hearing Speakers: None

The agenda was as follows:

Call to Order and Introduction of Committee	**Lindsey Baden, MD** Chairperson, AMDAC
Conflict of Interest Statement	**Lauren Tesh Hotaki, PharmD, BCPS** Designated Federal Officer, AMDAC
FDA Opening Remarks	**Jeffrey Murray, MD** Deputy Director Division of Antiviral Products (DAVP) Office of Antimicrobial Products (OAP) Office of New Drugs (OND), CDER, FDA
FDA PRESENTATIONS	
Background on Rabies and Why Monoclonal Antibodies (mAbs) are Being Developed for Rabies PEP	**Tanvir Bell, MD, FACP, FIDSA** Medical Officer DAVP, OND, CDER, FDA
Neutralizing Activity of Anti-Rabies Virus Antibodies in Cell Culture	**Damon Deming, PhD** Virologist DAVP, OND, CDER, FDA
SPEAKER PRESENTATION	
Use of Animal Models in Rabies Product Development	**James A Ellison, PhD** Microbiologist Poxvirus and Rabies Branch U.S. Centers for Disease Control and Prevention
BREAK	
FDA PRESENTATIONS (cont.)	
Clinical Trials to Evaluate Rabies mAb Cocktails as a Component of Post-Exposure Prophylaxis & A Proposed Development Pathway	**Stephanie Troy, MD** Medical Officer DAVP, OND, CDER, FDA
Clarifying Questions	
LUNCH	
OPEN PUBLIC HEARING	
Questions to the Committee/Committee Discussion	

BREAK

Questions to the Committee/Committee Discussion (cont.)

ADJOURNMENT

Questions to the Committee:

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.

   Committee Discussion: *The committee made several recommendations. For in vitro data required prior to evaluating a mAb cocktail in place of RIG in clinical trials in rabies-exposed subjects, the committee noted that preference should be given to target global, circulating rabies virus strains that cause human disease. It was proposed that mAb cocktail products should be globally employable if possible. One member suggested that the fifty percent effective concentration (EC_{50} value) should be measured independently for each mAb included in the cocktail in addition to the combined product. It was also suggested that the mAbs chosen for inclusion in cocktails should target different epitope binding sites, have well characterized mechanisms of resistance, and be complementary with respect to neutralizing activity against circulating rabies virus strains (e.g., at least one mAb should be active against all strains). One member suggested that the in vitro assays should be standardized in terms of rabies virus dose and the cell type used. Additionally, it was proposed that both human rabies immune globulin (HRIG) and equine rabies immune globulin (ERIG) be used as comparators in animal models due to differences in provincial use of HRIG and ERIG. On the other hand, a few members noted that they weren't concerned with using HRIG versus ERIG as the comparator because they did not suspect a difference in efficacy between these products. There were several suggestions to study the mAb cocktails and HRIG both alone and in combination with rabies vaccine in the animal studies. It was also suggested that animal challenge studies be used to compare the prophylactic windows of approved and investigational products by comparing survival rates when interventions are started at multiple times post-challenge (e.g., at 6 hours, 12 hours, 3 days and 7 days post rabies virus exposure) to emulate what is seen in clinical practice once a patient presents with potential rabies exposure.*

   For Phase 1, non-rabies exposed human pharmacokinetic and pharmacodynamic (PK/PD) data required prior to evaluating a mAb cocktail in place of RIG in clinical trials in rabies-exposed subjects, it was proposed that men and women should be studied to assess if there are differences in response based on gender. In addition, it was recommended that children and pregnant women only be studied in later studies in rabies-exposed patients, as there would be no prospect of clinical benefit from participation in the Phase 1 studies. Ranges of ages (e.g. 20s, 50s and 70s) were also suggested along with patients living inside and outside

of the United States (U.S.). It was discussed that enrolling a variety of subjects would be important as vaccine interference might be greater in people with low responses to the rabies vaccine, and vaccine response might be influenced by host factors such as age or genetic variations. It was also suggested that vaccine interference be evaluated with all the different types and routes of administration of rabies vaccine that the mAb cocktail might be paired with in the Phase 2/3 studies. Please see the transcript for details of the committee discussion.

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?

    Vote Result: Yes: 16 No: 0 Abstain: 0

    Committee Discussion: *The committee unanimously agreed that 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 elements a through c in question 2. Please see the transcript for details of the committee discussion.*

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.

    Committee Discussion: *The committee was in agreement that comparable early rabies virus neutralizing antibody levels and comparable vaccine interference of the mAb cocktail versus human rabies immune globulin (HRIG) in a clinical trial of rabies-exposed subjects is needed to support submission of a U.S. BLA for a rabies mAb cocktail as part of PEP. In addition, the committee agreed that a comparable safety profile of the mAb cocktail versus HRIG in at least 1000 subjects who receive the mAb cocktail and proven lack of mortality in ≥ 750 subjects are needed to support submission. The committee also recommended a post*

marketing study that accrued at least 6000 patients. Several committee members commented on the need for the pre-approval trial to be conducted as a randomized controlled trial with a HRIG/ERIG control arm, and several members recommended 1:1 randomization to the mAb cocktail versus HRIG/ERIG, both in combination with vaccine and wound washing. One member disagreed and thought that 1:1 randomization was not necessary given there would not be a noninferiority comparison for mortality, but several members noted that 1:1 randomization might still be important in case there were more cases of rabies deaths than anticipated in the mAb cocktail arm in order to determine if this was also seen in the control arm. It was discussed that comparison to HRIG versus ERIG might be more beneficial for the safety evaluation, and one member noted that use of HRIG instead of ERIG as the active comparator might make enrollment easier in rabies endemic countries where ERIG is more often used because this could be an incentive to enroll in the trial. One committee member suggested that documentation of the location and all other known aspects of the bite should be recorded for each participant (i.e., whether the bite was provoked, etc.). Several members commented on the need to include children and pregnant women either in the registrational trials or in post-marketing studies. Please see the transcript for details of the committee discussion.

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?

    Vote Result: Yes: 16 No: 0 Abstain: 0

    Committee Discussion: *The committee unanmioulsy agreed that a data package containing the elements a through c in question 4 would be sufficient to support submission of a U.S. BLA. Most members of the committee stated that the mAb cocktail with this data package should only be approved for second-line use in situations where HRIG is not available. It was also recommended, if approved, that the label should clearly state the rationale for second line treatment. One member suggested that administration should only be given*

within 72 hours of the rabid bite. Another committee member suggested that this mAb cocktail should not be given to patients with high risk bites until more assurance of its efficacy is obtained. Please see the transcript for details of the committee discussion.

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.

Committee Discussion: *The committee noted that a post-marketing study should include at least 6000 patients who receive the mAb cocktail as part of PEP in order to support a first-line indication. In addition, it was recommended that a control group who receive HRIG or ERIG as part of PEP would be useful, and that disproproportionate randomization at a 3:1 or 6:1 ratio to mAb cocktail versus HRIG/ERIG as suggested in the background materials sounded reasonable. It was also noted that there should be continued assessment of the types of rabies virus exposures in the U.S. One committee member noted that post-marketing studies should include immunocompromised patients in resource limited settings. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 4:30 p.m.