Mid-Cycle Communication Telecon

Application type and number: STN 125613/0
Product name: Rabies Immune Globulin (Human)
Proposed Indication: Passive, transient post-exposure prophylaxis of rabies infection, when given immediately after contact with a rabid or possibly rabid animal and in combination with rabies vaccine
Applicant: Kamada Ltd
Meeting date & time: February 23, 2017, 10:30 to 11:00 am
Committee Chair: Michael Kennedy, PhD
RPM: Jiahua Qian, PhD

FDA Participants
Kennedy, Michael, Ph.D. Chair, Team Lead/CMC
Schneider, Bruce, MD, Clinical, Team lead
Tang, Winson, MD, Clinical reviewer
Wang, Xiaofei, Ph.D. Clinical pharmacology
Scott, Dorothy, MD, Branch Chief/CMC
Mahmood Iftekhar, Ph.D. clinical pharmacology
Jiahua Qian Ph.D., RPM

Kamada Participants
Orit Pinchuk, MSc   Vice President Regulatory Affairs, Kamada Ltd.
Naveh Tov, MD   Vice President Medical Affairs, Kamada Ltd.
Lily Bar   Vice President, R&D
Alma Levy   Regulatory Affairs Director, Kamada Ltd.
Nir Sharon   Biostatistic, Kamada Ltd.
Garrett Bergman, MD, MBA   Sr. Director, Medical Affairs, Kedrion BioPharma, Inc.
Wang, Yu-Fen   Head of US Regulatory Affairs, Kedrion BioPharma, Inc.
Vladislava Zamfirova, MD   Clinical Operations, Kedrion BioPharma, Inc.
Ruth Ellis, MD, MPH   Sr. Clinical Consultant, Biologics Consulting
Holli S. Vaughan, MS, RAC   Regulatory Project Manager Biologics Consulting

Discussion Summary:

FDA has emailed the discussion outline to Kamada on February 21, 2017.

1. **Any significant issues/major deficiencies identified by the review committee to date. State during the telecon if there are no significant issues/major deficiencies identified at this time and document the statement in the telecon summary**

   The review is on going

2. Information regarding major safety concerns. State during the telecon if there are no major safety concerns identified at this time and document the statement in the telecon summary

At this time, review of the clinical data has not identified any major safety concerns.

3. Preliminary review committee thinking regarding risk management

Since the review of the clinical data has not identified any major safety concerns, the review committee does not think that a *Risk Evaluation and Mitigation Strategy* is required at this time.

4. Any information requests sent and not received

Waiting for a pending IR response on Sterility test qualification report from contractor Charles River. Kamada mentioned the report will be provided in Q1 of 2017.

Information requests have been sent to Kamada
    Feb. 13, 2017:   NDC
    Feb. 13, 2017:   CMC Viral Clearance
    Feb. 21, 2017;   Combined CMC information request

5. Any new information requests to be communicated

Clinical Review
  1. The most common lab abnormalities that were listed as AEs in the three studies were hematuria and leukocyturia. However, your integrated summary of safety did not discuss these two urinary abnormalities. Please provide an integrated summary of hematuria and leukocyturia and a literature review on the prevalence of hematuria and leukocyturia with intravenous immunoglobulin administration as well as a discussion on the potential mechanism(s).

  2. The most common AEs in this Application were injection-site reactions, particularly injection-site pain. You state that you cannot differentiate between the relationship of these to vaccine or KamRAB/HyperRAB. However, KamRAB/HyperRAB was administered in the lower extremity while vaccine was given in the right deltoid. Thus, one should be able to distinguish between local reactions at these two sites, in terms of association with vaccine or KamRAB/HyperRAB. Please reanalyze your data to differentiate between the local AEs at these two different sites of administration.

  3. In Study KamRAB-003, you have selected day 14 (D14) as the timepoint for the readout of your primary endpoint. However, by D14, the rabies virus neutralizing antibody (RVNA) that can be attributed to KamRAB has already decreased by ~35%

given that the half-life of the immunoglobulin is 21 days. In reality, the majority of the RVNA at D14 is due to the effects of the vaccine. Given that the rationale for HRIG administration is to provide immediate protection while awaiting the generation of an immune response to the vaccine, shouldn't the target endpoint be a RVNA ≥ 0.5IU/ML on days 3-7? Please discuss the rationale for selecting D14 as the timepoint for assessing this potential marker of efficacy as opposed to D3.

4. In Study KamRAB-003, Subject 0024 was not able to achieve a therapeutic RVNA titer until D28. Please provide a narrative for subject 0024 and a discussion of why Subject 0024 did not mount a greater immune response.

Time (days)	0	3	7	14	28	49	185
RVNA (IU/mL)	BLQ	0.12	0.12	0.18	0.81	0.88	0.38

5. You performed bioequivalence (BE) evaluation in two studies (study # RD 154/23630 and # KamRAB-003) comparing your test product, KamRAB, to the reference products, BayRAB®/HyperRAB® by Grifols Therapeutics Inc. However, your KamRAB failed to meet BE criteria in both studies despite satisfying the primary endpoint of RVNA >0.5IU/mL on Day 14. For example, in Study RD 154/23630, the following PK parameters were reported

	C_{max}	T_{max}	AUC_T	AUC_I
KamRAB	0.249	7	5.222	6.734
BayRAB	0.302	3	6.266	7.972

Similarly, in the KamRAB-003 study, the Cmax for KamRAB is statistically significantly lower than that of HyperRAB on D3 (0.183 ± 0.053 vs 0.224 ± 0.053, p=0.0003). Efficacy concerns are raised due to above observations. Please provide additional clinical data and/or other evidence to address whether the PK difference observed in these BE studies will have clinically significant impact on the efficacy of your product, KamRAB.

6. Please provide certificate of analysis (CoA) for all lots of your test and reference products used in clinical studies # RD154/23630 and # KamRAB-003. Please also submit the potency data if you performed potency test using your in-house (b) (4) method for both test and reference product prior to use. If you did not perform potency analyses with your in-house assay on both test and reference products, please provide this information.

7. The failure rate in the KamRAB group for the KamRAB-003 study was 1.8%, which would be unacceptable, especially if large numbers of patients were to be treated with KamRAB. In your Application, you state that KamRAB has been administered to over 250,000 patients in 10 countries around the world. To allay concerns regarding efficacy, please provide an analysis of PEP outcomes for Israel, S Korea, and Australia. We have chosen the latter two countries (in addition to Israel) because we note that you are marketing KamRAB under a "named patient" program. For this

analysis, please provide a table with the following information: route of exposure by percent and numbers of patients (bite, mucosal, other), animal vector by percent and numbers of patients (bat, skunk, dog, other), site of exposure by percent and numbers of patients (lower extremity, trunk, face, other), suspected vs confirmed rabid animal, and clinical outcome. As the numbers of patients receiving PEP are likely to be large, please focus your analysis on confirmed rabies exposures. The table should indicate how much missing data there are for each of the above categories. We believe that these clinical outcomes data are critically important in determining the effectiveness of your product.

8. A variety of factors may affect an individual's immune response. For example, the immune response wanes as we age. Similarly, hypersensitivity reactions to equine rabies immune globulin and HRIGs have been reported to occur more frequently in women. Please perform a subgroup analysis for the PK and safety of KamRAB and the Comparator HRIGs by age, sex, and BMI.

9. In your Application, you state that there were 236 subjects screened for study KAMRAB-003 with only 118 subjects enrolled, for a screen failure rate of 50%. Please provide a table giving the reasons for screen failures and numbers or percent who failed due to each reason. Similarly, there was no screen failure rate (and reason for failing screening) provided for Studies 23630 and 24061. Please provide these data.

Clinical Pharmacology

10. Per your clinical study KamRAB-003 report attachment 1 (non-compartmental pharmacokinetic analysis for study KamRAB-003, page 17-18), you stated that *the geometric mean was calculated using the repeated assayed plasma HRIG concentrations determined from the same sample* and *the geometric mean values were also used to calculate HRIG PK parameters*. This is not acceptable. For pharmacokinetic samples assayed multiple times, arithmetic mean values of each biosample should be used in PK calculation. Please re-conduct PK and bioequivalence analysis using the arithmetic mean values of your PK samples for your study KamRAB-003 and submit the results.

11. Additionally, please submit 1) the updated individual concentration-time data and PK parameter data in SAS-compatible dataset and variable definitions; and 2) the SAS codes used in your bioequivalence assessment for your clinical study KamRAB-003.

6. Proposed date for the late-cycle meeting

The late-cycle meeting is tentatively scheduled on June 8, 2017.

7. Updates regarding plans for the AC meeting

STN 125613 will not be presented before the Advisory Committee.

8. Other projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates

None