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LETTER

Letter to the editor: Safety and immunogenicity of a novel recombinant rabies vaccine

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The Editor,

We read with interest the recent publication on the safety and immunogenicity of a novel recombinant rabies vaccine.[1] We have the following observations for which we seek response from the authors:

(1) The Rapid Fluorescent Focus Inhibition Test (RFFT) for the estimation of the rabies virus neutralizing antibody (RVNA) titers, which is an indicator of the vaccine immunogenicity, was conducted at the Department of Neurovirology, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, which is a World Health Organization (WHO) collaboration center for Reference and Research on Rabies. The International Committee of Medical Journal Editors (ICMJE) recommends that all individuals who substantially contribute to the acquisition, analysis, or interpretation of data for the work should have the opportunity to review, drafting, and final approval of the manuscript.[2] Why is it that no individual from this center fulfilled the authorship criteria for this publication?

(2) The authors mention that the requisite for vaccination is to stimulate the immune system to produce antibody titers of at least 0.5IU/mL by day 14 as recommended by the WHO for seropositivity. However, there is no citation to this statement. The WHO recommendations, however, mention that an antibody concentration of 0.5IU per mL on days 14 and 28 or 30, after initial vaccination, is generally considered to be adequate.[3]

(3) The WHO also mentions that for post exposure prophylaxis regimens, the following schedules for antibody testing are recommended as a minimum: days 0, 14, 28 or 30, 90, 180, 360.[3] Why were antibody testing not planned and done according to these recommendations?

(4) The table on sero-response of the study subjects shows that six subjects seroconverted from negative to positive from days 14 to 42 in the reference vaccine group implying 100% seroconversion on day 42. However, in the test vaccine group, three subjects who were seropositive on day 14 became seronegative on day 42. Also, on day 42, in the test vaccine group, a total of seven subjects were still seronegative. An understanding of this sero-response would be incomplete without the follow-up testing and repeat booster vaccination of these seronegative subjects and to assess the durability of immunogenicity on days 90, 180, and 360 of the remaining seropositive subjects. How do the authors interpret this result and can such a result be taken as acceptable sero-response?

(5) The figure on disposition of the study participants shows that on day 42 immunogenicity visit, out of a total 800 participants who had been randomized, 795 subjects visited. However, out of these 795, only 576 (72.4%) samples were analyzed. In the test arm, 41.3% of the samples were unsatisfactory and in the reference arm 54.3% of the samples were unsatisfactory. Considering the fact that this is the only time point apart from 14 days when the immunogenicity of the vaccine was tested, why have the authors not provided any detail as to why these samples were unsatisfactory? Also, what were the measures taken by the authors to try to repeat sample collection or analysis based on the cause of the samples being unsatisfactory?

(6) The WHO recommendations mention that immunogenicity data should also include geometric mean titers (GMT) with confidence intervals and range of antibody titers.[3] The same would have added a more wholesome understanding of the immunogenicity of the novel vaccine. We would urge the authors to provide this data as a supplementary table , if possible.

(7) All authors declare no potential conflicts of interest. However, the corresponding author appears to be employed by Cadila Pharmaceuticals Ltd., which seems a conflict.

Being a novel vaccine manufacturing technology, the trial should have included administration of Rabies immunoglobulin (RIG) also, and then, the interference in titers due to all types of

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RIGs should have been estimated. We feel that real-world protection in rabies exposed patients should be assessed or a sample size of such a magnitude should be taken to cover probable rabies exposed patients too to find out vaccine effectiveness.

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