Fourth teleconference on Ebola vaccine clinical trials
in Guinea, Liberia, and Sierra Leone

30 March 2015

SUMMARY

The meeting was chaired by WHO Assistant Director-General, Dr Marie-Paule Kieny, on behalf of Dr Margaret Chan, Director-General, World Health Organization

AGENDA
Introduction: Dr Marie-Paule Kieny

STATUS OF PHASE III TRIALS
Update on implementation of Guinea Phase III ring vaccination trial
Dr Ana-Maria Henao Restrepo Medical Officer, Immunization, Vaccines and Biologicals, WHO
and Dr Grais, Director, Epidemiology and Population Health, Epicentre

Status of Liberia Phase II trial and plans for expansion to Phase III
Dr Higgs, Deputy Branch Chief, Collaborative Clinical Research Branch, NIH/NIAID

Plans for initiation of Sierra Leone rVSV-ZEBOV Phase III Trial
Dr Anne Schuchat, Assistant Surgeon General Director, NCIRD, CDC

Preparation for Ad26/MVA Sierra Leone Phase III trial
Dr Johan van Hoof, Global Therapeutic Area Head, Infectious Diseases and Vaccines, Johnson & Johnson

MANUFACTURERS’ SHORT UPDATES ON PHASE I/II TRIALS
GSK - ChAd3 ZEBOV
Dr Ripley Ballou, Vice President, GSK Biologicals

Merck/NewLink - rVSV-ZEBOV
Dr Mark Feinberg, Vice President and Chief Public Health and Science Officer; Merck Vaccines, Merck & Co., Inc.

Johnson & Johnson - Ad26 ZEBOV/MVA ZEBOV
Dr Johan van Hoof, Global Therapeutic Area Head, Infectious Diseases and Vaccines, Johnson & Johnson

SUMMARY OF PRESENTATIONS AND DISCUSSIONS
STATUS OF PHASE III TRIALS

Guinea

The Guinea collaboration has initiated implementation of two protocols targeting different population.

The Phase II protocol targets front-line workers (FLWs). The trial will assess safety and immunogenicity of the rVSV-ZEBOV vaccine. The trial started on 7 March with the vaccination of Guinean dignitaries. FLWs’ vaccination was then started in Donka Hospital in Conakry and the trial enrolled 3 volunteers on 24 March, 12 on 27 March, and 12 on 28 March. The plan is to gradually scale up to 20 volunteers/day followed by 40 volunteers/day in the coming weeks. The trial was well accepted by FLWs.

The Phase III protocol targets contacts of confirmed cases of Ebola virus disease (EVD). The trial will assess efficacy and effectiveness of the rVSV-ZEBOV vaccine in preventing EVD in contacts of confirmed EVD cases and in contacts of these contacts, thereby forming a “ring of immunity” around EVD cases. Rings will be randomized to be either vaccinated immediately or with a delay of 21 days. Residents of the rings will be visited every day for 21 days by surveillance officers as part of Ebola Response teams. A dedicated follow-up visit will be added at 3 days and 21 days after the vaccination to monitor possible adverse effects. Ninety percent (90%) of those who were vaccinated completed the 3-day follow-up, no adverse events were reported.

The first ring was vaccinated on 23 March in a village in the Prefecture of Coyah. Since then, four more rings have been vaccinated. Acceptance of the trial was very good (called Ebola ça suffit clinical trial) from the population. The first three rings were not randomized, as they served as a pilot to allow for adaptation of the design to the field and logistical realities. The objective is to finish inclusion of volunteers in early June 2015.

A question was raised about the acceptance of delayed vaccination and the exclusion of children. Dr Henao-Restrepo responded that communities were well informed of the nature of the study and understand the reason for the delay, provided all volunteers will be vaccinated within a relatively short period of time (21 days). An amendment to the protocol to include children will be requested, if safety in this population is demonstrated (in Gabon) before the end of the Phase III trial.

Another participant asked about the feasibility of defining the rings and whether people actually remained within the defined rings. Dr Henao-Restrepo clarified that contacts of EVD cases were asked to stay at home by the Ebola Response teams. The first three rings were located in different geographic areas: the first was around an isolated rural village surrounded by forest; the second was located in a semi-rural area; and the third was in Matoto in Conakry. In the three cases there was no difficulty in defining a ring.
A question was raised as to whether a second vaccine was still being considered for a follow-up ring vaccination trial. The investigators responded that implementation of a second trial would be dependent on epidemiological and logistical issues. The second study would test the GSK vaccine (either as a one-dose vaccine or in a prime-boost schedule). The Johnson & Johnson vaccine was also considered as a possible alternative candidate.

Finally, Dr Henao-Restrepo indicated that an article entitled “Ring vaccination for Ebola: a novel approach to evaluate vaccine efficacy and effectiveness during an outbreak” would soon be published and would discuss the methodology and detailed design of the trial.

**Liberia**

The Phase II/III double-blind, randomized, placebo-controlled study (called PREVAIL) will assess the efficacy and safety of the GSK ChAd3-ZEBOV and Merck rVSV-ZEBOV vaccines against a placebo control.

The Phase II segment has enrolled 24 volunteers/day at Redemption Hospital and will continue to enrol patients until the end of April. As of 27 March, a total of 876 participants were enrolled. The study was redesigned to include a total of 1,428 participants with 476 volunteers per group. Immune responses will be assessed at one week, one month, six months and 1 year post vaccination.

The DSMB is monitoring the trial and has completed three reviews to date. On 20 March, the Committee analysed the safety and immunogenicity data from the first participants and recommended expanding the Phase II portion of the trial. The analysis also revealed that only 16% of study participants were women, which is being corrected through priority inclusion of women.

Dr Higgs highlighted the climate of trust and partnership in the country, where NIH works very closely with national entities. In order to secure acceptability in the communities, an offensive strategy is being implemented for social mobilization, community engagement and communication.

A question was raised whether the trial should proceed to the Phase III segment, in view of the (very) low incidence of EVD in Liberia at this moment. Dr Higgs indicated, it was initially planned that enrolment for the Phase III trial in Liberia would be completed in a 4-month period, but that it was now most likely the trial would not be completed in this country. As a consequence, NIH has started discussions about compatibility and feasibility of two Phase III trials running at the same time in Sierra Leone or Guinea. Dr Higgs also clarified that the sample size of the trial might be increased, if needed, to ensure feasibility of an individually randomized trial in a context of low case incidence.

**Sierra Leone**

The CDC trial

Dr Schuchat indicated that the Sierra Leone Trial to Introduce a Vaccine against Ebola (STRIVE) would begin as soon as it gets final approval from the National Pharmacy Board of Sierra Leone and the United States Food and Drug Administration (US FDA). The design of the trial is a cluster-based, non-
blinded, individually-randomized vaccination of FLWs with rVSV-ZEBOV. In each cluster, FLWs will be randomized either to be vaccinated immediately or after 6 months. The trial will start in the Western Rural Area of Sierra Leone and then extended to other districts. The trial will enrol 6 000 volunteers (3 000 vaccinated immediately and 3 000 after 6 months). A sub-study will investigate reactogenicity in 400 subjects.

Volunteers will be monitored for 6 months after vaccination and called up every month. The design envisages several interim analyses. Every participant will be provided with medical care for any adverse events which may occur and compensation will be made for transportation or inconvenience linked to their participation in the trial.

A lot of communication was done around the trial and the FLW population seems to accept the principle of randomization and delayed vaccination.

A question was raised about the likelihood of the trial being able to draw a conclusion on the efficacy of the vaccine because of the current low incidence of EVD among health-care workers. Dr Schuchat answered that this was indeed a cause of concern, but that the reopening of health care facilities in the countries might, unfortunately, increase the number of cases in the future.

The London School of Hygiene and Tropical Medicine (LSHTM) trial
The Phase III trial with Ad26/MVA will be a cluster-randomized trial. It will be organized in three stages: stage one will enrol 40 patients; stage 2, 600 patients; and stage 3 will be extended, depending on feasibility and incidence of EVD, to up to 800 000 volunteers.

General discussion on the Phase III trials
A question was raised about the expected duration of protection induced by the vaccines. While no evidence exists at this moment to answer this question, it was indicated that long-term protection would be assessed as part of the LSHTM trial. On the Liberian side, the Phase II protocol was modified to assess antibody responses at 6 and 12 months. The Guinea trial also plans to collect blood samples to investigate antibody and cellular immune responses in FLWs.

Particular interest focused on the expected timelines to results, but all agreed that for the moment it is too early to provide a precise answer.

It was highlighted that African regulators were well involved in all steps of the regulatory process. A significant support was provided by stringent regulatory agencies (European Medicines Agency, Health Canada, and US FDA) to facilitate the review protocols for approval by national authorities.

Dr David Wood informed the group that the WHO prequalification group was preparing an emergency listing assessment procedure for Ebola vaccines. This new procedure was open to comment until 10 April 2015 at http://www.who.int/medicines/news/public_consult_med_prods/en/.
MANUFACTURERS’ SHORT UPDATES ON PHASE I/II TRIALS

GSK – ChAd3-ZEBOV
A Phase II trial is expected to start in mid-May in Mali as a likely first site; regulatory approval is pending.

Merck/NewLink – rVSV-ZEBOV
The Phase I trials are completed or nearing completion with close to 800 participants having been enrolled. Several hundred more volunteers were also enrolled in the Liberian Phase II trial. Immunogenicity and safety data would be publicly available in the near future (NOTE added after the teleconference: the NEJM articles reporting the results were published on April 1). In addition to its inclusion in the PREVAIL study in Liberia, the rVSV-ZEBOV candidate vaccine is now being studied in the ongoing Phase III trial in Guinea and will be studied in a Phase III trial in Sierra Leone that is scheduled to begin shortly. Merck/NewLink also plans to conduct additional Phase II studies, including those focusing on special populations.

Johnson & Johnson – Ad26 ZEBOV/MVA ZEBOV
Should efficacy of the vaccine be proven, J&J could rapidly provide doses for mass vaccination. The vaccine can be shipped at -20 C° and handled in domestic distribution channels at 2-8C°.

The Phase I trials are proceeding in the United States and in Europe, and all the booster doses have already been given in the United Kingdom study. Dr van Hoof indicated that the safety profile looked promising with no serious side effects reported. In a recent meeting in Washington, the first immunogenicity data post-prime were shared.

Recruitment for Phase I will also start in Ghana, Tanzania and Ugandaand is ongoing in Kenya. In upcoming Phase II trials, the investigators will look at safety and immunogenicity in adults and also in children and HIV-seropositive subjects.

The NEXT TELECONFERENCE will be organized by WHO in two months.