WHO Technical Advisory Group – candidate vaccine prioritization

Summary of the evaluations and recommendations on the four Marburg vaccines that are candidates for inclusion in the planned “A phase 1/2/3 study to evaluate the safety, tolerability, immunogenicity, and efficacy of vaccine candidates against Marburg disease in healthy individuals at risk of Marburg disease”

April 4, 2023
Background

With the recent occurrence of Marburg outbreaks in Equatorial Guinea and Tanzania the WHO R&D Blueprint has enacted its rapid research plan to deploy vaccines as part of a pre-agreed protocol to evaluate their performance and facilitate obtaining safety and efficacy data in humans under conditions of natural exposure that could ultimately facilitate licensure. This envisions a future scenario wherein there may be multiple approved products to deploy early in Marburg outbreaks, an illness that typically exhibits high case fatality rates.

The TAG-CVP is supporting this outbreak response by the rapid evaluation and prioritisation of candidate Marburg vaccines for use under the WHO protocol. The prioritisation process is undertaken according to agreed criteria covering the potential for efficacy, a suitable safety profile, logistical issues such as vaccine stability, current and future vaccine availability, and ease of implementation.

Depending on the stage of clinical development of a candidate vaccine, the TAG-CVP can recommend that it be evaluated in a Phase 1 or 2 trial in an inter-epidemic period, or that it can proceed to a Phase 3 ring vaccination efficacy trial if a Marburg outbreak is evolving. As necessary, a nested Phase 1/2 trial can precede the initiation of the Phase 3 ring vaccination assessment of efficacy.

WHO Technical Advisory Group – candidate vaccines prioritization (TAG-CVP) membership and meeting attendees

To date four candidate vaccines have been evaluated at meetings that took place between 20th February and 30th March 2023. The meetings were chaired by Prof Myron M Levine.

The following voting members took part in the evaluations: Dr Rebecca E. Chandler, Prof Dani Cohen, Dr Subhash Kapre, Dr Sergio Nishioka, Dr Suenie Park, Dr. Sudhanshu Vrati, and written comments from Dr Junzhi Wang. Together these TAG-CVP members have expertise in the areas of vaccine safety, clinical immunology, vaccine trials, virology, regulatory science, vaccine manufacturing and pre-clinical evaluation of vaccines. Prof Miles Carroll attended the meetings as observer and expert in filovirus.

Prof Elizabeth Miller acted as rapporteur and Prof César Muñoz-Fontela and Dr Simon Funnell provided specialist expert advice to the TAG-CVP.
Process

Developers of each of the four candidate vaccines provided written material for the TAG-CVP to review prior to the meeting. This comprised, as appropriate, Investigator’s Brochures and pre-clinical or clinical study reports. Each sponsor made a live presentation to the TAG-CVP and responded to questions either in the meeting or through written responses. The TAG-CVP members were asked to make a recommendation after each meeting as to whether the candidate vaccine was suitable for inclusion in the trial.

Summary reports of each meeting, the questions raised by the TAG-CVP, the sponsors’ responses, and the recommendations made by the TAG-CVP on each candidate were drafted by the Rapporteur and, after review and approval by the Chairman, were submitted to the WHO Secretariat as the formal record of the meeting and the TAG-CVP’s recommendations.

Evaluation criteria

The TAG-CVP assessed safety and potential for efficacy based on the following criteria in descending order of importance:

Safety: Experience with the vaccine platform with a different filovirus or when used with a different antigen; safety data from toxicity studies in animals and clinical trials with the candidate vaccine.

Potential for efficacy: Proven efficacy with the vaccine platform expressing antigens from a different filovirus; immunogenicity in clinical trials including rapidity of response and potential for interference with naturally-acquired or vaccine-induced antibodies to the vaccine backbone; challenge data in non-human primates (special weight is given to NHP challenge data as this is the preferred animal model for predicting efficacy of Marburg vaccines in humans); challenge data in a rodent model; evidence of cross-protection against different Marburg strains.

Availability and implementation: Took account of the delivery timeline for product to be ready for use in the trial having successfully completed all release tests, stability data and storage temperature, method of administration, injected volume, need for dilution of product at study site, potential for scale-up, and commitment by the manufacturer to take the product to licensure.

Candidate vaccines

The four candidate vaccines evaluated to date are all viral-vectored vaccines encoding the surface glycoprotein from the Marburg virus, which is the key antigen involved in generating protective antibody responses against the disease. Two of the candidates use the replicating Vesicular Stomatitis Virus (VSV) as the vector and two use a non-replicating chimpanzee adenovirus vector (ChAd3 or ChAdOx1).
One of the VSV-vectored vaccines is being developed by Public Health Vaccines in the USA and the other by the International AIDS Vaccine Initiative.

The ChAd3-vectored vaccine is being developed by the Sabin Vaccine Institute in the USA and the ChAdOx1-vectored vaccine by the University of Oxford in the UK.

**Evidence available.**

All four vaccines have shown protection in an animal model with induction of antibodies likely to be associated with protection. To date NHP challenge data are available for the two VSV-vectored vaccines and the ChAd3-vectored vaccine with protection demonstrated for the ChAdOx1-vectored vaccine in a murine challenge model.

Currently, only the Sabin ChAd3-vectored vaccine has Phase 1 clinical data.

For each of the four vaccines a substantial body of clinical evidence has been amassed supporting the safety of the vector in humans when used for vaccines targeting other diseases including those licensed for Ebola and Covid-19.

**Doses of candidate vaccines available**

Presently, the ChAdOx1-vectored investigational product from Oxford University and the ChAd3-vectored investigational product from the Sabin Vaccine Institute have sufficient GMP-manufactured doses available for entering a trial within the context of the current Marburg outbreak.

Oxford University has ~1000 doses available for the trial, while Sabin Institute has ~850 doses. Both have stated that they can quickly produce additional doses.

Public Health Vaccines has 300 doses available but plans for production of additional doses have not yet been finalised. No GMP manufactured vaccine is currently available for the IAV VSV-vectored vaccine but production is planned for late 2023.

**Conclusions and recommendations of the TAG-CVP**

After review of the available pre-clinical and clinical data for each candidate Marburg vaccine and for related vaccines using the same viral vector, the TAG-CVP concluded that each was a suitable candidate for evaluation under the adaptable WHO protocol. However, the TAG-CVP recognised that the four candidates are at different stages of development in terms of the immediate availability of doses for a clinical trial and with respect to the clinical experience with the vaccine.

Based on the TAG-CVP comments on the presentations and written material from the four vaccine candidate sponsors and written responses from sponsors to questions posed by the TAG-CVP, the TAG-CVP Executive (Chair and Rapporteur), in conjunction with the WHO Secretariat, prepared a preliminary prioritization list of the vaccines that were most likely to enter the trial expeditiously based on existing preliminary human clinical data, availability of GMP doses, and evidence of vaccine efficacy from challenge studies in NHPs.
**Recommendation 1.** The Sabin Institute Vaccine should be included in the proposed WHO trial and enter into the phase 2 part of the protocol.

**Recommendation 2.** The Oxford University and Public Health Vaccines should be included in the proposed trial and to enter phase 1 of the WHO protocol (if possible) as at present only preclinical data is available.

**Recommendation 3.** The TAG-CVP considers that when their GMP product becomes available, IAVI’s candidate vaccine would be highly suitable for use in a Phase 1 or 2 trial under the conditions outlined in the WHO protocol.

The TAG-CVP noted that a vaccine using the VSV-backbone and encoding expression of the Ebola glycoprotein had proven efficacy and safety in a ring vaccination trial during an Ebola outbreak and was now licensed for use by EMA and FDA. The experience with the licensed Ebola vaccine indicated that a VSV-vectorized vaccine encoding the Marburg glycoprotein could be similarly protective and its efficacy could be demonstrated in an evolving Marburg outbreak.

The TAG-CVP strongly endorsed the ongoing efforts to produce an international standard reagent that would allow comparative quantitation of antibodies across different Marburg vaccines. Such an international standard would facilitate the identification of a correlate of protection that could support licensure of vaccines without direct evidence of efficacy.