

# M72/AS01E TUBERCULOSIS VACCINE CANDIDATE: CONSENSUS-GENERATING CONSULTATION ON THE DEVELOPMENT PATHWAY

30-31 July 2019  
WHO, Geneva, Switzerland

## Executive Summary

On 30-31 July 2019, the WHO convened in Geneva a meeting to generate consensus on the clinical development pathway for the M72/AS01E tuberculosis (TB) vaccine candidate developed by GSK. This meeting is a follow-up to the high-level consultation on accelerating the M72/AS01E TB vaccine, held in Geneva on 5 April 2019 and convened in light of the significant degree of protection provided by this vaccine against the development of active TB disease among adults with latent *Mycobacterium tuberculosis* (*Mtb*) infection (LTBI) in a phase 2b trial conducted in South Africa, Kenya and Zambia. The point estimate of vaccine efficacy after at least two years of follow-up following vaccination was 54% (90% CI, 14-75; P = 0.04).

The meeting on 5 April 2019 highlighted a lack of consensus on the clinical development pathway forward. The purpose of this new consultation was to generate consensus recommendation about next steps and regulatory development strategic options for further development of the M72/AS01E vaccine candidate. This plan should then be conveyed to developers and funders. A forum for WHO to present its recommendations to funders is planned to be organized in the late 2019.

The following is a summary of the most important consensus recommendations generated by the panel of experts following two days of deliberations under the chairmanship of Dr. David Kaslow, PATH and Dr. Michel Dewilde, independent consultant.

1. **Sense of urgency.** There was unanimous assessment that the Phase 2b trial result is unprecedented in the history of TB vaccine development and represents a major scientific breakthrough in efforts to develop a vaccine to control the global epidemic of TB, the cause of more deaths worldwide than any other infectious disease. These results should be considered at least as important as if a vaccine providing approximately 50% protection against progression to AIDS in subjects with HIV infection had been discovered. Evidence shows that important impact in high endemicity settings could be derived from protection from protection to TB disease in individuals with evidence of LTBI (LTBI +/-) and that justifies moving forward even in the absence of evidence of protection in individuals without evidence of LTBI (LTBI -/-) population. The existing phase 2b trial data justifies advancing the clinical development of the M72/AS01E TB vaccine candidate towards licensure and policy decision for use.
2. **Proceeding with existing schedule and formulation.** Progress should proceed with licensure evaluations based on the dose and schedule used in the phase 2b trial. In absence

of a correlate of protection and without an efficacy endpoint to support a regimen change (especially change in adjuvant dose), any modification to the current dose and schedule would add an important risk to the program. Possible dose and schedule modifications could be considered in parallel with, or subsequent to licensure, but modifications are not on the critical path and should not distract from advancing development of the current dose and regimen.

3. **Correlates of protection important but not on the critical pathway.** It is imperative that the biomarker working group associated with this initiative move expeditiously to begin analysis of samples from TB 018 in an effort to identify possible correlates of protection that could expedite further TB vaccine development efforts. There is, however, no expectation that evidence will be available in the near future to support strategic decisions relevant to the critical pathway to licensure. In absence of a correlate of protection, immunogenicity characterization may support some product-related regulatory bridging steps but not efficacy generalizability assumptions.
4. **LTBI screening.** There was consensus that future program implementation of a TB vaccine in high endemicity countries cannot be dependent on the need for systematic screening for LTBI with an indication for vaccination dependent on the result. In contrast, in countries with lower endemicity, programs with active contact tracing and LTBI screening activities may be interested in incorporation of a vaccine in LTBI +/- individuals to prevent progression to TB disease. In view of the fact that evidence of protection has not been generated in subjects who are LTBI -/-, it will be important to further test for LTBI at study entry in M72/AS01 vaccine trials. Standard of care recommendation for preventive drug therapy to be administered to study participants who are LTBI +/- may influence the acceptability of candidate vaccine research study designs. Implications should be carefully considered and discussed with regulatory authorities and institutional review boards.
5. **Role of a Prevention of Infection signal.** There was a call for caution about interpretation of potential evaluation of M72/AS01E-induced prevention of infection test conversion. The result may not reliably predict ability to prevent pulmonary TB disease in LTBI -/- individuals ; and more specifically it was estimated that even if the vaccine administered to LTBI -/- individuals fails to prevent infection test conversion, it may still efficiently prevent progression to TB disease. A negative signal in a Prevention of Infection study should not lead to termination of vaccine development.
6. **Use of available doses.** Of the 7,000-9,000 M72 doses manufactured for the phase 2b trial and still remaining at GSK, assuming that stability testing will support availability for use, the panel recommends that
  - a. 2,000-3,000 doses be retained to support product evaluation and bridging steps in manufacturing process improvement and product/technology transfer
  - b. The rest made available for safety and immunogenicity evaluations supporting increased confidence for favorable vaccine use in HIV-infected individuals in priority, and for expansion of the geographical and age indication, including LTBI -/- individuals, with details to be defined in the context of the priority accelerated pathway (see below)
7. **Pathways to licensure**

- a. **Phase 3 RCT pathway.** Seek traditional licensure based on a phase 3 efficacy study. The following priority considerations were highlighted
- i. Such a trial could be conducted in a 'very' high endemicity setting, in a population with a significant, high proportion of LTBI +/- individuals, and provide a more precise, confirmatory estimate of efficacy in this population.
  - ii. The age band could include adolescents and adults with highest incidence (ex 16-30 years old) to ensure sufficient statistical power with a realistic sample size.
  - iii. An ambitious but pragmatic approach is needed to support generation of evidence that is generalizable to other settings and support policy decision for global use in large, high-TB-burden countries. For settings with lower prevalence of LTBI, evidence of protection in LTBI -/- individuals will be key to support mass introduction (but such settings may not all need mass introduction as benefit may derive from vaccine introduction in key target populations only).
  - iv. Sample size assumptions support the possibility to include LTBI -/- individuals and detect an effect size with a low (>0%) lower bound of the confidence interval.
  - v. This approach would likely meet classical recommendations for licensure by stringent regulatory agencies, such as the EMA or the U.S. FDA, along with other national regional authorities. The value of engaging regulatory networks such as AVAREF and WHO PreQualification was highlighted.
  - vi. Safety and immunogenicity studies would support further age and geographical expansion of indication, to be complemented by effectiveness studies post initial licensure (also see 8. 'Other trials' below). Post licensure investigations would likely be needed for confirmation of effectiveness in older populations, in children, in vulnerable groups such as people living with HIV/AIDS.
  - vii. Challenges identified include
    - 1. The Phase 3 study would require a large sample size, with a significant associated cost.
    - 2. The time to product availability for wide scale use is long. The earliest time to potential data submission for licensure was projected to be 2028, assuming funding is identified quickly, necessary activities (ie technology transfer) and the planning and conduct of the study proceeds expeditiously).
- b. **Accelerated Phase 2b-based licensure pathway.** With the objective to accelerate the overall timing to impact and decrease investments needed, the panel recommended to consult relevant regulatory authorities to discuss opportunities related to an accelerated licensure based on the efficacy and safety data generated from the phase 2b trial. The following key considerations were highlighted:
- i. This would represent a conditional licensure, with a commitment to be made to conduct a more extensive, confirmatory effectiveness assessment subsequent to licensure.

- ii. Although the phase 2b trial was limited to LTBI +/- adults 16-50 years old the panel recommends that the relevant regulatory agencies permit vaccine use to all persons within this age range living in areas endemic for *Mtb* infection, without need for pre-screening for LTBI status, given the impracticability and cost of performing such screening during mass vaccine administration campaigns and in light of the acceptable safety profile of the vaccine in LTBI +/- persons shown in previous clinical trials.
  - iii. Additional trials with Phase 2 clinical trial material could be conducted to strengthen the safety and immunogenicity data package for licensure (e.g. in LTBI +/- and in HIV +/- in priority).
  - iv. Positive aspects of this strategy include:
    - 1. The potential for delivering the M72 vaccine to at-risk populations in the shortest possible time (possibly licensure as early as 2022), and at the lowest development cost.
    - 2. Some country programs with active contact tracing and LTBI screening activities may be interested in early incorporation of M72/AS01 vaccination in their program
    - 3. The potential to obtain data on vaccine effectiveness, based on post-licensure studies, more rapidly, with more flexible designs, with less expense than might be possible via a traditional phase 3 efficacy trial
  - v. Challenges associated with this strategy include:
    - 1. The existing dataset is unlikely to support licensure in other countries than where the study was conducted.
    - 2. Prospects for WHO prequalification and policy decision are uncertain.
    - 3. Licensure utilizing this strategy may make future placebo-controlled studies of the vaccine in the licensing countries difficult due to ethical considerations.
    - 4. Considering potential generalizability and other remaining questions, whether this strategy truly accelerates time to global impact should be further evaluated.
- 8. **Additional trials.** The panel recommends that, in addition to any trial or trials deemed necessary to obtain licensure, additional supportive trials, outside the critical path to initial licensure, should be considered at this time. These trials may include additional safety and immunogenicity studies, but could also assess efficacy using case-control methodologies (controls selected from the community), thereby minimizing the actual size and duration of such studies. Studies should include, but may not be limited to, the following:
  - a. In priority, a trial in HIV-infected persons;
  - b. Younger children, ultimately permitting a lowering of the age bounds on the licensed vaccine
  - c. Persons >50 years old – particularly in China and/or other similar epidemiological settings in Asia or elsewhere, where most TB disease occurs in older populations
  - d. Trials in other geographic locations, including India, Brazil, others
  - e. Trials in pregnant women, lactating women and persons with diabetes or malnutrition;

- f. A study of the potential immunogenicity booster effect of an additional vaccine dose administered to participants previously enrolled in the phase 2b safety/efficacy study (TB 018);
  - g. Trials in LTBI +/- persons at high risk of acquiring *Mtb* infection (i.e. health care workers, household contacts)
    - i. Investigating possible effect on preventing *Mtb* infection (no consensus that this is a priority)
    - ii. Investigating possible effect on preventing TB disease
- 9. The end in mind.** Both strategies mentioned above should be contemplated with the pathway to global impact in mind. Licensure based on the proposals above should be considered as options able to respond to the medical need in various geographical settings and the imperative for affordable access in the context of functional health system delivery to those in need.
- 10. Product development partner.** It is now urgent that GSK determines the selected product development partner, leading to identification of future sponsor, license holder and manufacturer. This is on the critical pathway to near term discussions on the clinical development plan, options for funding, definition of the regulatory strategy.
- 11. Technology transfer.** Developing a robust process to manufacture and scale-up the antigen for use in a possible phase 3 trial, and for subsequent use post-licensure, represents a critical endeavor. It is estimated that 2 years or more may be necessary to reach availability of Phase 3 vaccine lots, from identification of a regulatory sponsor and a manufacturing organization. Investments for technology transfer, process improvement and production capacity to scale could be done in some incremental manner, whereby committed funding would only be released upon successfully passing pre-defined stage gates.
- 12. Adjuvant availability.** It is essential that GSK, in line with its expressed commitment to better health for all and corporate social responsibility principles make adjuvant available to support investigations outlined here. GSK and the global health funding community should work together to ensure long term sustainable availability of AS01 for vaccines against tuberculosis and other diseases, for use in public health markets including resource limited settings, on the basis of and public value-driven health economic and business assessments. In the long term, new adjuvants may become available and bridging tools (correlates of protection) may support adjuvant dose reduction or switch in adjuvants, but such perspectives should not be integrated in the critical path.
- 13. Regulatory roadmap.** It is imperative that a regulatory roadmap be created to clearly define the proposed clinical development plan for M72/AS01E. It is imperative that a regulatory sponsor be identified for this effort, requiring GSK to decide on its development partner/licensee. The following key considerations were highlighted:
- a. Close interaction with the South African Health Products Regulatory Authority (SAHPRA) will be particularly critical if an accelerated pathway to licensure, using the phase 2b data from TB 018, is pursued. Involvement of AVAREF also is strongly recommended to ensure outreach to African regulators beyond South Africa.
  - b. The involvement of EMA through the Article 58 procedure provides a major opportunity for a streamlined review informing WHO PreQualification and Policy decision making.

- c. The possibility of seeking a license under the authority of the U.S. FDA also should be considered. It should be noted that FDA licensure also may result in the granting of a priority review voucher (PRV), which have been valued on the open market at between \$66 million and \$315 million.
- 14. **Community engagement and collaboration.** The voices of civil society and community representatives from affected communities should be included in the continuum of bringing this vaccine to use where needed.
- 15. **Funding.** It is imperative that funding is found to support this effort.
  - a. The panel strongly endorses the WHO plan to convene a panel of potential funders in collaboration with interested stakeholders, before end 2019