M72/AS01E TUBERCULOSIS VACCINE CANDIDATE

CONSENSUS-GENERATING CONSULTATION ON THE DEVELOPMENT PATHWAY

30-31 July 2019
Geneva, Switzerland

Meeting Report

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

MEETING REPORT

Introduction

Dr. Soumya Swaminathan, Chief Scientist, WHO, welcomed the participants. Dr. David Kaslow, Chair of the Consultation and Vice President of Essential Medicines at PATH in Washington, DC, subsequently opened the meeting at 08:40, 30 July 2019. Dr. Kaslow presented the programme of the meeting and introduced the participants.

1. **Key perspectives from the WHO: public health targets.** ***Johan Vekemans, Initiative for Vaccine Research, WHO***

   Dr. Vekemans reviewed the status of the development for the M72/AS01E vaccine from the perspective of the WHO preferred product characteristics (PPC) for TB vaccines[1]. He noted that the development pathway for this vaccine met nearly all the preferred characteristics and that, from the WHO perspective, the development efforts for this vaccine represent a major success and an important step forward in TB vaccine development efforts. This was emphasized by the unanimous recommendation of the PDVAC in their June 2019 meeting to move the vaccine into late-stage development, including a phase 3 efficacy evaluation. Following this consultation on the clinical development pathway, next steps will include developing a full public value assessment and further interactions with the Company and potential funders. *(Slides available here)*

2. **Detailed Review of M72/AS01E TB 018 Results and Discussions.** ***Ann Ginsberg, International AIDS Vaccine Initiative (IAVI)***

   Dr. Ginsberg presented the results of the phase 2b study of M72/AS01E vaccine in preventing TB disease among *Mycobacterium tuberculosis* (Mtb)-infected (quantiferon-positive - QFT+) adults in South Africa, Kenya and Zambia. The results of the primary analysis of this study have been published[2]. Data on the third year of follow-up will be presented at the Union World Conference on Lung Health this autumn. Dr. Ginsberg noted that plans for a correlates of immunity (CoI) analysis have not yet been agreed upon but that a call to the scientific community to address this issue will be forthcoming.

3. **Impact Estimates.** ***Rebecca Harris, London School of Hygiene and Tropical Medicine***

   Dr. Harris presented models enabling the prediction of the potential public health impact of TB vaccines, models that also permitted the assessment of differences in impact between vaccines based on differences in key vaccine variables. Dr. Harris introduced a few different scenarios of modeled vaccine impact estimating the number of TB disease cases potentially averted between 2028 and 2050 for a vaccine introduced in 2028. Dr. Harris's models suggested that nearly 39 million TB cases could be averted in India, and 2.4 million TB cases

averted in South Africa, under her "high case" assumptions, which included a VE of 80% and a 10-year duration of effect when administered to QFT+ persons. If the vaccine were also effective in the pre-Mtb-infection scenario, the impact could be further accentuated. Increasing the reach of mass campaigns, and broadening models of the age groups included in such campaigns, were predicted to increase vaccine impact. Dr. Harris emphasized, however, that targeting strategies may need to be tailored to fit the particular epidemiological characteristics of TB in certain regions and countries.

4. **Of Incidence and Sample Size in TB Vaccine Efficacy Trials.** ***Kathryn Rutkowski, IAVI***

Dr. Rutkowski discussed the assumptions that impact the sample size needed for vaccine efficacy (VE) trials. Important factors driving sample size calculations cited by Dr. Rutkowski were disease incidence, duration of follow-up, the assumed "true" VE, the choice of significance level and the use of a non-zero lower bound of the confidence interval. She noted how other trial design considerations, including adaptive trial design strategies in which interim assessments are included to evaluate potential futility, overwhelming efficacy or the need to recalculate and possibly boost sample size is included in the initial trial design. Dr. Rutkowski also presented a list of potential priority studies, with associated sample size estimates, to advance M72/AS01E development. She concluded by noting that challenges in selecting appropriate sample sizes could be minimized by considering several factors including obtaining an accurate estimate of disease incidence in the study population, avoiding underpowering a trial by assuming a higher VE than expected, and by thinking about the most appropriate alpha and lower bound, considerations that require engagement with appropriate regulatory agencies, emphasizing the importance of including African regulators via organizations such as the African Vaccine Regulatory Forum (AVAREF).

5. **Role of Immunogenicity Markers and Correlates of Protection: What Can We Reasonably Expect?** ***Alex Schmidt, Gates Medical Research Institute***

Dr. Schmidt described three means by which the impact of a TB vaccine can be assessed utilizing measures of immunological response. The simplest is vaccine *take*, in which the ability of a vaccine to generate a physically observable reaction on the skin, such as an area of induration, a scab or an ulcer around the point of injection, due to an immune reaction to the vaccine. The second is through an assessment of immunological correlates of protection (CoP), or the negative image of a CoP, a correlate of risk (CoR). Understanding the actual mechanisms of protection represents the most difficult challenge and offers the greatest opportunity to impact the development of future TB vaccines. Dr. Schmidt proposed that CoP/CoR studies for the TB 018 trial of M72/AS01E be modeled after the governance program for the biological specimens collected under the recently completed study demonstrating an apparent protective effect of BCG revaccination against infection with Mtb. He noted that the Bill and Melinda Gates Foundation (BMGF), in collaboration with GSK, will be coordinating this effort.

6. **GSK Perspectives on Product Availability for Further Testing; Ordering New Material According to Current Process.** ***Marie-Ange Demoitie, GSK***

Dr. Demoitie noted that 8,800 doses of the M72/AS01E vaccine (antigen + adjuvant) remain at GSK. According to the current stability plan, these doses are considered stable until May 2020, 60 months post manufacture. GSK is looking into the possibility of providing data that would extend a stability determination until May 2021. She reviewed the M72 manufacturing process and timelines, stating that manufacturing a new lot would require at least a 1-year notification, pending the availability of facilities. Dr. Demoitie then described the challenges to be faced when scaling up from manufacturing lots for phase 2 assessments to commercially available lots, highlighting that freeze-drying represented a necessary step in the manufacturing process given that the M72 antigen is not stable in liquid and that freeze-drying capacity would need to be scaled up from the current 11,000 vial capacity to a 120,000 vial capacity, requiring construction of new manufacturing facilities. Dr. Demoitie stated that it would be optimal to have the commercial facilities completed at the time of initiating a phase 3 trial but that this was not a mandatory condition necessary to begin such a trial. She also noted that the freeze-drying step was the most difficult aspect of the manufacturing process to hand over via a technology transfer arrangement. Dr. Demoitie also noted that the shelf life for the current vaccine lot already had expired and that the remaining vaccine could be used until May 2020 under the current stability protocol, a date that GSK is trying to extend to 2021. Dr. Demoitie stated that GSK would work with the CoP group to enable the generation of CoP data as soon as possible, utilizing the data from the phase 2b trial. Participants emphasized that a regulatory strategy is urgently needed, including a path to licensure and a plan for the use of CoP data once such data is generated.

7. **Technology Transfer, Process Development, Manufacturing: Perspectives on Procedures, Timing, Costs.** ***David Kaslow, PATH***

Dr. Kaslow emphasized that the *process* of manufacturing M72 is the product that would be the focus of technology transfer efforts. He emphasized that coordinating technology transfer between two different organizations is much more difficult than accomplishing technology transfer within a single organization, with the transfer of regulatory sponsorship from one manufacturer to another being particularly challenging. Dr. Kaslow noted that both a technology transfer protocol and a comparability plan must exist prior to moving from manufacturing vaccine for research to commercial manufacturing efforts and cautioned that sufficient retention samples from the sending facility must be provided to the receiving facility to permit the latter to demonstrate comparability in accordance with ICH guidelines. Dr. Kaslow reviewed the timing of technology transfer efforts, describing typical installation and validation timelines of 1 to 2 years for packaging and 4 to 5 years for building a new facility. He noted that the cost of technology transfer for a vaccine antigen such as M72 generally ranges from $5 million to $50 million, depending on the investment needs for a list of issues which he reviewed. Dr. Kaslow cautioned against underinvestment

in robust analytics and stressed the need to maintain sufficient retention samples to mitigate and manage risk.

8. Key Considerations about Long-term Adjuvant Access. *Michel de Wilde (independent)*:

Dr. de Wilde described the AS01 adjuvant system noting that it contained monophosphoryl lipid A (MPL) derived from the membrane of *Salmonella minnesota*, along with the saponin QS21, derived from the bark of the Chilean tree *Quillaja saponaria* encapsulated together in a liposome. He noted that because both MPL and QS21 are derived from natural sources, challenges exist in maintaining an adequate supply of necessary raw materials and in formulating the finished product. Dr. de Wilde stated that although synthetic TLR4 ligands are available, attempts to utilize them would require a major investment in capacity building to scale up their manufacturing. Dr. de Wilde stated that attempts to utilize alternative adjuvants to AS01E would represent riskier and slower options than advancing the current M72/AS01E vaccine as tested in the phase 2b trial.

The question session that followed Dr. de Wilde's presentation was inclusive of the GSK presentation and Dr. Kaslow's discussion of technology transfer. During this session, participants emphasized the need for a new sponsor to take responsibility for manufacturing the M72 antigen, while GSK intended to continue to be the supplier of the AS01E adjuvant. It was emphasized that a solid business model, with a strongly stated value proposition, would be needed to attract the interest of a potential new supplier of M72. The value of identifying a CoP in the longer term was stressed, as this could be used to support the bridging steps necessary to speed product development. To demonstrate lot-to-lot consistency, it will be important to explore if an immunological marker, rather than a CoP, may be able to achieve this to the specification of relevant regulatory authorities, as relying of discovering a CoP for this purpose entails high risk. Regarding the transfer of M72 manufacturing technology, it was recommended that the whole cell bank (WCB) be transferred from GSK to the new manufacturer, rather than having a new manufacturer start with the master cell bank (MCB), given the existence of immune markers that would support assessments of the WCB rather than the MCB. Finally, the panel was urged to focus on achieving an end-to-end solution to manufacturing M72/AS01E for phase 3 trials and commercialization, rather than focusing in on the individual components of the vaccine. This will be key to attracting significant investment.

9. Accelerated Pathways focused on Reduction of Pulmonary TB in Moderate to High Endemicity Settings. *Dereck Tait, IAVI*

Dr. Tait recommended that the schedule and adjuvant dose used in the phase 2b trial be utilized in an upcoming phase 3 trial as well, a recommendation embraced by the panel members. Dr. Tait then led a discussion on inclusion and exclusion parameters that would be important to consider when attempting to allow the data from a pivotal phase 3 trial to result in broad acceptance among key regulatory agencies while permitting an efficient trial design given likely constraints on resources. Variables discussed included whether the age

range should be inclusive of adolescents and adults older than 50 years; whether the trial should include QFT- persons as well as those who are QFT+; whether HIV-infected (HIV+) individuals should be included; and what the lower bound (LB) of the 95% CI should be. Regarding this last point, Dr. Tait noted that, in the phase 2b trial, the LB of the 95% CI was set at >0%, but this was unlikely to be acceptable by many key regulatory agencies. After some discussion, a LB of >20% was deemed appropriate by many panel members. Dr. Tait then presented two options for the global development of the vaccine; one that would provide enough data to permit the likelihood of global licensure of the vaccine and one describing a staged approach to development that would reduce the time and cost of a phase 3 trial but likely result in the initial licensure of the vaccine in sub-Saharan Africa only, with subsequent licensure in India. In the panel discussion that followed, a third option for licensure was put forward: approaching key regulatory agencies such as the EMA to explore whether the efficacy data generated in the phase 2b study of M72/AS01E, in combination with an expanded safety study encompassing 3,000 or more persons, might be sufficient to merit an accelerated licensure, conditional on conducting 1) an expanded post-marketing efficacy study in the QFT-, HIV-negative (HIV-) population included in the phase 2 b study; and 2) conducting additional phase 3 safety and efficacy studies in QFT-, HIV+ persons, and ages younger than 16 and older than 50, exploring the potential for the expansion of the indicated population in the future. Members of the WHO expressed support for further exploring the potential for achieving conditional licensure for the vaccine in this manner, if the consensus of the panel was in support of this as well.

10. Testing of Alternative Schedules and Formulations in the Context of an Overall Clinical Development Plan: ***Dr. Alex Schmidt, Gates Medical Research Institute***

Dr. Schmidt stated that, in the view of the Gates Medical Research Institute (GMRI), conducting a phase 3 study of M72/AS03E represented an urgent need and should be initiated as soon as possible, without changes in dosing or administration schedule, as licensure of this vaccine represented the fastest route possible to effecting a public health impact concerning TB. From the perspective of the GMRI, a phase 3 study of M72/AS01E should be of sufficient size and duration to unequivocally establish VE in QFT+ individuals while supporting a licensed indication for use in persons regardless of QFT status. Accordingly, the phase 3 VE study should include enough QFT- individuals to establish the safety and immunogenicity of the vaccine in this population, and also should provide a reasonable assessment of VE in QFT- persons. Dr. Schmidt proceeded to present a possible study design based on these and other key parameters. In the discussion that followed, participants declared the urgent need to meet with regulators to discuss the quickest path forward, and to align behind that strategy. There was a consensus that experimenting with different antigen and/or adjuvant doses, or adjusting the vaccine administration schedule, did not represent critical path initiatives and should not delay a phase 3 VE study intended to support vaccine licensing/registration. WHO representatives noted that the WHO Global TB Program and Initiative for Vaccine Research (IVR) were planning to brief the Strategic Advisory Group of Experts on Immunization (SAGE), the main WHO advisory body relevant to vaccines, on the status of M72/AS01E development. Dr. Schmidt concluded the

discussion by reiterating that the BMGF and GMRI were keen on supporting M72AS01E development, but that further development would need to be led by the would-be regulatory sponsor.

11. Other Indications for M72/AS01E not on the Critical Path for Registration: When and How? *Mark Hatherill*

Dr. Hatherill cited four potential indications for the M72/AS01E vaccine that were not on the critical path for development: 1) preventing TB in household contacts; 2) preventing recurrent TB in persons successfully treated for active TB; 3) preventing TB in persons with HIV/AIDS; and 4) preventing TB in children. In his presentation, Dr. Hatherill discussed potential study strategies to use when assessing the vaccine for these endpoints and set forth pros and cons for each approach. In the discussion that followed, participants noted that the potential for use in other important sub-populations at increased risk for developing TB, including persons with diabetes mellitus, also should be explored. Dr. Vekemans highlighted the WHO Preferred Product Characteristic stating that once a vaccine is shown to be effective in adults, it should be studied for use in children as well. The importance, and challenges, of study the vaccine in pregnant women, particularly HIV+ pregnant women, also was cited.

Concluding discussion, first day:

Dr. Kaslow noted that there was unanimous support to move the M72/AS01E vaccine into late stage development and cited the sense of urgency among the panelists to make this happen. Critical needs that must be addressed to actualize this plan include the identification of a new regulatory sponsor (taking the place of GSK – defined as "the most urgent issue"); actualizing technology transfer between GSK and the new regulatory sponsor; ensuring that there is sufficient AS01 supply to meet phase 3 and early commercialization demand; and obtaining sufficient funding to assist in the technology transfer efforts and to conduct a pivotal phase 3 efficacy trial.

Dr. Vekemans noted that, from the perspective of the WHO, the outcome of the meeting represented major progress. In particular, he highlighted the urgent need to find a new regulatory sponsor. He emphasized the need to seek active participation from other key institutions and organizations supporting global public health initiatives such as the NIH and the Wellcome Trust.

DAY 2 Discussion

Dr. Michel de Wilde, Recap of Day 1
Dr. de Wilde outlined the points of discussion upon which there was broad agreement on Day 1.

- There was a consensus that the phase 2b data justified moving the M72/AS01E vaccine forward, "diligently and as aggressively as possible";

- There is a need to develop a regulatory roadmap and an associated clinical development plan (CDP);
- There is a need to identify a regulatory sponsor to move the vaccine forward. This responsibility falls to GSK;
- There is a critical need to identify a source of initial funding;
- There was consensus that a phase 3 trial should not be delayed by efforts to alter the phase 2b dosage or administration schedule in efforts to achieve dose-sparing;
- There was consensus that of the 8,800 M72 vaccine doses remaining with GSK, approximately 2,000 should be set aside as retention samples, leaving approximately 6,800 available for use in further trials.

Dr. de Wilde also reviewed key points of discussion from Day 1 that required further clarification and discussion;

- GSK is requesting clarity not just on initial funding but stated a strong preference for a line of sight that included the source and amount of total funding;
- GSK is seeking further clarity on expectations regarding their further preparation of the M72 antigen for a phase 3 trial. In particular, they are asking whether there is an expectation that antigen scale up would start early, prior to initiation of a phase 3 trial, or whether scale-up would occur in parallel to the conduct of a phase 3 trial;
- What is the perspective of the panel on the suggestion that key regulatory authorities be approached with the idea of utilizing the existing VE data from the phase 2b study in support of licensure, with additional safety data to be added?
- What will be the proposed initial indication for the vaccine?
- What initial geographical location(s) will be targeted for first licensure efforts?
- What secondary indications for the vaccine should be pursued, and in what hierarchy of priority?
- Subsequent to the phase 3 trial, should efforts be made to further adjust dose and administration schedule?

In the discussion that followed, participants reflected that:

- A regulatory filing in support of vaccine licensure could be made by 2021, with potential licensure by 2022, if a regulatory body were to accept the phase 2b efficacy data in support of licensure, without require additional efficacy data. It was suggested that the South African Health Products Regulatory Authority (SAHPRA) be approached with this proposal, with the European Medicines Agency (EMA) and AVAREF included in these discussions.
- Efficacy data generated primarily in SA may not satisfy regulatory authorities in other countries. It will be important to generate additional efficacy data that is globally relevant to achieve global registration of the vaccine. The possibility of achieving initial licensure in SA, possibly based on existing phase 2b efficacy data, and then moving on to conducting a phase 3 efficacy study that could support vaccine prequalification (PQ) and global use of the vaccine, was discussed.
- As the phase 2b study was performed in QFT+ persons only, a study could be performed quickly in QFT- individuals, both to provide additional safety data and to assess efficacy, possibly via a case-control strategy. This would prevent a situation where the vaccine label

would indicate that vaccine use was restricted to QFT+ persons only, a situation that would not be practical when attempting to implement a vaccination program.

- A first order of business is to develop a robust process to scale up the manufacturing of the M72 antigen. Representatives from GSK stated that this would require a 3-year process to achieve a final product, with the product potentially being licensed as early as 2025.
- It will be important to develop a licensure strategy that will be acceptable to regulatory authorities in India and China given the pressing need for deployment of a TB vaccine in these countries.
- It will be important to utilize the 6,800 remaining vaccine doses being made available for human studies before they reach the end of their official stability date (May 2020; GSK noted that they are looking into the possibility to extend this until May 2021). This remaining vaccine represents phase 2 clinical material that could be used to assess safety and immunogenicity in various populations such as HIV+ persons, QFT- individuals, pregnant women, adults age 65 years and older and children age 12 years or younger, as well as in varied geographical locations such as India and China. Participants emphasized that such studies needed to be large enough to perform meaningful assessments, thereby permitting the accrual of additional efficacy data.
- Financial support will need to come from a number of major funders within the global health space. To attract potential funders, developers will need to present to them a compelling integrated vision of the entire development process and implementation plan for the vaccine, not just a focus on what the next phase 3 efficacy trial will look like.
- As the key decision-makers regarding licensure/registration are the regulatory and procurement agencies in the countries where the vaccine is most likely to be utilized, it will be important to include authoritative voices from these agencies in the decision-making process for further vaccine development. It would be a tragic error to generate clinical trial data that will not prove useful in allowing countries to make registration or procurement decisions.

Dr. Vekemans summarized this session by noting that this meeting represented an important advance over the 5 April 2019 high-level consultation of the M72/AS01E vaccine candidate given the major points of consensus regarding the development plan for the vaccine expressed during this meeting (please see the Executive Summary for details). WHO will be hosting a Full Public Value assessment of TB vaccines in September. It will be important to involve civil society members from end user countries when moving forward with clinical development plans.

Dr. Swaminathan congratulated meeting participants on the collaborative approach to advancing the M72/AS01E vaccine displayed in the meeting. She encouraged the participants to keep the momentum going. She noted that the first critical decision point would be GSK's selection of a partner to manufacture future lots of M72 and to take regulatory responsibility for vaccine registration efforts. Dr. Swaminathan also highlighted the importance of engaging regulatory bodies, particularly in countries targeted for early vaccine registration and use. Dr. Swaminathan concluded the meeting by emphasizing the WHO commitment to making sure that this effort continues to move forward.

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