Questions from Spotlight on M72/AS01E phase 3 clinical trial.

Answers from Gates MRI, attributed to Dr Lee Fairlie, Country Principal Investigator, and Dr Alemnew Dagnew, Clinical Lead.

1. In previous press statements and on the ClinicalTrials.gov page it is said that the trial would recruit 26,000 participants, but in the new statement it says "up to 20,000". Can you confirm that 20,000 is indeed the correct number and explain why the number has come down by so much?

Answer: As a result of ongoing discussions between the institute and our funders, the decision was taken to review the study protocol with the intent of simplifying the study given its size and complexity. This will not affect the safety of the trial. It is common to continue to refine a protocol. We found a way to expedite the study that would potentially allow us to offer the public health impact of this vaccine to those in need sooner. All partners, including the trial funders, are fully aligned to the protocol refinements. The trial will include 20,000 participants. Some assumptions used to inform the design of the first protocol were deemed overly conservative, so the clinical team used slightly less conservative assumptions on Vaccine Efficacy (VE) and TB incidence rate thus allowing for a reduction in the number of participants in the trial, while still retaining the primary goal of confirming the safety and efficacy of the M72/AS01-E-4 vaccine for prevention of TB, guided by the final results of the phase 2b study completed several years ago.

2. Can you provide details on how many people living with HIV will be recruited and how many people without TB infection?

Answer: The Gates MRI is expecting to recruit around 20,000 study subjects aged 15 to 44 across up to 60 trial sites. The trial will include three cohorts based on HIV and Interferon-Gamma Release Assays (IGRA) statuses: 18,000 HIV- IGRA+ cohort, 1,000 HIV- IGRA- cohort and 1,000 HIV+ cohort (of either IGRA status).

3. Can you give our readers an accessible explanation of why the study includes the three cohorts (LTBI/No LTBI/HIV)?

Answer: This is the first vaccine candidate to be evaluated in an adult population with latent TB infection, and it is the first subunit vaccine candidate ever to demonstrate efficacy against pulmonary TB in adults, the most common manifestation of the disease in people. It has met key criteria for the WHO's preferred product characteristics for new adult/adolescent TB vaccines. A study group includes panelists who are IGRA-negative so we can obtain more data on the safety of the vaccine candidate in this population. The Gates MRI recently completed the MESA-TB study which, funded by Wellcome and the Gates Foundation, which assessed the safety and ability to induce an immune response of the M72/AS01E vaccine in people living with controlled HIV infection on antiretroviral therapy (ART), to inform and support their inclusion in the phase 3 trial of this vaccine. This trial was completed and supported the inclusion of such participants in a phase 3 trial, they are an important population of people at risk from developing pulmonary TB.

4. Sorry, a very basic science question. Can you give an accessible explanation of why M72 is targeted at people with LTBI? Is it mainly that people with LTBI are simply a higher risk group and therefore worth targeting, or is there an immunological reason to think M72 would have greater efficacy in people with LTBI?
   Answer: The WHO estimates that up to a quarter of the world's population carries latent TB. If shown to be well-tolerated and effective, M72/AS01E could potentially become the first vaccine to help prevent pulmonary TB in adolescents and adults, the most common form of the disease, and the first new TB vaccine in over a century.
5. Can you say something about the challenges with recruitment? We know LTBI is very common in SA, but we don't have a clear idea of how hard it would actually be to recruit a sufficient number

of people with LTBI for this study (we assume they'll be the biggest cohort). Anything you can say to help us understand the dynamics/challenges here would be helpful.
Answer: We need to be quite careful in our recruitment approach, and need to recruit in places where there is a high TB burden and high TB transmission, called a TB hotspot. Latent TB rates differ between communities, some as high as 60% others much lower and we'll need to map these latent TB prevalences to make sure that we recruit enough people with latent TB. These tend to be people in high density, impoverished communities and because they're at highest risk of TB disease, they're also likely to have the greatest benefit from a TB vaccine with efficacy against pulmonary TB.

6. On ClinicalTrials.gov quite a lot of the study sites are listed as being in South Africa. Do you have a rough estimate as to what percentage of study participants will be in SA?
Answer:We anticipate enrolling between 50% and 60% of the trial participants in SA.
7. We understand from the statement that the first site where shots have been administered is at Wits, but can you please provide precise details of the site? Is it a specific clinic or hospital?
Answer: Wits RHI Shandukani falls under the Maternal and Child Directorate at Wits RHI (there are 6 directorates). Wits RHI is the largest Institute of The University of the Witwatersrand.
8. Are the primary and secondary endpoints for the trial indicated on ClinicalTrials.gov still accurate? (We see it was last updated in October 2023 - https://classic.clinicaltrials.gov/ct2/show/NCT06062238) If they have changed, could you share the updated ones with us?
Answer: Yes, they are accurate. The information currently on ClinicalTrials.gov is based on version 1 of the protocol. All study endpoint definitions in version 2 are unchanged relative to version 1. We will update the information on ClinicalTrials.gov as soon as possible.
9. According to the ClinicalTrials.gov page follow-up will essentially be five years. Are we correct in assuming that most vaccinations in the trial will happen in year 1 and the rest of the time would be monitoring/follow-up?
Answer: In version 2 of the protocol, we have 4 years of follow up from the first participant enrolled. The plan is to complete enrollment in 2 years. The actual duration of the trial will depend on how long it takes to accrue 110 cases of lab-confirmed pulmonary TB in the per-protocol analysis set.
10. Based on the phase 2 studies, are there any biomarkers that you will be looking at as indications that the jab is working?
Answer: Yes, we will look at different markers.
11. We've seen some studies stopped early in recent years when a routine DSMB peak at the data showed clear efficacy or futility. How often will data from this study be looked at to see if there are early signs of high efficacy or futility?
Answer: The independent data monitoring committee (IDMC) will review safety data every quarter. There is currently no plan to stop the trial early for high efficacy or futility. We will analyze the data after accruing 110 cases of laboratory confirmed pulmonary TB.
12. Are any sub-studies planned and can you provide details of what these sub-studies will look at? We are thinking of e.g. qualitative studies on acceptability (given issues like vaccine skepticism).
Answer: There are ongoing discussions to conduct qualitative studies on acceptability and related topics.
13. Just to be 100% clear, m72 is administered as two intramuscular injections a month apart? Can you say which muscles are used? How different/similar would it be to getting e.g. a SARS-CoV-2 jab?
Answer: Yes, it is administered as two intramuscular injections a month apart. The site of administration is the deltoid muscle.
14. On the face of it $550m seems very expensive, even given the size of this study. Can you help our readers understand why the study costs so much to run?
Answer: This is a large study over seven countries and up to 60 sites, we expect the study to run for 5-6 years. The total cost of the study includes manufacturing costs, analysis and other support activities.