M72/AS01$_E$ & PREVENTION OF TB DISEASE
PHASE 2B TRIAL IN A IGRA-POSITIVE POPULATION

- 49.7% (95% CI 2.1 to 74.2%) vaccine efficacy (VE)
- Acceptable safety profile

DOI: 10.1056/NEJMoa1803484 & DOI: 10.1056/NEJMoa1909953
M72/AS01\textsubscript{E} PRODUCT DEVELOPMENT

- GSK, supported by Aeras and BMGF, developed M72/AS01\textsubscript{E} through Phase 2b
- Gates MRI obtained a commercial license from GSK in 2020 to enable continued vaccine development and potential use in LMICs
- GSK actively supports technology transfer & provides adjuvant for the program
PHASE 3 DEVELOPMENT: KNOWLEDGE GAPS & CHALLENGES

• Significant uncertainty with regards to incidence of *Mtb* infection & TB disease
  / Highest possible TB incidence rate needed to increase probability of success
  / Clinical trials capacity needed in poor communities in LMICs

• Significant uncertainty with regards to true vaccine efficacy (VE)
  / Primary endpoint definition appears to have impact on VE and incidence rate in IGRA-positives
  / No data on VE in IGRA-negative populations
  / No data on VE in PLHIV

• How to mitigate uncertainties?
  / Determine IGRA-positivity by age at site-level, include high burden sites only
  / Build clinical trials capacity where it is needed
  / Adaptive trial design & event-triggered primary endpoint analyses
KEY QUESTIONS FOR M72/AS01E

• Phase 3 study
  / Does M72/AS01E protect IGRA-positive individuals from disease (POD) and for how long)?
  / Does M72/AS01E protect IGRA-negative individuals from infection (POI) and/or disease?

• What data needed for first dossier in South Africa?
  / Lower bound of 95% CI? Submission with interim data (e.g., 95%CI LB>0), followed by primary analysis data (e.g., 95%CI LB>15%)?

• Delivery considerations
  / Target age group for implementation? - Will depend on VE for POI in IGRA-negative individuals
  / Delivery channels, payors, etc. ?

• What needs to be included in the Phase 3 and what implementation research is needed to support WHO policy recommendation, PQ and financing?
CRITICAL PATH

Clinical & Regulatory:

• Generate Safety & Immunogenicity data to support inclusion of PLHIV in Phase 3 VE trial
• Select highest incidence sites for Phase 3 VE trial, based on large epi trial
• Develop Phase 3 protocol jointly with stakeholders
• Reach agreement on protocol design & initial registration package with health authorities
• Conduct a high-quality Phase 3 VE trial

Technical Development:

• Develop M72 antigen manufacturing process to support Phase 3 and commercialization
• Manufacture new drug product to supply Phase 3
• Identify Commercial Manufacturer
PHASE 2 STUDY IN PEOPLE LIVING WITH HIV

- Observer-blind, randomized, placebo-controlled safety & immunogenicity study
- PLHIV on ART for > 3 months (VL<200 copies, CD4 ≥ 200)
- Six sites in South Africa
- Enrollment ongoing, completion of enrollment anticipated in July 2021

www.clinicaltrials.gov NCT04556981
EPI STUDY TO PREPARE FOR PHASE 3 VE TRIAL

Objectives
• IGRA-positivity at site-level, by age (as proxy for high infection rates in young adults)
• Incidence of pulmonary TB (overall)

Operational goals:
• Build site capacity & train teams
• Establish operational feasibility for each site

Design:
• 8,000 study participants, 50 sites, study duration flexible, 12 - 24 months
• Study to end at a given site once site is ready to start Phase 3 enrolment
• IGRA status at baseline & at Month 12, follow-up every 2 months for suspected TB
PHASE 3 EFFICACY STUDY DESIGN FOR M72/AS01\textsubscript{E}

- Demonstrate VE for POD in IGRA-positive participants
- Support licensure for use irrespective of IGRA status

\hspace{1em} / Include enough QFT-neg participants to establish safety, immunogenicity & VE for POI

- Support licensure including people living with HIV
- Trial simulations suggest that at least 14,000 subjects in very high incidence settings are needed to demonstrate VE in a randomized placebo-controlled trial
- An interim analysis for VE could be explored to potentially accelerate submission of a first dossier
TO CONCLUDE

• M72/AS01E can potentially contribute to accelerating the end of the TB epidemic

• A large clinical endpoint trial in high incidence settings is needed to demonstrate vaccine efficacy in a population at high risk of infection & disease

• Identification of candidate correlates of protection is a key priority for Gates MRI to accelerate vaccine development
THANK YOU