

2024 Annual Meeting

12 November 2024

Bali, Indonesia



Updates on Phase 3 candidates MTBVAC and M72/AS01E



BILL & MELINDA
GATES *foundation*

TB Vaccine Pipeline

Ann Ginsberg

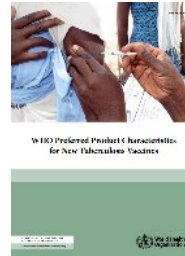
November 12, 2024

End-to-End TB Vaccine Development

Selection of Useful Reference Resources:



- [Preferred Product Characteristics \(WHO\)](#)
- [Global Roadmap of R&D for TB Vaccines \(AIGHD, EDCTP\)](#)
- [Investment Case for a New TB Vaccine \(WHO\)](#)
- [Global Framework to Prepare for Country Introduction of New TB Vaccines for Adults and Adolescents](#)
- [Evidence Considerations for Vaccine Policy Development for Tuberculosis Vaccines Intended for Adults and Adolescents \(WHO\)](#)
- [Conducting market analyses for new tuberculosis vaccines for adolescents and adults: A summary of one approach applied to M72/AS01E](#)



Key Preferred Product Characteristics (PPC) for new adolescent and adult TB vaccines

<https://www.who.int/publications/i/item/WHO-IVB-18.06>

Parameter	Preferred Characteristic
Indication	Immunization for prevention of active pulmonary TB disease
Target Population	Adolescents and adults
Outcome Measure and Efficacy	50% or greater efficacy in preventing confirmed pulmonary TB
Duration of Protection	Ten years or more, ideally Demonstrated efficacy over at least 2 years after completion of the primary immunization regimen to support initial policy decisions.
Safety	Safety and reactogenicity profile should be favorable, similar to other current WHO-recommended routine vaccines for use in adolescents and adults.
Schedule	A minimal number of doses and boosters required. A requirement for more than three doses to achieve primary immunization would not be desirable due to logistical and cost concerns.

TB Vaccine Pipeline

Vaccine candidates under clinical development

There are 15 vaccine candidates in the pipeline as of September 2024, of which 12 are in active trials. The candidates are placed under the phase which corresponds to the most advanced ongoing or completed trial.

Platform

-  Mycobacterial - Live attenuated
-  Mycobacterial - Inactivated
-  Viral vector
-  Protein/Adjuvant
-  RNA

Candidate target population

-  Elderly
-  Adults
-  Adolescents
-  Children
-  Infants
-  People living with HIV
-  People without Mtb infection
-  People with Mtb infection
-  People with active TB disease
-  People with MDR-TB
-  People cured of active TB

Trial status

-  Active trials
-  No active trials

Primary candidate indication

-  Prevention of Infection
-  Prevention of Disease
-  Prevention of Recurrence
-  Therapeutic

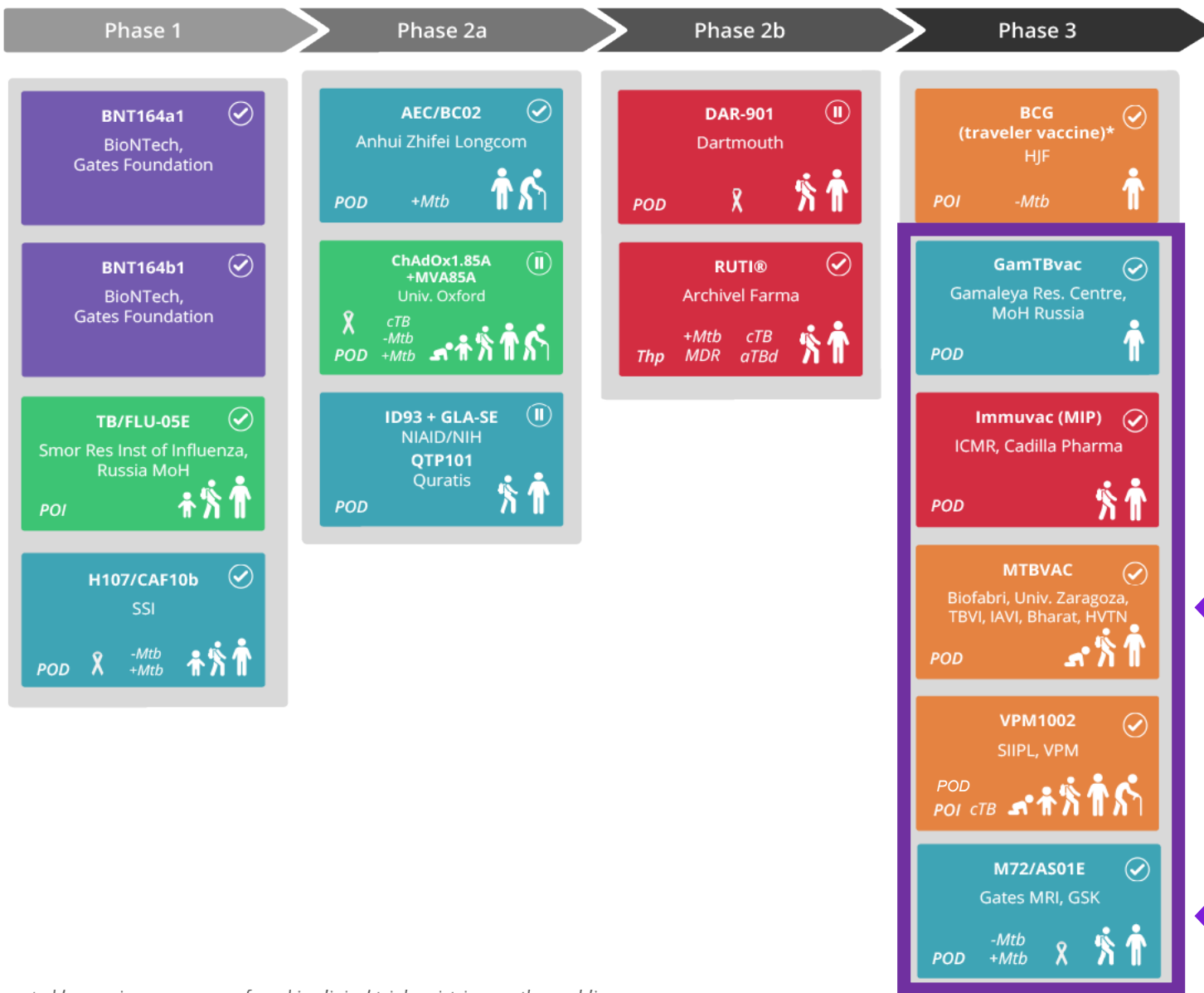


Information reported by vaccine sponsors or found in clinical trial registries or other public sources

Institutions listed are vaccine sponsors and development partners

Additional information, including the full list of clinical trials for each candidate, can be accessed via the QR code or at newtbvaccines.org/tb-vaccine-pipeline/

Last update: 2 September 2024



**Next 5 years –
an unprecedented
bolus of efficacy
trial results**

Vaccine candidate	Results anticipated (my best guess)
VPM1002	
POD; also, IMMUVAC (MIP)	4Q 2024
POR	2024
POI	2026
MTBVAC	
POD (infants)	4Q 2028
POD (adolescents/adults)	2028-2029
BCG revac - POI	2024 – No VE demonstrated
M72/AS01 _E - POD	2028
H56:IC31 - POR	2024 – No POR demonstrated
RUTI (adjunct to treatment; improved outcomes)	4Q 2025
GAMTBVAC - POD	4Q 2025

Trials complete; results pending

Thank
you!



Annual Meeting
12 November 2024
Bali, Indonesia



Clinical Development Update: MTBVAC

Mark Hatherill

South African Tuberculosis Vaccine Initiative

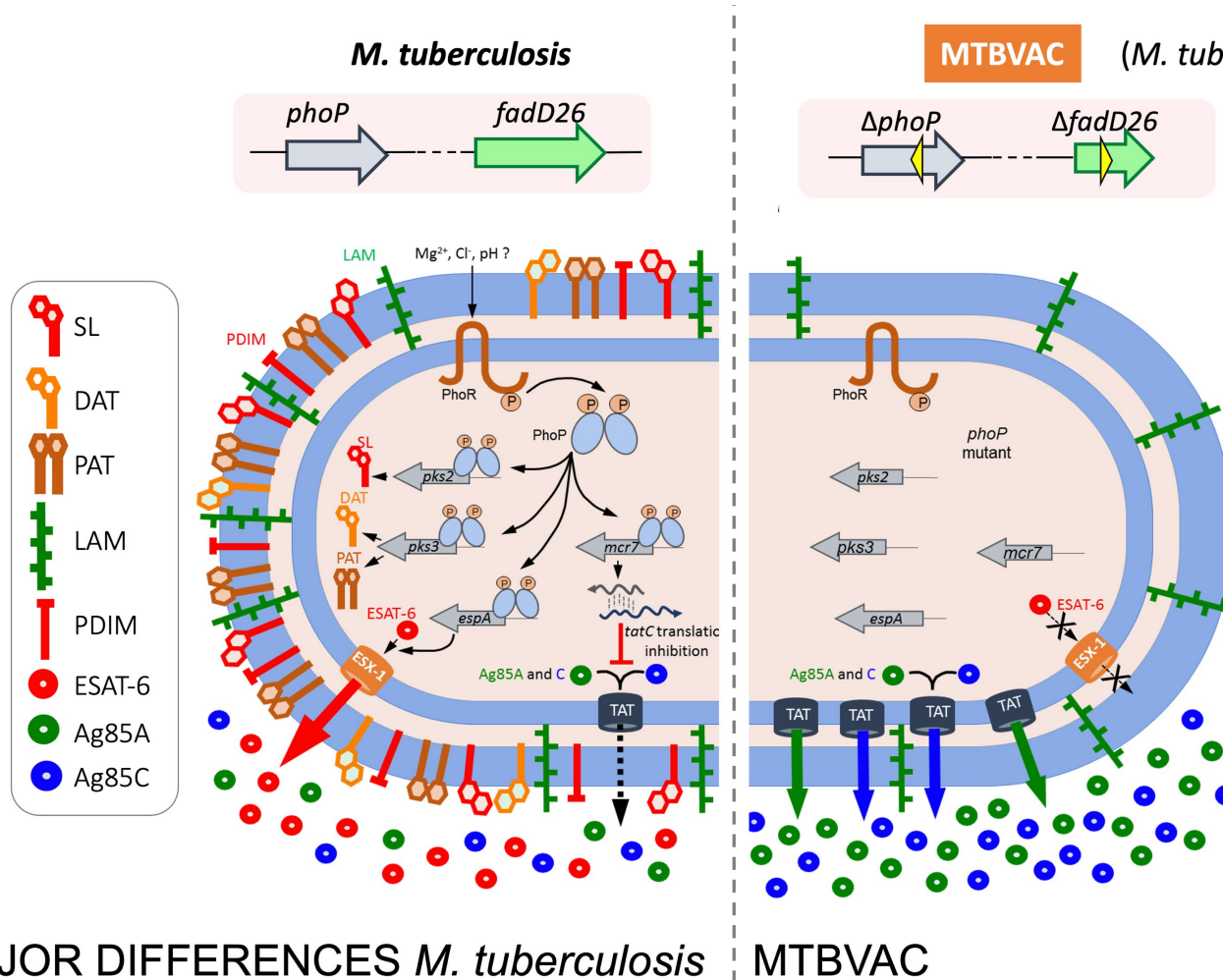
University of Cape Town

Slide presentation courtesy of Ingrid Murillo Jelsbak, Biofabri



MTBVAC: Live attenuated *M. tuberculosis* vaccine

Two stable deletions in independent virulence factors



phoP: controls expression
2% of MTB genes

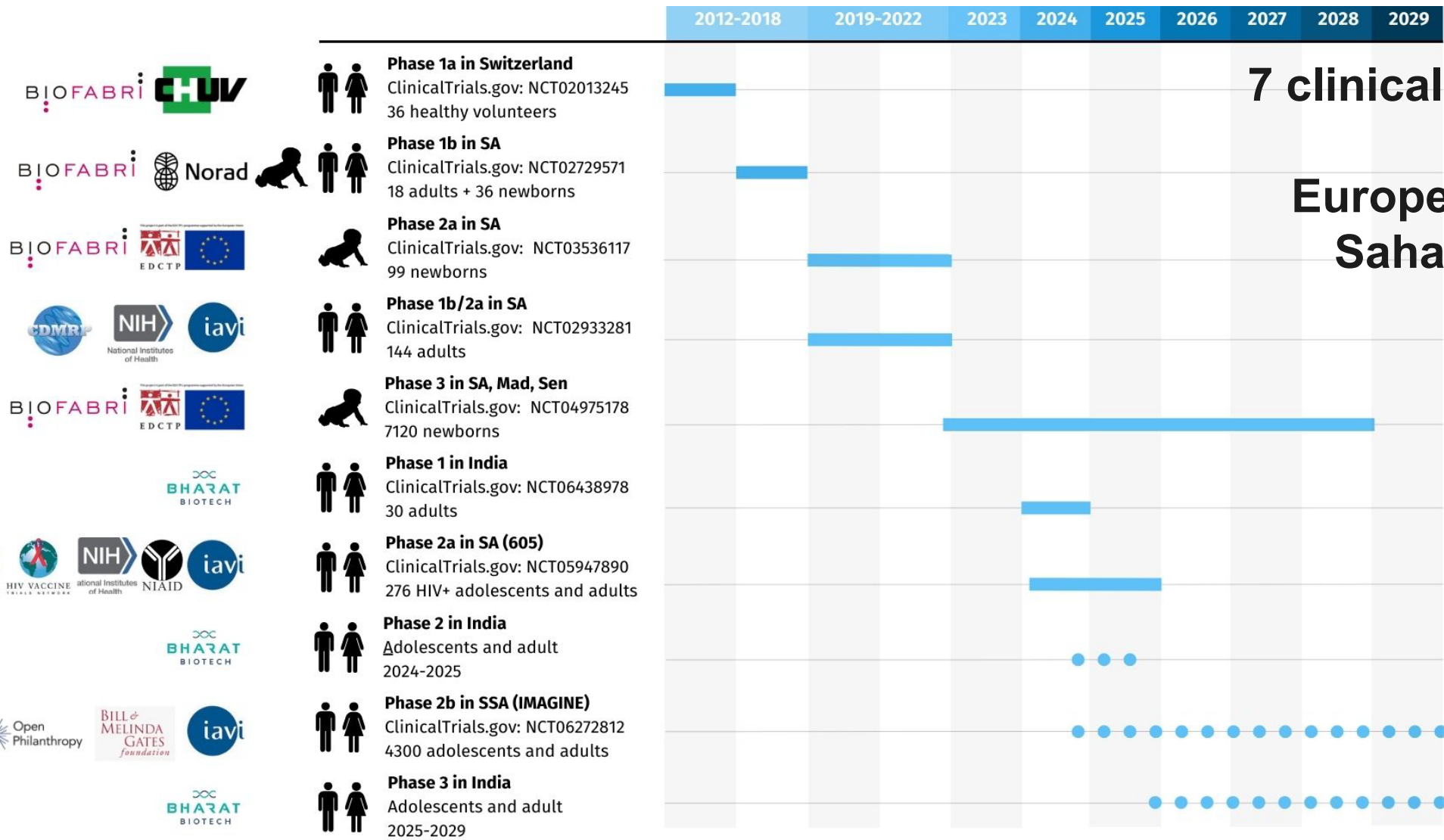
fadD26: synthesis PDIM
Major Virulence Lipid in MTB

**Major difference
MTBVAC/ BCG
contains RD1:**

ESAT6/CFP10/PPE68:
311 epitopes

J Gonzalo Asensio

MTBVAC: Timeline



7 clinical since FIH (2012)
Europe and Sub-Saharan Africa

3 clinical trials pending Sub-Saharan Africa and India



MTBVAC: First-in-human and Phase 1b

Phase 1a: BCG-naïve adults in

Safety of human immunisation with a live-attenuated *Mycobacterium tuberculosis* vaccine: a randomised, double-blind, controlled phase I trial

François Spertini¹, Régine Audran², Reza Chakour², Olfa Karoui², Viviane Steiner-Monard², Anne-Christine Thierry², Carole E Mayor², Nils Rettby³, Katia Jaton⁴, Laure Vallotton⁵, Catherine Lazor-Blanchet⁶, Juana Doce⁷, Eugenia Puentes⁷, Dessislava Marinova⁸, Nacho Aguilo⁸, Carlos Martin⁹

Affiliations + expand

PMID: 26598141 DOI: 10.1016/S2213-2600(15)00435-X

Phase 1b: BCG-vaccinated adults and BCG-naïve

Live-attenuated *Mycobacterium tuberculosis* vaccine

MTBVAC versus BCG in adults and neonates: a randomised controlled, double-blind dose-escalation trial

Michele Tameris¹, Helen Mearns¹, Adam Penn-Nicholson¹, Yolande Gregg¹, Nicole Bilek¹, Simbarashe Mabwe¹, Hennie Geldenhuys¹, Justin Shenje¹, Angelique Kany Luabeya¹, Ingrid Murillo², Juana Doce², Nacho Aguilo³, Dessislava Marinova³, Eugenia Puentes², Esteban Rodríguez², Jesús Gonzalo-Asensio³, Bernard Fritzell⁴, Jelle Thole⁴, Carlos Martin⁵, Thomas J Scriba¹, Mark Hatherill⁶; MTBVAC Clinical Trial Team

Collaborators, Affiliations + expand

PMID: 31416768 DOI: 10.1016/S2213-2600(19)30251-6

Spertini et al, Lancet Respir Med 2015

- MTBVAC is as safe and immunogenic as BCG in healthy BCG-naïve, HIV negative adults

Tameris et al, Lancet Respir Med 2019

- MTBVAC is as safe as BCG and more immunogenic than BCG in newborn infants
- Dose-related IGRA conversion → reversion

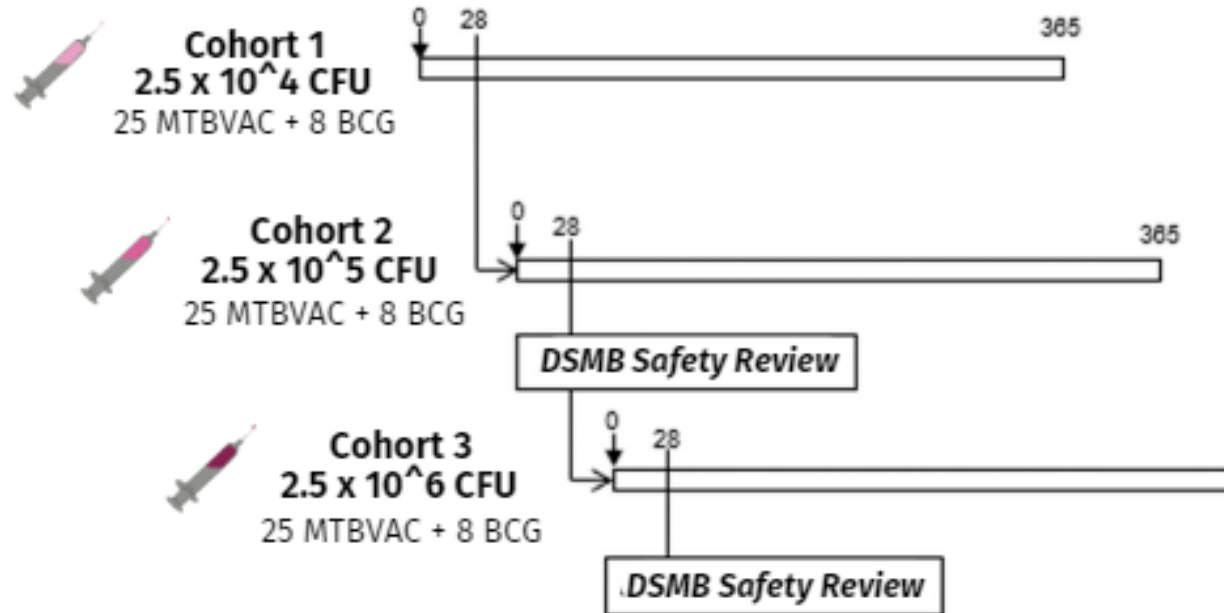
MTBVAC Phase 2a in Newborn infants

NCT03536117A: Completed

Phase 2a Randomized Controlled Dose-Defining Trial of the Safety and Immunogenicity of MTBVAC in Healthy, BCG Naïve, HIV Unexposed, South African Newborns

N=99; MTBVAC @ 3 dose levels (n=25 x 3)

or BCG (n=24)



Study Site



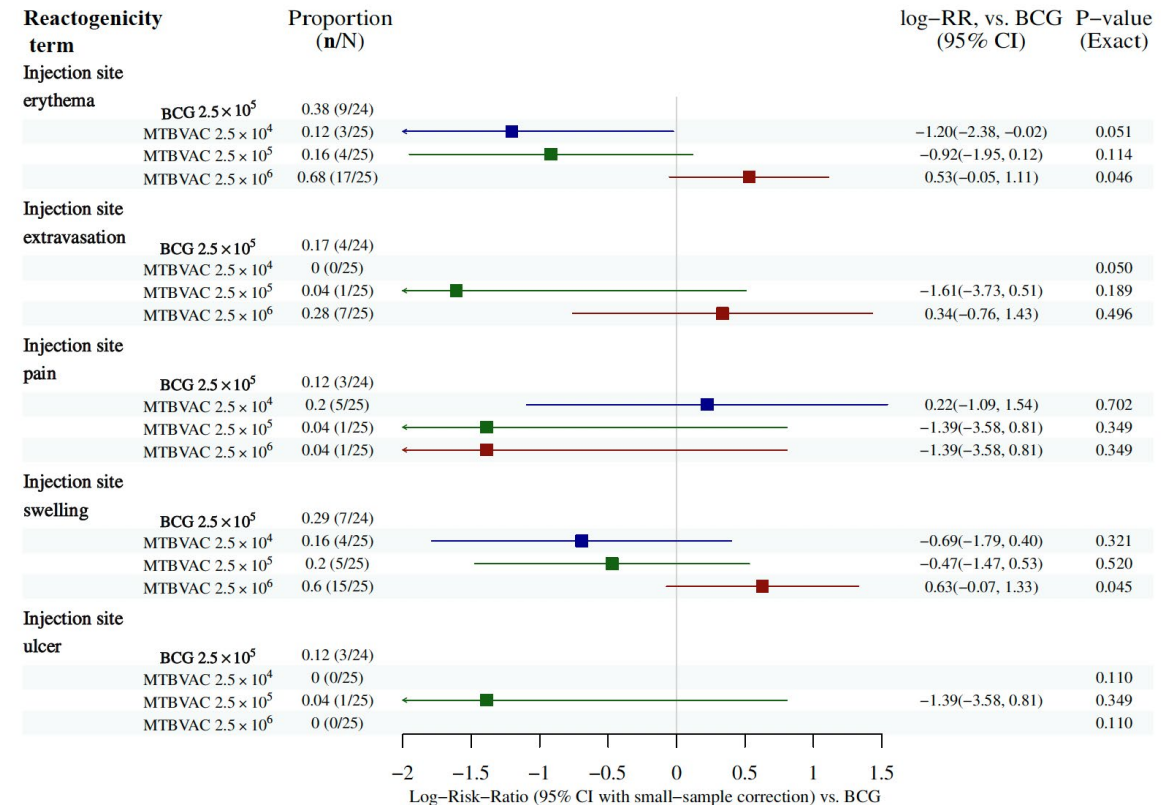
MTBVAC Phase 2a in Newborn Infants

NCT03536117A: Completed

Phase 2a Randomized Controlled Dose-Defining Trial of the Safety and Immunogenicity of MTBVAC in Healthy, BCG Naïve, HIV Unexposed, South African Newborns

Manuscript under review, Tameris et al, EbioMedicine

- All MTBVAC doses appeared safe and well tolerated (2.5 x 10⁴, 10⁵ and 10⁶ CFU)
- MTBVAC appeared as safe as BCG and more immunogenic at the equivalent dose (10⁵ CFU)
- 8 infants were treated Unconfirmed pulmonary TB (4 x BCG and 4 x MTBVAC 2.5×10⁴ CFU)
- 1 infant treated for Unconfirmed TB meningitis (1 x BCG)
- 2.5×10⁵ CFU MTBVAC dose selected for the Phase 3



MTBVAC Phase 1b/2a in Adults

NCT02933281: Completed

Live-attenuated *M. tuberculosis* vaccine, MTBVAC, in adults with or without *M. tuberculosis* sensitization: a Phase 1b/2a randomized, controlled, double-blind, dose-escalation trial

N= 144; MTBVAC @ 4 dose levels (12 IGRA- / 12 IGRA+) or BCG (24 IGRA- / 24 IGRA+)

8 Cohorts



Manuscript under review, Luabeya et al, Lancet Global Health

- MTBVAC 5 x 10⁵ CFU dose showed comparable safety and reactogenicity, greater immunogenicity compared to BCG in Mtb-unsensitised and Mtb-sensitised individuals

Study Site



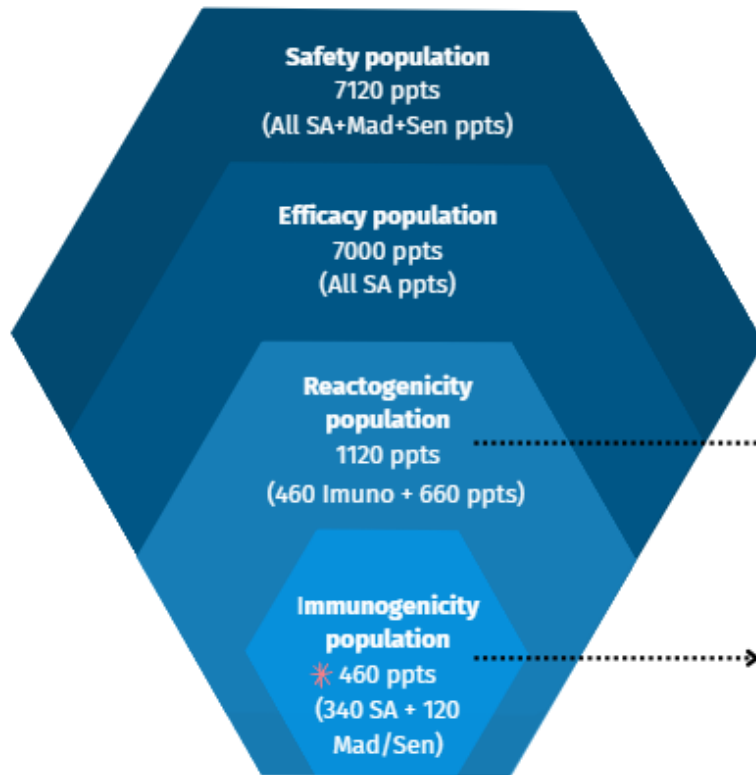
Cape Town

MTBVAC Phase 3 in Newborn Infants

NCT04975178: Recruiting

Randomized, Double blind, Controlled Phase 3 to evaluate the Efficacy, Safety and Immunogenicity of MTBVAC administered in healthy HIV unexposed uninfected and HIV exposed uninfected newborns in Tuberculosis-Endemic Regions of Sub-Saharan Africa

Study Population



- * - 100 HEU (HIV exposed uninfected)
- 240 HU (HIV unexposed)

N= 7,120 newborn infants, HEU and HUU

South Africa (4), Madagascar (1), Senegal (1)

Completed for SA ✓

Completed for SA ✓

Study Sites



MTBVAC Phase 3 in Newborn Infants

NCT04975178: Recruiting

Randomized, Double blind, Controlled Phase 3 to evaluate the Efficacy, Safety and Immunogenicity of MTBVAC administered in healthy HIV unexposed uninfected and HIV exposed uninfected newborns in Tuberculosis-Endemic Regions of Sub-Saharan Africa

MTBVAC 2.5×10^5 CFU dose vs BCG

- Efficacy (min 24 – max 72 months)
- Safety
- Non-specific effects (hospitalization, death, non-TB infectious diseases)
- Immunogenicity (subset)
- Biobank immune correlate samples (all)

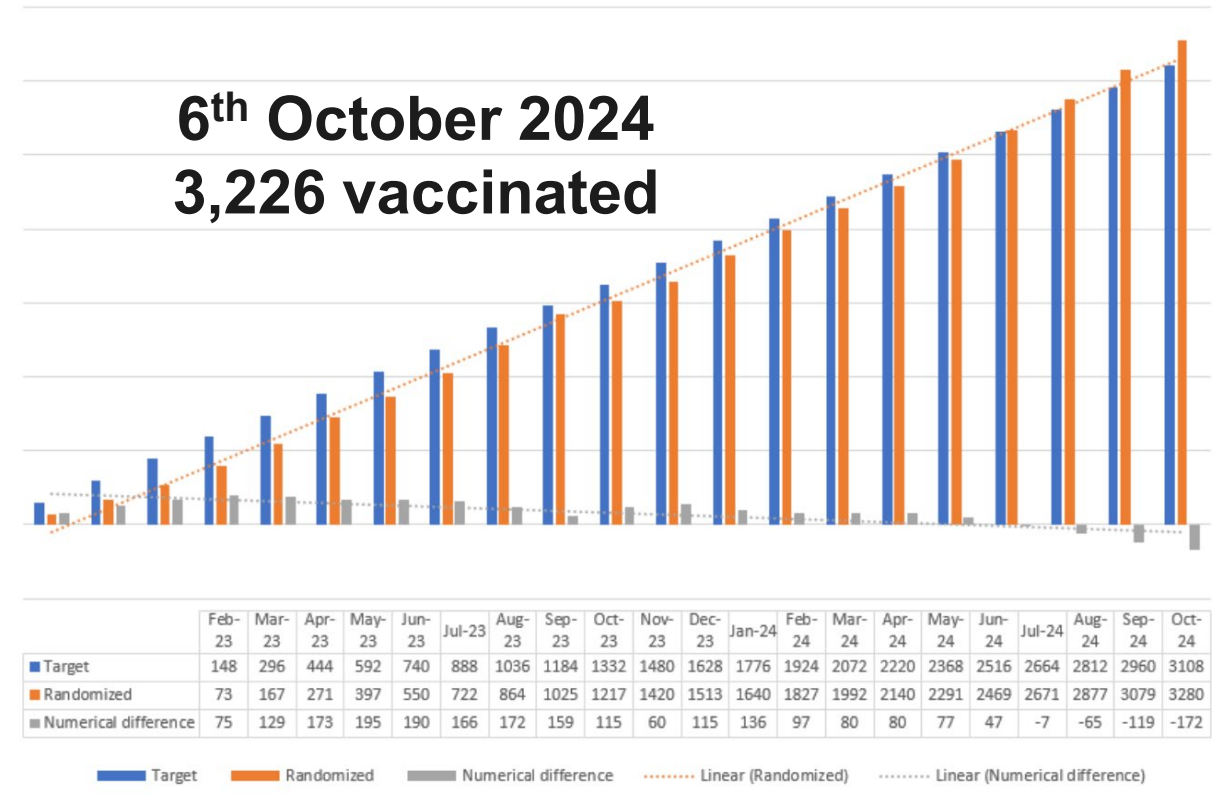
Rigorous, adjudicated 1^o endpoint definition
(Confirmed / Unconfirmed TB)

144 TB Cases powered for Hazard Ratio 0.5
(50% efficacy MTBVAC relative to BCG)

Interim analyses @ 49 (futility) and 97 (futility/efficacy)

Primary completion date estimated 2028

Cumulative target vs actual randomized 31Oct2024



MTBVAC: Phase 2a in PLWHIV

NCT05947890 (HVTN605/A5421): Recruiting

A Phase 2a Clinical Trial to Evaluate the Safety and Immunogenicity of MTBVAC in Adolescents and Adults Living With and Without HIV in South Africa

Goal: To allow PLWHIV to participate in planned efficacy evaluation

N=276 volunteers aged 12 - 55 years, IGRA-positive and IGRA-negative

Cohort 1: Adolescents and adults without HIV

Cohorts 2: Adolescents and adults with HIV viral suppression, ART (>6 months), TPT

CD4 count ≥ 200 cells/mm³ at screening

WHO clinical stage 1/2 prior to ART

Cohort 3: Adults with HIV viral suppression, ART (>6 months), TPT

CD4 count ≥ 100 cells/mm³ at screening

CD4 count < 200 cells/mm³ or WHO clinical stage 3/4 prior to ART

Cohort 1 fully enrolled, Cohort 2 >90% enrolled

Cohort 3 enrolls if acceptable safety data → D28 in Cohorts 1 & 2



MTBVAC Phase 2b in Adolescents and Adults

NCT06272812: Pending

A Phase 2b, double-blind, randomized, placebo-controlled study to evaluate the efficacy, safety and immunogenicity of a candidate tuberculosis (TB) vaccine, MTBVAC, against TB disease in interferon gamma release assay positive adolescents and adults aged 14-45 years, living in a TB endemic region

N=4,300 BCG-vaccinated, IGRA+, HIV- adolescents and adults (14 - 45 years) 15 sites in Sub-Saharan Africa

MTBVAC vs placebo

- Efficacy (FU 36 months)
- Safety
- Immunogenicity

IMAGINE

IMAGINE

BILL &
MELINDA
GATES
foundation

iavi

Open
Philanthropy

BIOFABRI

Study Sites



MTBVAC Phase 1 in Adults (India)

NCT06438978: Completed

Phase I Clinical Trial, open label to Assess the Safety, Reactogenicity, Tolerability and Immunogenicity of a Tuberculosis Vaccine BBV169 (MTBVAC), in Healthy Indian Adults





Thank you!

Participants, families and
communities

Investigators and Study Teams

Funders and Collaborators



Phase 1a in Switzerland

ClinicalTrials.gov: NCT02013245

36 healthy volunteers



Phase 1b in SA

ClinicalTrials.gov: NCT02729571

18 adults + 36 newborns



Phase 2a in SA

ClinicalTrials.gov: NCT03536117

99 newborns



Phase 1b/2a in SA

ClinicalTrials.gov: NCT02933281

144 adults



Phase 3 in SA, Mad, Sen

ClinicalTrials.gov: NCT04975178

7120 newborns



Phase 1 in India

ClinicalTrials.gov: NCT06438978

30 adults



Phase 2a in SA (605)

ClinicalTrials.gov: NCT05947890

276 HIV+ adolescents and adults



Phase 2 in India

Adolescents and adult

2024-2025



Phase 2b in SSA (IMAGINE)

ClinicalTrials.gov: NCT06272812

4300 adolescents and adults



Phase 3 in India

Adolescents and adult

2025-2029



BILL & MELINDA GATES MEDICAL RESEARCH INSTITUTE

M72/AS01_E Clinical Development Program Overview

Alemnew Dagne (MD), Clinical Development Leader
Gates MRI

Agenda

- M72/AS01_{E-4} Product Development Background
- Past Studies
- Gates MRI Completed & Ongoing Studies
- Phase 3 Vaccine Efficacy Trial Assumptions & Trial Design
- Proposed Label Indication & Rationale
- M72/AS01_{E-4} Phase 3 Trial Progress

M72/AS01_{E-4} Product Development Background

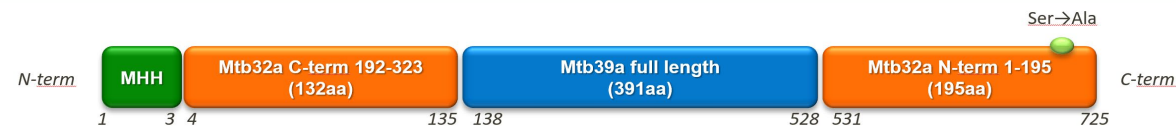
- GSK led product development through Phase 2b
- In 2020, Gates MRI obtained a license from GSK for M72/AS01_{E-4} to continue vaccine development and to register & commercialize the vaccine in many LMICs
- Gates MRI & GSK collaborate to ensure an efficient transfer of the asset technology
- GSK will provide AS01_{E-4} adjuvant for product development & commercial product
- Gates MRI will lead product development & sponsor clinical trials

M72/AS01_{E-4} Product Overview

- Recombinant fusion protein plus GSK proprietary adjuvant system
- 2-vial presentation (reconstitution of antigen + adjuvant) x 2 doses (1 mo. apart)

M72 is a 72kDa recombinant fusion protein derived from the two *M. tuberculosis* antigens

- Mtb39a : membrane-associated protein, putative evasion factor
- Mtb32a : secreted protein, putative serine protease

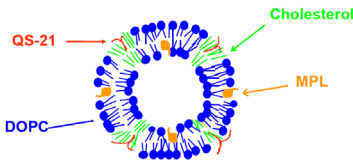


Composition of M72 lyophilized formulation per dose

Ingredient	Quantity per dose*	Function	Reference
M72	10 µg	Active ingredient	GSK Bio 300723
Sucrose	25 mg	Cake stability	Ph. Eur. 0204
Polysorbate 80	0.1 mg	Protein recovery	Ph. Eur. 0428
Tris	0.97 mg	Buffering agent	Ph. Eur. 1053

* Does not include overage
Ph. Eur.: European Pharmacopoeia
Pharmaceutical form: freeze-dried, white pellet

AS01_{E-4} adjuvant system (GSK proprietary) is composed of immunoenhancers, liposome and other excipients



- QS-21 (a triterpene glycoside purified from the bark of Quillaja Saponaria Molina)
- MPL (3-D Monophosphoryl lipid A)
- DOPC
- Cholesterol
- Buffer



Past Studies: GSK-sponsored Phase 1 & 2 trials

M72/AS01_E has been evaluated in a series of Phase 1 and 2 studies and was shown to be immunogenic & have a clinically acceptable safety profile in the following populations:

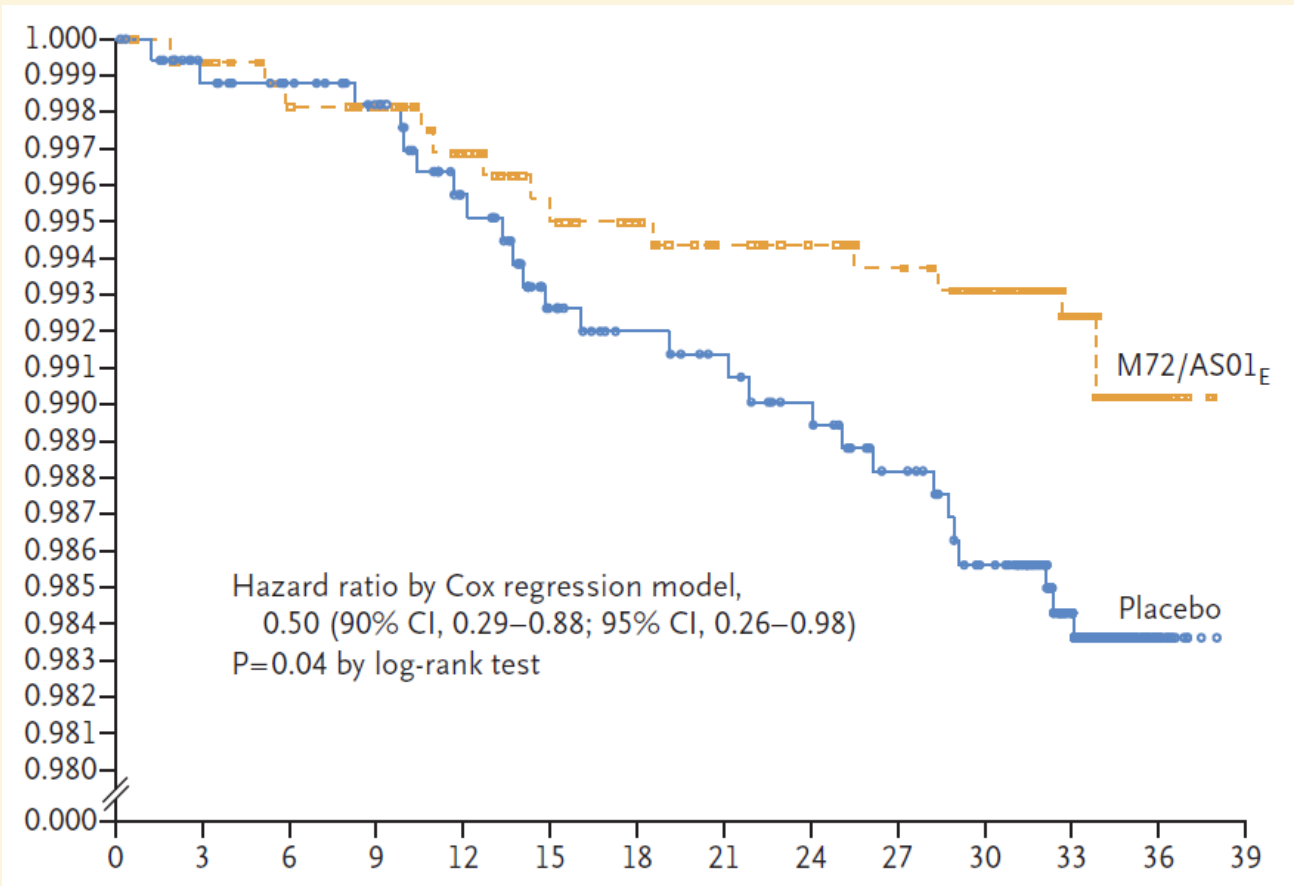
- Purified Protein Derivative (PPD)-negative and -positive adults in South Africa (TB-010)
- PPD-positive adults in the Philippines (TB-009)
- HIV-positive adults on anti-retroviral therapy (ART) in Switzerland (TB-011)
- South African adolescents aged 13 to 17 years (TB-012)
- Healthy infants in Gambia (TB-013)
- HIV-positive adults (ART-naïve), and HIV-positive adults on ART, in India (TB-014)
- Healthy BCG-primed adult participants in Belgium (TB-019)

Phase 2b vaccine efficacy trial in IGRA-positive adults in Kenya, South Africa, and Zambia:

- VE of 49.7% (95% CI 2.1-74.2) for Prevention of Disease (POD) in IGRA+ participants

Phase 2b Results: Prevention of Disease (POD) in IGRA-positive adults

- Vaccine Efficacy Point Estimate: 50% (68%)
- Acceptable safety profile



DOI: [10.1056/NEJMoa1803484](https://doi.org/10.1056/NEJMoa1803484) & DOI: [10.1056/NEJMoa1909953](https://doi.org/10.1056/NEJMoa1909953)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 2b Controlled Trial of M72/AS01_E Vaccine to Prevent Tuberculosis

O. Van Der Meeren, M. Hatherill, V. Nduba, R.J. Wilkinson, M. Muyoyeta, E. Van Brakel, H.M. Ayles, G. Henostroza, F. Thienemann, T.J. Scriba, A. Diacon, G.L. Blatner, M.-A. Demoitié, M. Tameris, M. Malahleha, J.C. Innes, E. Hellström, N. Martinson, T. Singh, E.J. Akite, A. Khatoon Azam, A. Bollaerts, A.M. Ginsberg, T.G. Evans, P. Gillard, and D.R. Tait
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Final Analysis of a Trial of M72/AS01_E Vaccine to Prevent Tuberculosis

D.R. Tait, M. Hatherill, O. Van Der Meeren, A.M. Ginsberg, E. Van Brakel, B. Salaun, T.J. Scriba, E.J. Akite, H.M. Ayles, A. Bollaerts, M.-A. Demoitié, A. Diacon, T.G. Evans, P. Gillard, E. Hellström, J.C. Innes, M. Lempicki, M. Malahleha, N. Martinson, D. Mesia Vela, M. Muyoyeta, V. Nduba, T.G. Pascal, M. Tameris, F. Thienemann, R.J. Wilkinson, and F. Roman

M72/AS01_{E-4} Phase 2b: VE Estimates for Different Case Definitions

Table 1. Vaccine Efficacy of M72/AS01_E as Compared with Placebo against Pulmonary Tuberculosis in Adults with Evidence of Tuberculosis Infection.*

Cohort and Case Definition	M72/AS01 _E			Placebo			Vaccine Efficacy	
	No. of Participants†	Person-yr of Follow-up	Rate per 100 Person-yr (90% CI)	No. of Participants†	Person-yr of Follow-up	Rate per 100 Person-yr (90% CI)	% (90% CI)	% (95% CI)
According-to-protocol efficacy cohort								
First definition	13	4427.62	0.3 (0.2 to 0.5)	26	4463.06	0.6 (0.4 to 0.8)	49.7 (12.1 to 71.2)	49.7 (2.1 to 74.2)
First definition: sensitivity analysis‡	7	4429.29	0.2 (0.1 to 0.3)	22	4467.51	0.5 (0.3 to 0.7)	68.0 (34.7 to 84.3)	68.0 (25.1 to 86.3)
Second definition	8	4429.69	0.2 (0.1 to 0.3)	21	4467.51	0.5 (0.3 to 0.7)	68.0 (34.7 to 84.3)	68.0 (25.1 to 86.3)
Third definition	19	4427.62	0.4 (0.3 to 0.6)	30	4463.06	0.6 (0.4 to 0.8)	49.7 (12.1 to 71.2)	49.7 (2.1 to 74.2)
Fourth definition§	19	4427.62	0.4 (0.3 to 0.6)	32	4463.06	0.6 (0.4 to 0.8)	49.7 (12.1 to 71.2)	49.7 (2.1 to 74.2)
Fifth definition§	26	4434.21	0.6 (0.4 to 0.8)	38	4472.91	0.6 (0.4 to 0.8)	49.7 (12.1 to 71.2)	49.7 (2.1 to 74.2)
Modified fifth definition	25	4434.21	0.6 (0.4 to 0.8)	36	4471.56	0.6 (0.4 to 0.8)	49.7 (12.1 to 71.2)	49.7 (2.1 to 74.2)
Total efficacy cohort								
First definition	13	5055.30	0.3 (0.2 to 0.4)	28	5005.18	0.6 (0.4 to 0.8)	49.7 (12.1 to 71.2)	49.7 (2.1 to 74.2)
Second definition	8	5057.38	0.2 (0.1 to 0.3)	22	5011.28	0.5 (0.3 to 0.7)	68.0 (34.7 to 84.3)	68.0 (25.1 to 86.3)
Third definition	20	5055.30	0.4 (0.3 to 0.6)	32	5005.18	0.6 (0.4 to 0.8)	49.7 (12.1 to 71.2)	49.7 (2.1 to 74.2)
Fourth definition	20	5055.30	0.4 (0.3 to 0.6)	34	5005.18	0.6 (0.4 to 0.8)	49.7 (12.1 to 71.2)	49.7 (2.1 to 74.2)
Fifth definition	28	5061.90	0.6 (0.4 to 0.8)	38	5016.93	0.6 (0.4 to 0.8)	49.7 (12.1 to 71.2)	49.7 (2.1 to 74.2)
Modified fifth definition	27	5061.90	0.5 (0.4 to 0.7)	36	5015.58	0.7 (0.5 to 0.9)	33.3 (10.1 to 56.5)	33.3 (10.1 to 56.5)

The first case definition (blue box) for the primary endpoint (definite pulmonary TB) required **≥1** positive sputum test. The sensitivity analysis of the primary endpoint (red box) required **≥2** positive sputum tests.

The more stringent case definition (**≥2 positive** sputum tests) will be used as primary case definition for the Phase 3 VE trial.

Gates MRI Completed & Ongoing Studies

- Phase 2 trial in people living with HIV (PLHIV) in South Africa (MESA-TB)
 - Generate safety & immunogenicity data to support inclusion of PLHIV in Phase 3 VE trial, approx. 400 participants
- Global epidemiology study
 - Identify sites with high TB incidence and build capacity for Phase 3, approx. 160 participants/site
- Phase 3 vaccine efficacy trial
 - Pivotal registration trial, approx. 20,000 participants

Phase 3 Vaccine Efficacy Trial Assumptions & Trial Design

Protocol Version 2, 08 Jan 2024

- Vaccine Efficacy (VE) against Disease (D) in IGRA+ in per-protocol (PP) cohort is **≥55%**
- Null hypothesis: $H_0: VE(D) \leq 10\%$ ($\alpha < 2.5\%$, lower bound of 95% confidence interval **>10%**)
- Event-triggered VE analysis
- Final analysis of primary endpoint once 110 cases are observed
- >90% power to demonstrate VE of 55% with LB>10%
- TB incidence: **0.4%** per year in IGRA+
- Placebo-controlled, double-blind, 1:1 randomized trial
- N=20,000, 15 to 44 years of age
- 2 years to full enrolment
- Follow-up up to 4 years

Cohort	N
HIV-, IGRA+ cohort	18,000
HIV-, IGRA- cohort	1,000
HIV+ cohort	1,000
Total	20,000

Proposed Label Indication & Rationale

- Indication: “Active immunization to prevent active pulmonary TB in children and adults, 15 years of age and older”
 - Sample size and power calculations estimated through trial simulations
 - Demonstration of VE(D) in a baseline IGRA-negative population is not feasible in a Phase 3 registration trial
- Benefit/risk assessment for the overall population in high TB burden countries is very likely positive
 - If safety and VE(D) are demonstrated in an IGRA+/ HIV- population AND
 - If safety profile is acceptable in PLHIV of either IGRA status AND
 - If safety profile is acceptable in IGRA-/ HIV- populations

M72/AS01_{E-4} Phase 3 Trial Progress

- As of November 11, 2024, 52 sites across Africa and Asia have been activated, with over 15,000 participants enrolled.
- Based on modeling, we anticipate reaching the 110 endpoints needed for the primary analysis in about 4 years, assuming a TB incidence rate of 0.4%.
 - / This timeline may be shorter or longer depending on the actual observed incidence rate of TB.
- Further information on the trial can be found at <https://clinicaltrials.gov/study/NCT06062238>.

Thank You!