Stop TB Partnership

WORKING GROUP ON NEW TB VACCINES

2024 Annual Meeting

12 November 2024

Bali, Indonesia

Updates on Phase 3 candidates MTBVAC and M72/AS01E

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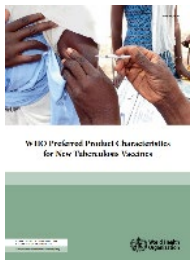
TB Vaccine Pipeline

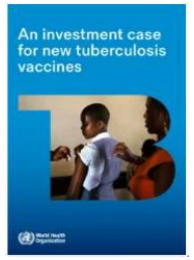
Ann Ginsberg

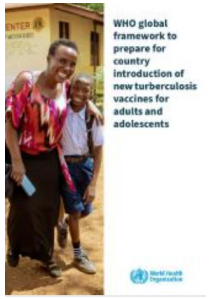
November 12, 2024

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

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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.

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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

Trial staus

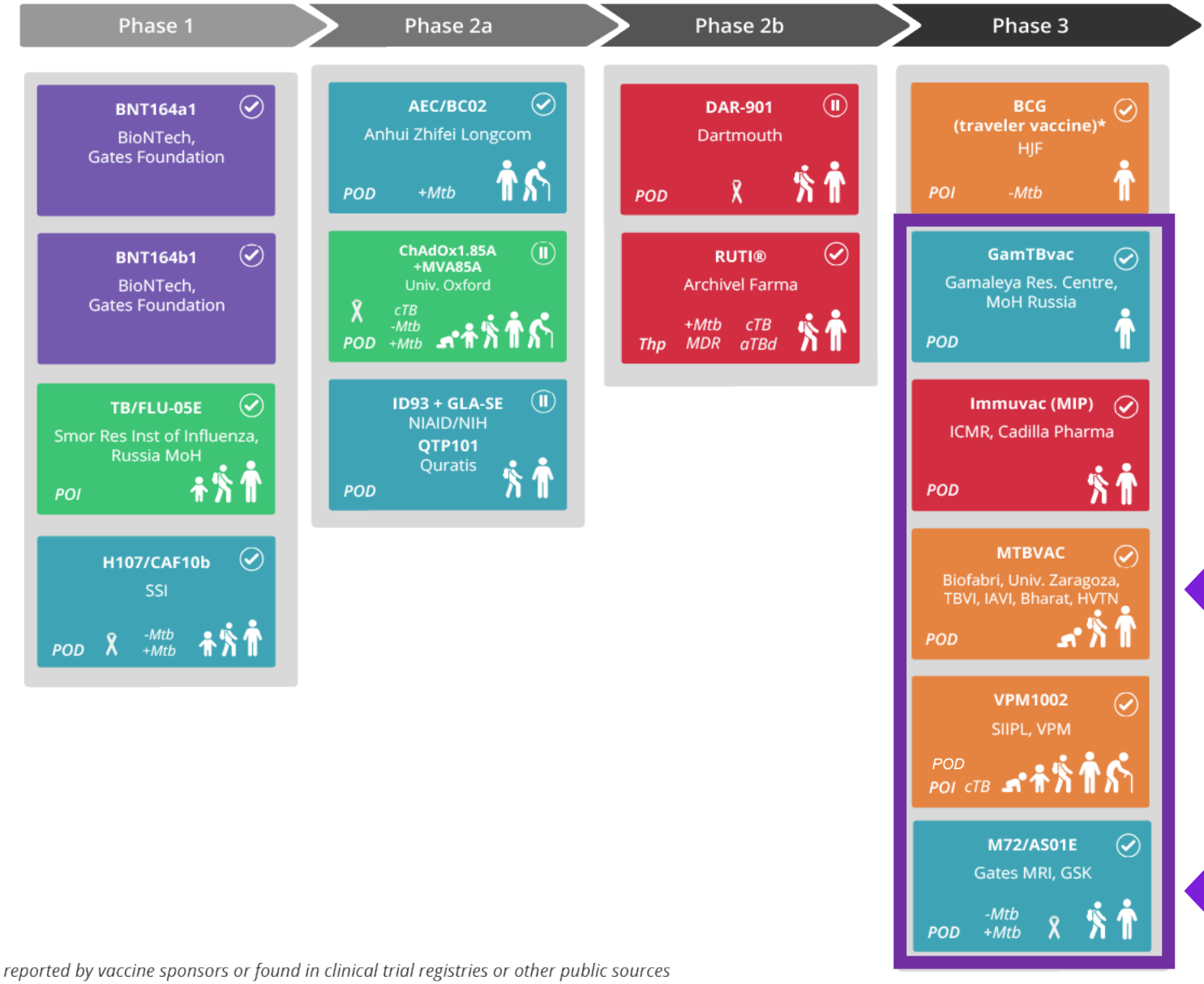
- Active trials
- No active trials

Candidate target population

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

Primary candidate indication

- *POI* — Prevention of Infection
- *POD* — Prevention of Disease
- *POR* — Prevention of Recurrence
- *Thp* — Therapeutic



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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

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Clinical Development Update: MTBVAC

Mark Hatherill
South African Tuberculosis Vaccine Initiative
University of Cape Town

Slide presentation courtesy of Ingrid Murillo Jelsbak, Biofabri

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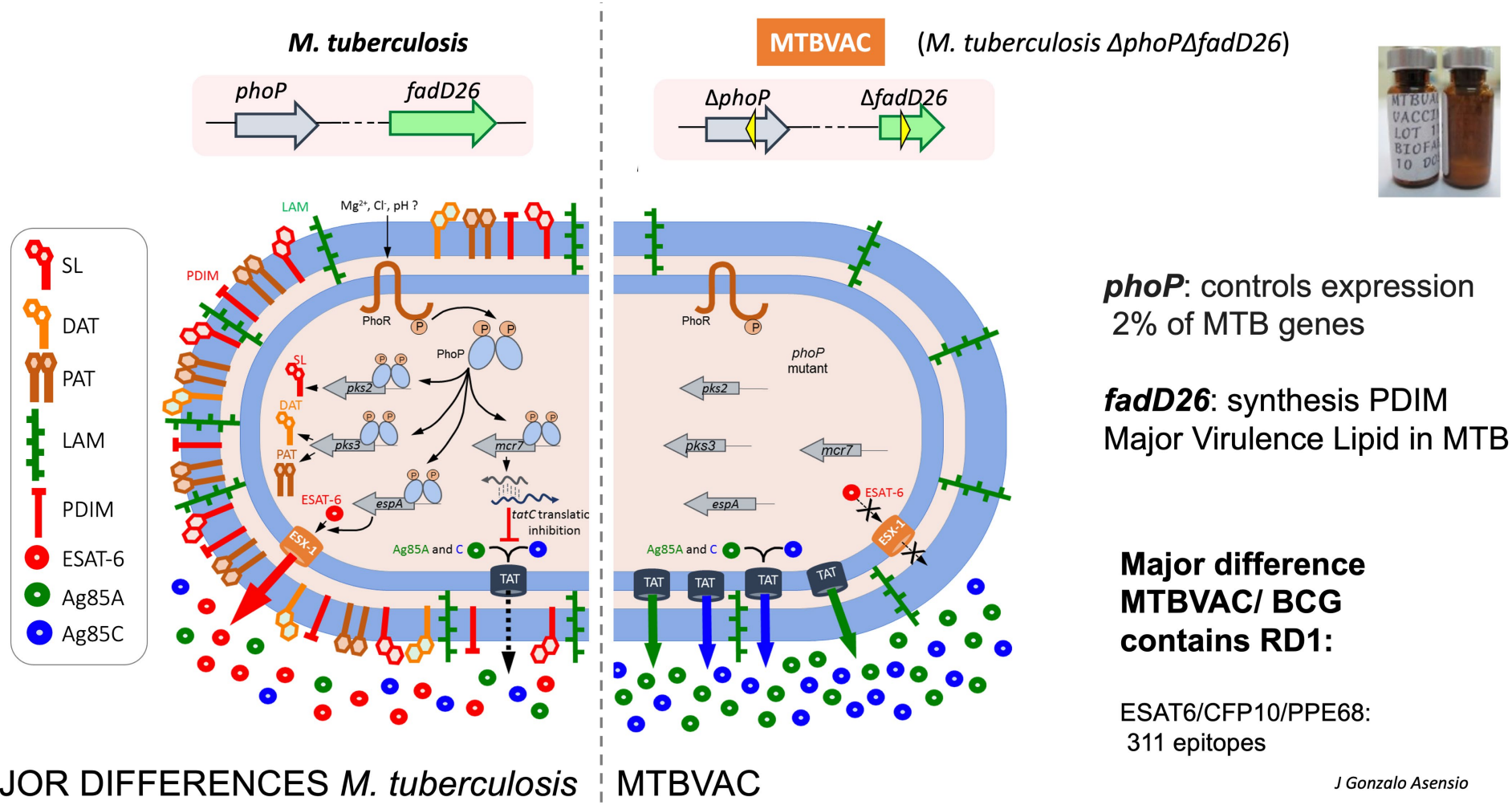
University of Cape Town · iYunivesithi yaseKapa · Universiteit van Kaapstad

MTBVAC: Live attenuated *M. tuberculosis* vaccine

Two stable deletions in independent virulence factors



phoP: controls expression
2% of MTB genes

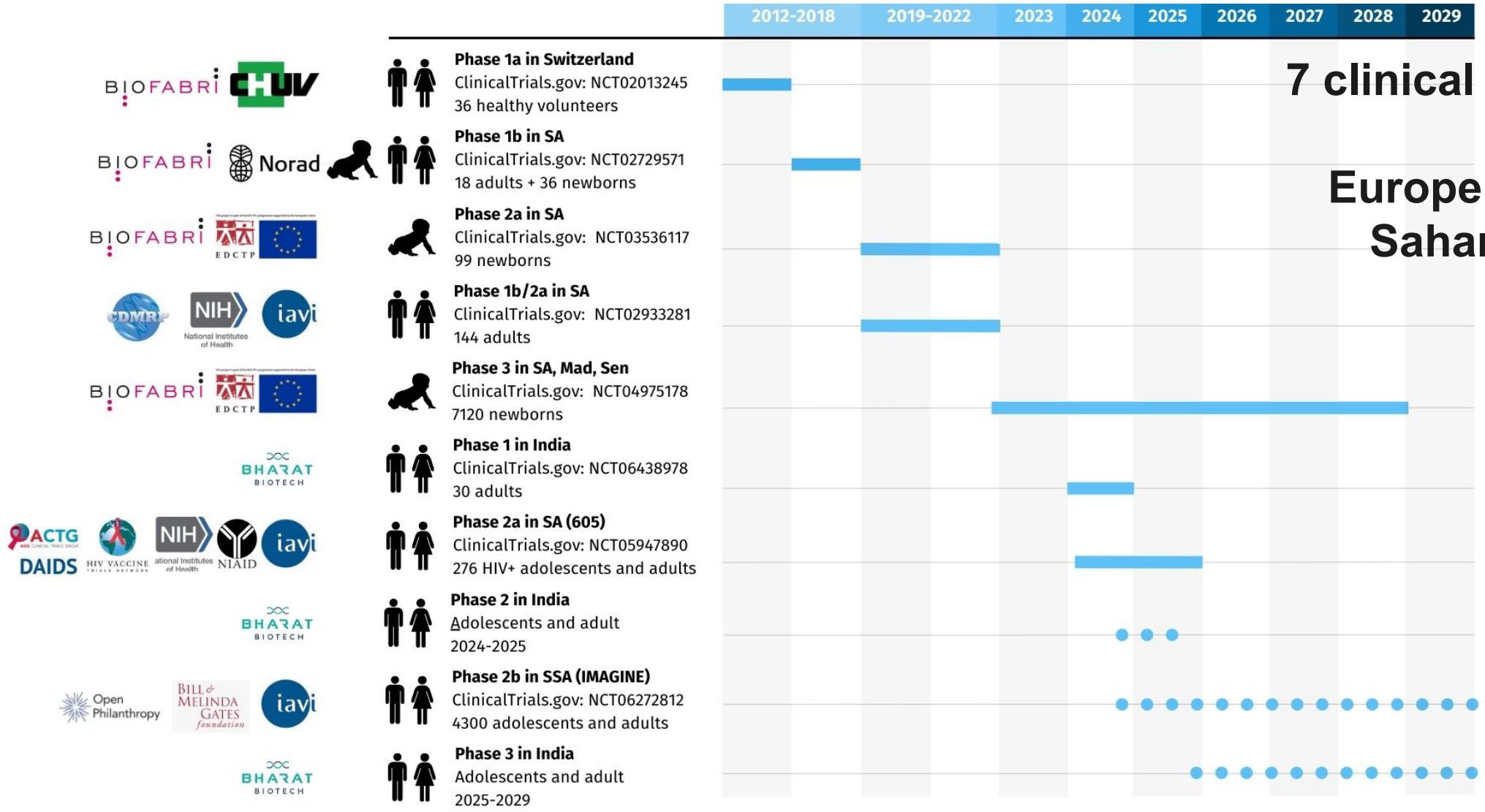
fadD26: synthesis PDIM
Major Virulence Lipid in MTB

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 Spertini [1], Régine Audran [2], Reza Chakour [2], Olfa Karoui [2], Viviane Steiner-Monard [2], Anne-Christine Thierry [2], Carole E Mayor [2], Nils Rettby [3], Katia Jaton [4], Laure Vallotton [5], Catherine Lazor-Blanchet [6], Juana Doce [7], Eugenia Puentes [7], Dessislava Marinova [8], Nacho Aguilo [8], Carlos Martin [9]

Affiliations + expand

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

Spertini et al, Lancet Respir Med 2015

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

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 Tameris [1], Helen Mearns [1], Adam Penn-Nicholson [1], Yolande Gregg [1], Nicole Bilek [1], Simbarashe Mabwe [1], Hennie Geldenhuys [1], Justin Shenje [1], Angelique Kany Kany Luabeya [1], Ingrid Murillo [2], Juana Doce [2], Nacho Aguilo [3], Dessislava Marinova [3], Eugenia Puentes [2], Esteban Rodríguez [2], Jesús Gonzalo-Asensio [3], Bernard Fritzell [4], Jelle Thole [4], Carlos Martin [5], Thomas J Scriba [1], Mark Hatherill [6]; MTBVAC Clinical Trial Team

Collaborators, Affiliations + expand

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

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

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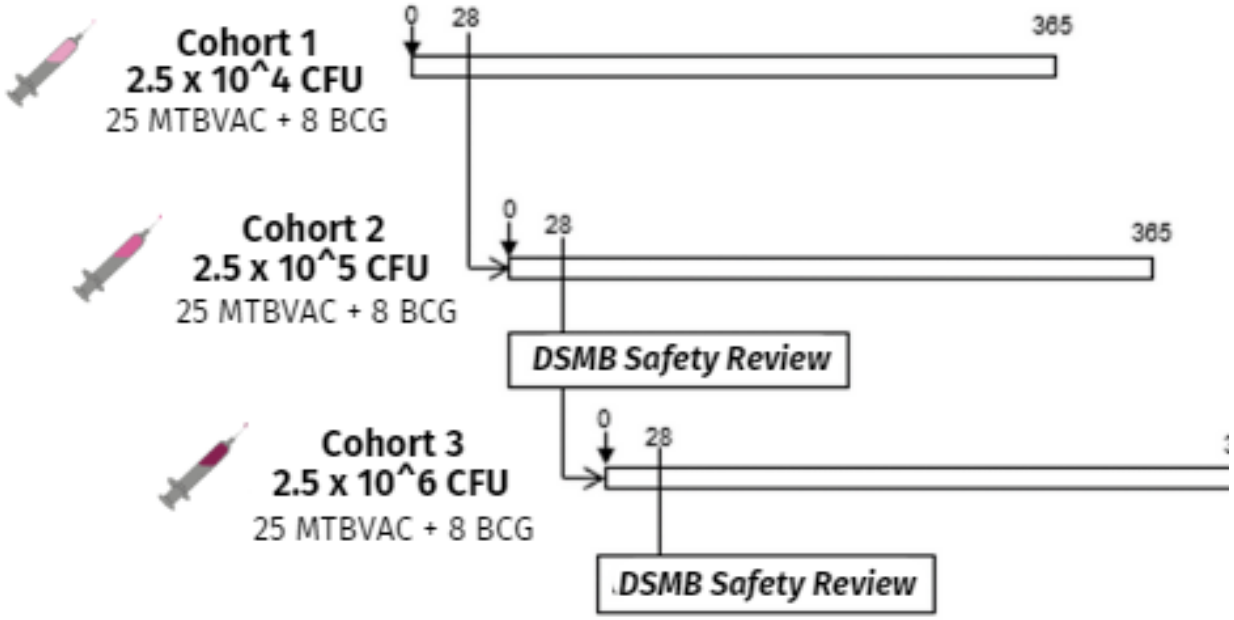
MTBVAC Phase 2a in Newborn infants

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)



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

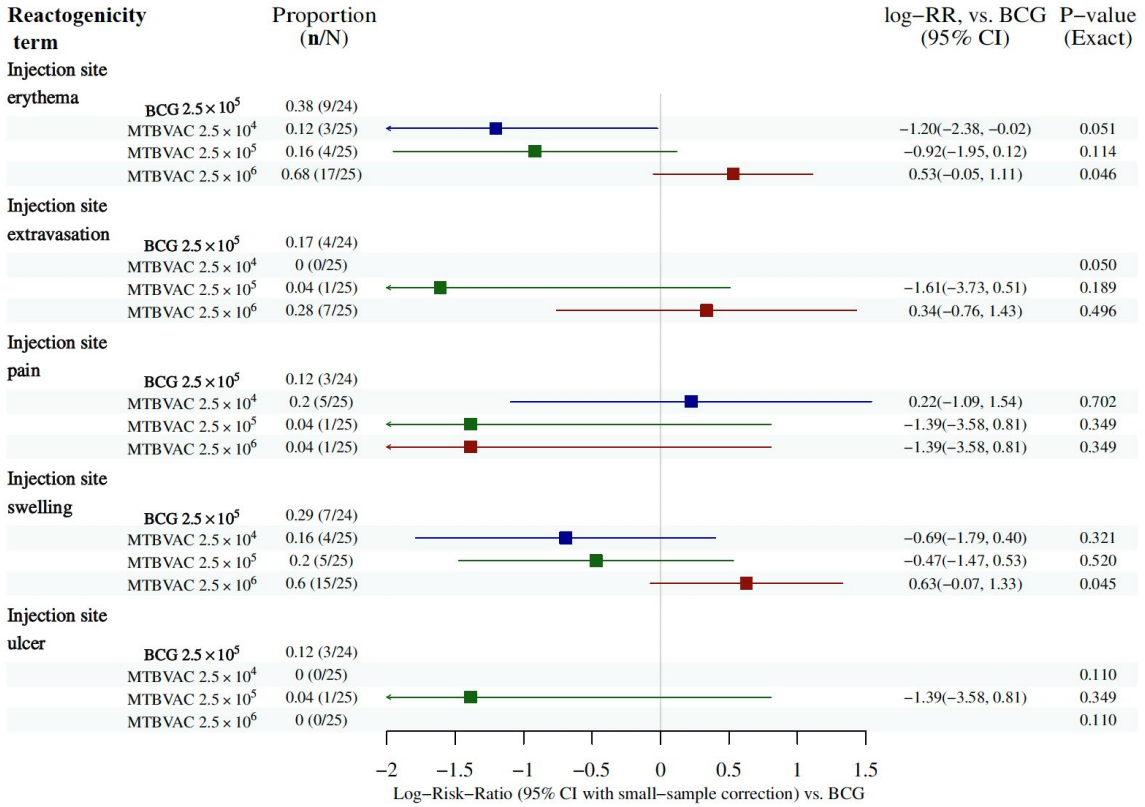
Manuscript under review, Tameris et al, EbioMedicine

- **All MTBVAC doses appeared safe and well tolerated**
- (2.5 x 10^4, 10^5 and 10^6 CFU)

- **MTBVAC appeared as safe as BCG and more immunogenic at the equivalent dose (10^5 CFU)**

- **8 infants were treated Unconfirmed pulmonary TB**
  (4 x BCG and 4 x MTBVAC 2·5×10^4 CFU)
- **1 infant treated for Unconfirmed TB meningitis**
  (1 x BCG)

- **2·5×10^5 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+)

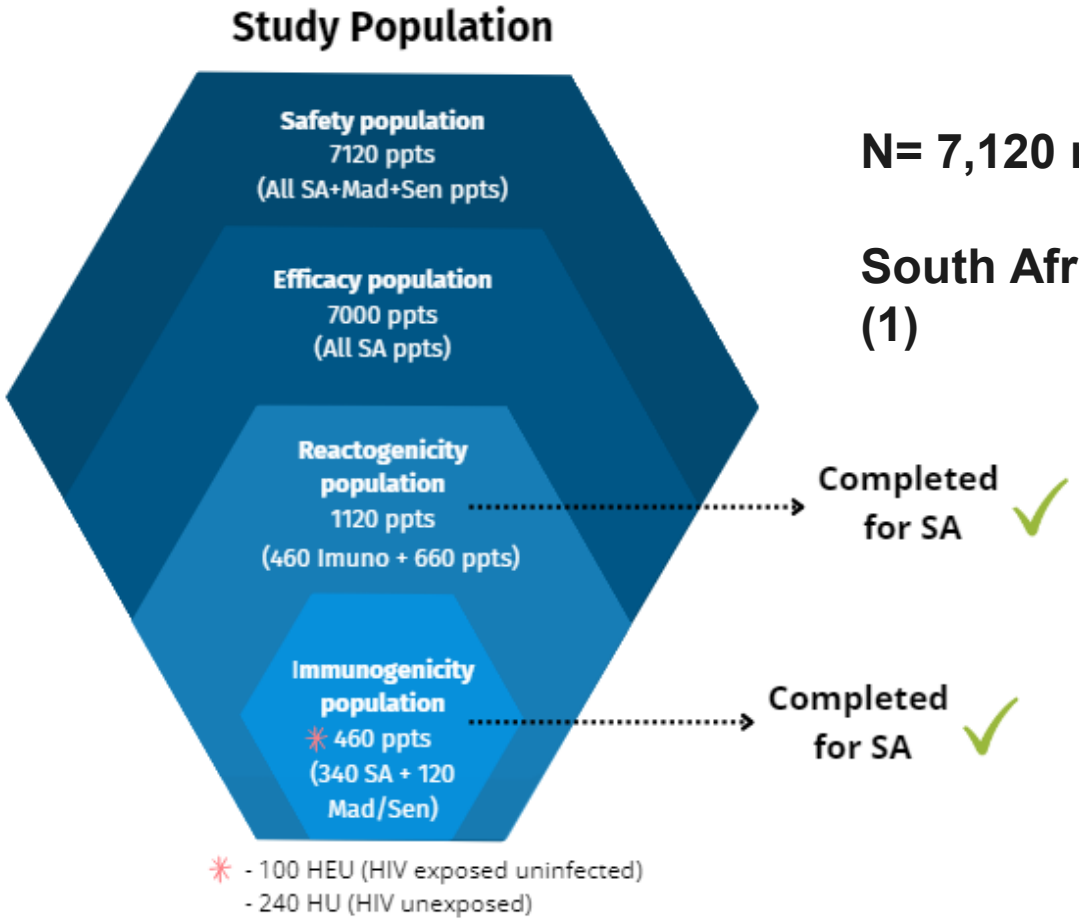
8 Cohorts

Manuscript under review, Luabeya et al, Lancet Global Health

- **MTBVAC 5 x10^5 CFU dose showed comparable safety and reactogenicity, greater immunogenicity compared to BCG in Mtb-unsensitised and Mtb-sensitised individuals**

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



N= 7,120 newborn infants, HEU and HUU

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

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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 x 10^5 CFU dose vs BCG

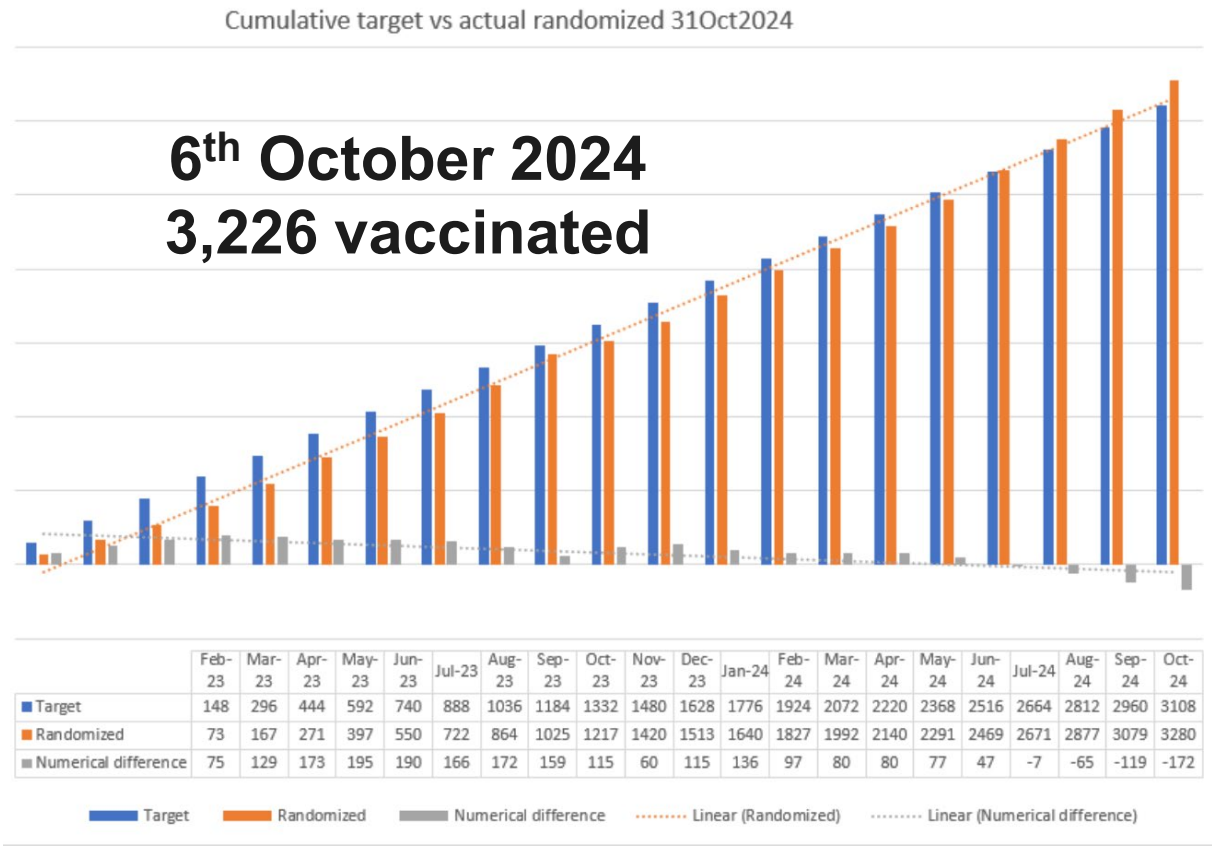
- **Efficacy (min 24 – max 72 months)**
- **Safety**
- **Non-specific effects** (hospitalization, death, non-TB infectious diseases)
- **Immunogenicity (subset)**
- **Biobank immune correlate samples (all)**

Rigorous, adjudicated 1^0 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



	Feb-23	Mar-23	Apr-23	May-23	Jun-23	Jul-23	Aug-23	Sep-23	Oct-23	Nov-23	Dec-23	Jan-24	Feb-24	Mar-24	Apr-24	May-24	Jun-24	Jul-24	Aug-24	Sep-24	Oct-24
Target	148	296	444	592	740	888	1036	1184	1332	1480	1628	1776	1924	2072	2220	2368	2516	2664	2812	2960	3108
Randomized	73	167	271	397	550	722	864	1025	1217	1420	1513	1640	1827	1992	2140	2291	2469	2671	2877	3079	3280
Numerical difference	75	129	173	195	190	166	172	159	115	60	115	136	97	80	80	77	47	-7	-65	-119	-172

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/mm^3 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/ mm^3 at screening
CD4 count <200 cells/mm^3 or WHO clinical stage 3/4 prior to ART

Cohort 1 fully enrolled, Cohort 2 >90% enrolled
Cohort 3 enrols 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**

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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

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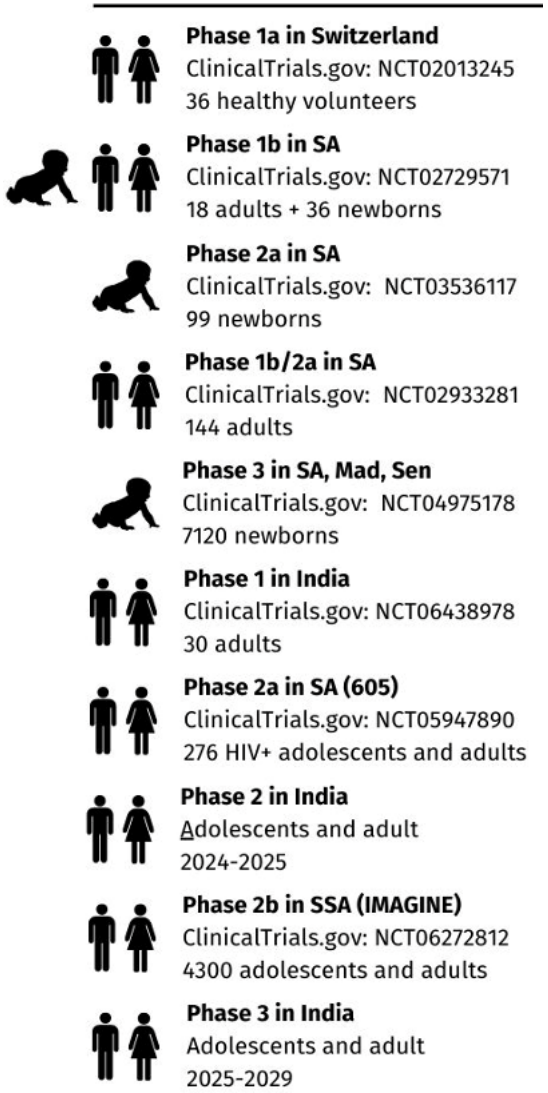
BHARAT BIOTECH

Thank you!

Participants, families and communities

Investigators and Study Teams

Funders and Collaborators



BILL & MELINDA GATES MEDICAL RESEARCH INSTITUTE

M72/AS01$_E$ Clinical Development Program Overview

Alemnew Dagnew (MD), Clinical Development Leader
Gates MRI

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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

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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

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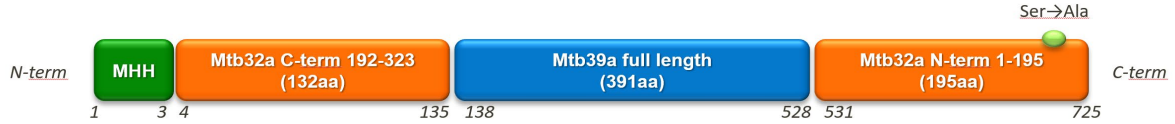
M72/AS01$_{E-4}$ Product Overview

- 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

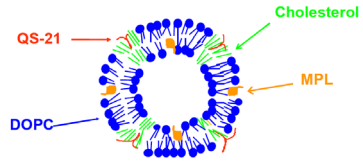


Composition of M72 lyophilized formulation per dose

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

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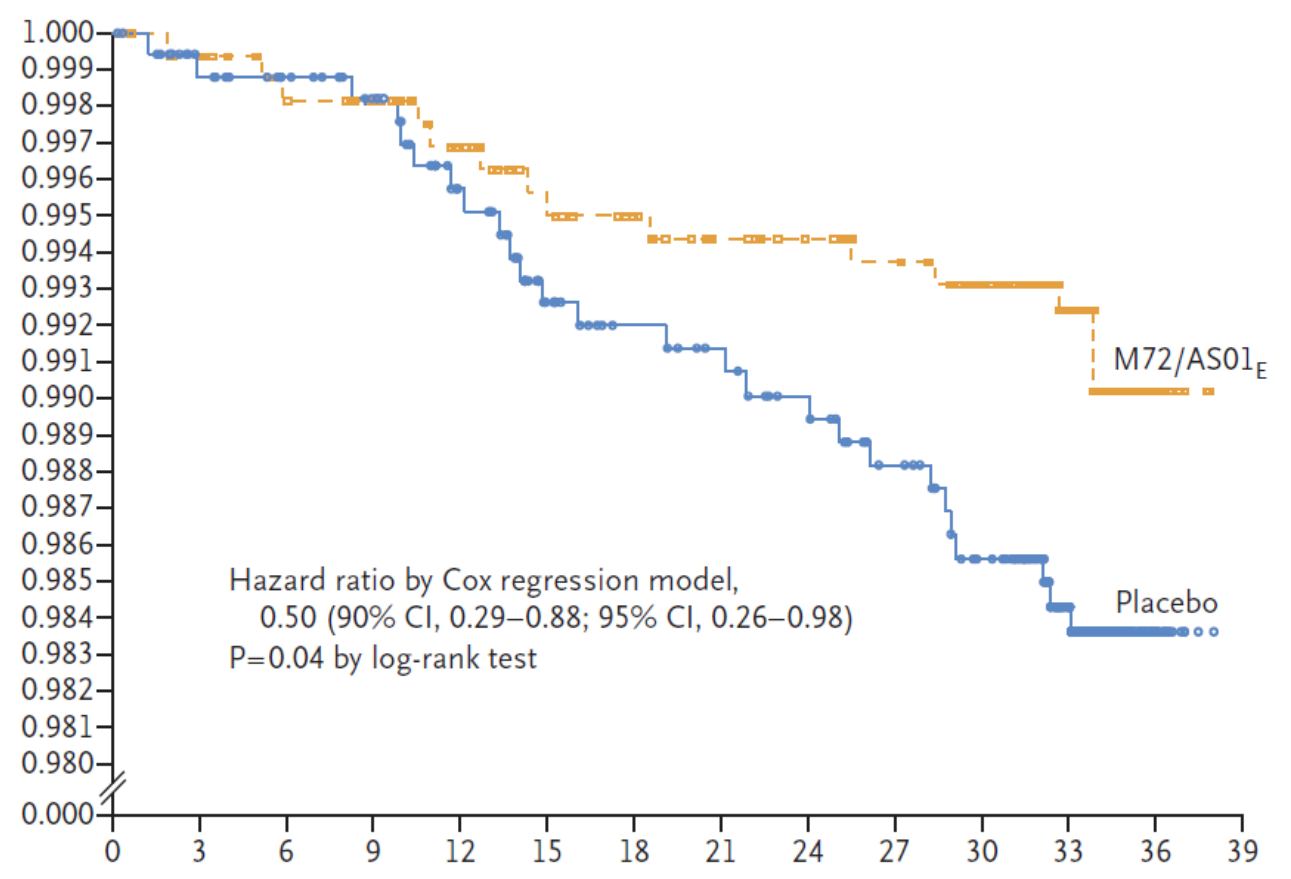
Phase 2b Results: Prevention of Disease (POD) in IGRA-positive adults

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



DOI: 10.1056/NEJMoa1803484 & DOI: 10.1056/NEJMoa1909953

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 2b Controlled Trial of M72/AS01E 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/AS01E 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

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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 (		
Third definition	19	4427.62	0.4 (0.3 to 0.6)	30	4463.06	0		
Fourth definition§	19	4427.62	0.4 (0.3 to 0.6)	32	4463.06	0		
Fifth definition§	26	4434.21	0.6 (0.4 to 0.8)	38	4472.91	0		
Modified fifth definition	25	4434.21	0.6 (0.4 to 0.8)	36	4471.56	0		
Total efficacy cohort								
First definition	13	5055.30	0.3 (0.2 to 0.4)	28	5005.18	0		
Second definition	8	5057.38	0.2 (0.1 to 0.3)	22	5011.28	0		
Third definition	20	5055.30	0.4 (0.3 to 0.6)	32	5005.18	0		
Fourth definition	20	5055.30	0.4 (0.3 to 0.6)	34	5005.18	0		
Fifth definition	28	5061.90	0.6 (0.4 to 0.8)	38	5016.93	0		
Modified fifth definition	27	5061.90	0.5 (0.4 to 0.7)	36	5015.58	0.7		

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.

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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

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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: H0: VE(D) ≤ 10% (α <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

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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

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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.

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Thank You!

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