BILL & MELINDA GATES MEDICAL RESEARCH INSTITUTE

Update on Gates MRI TB Activities

Charles D. Wells, MD

TBTC, 16 OCT 2020

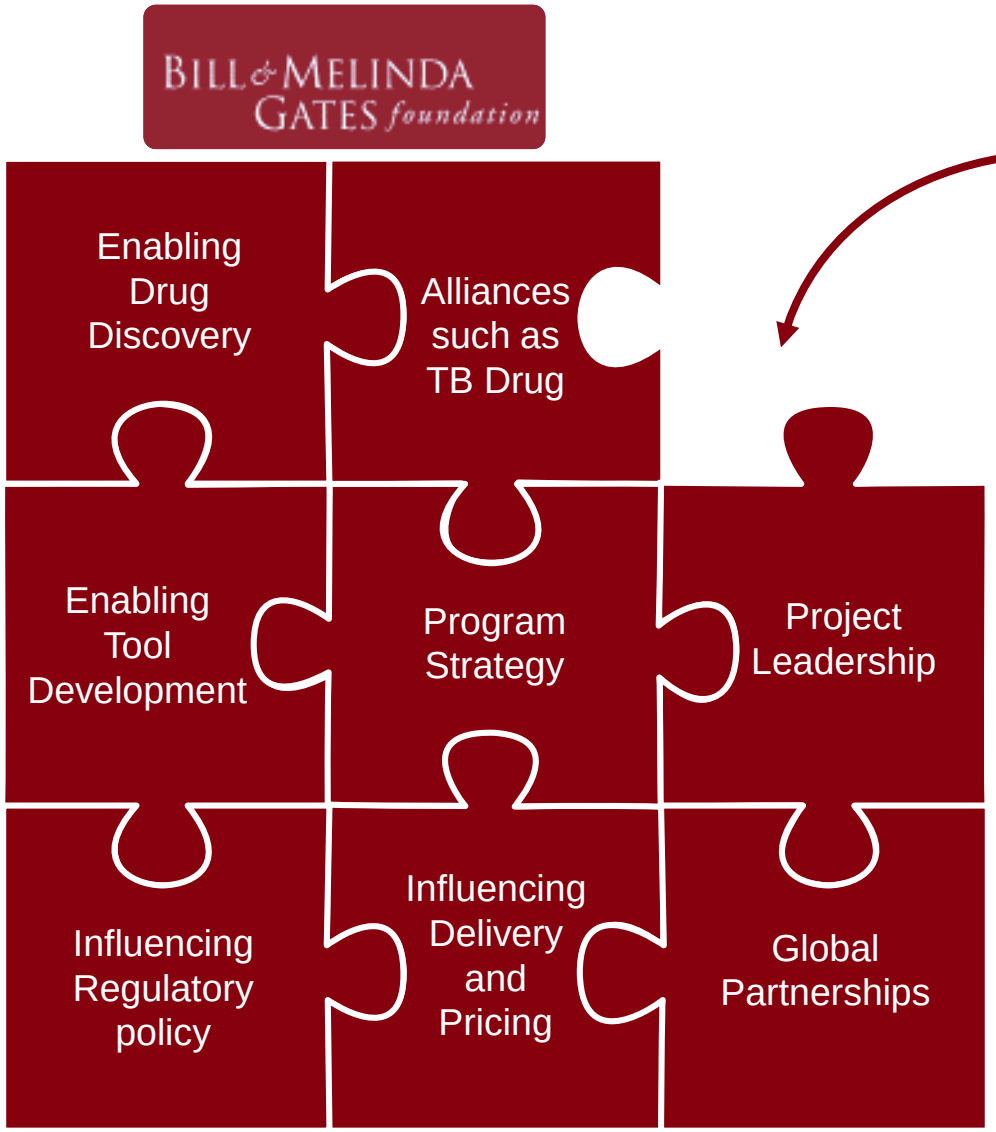
OVERVIEW

1. Gates MRI – who we are & what we do

2. Vaccines
   - Phase 2b BCG Revaccination study
   - M72/AS01 Product Development

3. TB drugs/regimens
   - PAN-TB Collaboration for regimen development
   - Early phase work on individual agents

/ THE FOUNDATION: WE SEEK TO EXECUTE



And many other capabilities…..

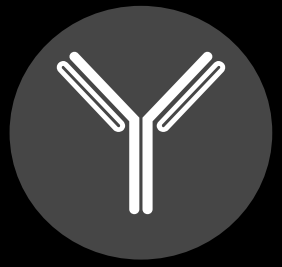
- **Foundation & MRI have one common strategy and share common belief: all lives have equal value**
- **Non-profit biotech organization committed to bringing industry innovations to Global Health**
- **Wholly owned subsidiary of the Foundation**
- **The Foundation's extensive skills, expertise and long-standing relationships across academia, PDPs and industry provide synergy.**

DISEASE AREA & MODALITIES

SMALL MOLECULE THERAPEUTICS

DIAGNOSTICS/ BIOMARKERS[1]

VACCINES



BIOLOGICS[2]

1 Biomarker optimization for early hand over to diagnostic companies
2 Includes mAbs and other non-small-molecule modalities, e.g., RNA, DNA, viral and cell platforms

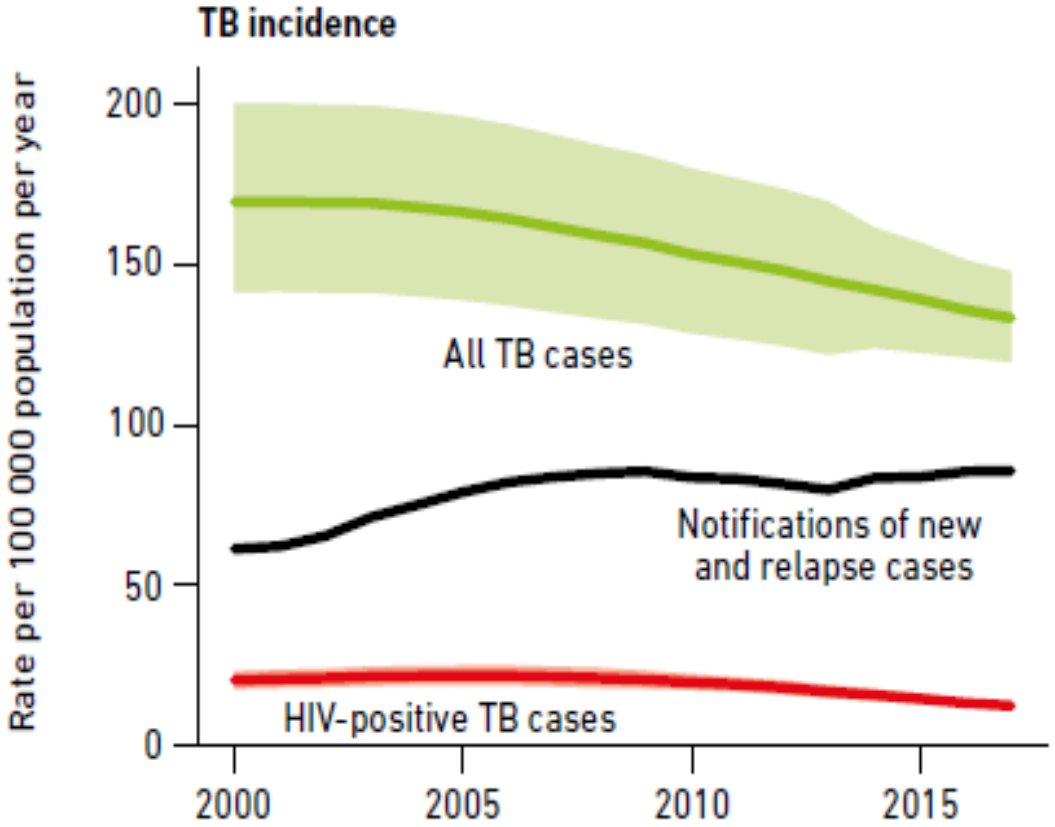
ENTERIC AND DIARRHEAL DISEASES

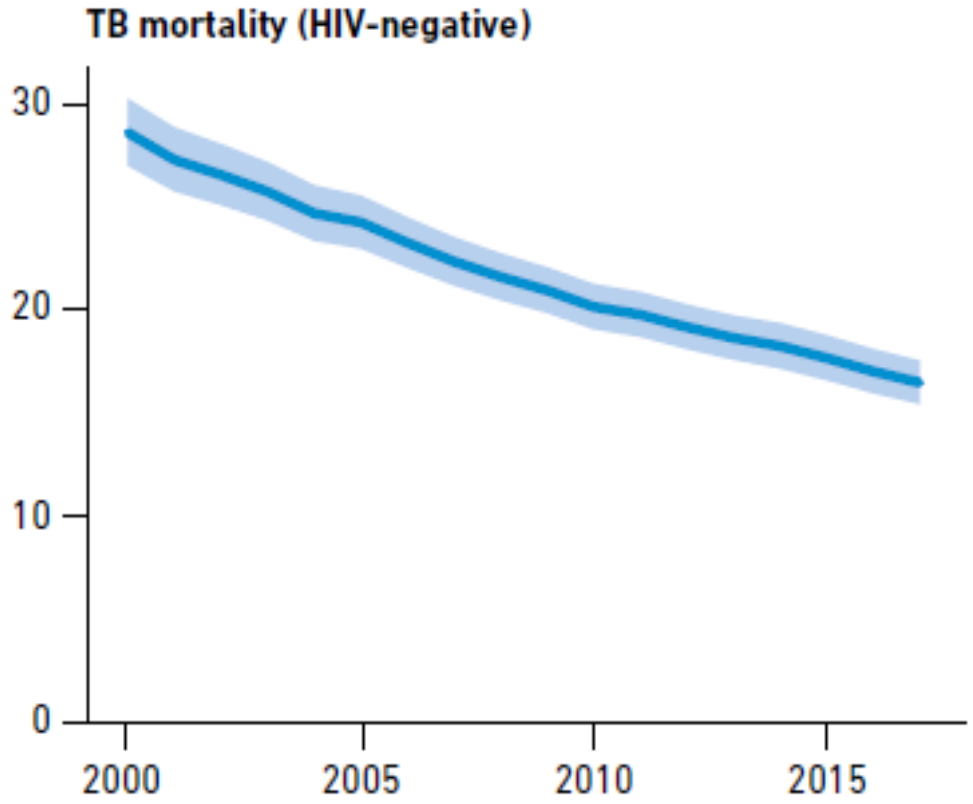
MALARIA

TUBERCULOSIS

MNCH

ACCELERATING DECLINE AS KEY PRIORITY FOR THE FOUNDATION & GATES MRI





/ HOLISTIC APPROACH TO COMPLEXITY OF TB

- Prevent infection with vaccine approaches
  - Identify correlates of protection
  - Goal is cost-effectiveness without pre-screening for Mtb infection
- Prevent disease progression vaccines & drugs
  - Vaccine options may stem latent disease development
  - Treat with shorter, tolerable combination regimens
- Transform treatment with substantially shorter and better regimens
  - Improve adherence and treatment outcomes
  - Prevent further emergence of drug-resistant TB

/ 2018: HISTORIC YEAR FOR TB VACCINES

The NEW ENGLAND JOURNAL of MEDICINE

Phase 2b Controlled Trial of M72/AS01E Vaccine to Prevent Tuberculosis

Olivier Van Der Meeren, M.D., Mark Hatherill, M.D., Videlis Nduba, M.B., Ch.B., M.P.H., Robert J. Wilkinson, F.Med.Sci., Monde Muyoyeta, M.B., Ch.B., Ph.D., Elana Van Brakel, M.B., Ch.B., Helen M. Ayles, M.B., B.S., Ph.D., German Henostroza, M.D., Friedrich Thienemann, M.D., Thomas J. Scriba, Ph.D., Andreas Diacon, M.D., Ph.D., Gretta L. Blatner, M.S., M.P.H., et al.

October 25, 2018
N Engl J Med 2018; 379:1621-1634
DOI: 10.1056/NEJMoa1803484

The NEW ENGLAND JOURNAL of MEDICINE

Prevention of M. tuberculosis Infection with H4:IC31 Vaccine or BCG Revaccination

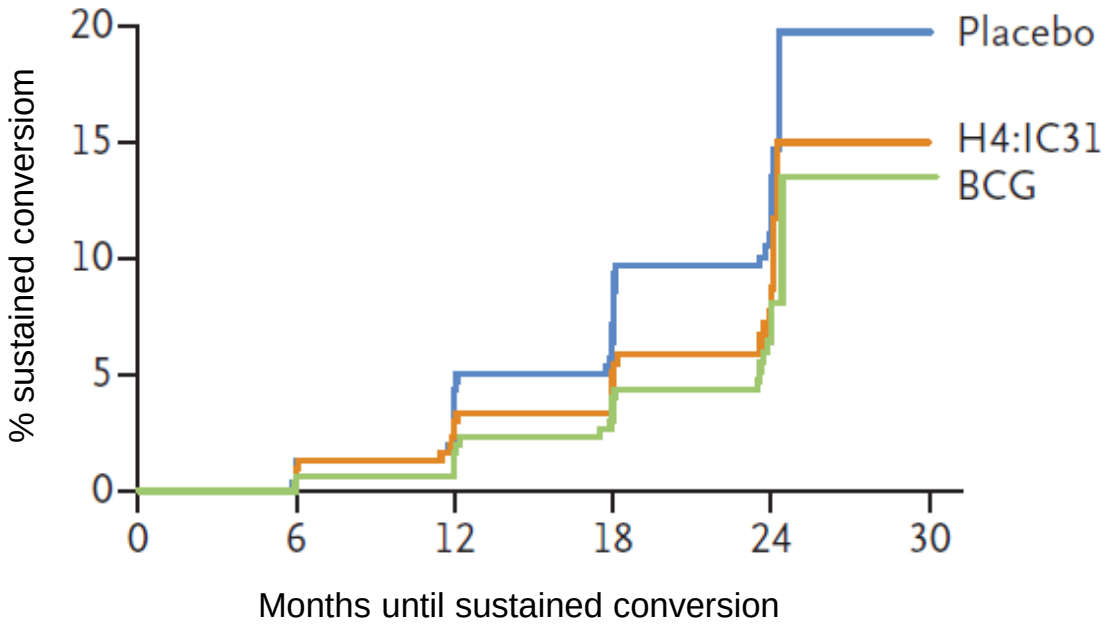
Elisa Nemes, Ph.D., Hennie Geldenhuys, M.B., Ch.B., Virginie Rozot, Ph.D., Kathryn T. Rutkowski, M.Sc., Frances Ratangee, B.N., Nicole Bilek, Ph.D., Simbarashe Mabwe, M.Sc., Lebohang Makhethe, B.Sc., Mzwandile Erasmus, B.Sc., Asma Toefy, B.Sc., Humphrey Mulenga, M.P.H., Willem A. Hanekom, M.B., Ch.B., et al., for the C-040-404 Study Team†

July 12, 2018
N Engl J Med 2018; 379:138-149
DOI: 10.1056/NEJMoa1714021

PHASE 2B BCG REVACCINATION STUDY

BCG REVACCINATION

- N=990, 1:1:1, primary endpoint: initial QFT-conversion, secondary EP: sustained QFT-conversion
- BCG: 45% (95%CI 6.4-68.1%) vaccine efficacy for sustained QFT conversion



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prevention of *M. tuberculosis* Infection with H4:IC31 Vaccine or BCG Revaccination

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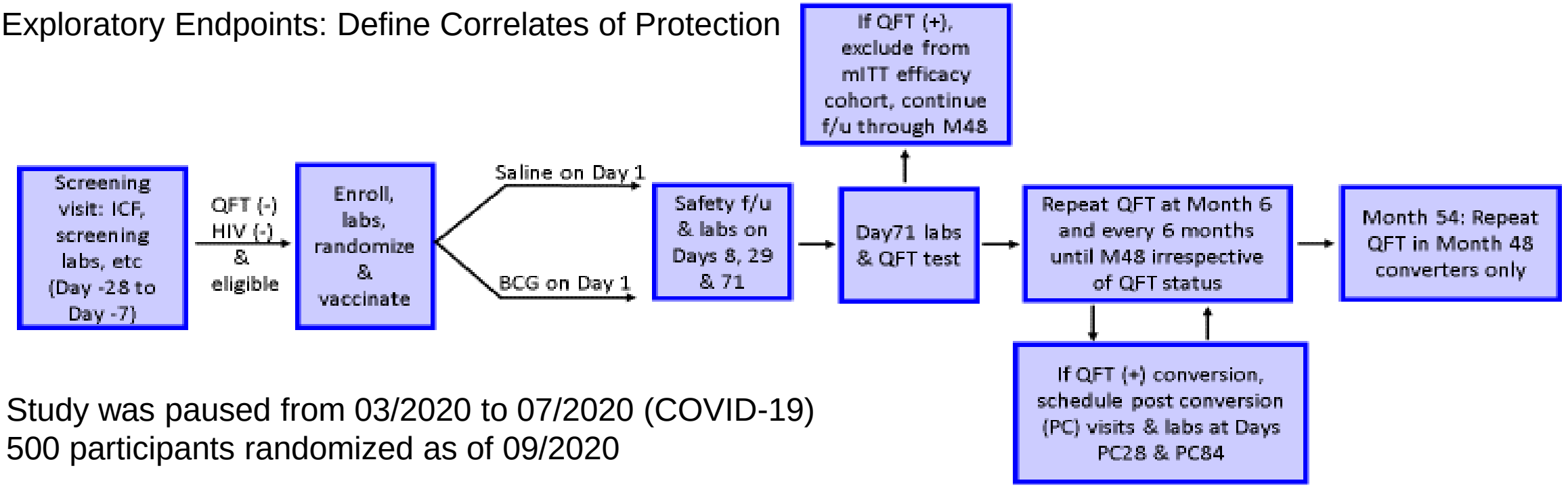
DOI: 10.1056/NEJMoa1714021

GATES MRI BCG REVACCINATION STUDY

Goal: generate data that can support potential policy changes and/or further study in additional epidemiologic settings

- Randomized, placebo controlled, observer-blind, Phase 2b study with two arms (BCG vaccine and saline placebo)
- 1,800 QFT-negative participants 10-18 years of age are randomized 1:1 to receive a single intradermal injection
- Primary Endpoint: Sustained QFT conversion
- Exploratory Endpoints: Define Correlates of Protection



Study was paused from 03/2020 to 07/2020 (COVID-19)
500 participants randomized as of 09/2020

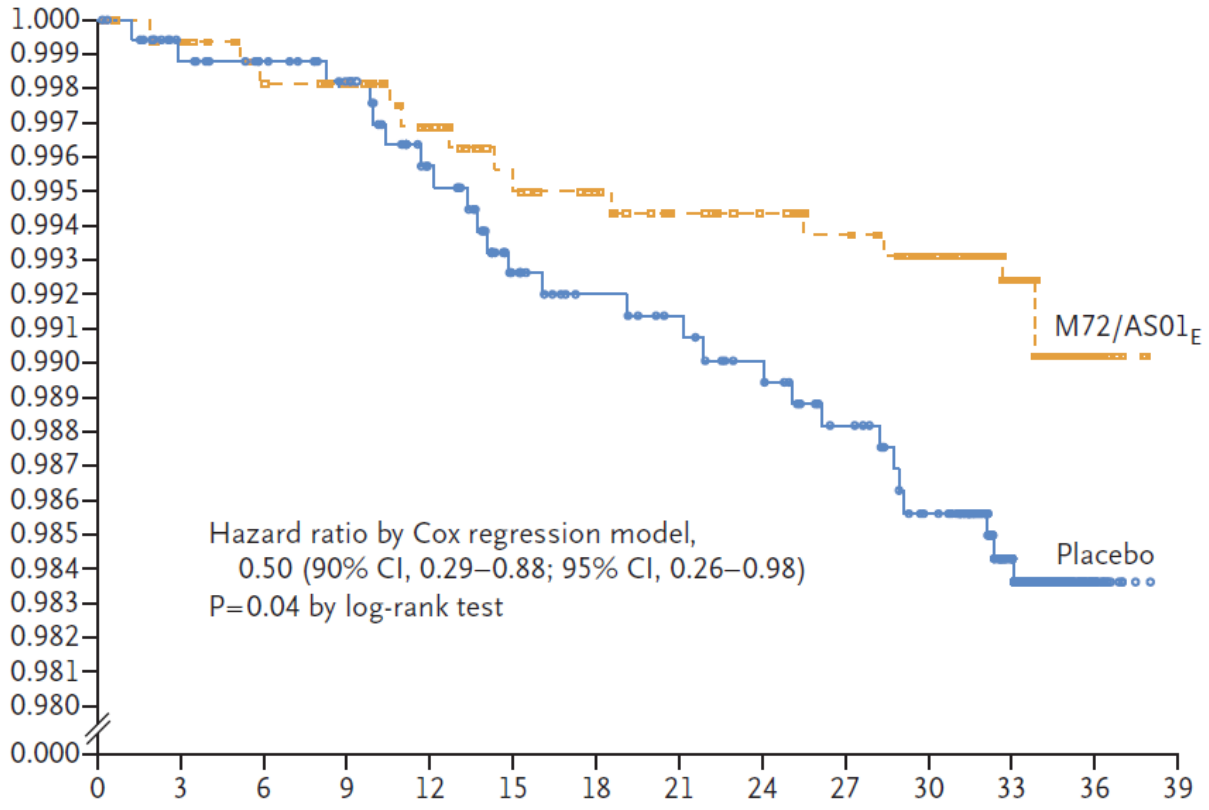
Clinicaltrials.gov ID NCT 04152161
Alexander.Schmidt@gatesmri.org

M72/AS01 PRODUCT DEVELOPMENT

M72/AS01$_E$ & PREVENTION OF DISEASE

PHASE 2B TRIAL IN QFT-POSITIVE POPULATION

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



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Phase 2b Controlled Trial of M72/AS01$_E$ Vaccine to Prevent Tuberculosis

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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

DOI: 10.1056/NEJMoa1803484 & DOI: 10.1056/NEJMoa1909953

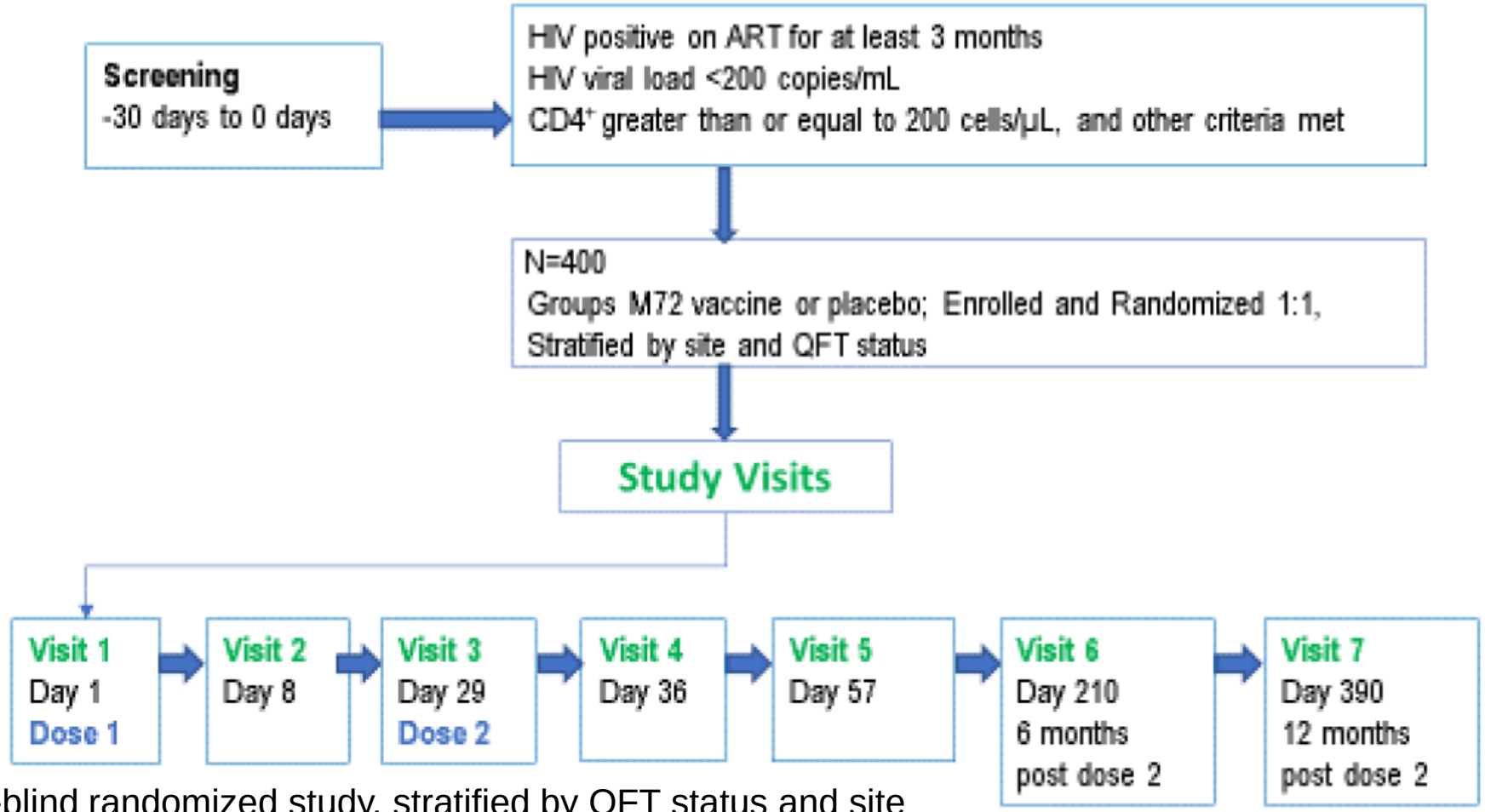
M72/AS01$_E$ PRODUCT DEVELOPMENT

Goal: Product Development

Generate data to support licensure of the vaccine and recommendations for effective use

- GSK licensed M72/AS01$_E$ to Gates MRI, paving way for continued vaccine development and potential use in LMICs
- GSK will support with scientific expertise and ensure efficient transfer of asset technology
- GSK will provide AS01 adjuvant for development program
- Gates MRI will lead product development and sponsor future clinical trials
- Gates MRI will actively reach out to and collaborate with many partners and stakeholders committed to accelerating end of TB epidemic.

M72/AS01E IN PEOPLE LIVING WITH HIV: PHASE 2 STUDY TO GENERATE ADDITIONAL SAFETY DATA PRIOR TO PHASE 3



- Double-blind randomized study, stratified by QFT status and site
- 400 participants, 1:1 randomization to M72 vs. placebo
- Study start anticipated for 11/2020

INITIATING PHASE 3 STUDY ASAP AS QUICKEST PATH TO PUBLIC HEALTH IMPACT

1. Phase 3 study should be of sufficient size and duration to unequivocally demonstrate vaccine efficacy (VE) in QFT-positive recipients while supporting licensure for use irrespective of QFT status
2. Phase 3 VE should include enough QFT-negatives to establish safety & immunogenicity, and to obtain 1st assessment of vaccine's potential in QFT-negative vaccinees
   - Screening for QFT status as part of national vaccination program likely not feasible
3. Trial simulations suggest ≥ 14,000 subjects in high burden settings needed to demonstrate VE in RCT (1:1 vs placebo); number of cases needed to conclude is very sensitive to observed VE
4. Interim analysis for VE could be explored to accelerate submission of first dossier

SUMMARY

- Primary endpoint, case definition and trial design need thorough discussion with stakeholders; consultations with regulators and other stakeholders will inform trial design.
- Clinical operations activities and epidemiology studies will need to start now
  - / Country and site selection activities have been initiated
- Phase 3 will take 2 years to enroll & 5 years of follow-up (event-driven analysis)
  - / Sample size TBD but likely 15,000 to 20,000 participants
- Active, timely and transparent communication, as well as regular updates on progress of candidate to relevant health authorities and policy makers will be key to program success
  - / Presented Phase 3 plans to WHO PDVAC in September 2020, SAB planned for Q1, 2021

TB DRUG & REGIMEN DEVELOPMENT

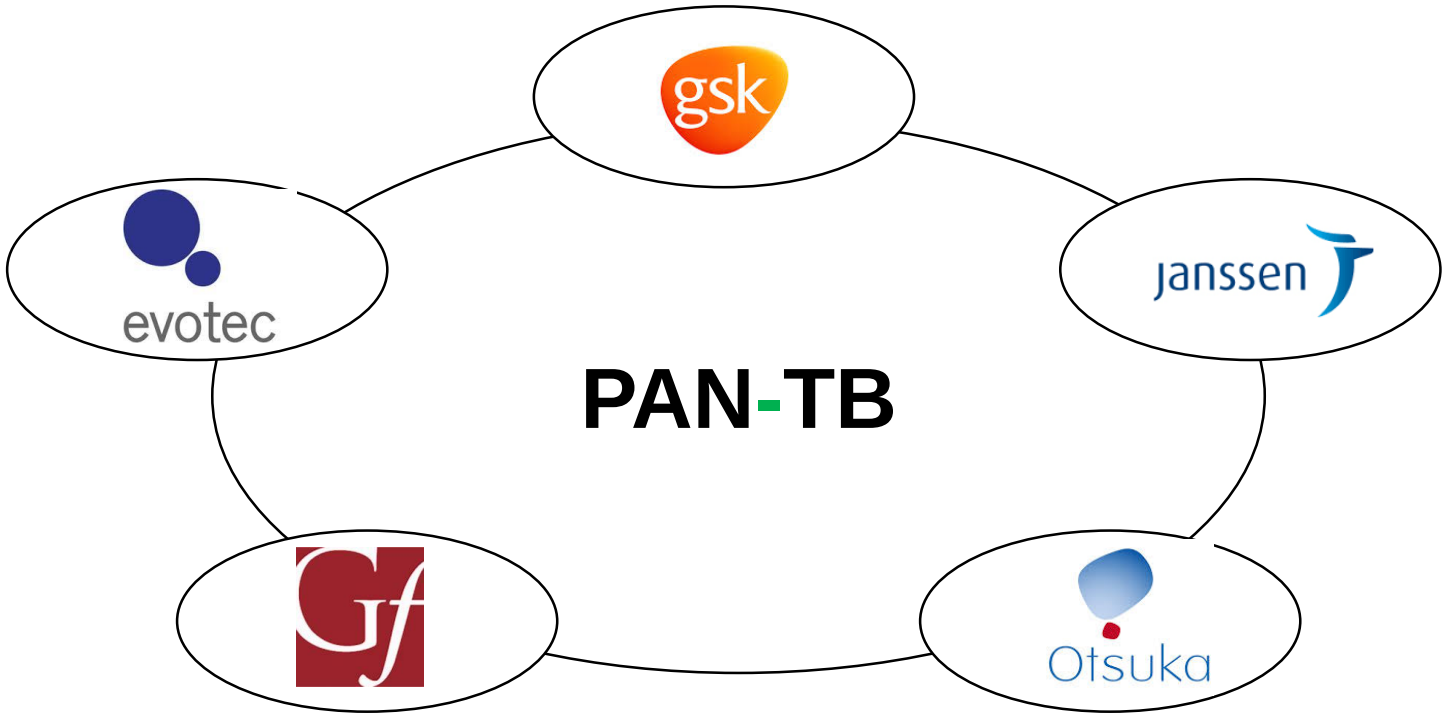
PAN TB TARGET REGIMEN PROFILE

TRP Attribute	Criteria
Indication	1st line treatment WITHOUT the need for DST
Efficacy/Duration Forgiving	< 2-month regimen; not inferior to HRZE PK/PD forgiving to non-adherence
Safety	No baseline or monitoring safety labs. No clinical monitoring.
Drug-Drug Interactions	No clinically relevant DDI's (i.e., no clinical management required)
Resistance	No pre-existing resistance. In vitro mutation rate < $1/10^6$
Affordable	Accessible for all LMICs

PAN-TB

PROJECT TO ACCELERATE NEW TREATMENTS FOR TUBERCULOSIS

PAN-TB FOUNDING PARTNERS AND ROLE OF GATES MRI

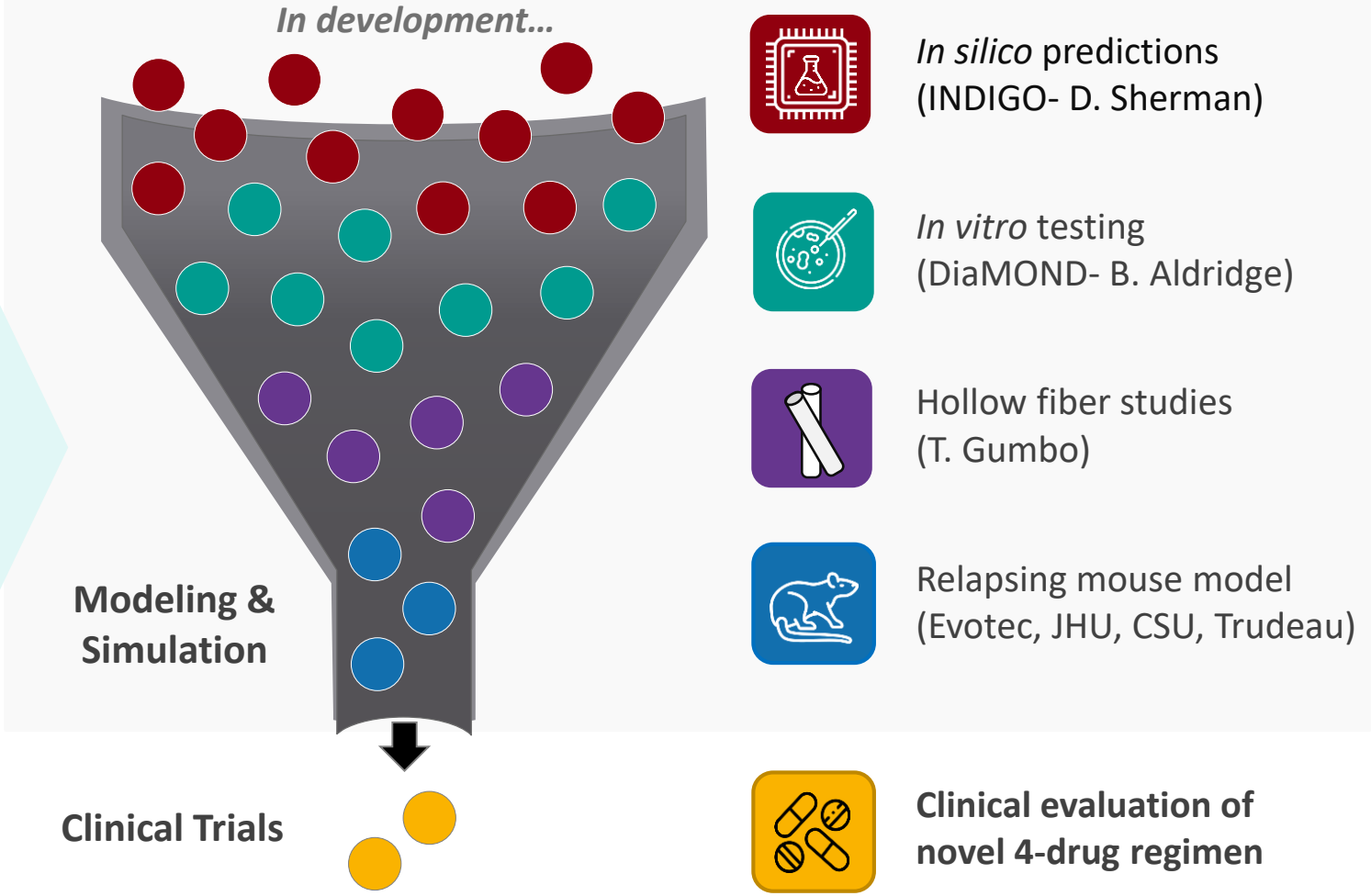


GATES MRI Execution of clinical trials within PAN-TB to be coordinated and conducted by Gates MRI.

Platform to expedite the development of new drug regimens in TB

An experimental funnel to rapidly test and rank order potential drug and target combinations:

1. Designed to leverage *in silico*, *in vitro*, *and in vivo* methods coupled to quantitative modeling.
2. Major focus on increasing speed and throughput of the relapsing mouse model:
   a) Aiming to reduce time to results from 9 months to 3 while also
   b) Reducing group size to allow a larger number of compounds to be tested simultaneously.



SUMMARY - NON-CLINICAL APPROACH (FIRST WAVE OF STUDIES)

- ✓ Aligned on the TB Priority Candidate list for Wave 1
- ✓ Aligned on use of JHU BALB/C Relapsing Mouse Model

Wave 1 Priority Candidate:

- BDQ
- DEL
- Pa
- GSK
- GSK
- OPC
- SUT

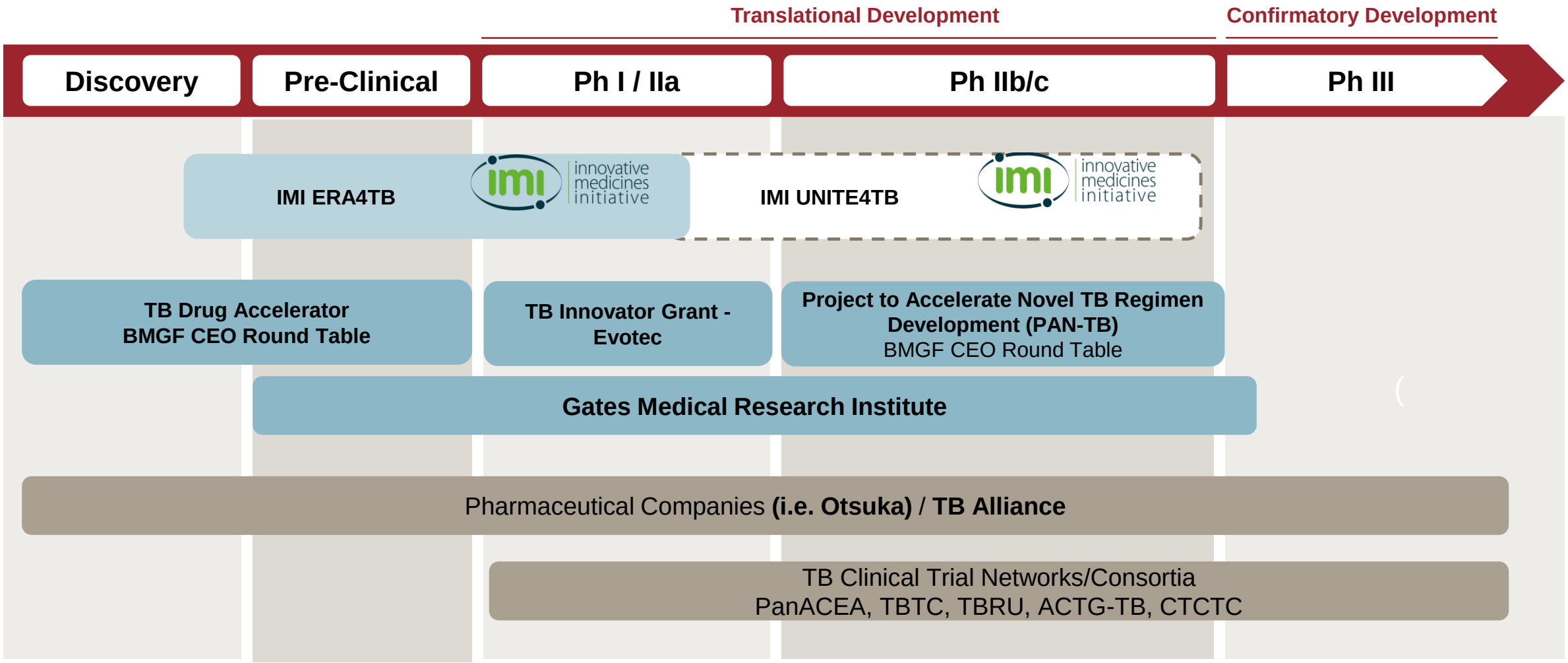
55

Number of resulting 3-4 candidate regimens reviewed and prioritized by Non-Clinical Working Group

4-drug regimens reviewed and Prioritized by Non-Clinical Working Group for Wave 1

Studies began 01 MAR 20

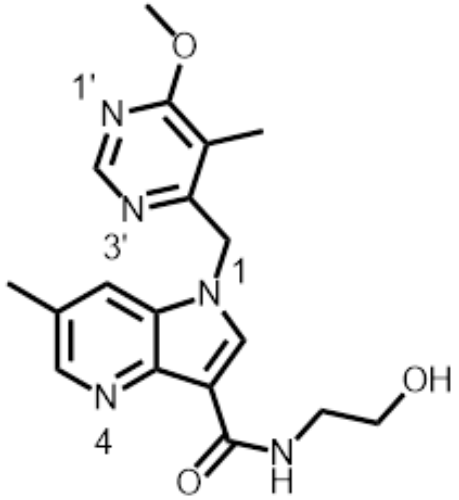
EVOLVING TB DRUG DEVELOPMENT LANDSCAPE



ASSESSMENT OF INDIVIDUAL TB AGENTS FOR ENTRY INTO PAN-TB

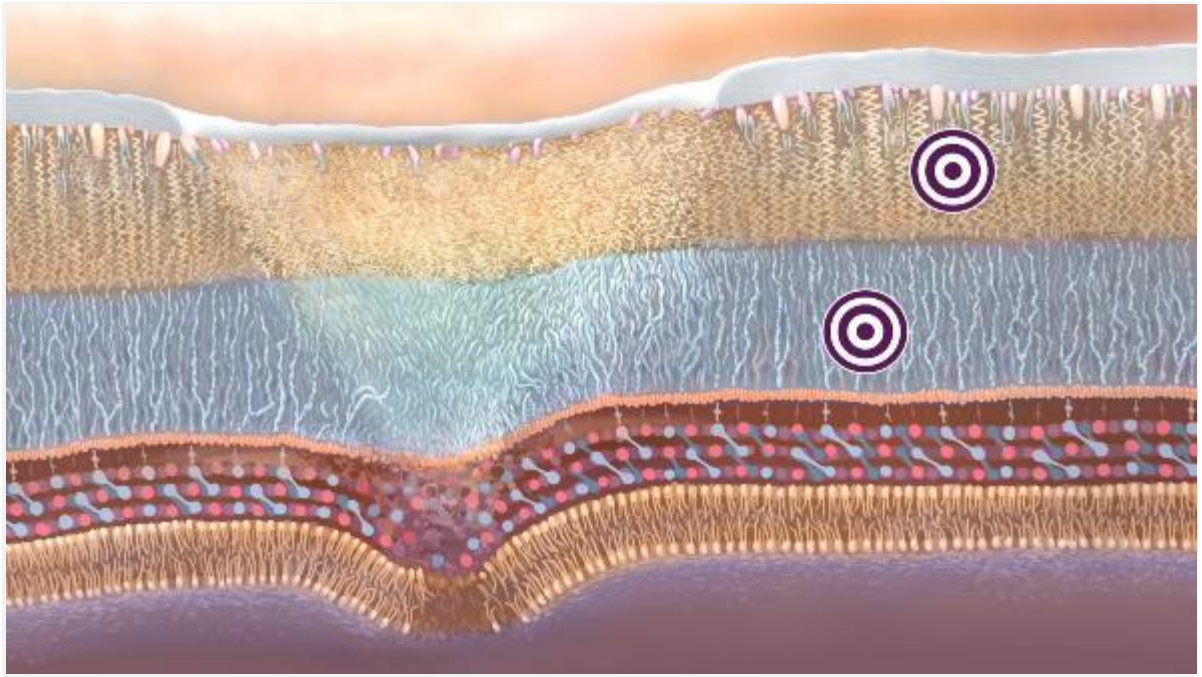
/ TBA-7371 - INVESTIGATIONAL PHASE 2A COMPOUND

- **Novel mechanism of action**
- **Target: DprE1 enzyme**



- **Partnership with TB Alliance**

  Non-exclusive licenses to Gates MRI to develop TBA-7371 and to FNDR[†] (in India)



Mechanism of Action

Cell Wall Metabolism

Compounds are able to disrupt the TB bacterium's ability to build its cell wall, which is critically important during reproduction.

[†] FNDR - Foundation for Neglected Disease Research

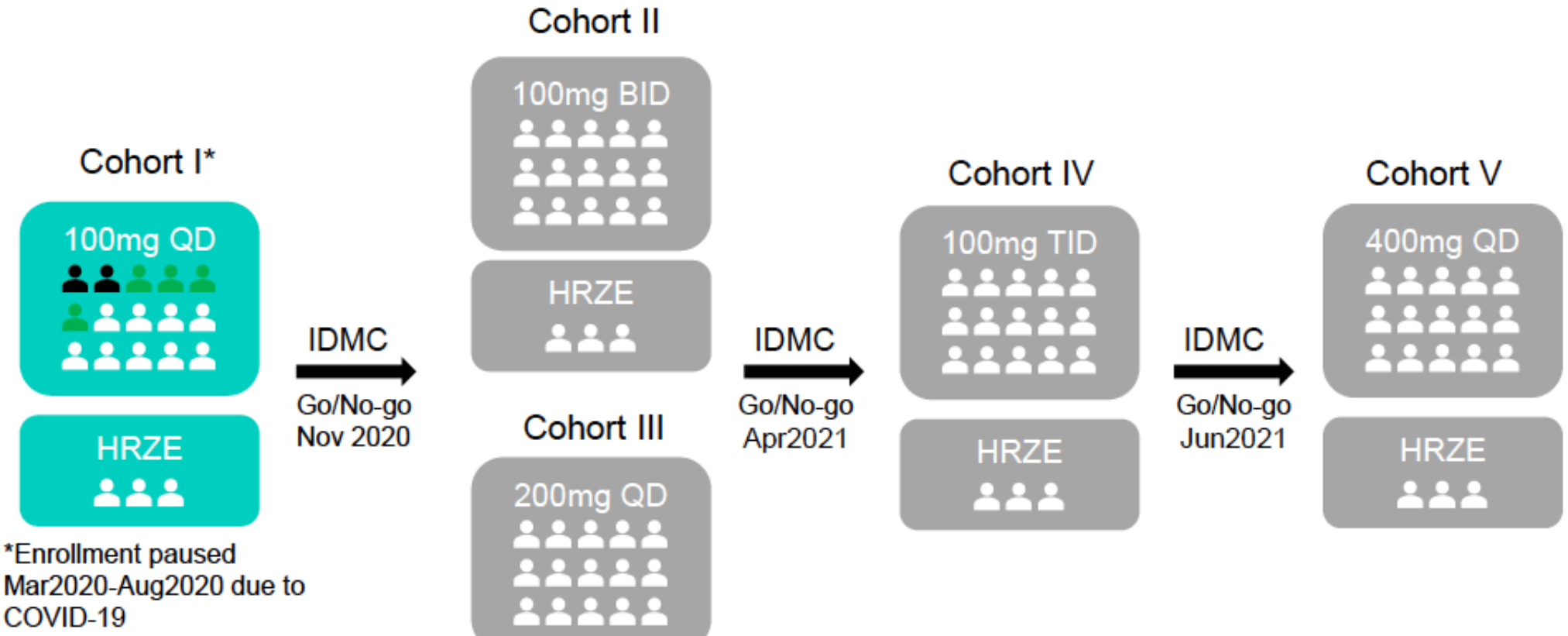
TBA-7371 - PHASE 2A EBA TRIAL OBJECTIVES AND ENDPOINTS

CHARACTERIZING 5 DOSE REGIMENS OF TBA-7371 (AND HRZE)

		Objectives	Endpoints
1°	Bactericidal activity	Demonstrate 14-day EBA† by CFU counts (solid media)	Slope: average Δ / day – baseline to Day 14 of log CFU counts
	Safety	Assess severe/serious AEs over 14-day Rx period	Freq. of participants experiencing ≥ 1 severe and/or SAEs from Days 1 to 15
2°	Bactericidal Activity	Demonstrate EBA of Day 0-2 and Days 2-14 by CFU counts (solid media)	Slope - average Δ / day – Day 0-2 and Day 2-14 of log CFU counts.
		Demonstrate BA by: - TTP in MGIT - Sputum LAM assay	- Slope of TPP (MGIT): Day 0-14, Day 0-2, and Day 2-14 - Slope of log concentration of sputum LAM: Day 0-14, Day 0-2, and Day 2-14
	Safety	Assess AE profile over 14-day Rx period	Freq. of participants with AE by: body system, preferred term; seriousness, intensity, expectedness and relatedness to IMP

†EBA - early bactericidal activity
Clinicaltrials.gov ID NCT 04176250

TBA-7371 EBA TRIAL UPDATE – SEP 2020



*Enrollment paused Mar2020-Aug2020 due to COVID-19

EBA Design Features

- Treatment: 14d
- Follow-up: 28d
- Escalation decision made after cohort treatment period complete for all participants

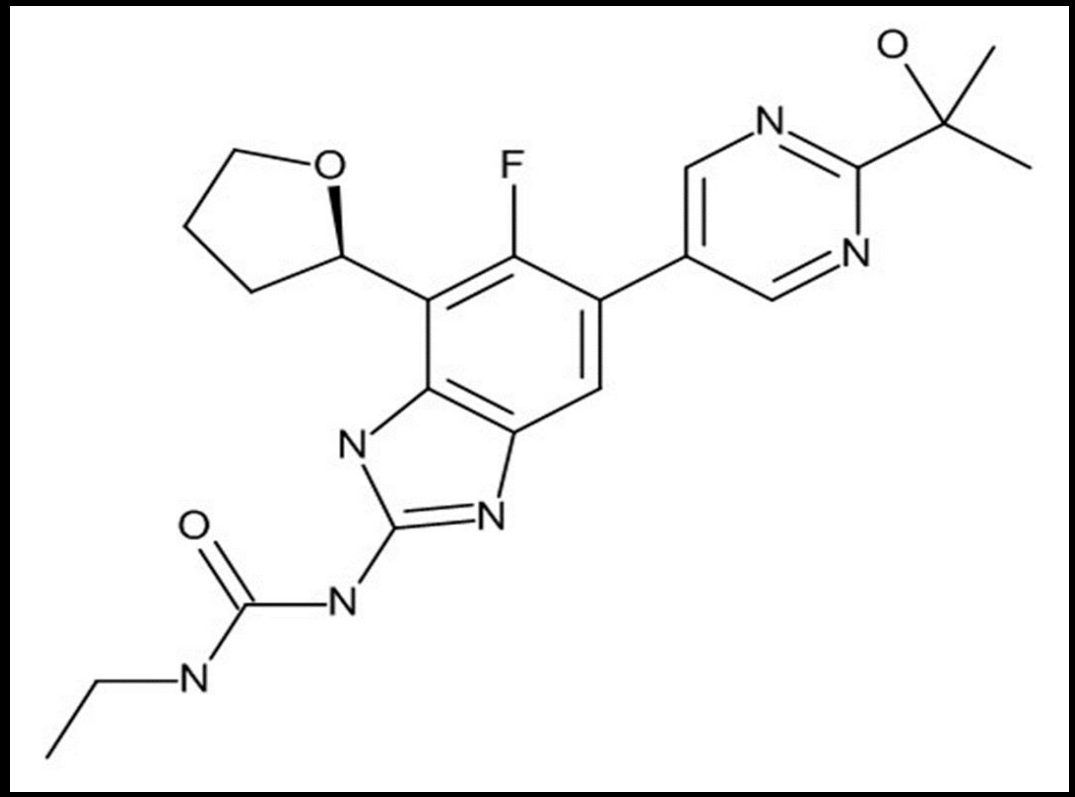
Open slot
Randomized, on study
Discontinued
Completed

= Open cohort
= Cohort not open

IDMC = Independent Data Monitoring Committee

/ SPR 720

Gates MRI and Spero Therapeutics collaboration to develop Spero's investigational compound SPR 720 (amino-benzimidazole inhibitor of gyrase B/ParE) for the treatment of pulmonary TB.



THANK YOU & QUESTIONS