MTBVAC an attenuated TB vaccine - Looking towards the efficacy trial

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**MTBvAC – CLINICAL DEVELOPMENT OVERVIEW**

- **2012**
  - **Phase 1a**: ClinicalTrials.gov: NCT02013245
  - 36 healthy volunteers
  - [Centre Hospitalier Universitaire Vaudois](https://www.chuv.ch/en)

- **2013**
  - **Phase 1b**: ClinicalTrials.gov: NCT02729571
  - 18 adults + 36 neonates

- **2014**
  - **Phase 2a**: ClinicalTrials.gov: NCT03536117
  - 99 neonates

- **2015**
  - **Phase 1b/2a**: ClinicalTrials.gov: NCT02933281
  - 144 adults

- **2016**
  - **Phase 3**: 6,500 neonates

- **2017**
  - **Phase 3**: 6,500 neonates

- **2018**
  - **Phase 3**: 6,500 neonates

- **2019**
  - **Phase 3**: 6,500 neonates

- **2020**
  - **Phase 3**: 6,500 neonates

- **2021**
  - **Phase 3**: 6,500 neonates

- **2022 - 2028**
  - **Phase 3**: 6,500 neonates

**Clinical Trials:**
- ClinicalTrials.gov: NCT02013245
- ClinicalTrials.gov: NCT02729571
- ClinicalTrials.gov: NCT03536117
- ClinicalTrials.gov: NCT02933281
- ClinicalTrials.gov: NCT02933281

**Partners:**
- Universidad Zaragoza
- EDCTP
- TBVI
- VPD RMPRU
- EPIS
- EPLS
- UNIVERSITY OF KWAZULU-NATAL
- UNIVERSITEIT STELLENBOSCH UNIVERSITY
- INYIYASE VAKWAZULU-NATALI
- Institut Pasteur de Malagasy
MTBVAC Phase 1a in adults – Conclusions

Phase I Double Blind, Randomized, Controlled, Dose-Escalation Study to Evaluate the Safety and Immunogenicity of MTBVAC in Comparison with BCG in Elispot Tb (ESAT-6, CFP10, PPD)- and HIV-negative volunteers

IP: Dr. François Spertini

- Vaccination with MTBVAC demonstrated an excellent safety profile, comparable to BCG
- Negativity of IGRA tests 7 months after MTBVAC immunization is a key element for progressing MTBVAC to efficacy and prevention of infection trials
- At the same dose level as BCG, the MTBVAC group showed greater frequency of polyfunctional CD4+ central memory T-cells. A transient increase in CFP-10-specific ELISPOT positivity was observed at day 28 in three adult participants who received MTBVAC

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

François Spertini*, Régine Audran, Reza Chakoor, Olfa Karoui, Viviane Steiner-Monard, Anne-Christine Thierry, Carole E Mayor, Nils Retthy, Katie Jaton, Laure Vallotton, Catherine Lazé-Blanchet, Joana Doce, Eugenia Puentes, Dessislava Marinova, Nacho Agüila, Carlos Martín*
MTBVAC - Phase 1b. Design

A randomized, double-blind, dose-escalation clinical trial of the safety, reactogenicity and immunogenicity of MTBVAC compared to BCG Vaccine SSI, in newborns living in a tuberculosis endemic region with a safety arm in adults

IP: Dr. Michele Tameris

18 healthy adults randomized 1:1

- MTBVAC (5 x 10^5 CFU) or BCG SSI (5 x 10^5 CFU) (9+9)
- HIV negative, QuantiFERON (QFT) negative, previously BCG-vaccinated

36 healthy, HIV-unexposed, BCG-naïve, newborns randomized 3:1

- MTBVAC (2.5x 10^3 CFU) or BCG SSI (2.5x10^5 CFU) (9+3)
- MTBVAC (2.5x10^4 CFU) or BCG SSI (2.5x10^5 CFU) (9+3)
- MTBVAC (2.5x10^5 CFU) or BCG SSI (2.5x10^5 CFU) (10+2)

MTBVAC IS WELL TOLERATED

Lancet Respir Med 2019; 7: 757–70
Published Online August 12, 2019 http://dx.doi.org/10.1016/S2213-2600(19)30251-6
Longitudinal kinetics of antigen-specific CD4 T cells expressing the indicated cytokine responses in participants after vaccination and measured by whole blood intracellular cytokine staining assay.

CD4 T cells indicate a significant difference between the groups: Any Cytokine +, Th1+, Th1 + polyfunctional.
MTBVAC - Phase 1b. Summary conclusions

- MTBVAC in infants appears to be as, and more, safe than BCG
- MTBVAC is less reactogenic as compared to same dose of BCG
- MTBVAC induces a dose dependent, and stronger Th1 response as compared to BCG at peak response
- QFT conversion was observed in 80% in infants at M6 with MTBVAC highest dose reverting to less than 50% in M12 (QFT lower than 4IU/ml !)
- Based on these immunogenicity results, the low MTBVAC dose could be omitted from future studies

### PHASE 1B IN NEWBORNS, SA - MTBVAC QFT CONVERSION

<table>
<thead>
<tr>
<th>GROUP</th>
<th>D180 QFT +</th>
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<tbody>
<tr>
<td>MTBVAC - Cohort 1</td>
<td></td>
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<tr>
<td>2.5X10^3, N=9</td>
<td>3 of 8</td>
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<tr>
<td>MTBVAC - Cohort 2</td>
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<tr>
<td>MTBVAC - Cohort 3</td>
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<tr>
<td>BCG SSI</td>
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<tr>
<td>2.5X10^5, N=8</td>
<td>0 of 7</td>
</tr>
</tbody>
</table>
MTBVAC - Phase 2a in neonates RIA2019V-1637

Dose-Defining Safety and Immunogenicity Study and Capacity Building to Support Vaccine Efficacy Trials in TB-Endemic Regions of Sub-Saharan Africa

Selection dose, Safety, Reactogenicity and Immunogenicity

IP: Dr. Michele Tameris

99 healthy, HIV-unexposed, BCG-naïve, newborns randomized 3:1

- MTBVAC (2.5x10^4 CFU) or BCG (2.5x10^5 CFU) (25+8)
- MTBVAC (2.5x10^5 CFU) or BCG (2.5x10^5 CFU) (25+8)
- MTBVAC (2.5x10^6 CFU) or BCG (2.5x10^6 CFU) (25+8)

Enrolment completed  FUP – 12 months  LPLV March 2022

PARTNERSHIP

Biofabri / Spain / Coordinator
Stichting TuBerculosis Vaccine Initiative (TBVI) / The Netherland
University of Zaragoza / Spain
University of Cape Town (UCT) / South Africa
Center de Recherche Biomedicale Espoir Pour La Santé (BRC-EPLS) / Senegal
Institut Pasteur de Madagascar (IPM) / Madagascar

Lowest dose level deselected
MTBVAC  Phase 1b/2a in adults and adolescents

Phase 1b/2a Randomized, Double-blind, Active-controlled, Safety, Immunogenicity, and Dose-escalation Study in Adults with and without Latent Tuberculosis Infection in South Africa

Trial Population – 144 (96 +48 )

QFT negative individuals:
- Cohort 1: n =12 MTBVAC (5 x 10³ CFU) and n=6 BCG
- Cohort 2: n= 12 MTBVAC (5 x 10⁴ CFU) and n=6 BCG
- Cohort 3: n= 12 MTBVAC (5 x 10⁵ CFU) and n=6 BCG
- Cohort 4: n= 12 MTBVAC (5 x 10⁶ CFU) and n=6 BCG

QFT positive individuals:
- Cohort 5: n =12 MTBVAC (5 x 10³ CFU) and n=6 BCG
- Cohort 6: n= 12 MTBVAC (5 x 10⁴ CFU) and n=6 BCG
- Cohort 7: n= 12 MTBVAC (5 x 10⁵ CFU) and n=6 BCG
- Cohort 8: n= 12 MTBVAC (5 x 10⁶ CFU) and n=6 BCG

Enrolment completed  FUP – 12 months  LPLV September 2021
Objectives:

• To study the protective efficacy conferred by a single intradermal vaccine with MTBVAC or BCG against exposure to low doses of aerosol with M. tuberculosis in rhesus macaques.

• Characterize the immune response induced after vaccination and compare the immune responses in macaques with the responses in humans immunized with BCG and MTBVAC.
A single intradermal vaccination with MTBVAC given to adult rhesus macaques was well tolerated and conferred a significant improvement in outcome following aerosol exposure to M. tuberculosis compared to by a single BCG vaccination.

Vaccination with MTBVAC resulted in a significant reduction in M. tuberculosis infection-induced disease pathology following challenge:

- In vivo medical imaging
- Gross pathology lesion counts
- Pathology scores recorded at necropsy
- Frequency and severity of pulmonary granulomas
- Frequency of recovery of viable M. tuberculosis from extrapulmonary tissues

Concordance between immune profiles measured in clinical trials and a macaque pre-clinical study demonstrating significantly improved outcome after M. tuberculosis challenge as evidence to support the continued development of MTBVAC as an effective prophylactic vaccine for TB vaccination campaigns.

White et al/ npj Vaccines (2021) 6:4 ; https://doi.org/10.1038/s41541-020-00262-8
www.nature.com/npjvaccines
MTBVAC - Phase 3 Efficacy trial in neonates
MTBVAC Phase 3 in neonates - RIA2019S-25652

A Phase 3, Randomised, Double blind, Controlled of the Safety, Immunogenicity and Efficacy Evaluation Study in TB-Endemic Regions of Sub-Saharan Africa of MTBVAC in Healthy, BCG Naïve, HIV Unexposed and Exposed, South African newborns

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- Institut Pasteur de Madagascar (IPM) / Madagascar
- The University of Stellenbosch (SUN), Cape Town
- The Respiratory and Meningeal Pathogen Research Unit /RMPRU), Johannesburg, South Africa
- The University of KwaZulu Natal (UKZN), Durban, South Africa
MTBVAC Phase 3 in neonates - Timelines

- Phase 3 Safety, Immunogenicity and Efficacy in neonates
  - 6 African sites
- Protocol Submission May 2021
  - Pre-dose definition
- Protocol Submission Sep 2021
  - Definitive Dose
- Protocol Approval Jan 2022
- First vaccination Feb 2022

Study duration
- From 2022 to 2028
MTBVAC for Neonates – Wrap up

2001
- Vaccine discovery (2001 – 2008)
- GMP Process development (2008-2011)
- Preclinical studies (2008 – 2012)

2012
- Ph. 1a FIH Adults

2015
- Ph. Ib Newborns Endemic region

2019
- Ph. 2a newborns Endemic region

2021
- Ph. 3 Newborns Endemic region

2022
- Art.58 EMA

2028
- WHO PQ
- NRA MAA

Confidential
MAA – Marketing Authorisation Application; NRA – National Regulatory Authority; PQ- Prequalification
Thank you

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