TB Vaccines: Pipeline Overview and Status of Late-stage Candidates

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PDVAC
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New TB vaccines: a critical, unmet global health need

- 10M new TB cases in 2017
- 1.6M deaths
- >1/4 of all AMR-related deaths

Deaths in 2017

Source: WHO Global TB Report 2018
Multiple Target Populations

- Infants/children
- Adolescents/Adults
- TB patients – during or post-cure
Multiple Therapeutic Indications

- Prevention of Infection – e.g., infant BCG replacement with improved BCG*
- Prevention of TB disease
  - BCG replacement
  - BCG boost (proximal)
  - BCG boost (distal)
- Prevention of recurrent TB
- TB treatment shortening +/- or increased cure rates (adjunct to treatment)

* Under discussion with regulators
Overview of Global Pipeline

Candidates in preclinical development are representative and include those in the IAVI and/or TBVI portfolios that have completed Gate 1 as published in Barker L, Hessel L, Walker B, *Tuberculosis*, 92S1 (2012) S25–S29.
Recent Progress in preclinical and translational science:

- Alternate Routes of Administration
  - iv BCG in mice\(^1\) and NHP\(^2\) – high levels of protection and evidence of role for trained innate immunity\(^3\)
  - Phase 1 studies of aerosol delivery in humans\(^4\)
- Novel vectors: e.g., CMV-TB (Picker/Aeras collaboration)\(^5\)
- New tools – e.g.:
  - Bar-coded Mtb strains\(^6\)
  - Controlled human infection models\(^7\)
  - Biorepository to support correlates discovery

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Global Clinical Pipeline of TB Vaccine Candidates

**Phase 1**
- Ad5 Ag85A  
  McMaster, CanSino
- ChAdOx185A/MVA85A  
  (ID/IM/Aerosol)  
  Univ of Oxford
- AEC/BC02  
  Anhui Zhifei Longcom

**Phase 2a**
- RUTI  
  Archivel Farma, S.L
- TB/FLU-04L  
  RIBSP
- MTBVAC  
  Biofabri, TBVI, Zaragoza, Aeras/IAVI

**Phase 2b**
- DAR-901  
  Dartmouth, GHIT
- VPM 1002  
  SIIL, Max Planck, VPM, TBVI  
  (Ph2b/3)
- M72/AS01E  
  GSK, Aeras/IAVI
- BCG Revaccination
- H56: IC31®  
  SSI, Valneva, Aeras/IAVI
- ID93 + GLA-SE  
  IDRI, Wellcome Trust

**Phase 3**
- Vaccae™  
  Anhui Zhifei Longcom
- VPM 1002  
  SIIL/VPM, Gol
- MIP  
  Cadila, Gol

**Legend**
- Viral Vector
- Protein / Adjuvant
- Mycobacterial – Killed
- Mycobacterial – Live attenuated

Revised on October 20, 2018 – personal view!
2018 – a Year of Unprecedented Progress

- New use for 98 year old current vaccine - protect high risk, uninfected populations from Mtb infection with BCG revaccination
- Proof of concept that a subunit vaccine (2 Mtb antigens plus adjuvant) can protect against TB disease
- First demonstration that a vaccine can protect Mtb-infected adults from developing TB disease
- First opportunity to discover correlates of protection and increase understanding of protective human immune responses
Phase II Prevention of Infection Trial
H4:IC31 and BCG revaccination

Clinical Trial Sites:
SATVI and DTHF/Emavundleni
Overview – First TB Vaccine POI Trial

Objectives:
Phase 2 Proof of Concept Prevention of Infection study to evaluate safety, efficacy and immunogenicity

3 Study Arms:
- H4:IC31 (IM, 2 doses, 56 days apart)
- BCG revaccination (ID, 1 dose; SSI BCG)
- Placebo (saline; IM, 2 doses, 56 days apart)

Population:
- QFT*-negative adolescents (12–17y.o.)
- Western Cape, South Africa
- High risk of infection (~10% per year)

Design:
- Randomized (1:1:1)
- Placebo-controlled
- Partially blinded

Study Size:
N=990 (330/arm)

*QFT = QuantiFERON Gold In-Tube interferon gamma release assay
POI Trial Results and Conclusions

• Both H4:IC31® and BCG revaccination appeared safe and immunogenic

• Neither vaccine showed statistical significance in preventing initial infection (initial QFT conversion)

• BCG revaccination demonstrated statistically significant prevention of sustained infection (sustained QFT conversion): VE: 45.4%; p=0.01

• H4:IC31 did not demonstrate statistically significant prevention of sustained QFT conversion: VE: 30.5%; p=0.08

• Biobank created and analysis plan being developed for discovery of candidate correlates of risk and/or protection against sustained infection
First POI Trial: conclusions and next steps

BCG Revaccination
- Statistically significant protection against sustained infection
- Confirm then evaluate in Prevention of TB Disease trial
- Potential correlates of protection discovery

H4:IC31
- First signal of any protection against TB infection or disease in humans by a subunit vaccine
- Suggests benefit of studying other subunit vaccines
- Not being further developed

POI Trial Design
- Is feasible and may be useful tool for decision-making.
- Should be validated with a Prevention of Disease trial

Trial: NCT02075203
M72/AS01_E Phase IIb Prevention of Disease Trial

Results of the primary analysis
**M72/AS01<sub>E</sub> Candidate Vaccine**

M72 antigens were initially identified in the context of controlled human infection.

**Antigen – M72**

- Recombinant protein comprising full length Mtb39A flanked by inverted halves of Mtb32A<sup>1,2</sup>
- Mtb 32A and 39A are highly immunogenic<sup>2</sup>
  - Genes present in virulent and avirulent strains of Mtb complex and in BCG<sup>1</sup>

**Adjuvant – AS01<sub>E</sub>**

- Immunostimulants (MPL and QS21) in a liposome formulation<sup>3</sup>

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2. AS01<sub>E</sub>, Adjuvant System containing 3-O-desacyl-4'-monophosphoryl lipid A (MPL [25 μg], produced by GSK), *Quillaja saponaria* Molina, fraction 21 (QS-21 [25 μg], licensed by GSK from Antigenics LLC, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation) and liposome.
M72/AS01E Candidate Vaccine
Goal: induce a robust Th1 CD4+ T cell response against Mtb antigens

Clinical safety and immunological profiles to date

- Generally well tolerated although higher reactogenicity observed in patients with active tuberculosis
- High seroconversion rate & long lasting humoral response
- Poly-functional CD4 Th1 cells (IFNγ TNFα IL-2+)
  - 3 years persistence*
- CD8 Th1 cells
- IL-17-expressing CD4 T cells
- T cell responses in lung

Phase IIb Study Design

- **Subjects**
  - HIV negative healthy adults (18 - 50 years)
  - Negative sputum by PCR (Xpert MTB/RIF)
  - Mtb-infected: positive by QuantiFERON

- **Design**
  - Double-blind, randomized (1:1)
  - M72/AS01E or Placebo
  - 2 doses 1 month apart

- **TB cases determination by**
  - Active follow-up every 2 months either by calls, home visits or SMS
  - TB symptoms and bacteriological confirmation (3 sputum samples)
    - By PCR and/or MGIT culture

- **3 years follow up**
  - Primary analysis at year 2
  - LSLV November 2018
Study Participants

**Screened:** n=8,336

- **Enrolled:** n=3,575
  - **Total Vaccinated:** n=3,573
    - ATP Efficacy: n=3,283
    - Not ATP Efficacy: n=290
  - **Not vaccinated:** n=2
- **Screening failure:** n=4,761

**Trial sites:**
- KEMRI
- CIDRZ
- Zambart
- SATVI
- TASK
- CIDRI
- Aurum Inst.
- Tembisa
- Klerksdorp
- BePart
- Setshaba
- PHRU

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Figure adapted from Van Der Meeren et al, presented at IDWeek, October 2018, San Francisco CA, Abstract 70677

http://www.idweek.org

Van Der Meeren et al., NEJM, 2018
### All Efficacy Endpoints: primary analysis

**Vaccine efficacy against TB for each case definition**

<table>
<thead>
<tr>
<th>Efficacy endpoints</th>
<th>TB diagnosis</th>
<th>HIV status</th>
<th>Sputum testing</th>
<th>Vaccine efficacy % (90% CI)</th>
<th>p-value</th>
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<tr>
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<td>Culture, PCR</td>
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<td>Timing vs TB treatment start</td>
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<td><strong>Case definition 1</strong></td>
<td>Pulmonary TB Clinical suspicion</td>
<td>HIV–</td>
<td>Any positive</td>
<td>54</td>
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<td>Sensitivity analysis</td>
<td>Pulmonary TB Clinical suspicion</td>
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<td>TB diagnosed and treated by clinician</td>
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<td>Modified case definition 5</td>
<td>TB diagnosed and treated by clinician</td>
<td>HIV–</td>
<td>Any</td>
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</table>

*All EfficacyEndpoints: primary analysis*  

Vaccine efficacy against TB for each case definition

Vaccine Efficacy for Case Definition 1

Kaplan-Meier (ATP cohort for efficacy)

Figure adapted from Van Der Meeren et al, presented at IDWeek, October 2018, San Francisco CA, Abstract 70677.

http://www.idweek.org

Van Der Meeren et al., NEJM, 2018
Conclusions and Next Steps

- M72/AS01E prevented TB disease in Mtb-infected adults
  - Efficacy of 54% [CI 90% 14-75%, p=0.04] - primary endpoint met
  - Secondary endpoint met (VE of 58%; p=0.05)
  - VE calculated for the other case definitions ranged from 28-70%
  - Acceptable safety profile

- More research is warranted
  - End of study analysis
  - Aeras (now IAVI) Biobank to enable correlates discovery

- Next steps for M72 development are under discussion with key stakeholders and funders
Proof of Concept Study Acknowledgments

**Study participants and their communities**

In the Study, the following individuals and their communities were involved:

- **AERAS**
  - Dereck Tait
  - Maria Lempicki
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  - Tom Evans
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**Investigators and their teams**

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**Funders:**

Aeras/IAVI (BMGF, DFID, DGIS, AusAID); GSK

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* *Aeras TB vaccine clinical program was recently transferred to IAVI*
A new model with novel partnerships and networks required to achieve ‘end-to-end’ program impact.
A coalition of critical upstream and downstream partners will enable program funding, accelerated M72 development and rapid access.

**Identify Medical Needs & Product Requirements**
- Unmet Medical Need
- Target Product Profile (TPP)

**Research & Development**
- Discovery, Product Optimization, Preclinical Development
- Clinical Development Regulatory Strategy

**Licensure**

**Enabling Access & Supply**
- Low Cost Manufacturing, Packaging, Supply, Delivery

**Financing, Procurement**
- Market Potential
- Demand Forecasts
- Access Agreements
- Public Health Value Proposition

**Launching & Delivery, Demand Generation**
- Cost-Effectiveness
- Population Impact
- Epidemiology
- Access Roadmap

**Country Decisions**
- TPP
- WHO SAGE
- WHO Prequalific.
- Acceptability assessments

Potential Program Partners/Funders:
- Bill & Melinda Gates Foundation
- Unitaid
- WHO
- IDCT
- The World Bank
- The Global Fund

TPP

M72/AS01 Phase 2b development partner
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- USAID FROM THE AMERICAN PEOPLE
- PEPFAR U.S. President’s Emergency Plan for AIDS Relief
- BILL & MELINDA GATES FOUNDATION
- THE WORLD BANK
- UKaid from the British people
- CEPI New vaccines for a safer world
- JAPAN
- Ministry of Foreign Affairs of the Netherlands
- Ministry of Foreign Affairs of Denmark
- MINISTRY OF FOREIGN AFFAIRS OF DENMARK
- Ministry of Foreign Affairs of The Netherlands
- Ministry of Science & Technology, Government of India
- Ministry of Foreign Affairs of Denmark
- Ministry of Foreign Affairs of The Netherlands
- Ministry of Science & Technology, Government of India
- National Institute of Allergy and Infectious Diseases
- Norwegian Ministry of Foreign Affairs
- U.K. Department for International Development
- The U.S. President’s Emergency Plan for AIDS Relief through the U.S. Agency for International Development
- The World Bank
- As of May 2018

And many other generous individuals and partners around the world
Thank you
ANNEX

<table>
<thead>
<tr>
<th>Duration (years)</th>
<th>VE(%)</th>
<th>% decrease in cases</th>
<th>CE vaccine price (USD)</th>
<th>% decrease in cases</th>
<th>CE vaccine price (USD)</th>
<th>% decrease in cases</th>
<th>CE vaccine price (USD)</th>
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