VPM1002
A new TB vaccine on the horizon
Post exposure Vaccine/PoR

Leander Grode
CSO/Director BD

Umesh Shaligram
Director R&D

Prasad Kulkarni
Director Medical

Sunil Gairola
Director Q A/C

Vakzine Projekt Management GmbH
Serum Institute of India Ltd
Development of a **safe, well tolerated and efficacious** vaccine (rBCGΔureC:Hly/VPM1002) against tuberculosis for residents in *endemic areas* and persons at risk in *non-endemic areas*
VPM1002 - Mode of action

S.H.E. Kaufmann et. al
< 4 years to bridge the gap from lab to clinics

VPM1002 - Fast Translational Product Development

- 2004/05: In-Licensing
- 2006: GMP-Material
- 2007: First in Man (ph Ia)
- 2008/09: ph Ib
- 2010/11: ph Ila
- 2012/13: ph II
- 2014-17: ph III/IV

- 2015-2018: phase I/II
- 2015-2018: NMIBC

VPM1002
- 2018-2020: phase III
- 2018-2018: as TB prime vaccine

VPM1002BC
- 2015-2018: phase I/II
- 2015-2018: NMIBC

Immunotherapeutic (non-muscle invasive bladder cancer)

VPM1002
- 2018-2018: with HH contact

 confidential
## Target Product Profile for VPM1002

<table>
<thead>
<tr>
<th>Product name</th>
<th>Prime TB vaccine</th>
<th>Post-exposure TB vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product</strong></td>
<td>Freeze-dried cake of live-attenuated, recombinant mycobacterium bovis BCG ΔureC::hly (multi-dose vial)</td>
<td>Freeze-dried cake of live-attenuated, recombinant mycobacterium bovis BCG ΔureC::hly (multi-dose vial)</td>
</tr>
<tr>
<td><strong>Target indication and patient segments</strong></td>
<td>Immunization of neonates to prevent severe childhood forms of TB in children.</td>
<td>Immunization of adults after successful completion of therapy for pulmonary TB to prevent recurrence of disease.</td>
</tr>
<tr>
<td><strong>Target population</strong></td>
<td>Neonates in endemic areas and infants at risk in non-endemic areas.</td>
<td>Adults who previously suffered from TB and have been cured.</td>
</tr>
<tr>
<td><strong>Key geographical markets</strong></td>
<td>Global, particularly tender business</td>
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</tr>
<tr>
<td><strong>Key efficacy claim</strong></td>
<td>Higher safety and efficacy than BCG (in terms of local and systemic tolerance, abscess formation and prevention of childhood forms of TB)</td>
<td>Prevention of TB recurrent disease (no current prevention available)</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Less side effects than BCG (safety, tolerability), reduced risk for BCGosis</td>
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</tr>
<tr>
<td><strong>Dosage / volume / route</strong></td>
<td>1-4 x 10^5 CFU / in 0.05 ml /intradermal injection</td>
<td>2-8 x 10^5 CFU / in 0.1 ml / intradermal injection</td>
</tr>
<tr>
<td><strong>Onset / duration of effect</strong></td>
<td>1-3 months after vaccination / life-long</td>
<td>1-3 months after vaccination / life-long</td>
</tr>
<tr>
<td><strong>Stability / shelf life</strong></td>
<td>Up to now, data confirming stability for 36 months at +2 to +8°C (and also below -18°C) are available for clinical material. The stability program for the current batches of the investigational medicinal product is still ongoing and data will be added successively.</td>
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</tr>
<tr>
<td><strong>Presentation / formulation</strong></td>
<td>Lyophilized cake of live recombinant <em>Mycobacterium bovis</em> rBCGΔureC::Hly+, vial contains 2-8 x 10^6 CFU of the IMP. To be dissolved with water for injection.</td>
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</tr>
<tr>
<td><strong>Doses per reconstituted vial</strong></td>
<td>One reconstituted vial will contain 20 doses for neonates</td>
<td>One reconstituted vial will contain 10 doses for adults.</td>
</tr>
<tr>
<td><strong>Price</strong></td>
<td>Tbd</td>
<td>Tbd</td>
</tr>
<tr>
<td><strong>Current Gold-standard</strong></td>
<td>BCG vaccine</td>
<td>none</td>
</tr>
</tbody>
</table>
The Recombinant BCG ΔureC::hly Vaccine Targets the AIM2 Inflammasome to Induce Autophagy and Inflammation

Hiroyuki Saiga, Natalie Nieuwenhuizen, Martin Gengenbacher, Anne-Britta Koehler, Stefanie Schuerer, Pedro Moura-Alves, Ina Wagner, Hans-Joachim Mollenkopf, Anca Dorhoi and Stefan H. E. Kaufmann

1Department of Immunology
2Core Facility Microarray, Max Planck Institute for Infection Biology

Correspondence: Stefan H. E. Kaufmann, PhD, Max Planck Institute for Infection Biology, Charitéplatz 1, 10117 Berlin, Germany


Central Memory CD4+ T Cells Are Responsible for the Recombinant Bacillus Calmette-Guérin ΔureC::hly Vaccine’s Superior Protection Against Tuberculosis

Alexis Vogelzang,1 Carolina Perdomo,1 Ulrike Zedler,1 Stefanie Kuhlmann,1 Robert Hurwitz,1 Martin Gengenbacher,1,4 and Stefan H. E. Kaufmann1

1Department of Immunology and 2Core Facility Protein Purification, Max Planck Institute for Infection Biology, Berlin, Germany
3 Scientific Advises at **Paul Ehrlich Institute**/ German authority
May 2014: Scientific Advise at **Swissmedic** on bladder cancer study
In India the project was introduced to **DCGI** and **RCGM**
Meetings with **EMA, FDA**
International meetings at **WHO**:
  - 2012: Potency testing of new TB vaccines
  - 2011: Consensus statement on diagnostic endpoints for infant TB vaccine trials
  - 2009: 2\textsuperscript{nd} Geneva consensus: Recommendations for novel life TB vaccines
  - 2009: Standardization and evaluation of BCG vaccines
  - 2004: Geneva consensus: Essential steps towards clinical development

New live mycobacterial vaccines: the Geneva consensus on essential steps towards clinical development*
GMP Manufacture

Fully scalable state of the art fermentation process.
Prospect for overcoming BCG shortage.
1. **Pre-exposure vaccine**

A Multicenter phase III double-blind; randomized; controlled study to evaluate the efficacy and safety of VPM1002 in comparison with BCG in HIV-exposed and HIV-unexposed newborn infants

- expansion of current phase IIb trial
- **VPM1002-ZA-3.21TB**
- Location: South Africa, Tanzania, Gabon, Kongo (and India)

2. **Post-exposure vaccine - prevention of recurrent TB**

A multicenter phase III double-blind, randomized, placebo controlled study to evaluate the efficacy and safety of VPM1002 in the prevention of Tuberculosis (TB) relapse after successful TB treatment in India

- **VPM1002-IN-3.01TBR**
- Location: India
- Status: CTA approval, trial started QIV 2016
VPM1002
Clinical Development as Prime TB vaccine

Phase II South Africa
HIV-unexposed and HIV-exposed infants

(currently ongoing, 416 enrolled and complete)
Study cohort (n=416)

Randomization
Newborn infants
(0-12 days old)

Allocated to BCG (n=104)
- HIV-unexposed (n=52)
- HIV-exposed (n=52)

Allocated to VPM1002 (n=312)
- HIV-unexposed (HIV-exposed Hyg+ (n=52)
- HIV-unexposed (n=104)
- HIV-exposed (n=156)

12 months follow-up*

*structured medical surveillance will be conducted for 24 months post-trial completion

Primary objective
Safety & tolerability:
VPM1002 (total) vs. BCG (total)

Secondary objective
1. Safety & tolerability: VPM1002 (HIV-exposed) vs. VPM1002 (HIV-unexposed)
2. Immunogenicity

24 months structured medical surveillance period
VPM1002-ZA-2.13TB
Phase IIb South Africa - Study Design

- Multi-center trial in South Africa (3 sites Cape Town, 1x Johannesburg)
- Sponsor: SIIL
- Double-blind, randomised, controlled
  - VPM1002 vs. BCG
  - parallel-group
- Single administration - Intradermal (1-4x10e5 CFU)
  - HIV-unexposed and -exposed
- 12 month follow-up
  (additional 24 month surveillance period)
- Total of 416 neonates
  - First infant vaccinated in June 2015
  - Enrolled infants: 416 and complete
  - Last infant vaccinated October 2016
priMe
pivotal phase III trial
A Multicenter phase III double-blind; randomized; controlled study to evaluate the efficacy and safety of VPM1002 in comparison with BCG in HIV-exposed and HIV-unexposed newborn infants
Study conduct

- 9 sites in:
- South Africa
- Uganda
- Kenia
- Tanzania
- Gabon
priMe - Study design

Study cohort (n~10,000)

Randomization
Newborn infants
(0-12 days old)

Allocated to BCG (n~5,000)
HIV-unexposed HIV-exposed

Allocated to VPM1002 (n~5,000)
HIV-unexposed HIV-exposed

Average 24 months follow-up

Primary objective
Efficacy & Safety: VPM1002 vs. BCG

Secondary objective
Safety and efficacy parameters in HIV-exposed vs. HIV-unexposed infants

structured medical surveillance period
VPM1002
Clinical Development
as Post-exposure TB vaccine

Phase III India
HIV-negative, successfully treated TB patients

(The study started in QIV 2016)
VPM1002-IN-3.01TBR

A multicenter phase III study to evaluate the efficacy and safety of VPM1002 in the prevention of Tuberculosis (TB) Recurrence after successful TB treatment in India
Pre-clinical development of VPM100 Potential as a therapeutic vaccine

Perfomred by Martin Gengenbacher / Stefan H.E. Kaufmann at Max Planck Institute for Infection Biology, Berlin (publication submitted)
Pre-clinical development of VPM1002
Potential as a therapeutic vaccine

Performed by Martin Gengenbacher / Stefan H.E. Kaufmann at Max Planck Institute for Infection Biology, Berlin (publication submitted)
VPM1002-IN-3.01TBR
Planned study design

VPM1002 / placebo vaccination

In-study phase

0m
3m 6m 9m 12m

anti-tuberculosis treatment (ATT)

-4w to -2w

Active TB

"cured"

Screening

Sputum smear/culture negative

TB recurrence?

TB recurrence?

TB recurrence?

TB recurrence?

Bacteriologically confirmed TB and/or Clinically confirmed TB
Study cohort (n=2000)

Randomization
Successfully treated TB patients

Allocated to placebo (n=1000)

Allocated to VPM1002 (n=1000)

12 months follow-up (every 3 month sputum collection)

**Primary objective**
Efficacy in prevention of recurrence

**Secondary objective**
1. Safety & tolerability: VPM1002 after successful ATT
2. Immunogenicity in 200 patients
Acknowledgement

VPM1002-ZA-2.13 Team
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Anneke Hesseling, Desmond Tutu
Center
Victor Strugo, Triclinium

VPM1002-IN-3.01TBR) Team
Soumya Swaminatan and NIRT Team

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Amita Gupta, Vidya Mave, Padmini
Salgame and others.

Peter Kim NIH
Nandita Chopra NIH

Bladder Cancer Team
Schweizerische Arbeitsgemeinschaft für
klinische Krebsforschung (SAKK)
Cyrill Rentsch Uni Basel
Burger und Michael Giert Uni Regensburg
NKI Amsterdam
Francoirs Spertini CHUV

Max-Planck-Institut
für Infektionsbiologie

EDC T P
European & Developing Countries
Clinical Trials Partnership

HELMHOLTZ
ZENTRUM FÜR
INFECTIOnSFORSCHUNG

Partner of the
Stop TB Partnership

Bundesministerium für Bildung
und Forschung