



Vakzine Projekt
Management GmbH

eine Initiative des
Bundesministeriums für Bildung und Forschung (BMBF)

**Induction of antigen specific multifunctional T-cells
after vaccination with the live recombinant
tuberculosis vaccine VPM1002 (rBCG Δ ureC::Hly)
a live Vaccine in a Phase I clinical trial**

Dr. Bernd Eisele, CEO
Dr. Leander Grode, . Director BD

Vakzine Projekt Management GmbH

www.vakzine-manager.de

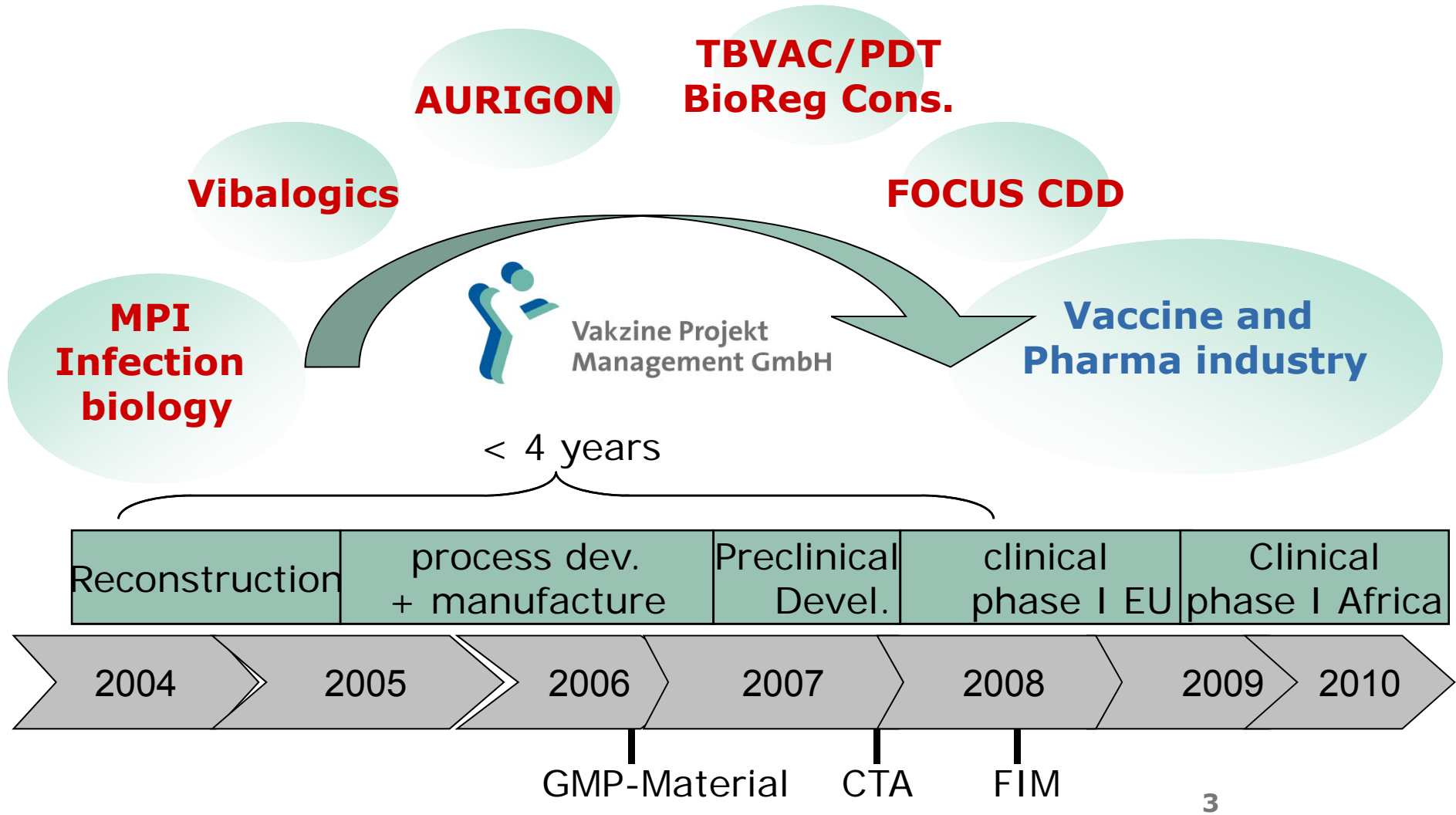
VPM's Mission



**Vakzine Projekt Management GmbH (VPM)
acquires promising vaccine candidates and biologics from
academia, develops them with a consortium of partners
and commercializes the results.**



Timeline along the value chain of development



Critical Success Factor: Several Scientific Advice Meetings with PEI ● ● ●

Product Profile VPM1002



Parental Strain:

BCG subtype Prague

Genetic Modification:

Listeriolysin gene inserted into bacterial genome (Urease C gene)

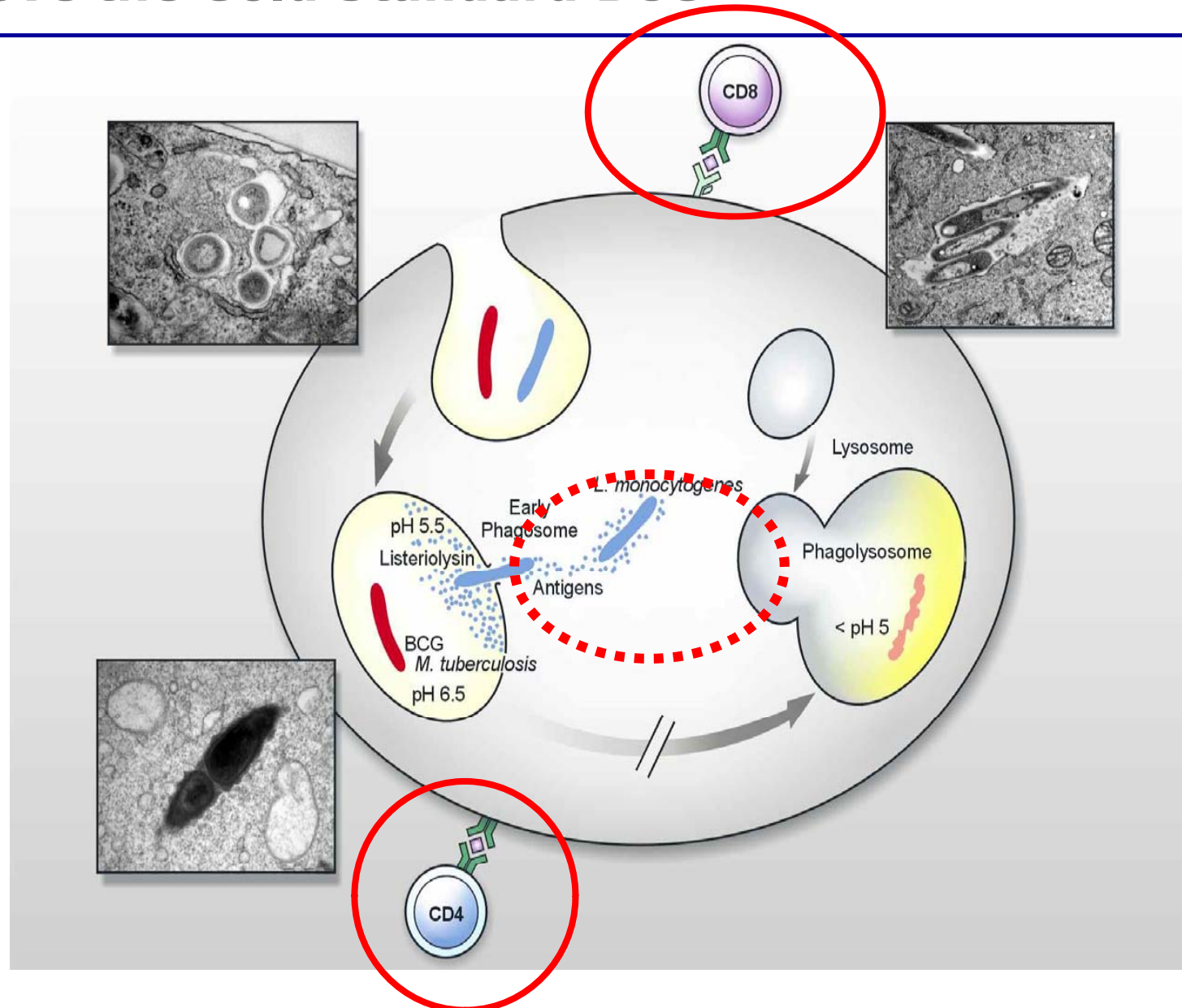
Resistance to Hygromycin

Classification: S1 / P1

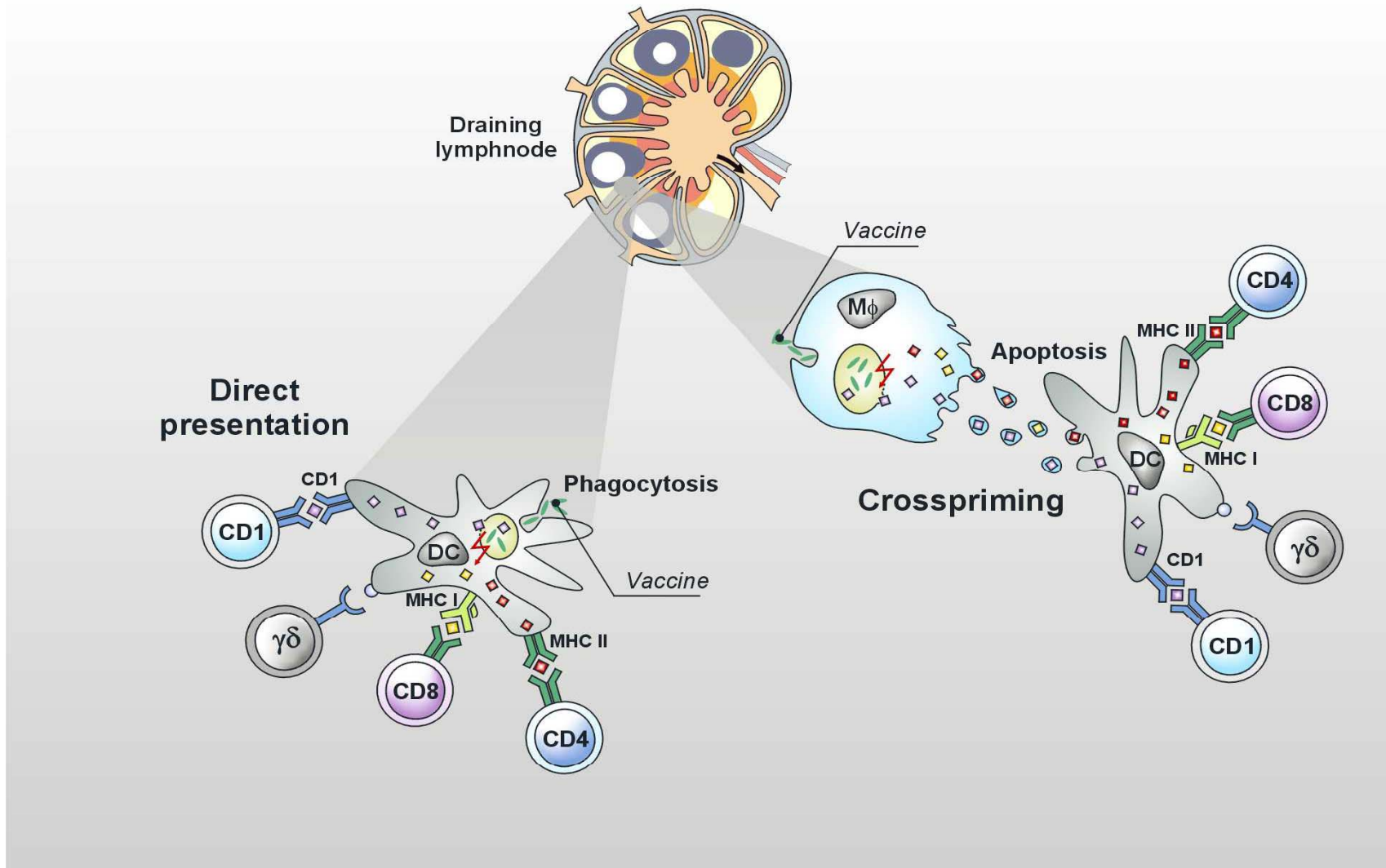


The Challenge in Translational Research: - Improve the Gold Standard BCG -

VPM1002

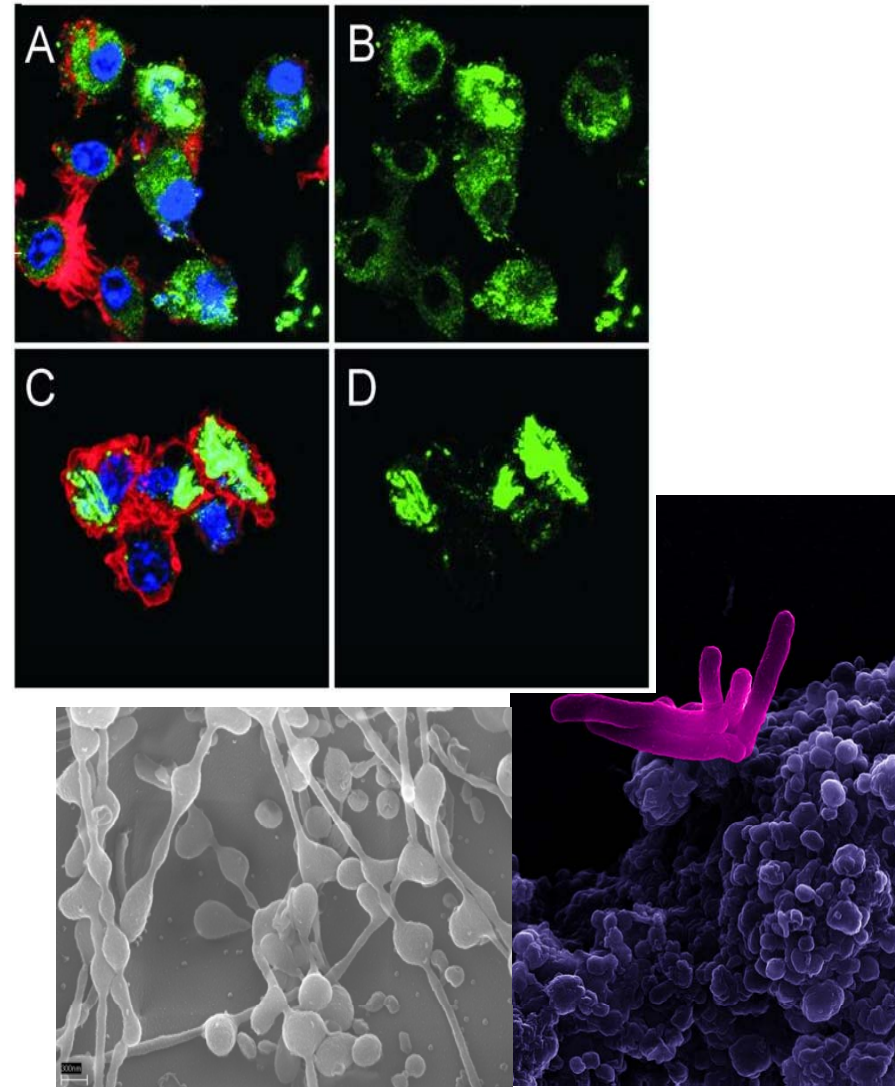


Antigen presentation



Mode of action

- **Perforation** → **Antigen translocation into cytosol** → **direct MHC I loading in infected cells**
- **Antigen translocation: improved CD8 T cell responses**
- **Perforation** → **translocation of cathepsins** → **activation of caspase cascade** → **apoptosis** → **crosspriming**
- **Crosspriming: improved CD8 as well as CD4 and CD1-restricted T cell responses**



VPM1002: manufacture

Product Profile

Manufacturing:

VPM1002 is manufactured by submerge fermentation in minimal medium. The final product is a lyophilised cake of live bacteria. Establishment of a GMP process is completed. The process has been designed to offer full scalability.

- Modern submers 30 liter fermentation
- Lyophilization (we are able to test 4 different formulations in one run)

The pilot lyophilization currently ~3000 GMP vials

Each vial contains 10 human doses ($\sim 5 \times 10^6$ CFU/vial)

Stability >29 months

VPM1002: non-clinical overview

Preclinical Studies

- 6 months toxicology study in **guinea-pigs** including one PPD skin test; **Successfully completed**, no adverse events, normal weight gain
- 42 days safety studies (highest dose $1-4 \times 10^7$ CFU/animal) in **guinea-pigs**; in-life phase **successfully completed** without adverse events, normal weight gain; gross necropsy and histology findings similar to control groups
- **Rabbit** toxicology study (**successfully completed**)
- **Safety studies in immune deficient mice**
 - 105 days SCID mouse studies four doses ranging from $1-4 \times 10^5$ to $1-3 \times 10^8$ CFU/animal; in-life phase **successfully completed** even the highest dose below LD50
 - 105 days IFN-gamma k.o. mouse study; two dose $1-4 \times 10^5$ and $1-4 \times 10^6$ CFU/animal; **successfully completed** 100% survival
- Protection / Challenge in a **murine model** (**successfully completed**)
- Safety in **macaques** (**successfully completed**)

VPM1002: clinical

VPM1002 Phase I: 80 volunteers in Germany

First Vaccinee enrolled on Sep 08, 2008



Last Vaccinee enrolled on June 2, 2009

13



VPM1002-GE-1.01TB: N=80

Dosage Group	Pre-Disposition (BCG-vaccination and PPD status)	N per group	N for interim safety monitoring	
BCG	No (neither vaccinated nor PPD-pos.)	10	3	
1	No (neither vaccinated nor PPD-pos.)	10	3	
2	No (neither vaccinated nor PPD-pos.)	10	3	
3	No (neither vaccinated nor PPD-pos.)	10	3	
BCG	Yes (vaccinated or PPD-pos.)	10	3	
1	Yes (vaccinated or PPD-pos.)	10	3	
2	Yes (vaccinated or PPD-pos.)	10	3	
3	Yes (vaccinated or PPD-pos.)	10	3	
Total		80	24	

Group 1: 5 x 10³ CFU VPM1002
Group 2: 5 x 10⁴ CFU VPM1002
Group 3: 5 x 10⁵ CFU VPM1002
BCG: 5 x 10⁵ CFU BCG

1-2-3-4 exposition

Stratification regarding the status of pre-disposition:

No = lack of BCG-vaccination in the personal vaccination documents and no BCG-scar and PPD-Skin-Test negative (< 1 mm)

Yes = documented BCG-vaccination in the personal vaccination documents or BCG-scar or PPD-Skin-Test positive (at least 1 mm but less than 10 mm)

Primary Objective

The primary objective of this study was to investigate the safety of single doses of VPM1002.

Primary parameters:

→ **Tolerability**

According to the study protocol 56 days and 6 months after vaccination the subjects were asked.

- 57% stated the tolerability as **very good**
- 40% good
- 3% bad (only in the BCG group)

→ **Safety**

- **No** Serious Averse Events
- (Expected!) Adverse Drug Reactions, mostly induration, erythema and swelling at the injection side

Secondary Objective

The secondary objective of this study was to investigate the immunogenicity of single doses of VPM1002 for vaccination against Tuberculosis.

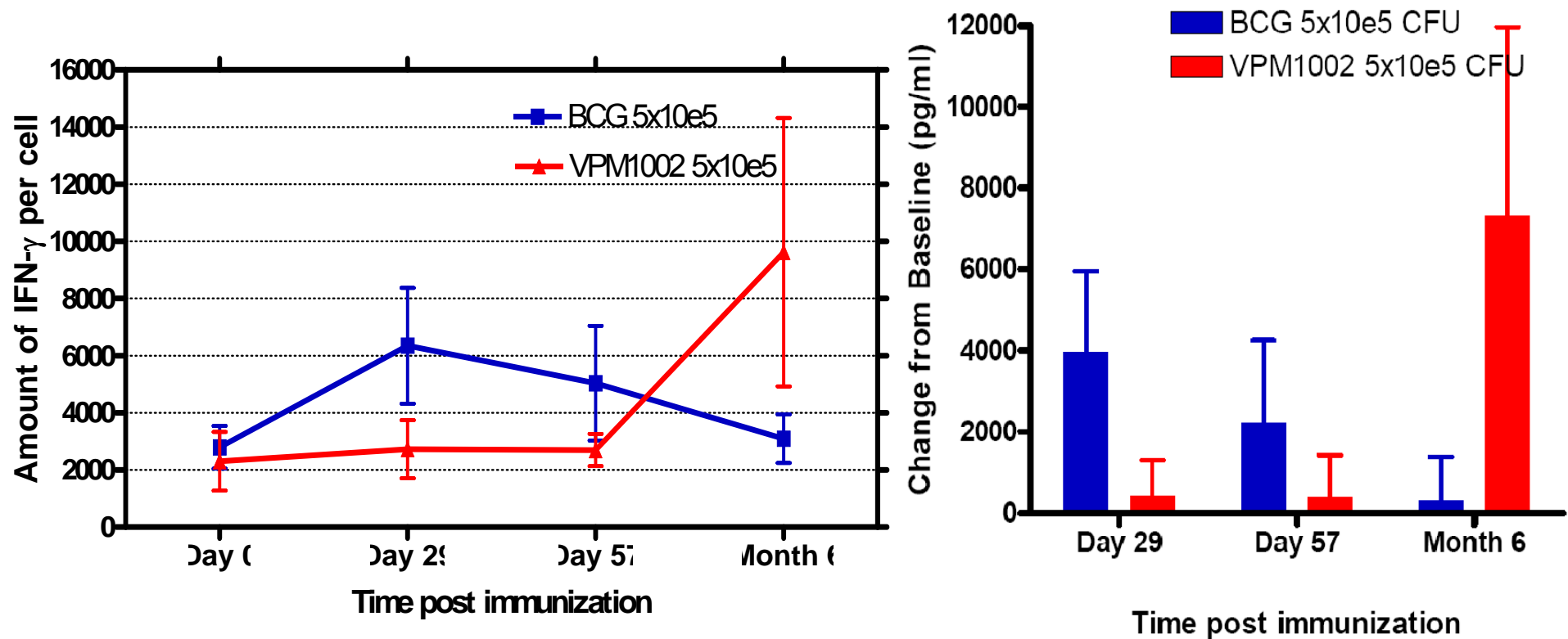
To determine the immune response the following assays were used:

- PBMC ELISA for IFN- γ restimulated with PPD
- Whole Blood Elisa for IFN- γ restimulated with PPD
- ELISpot Assay for IFN- γ restimulated with PPD

IFN- γ Release by PBMC

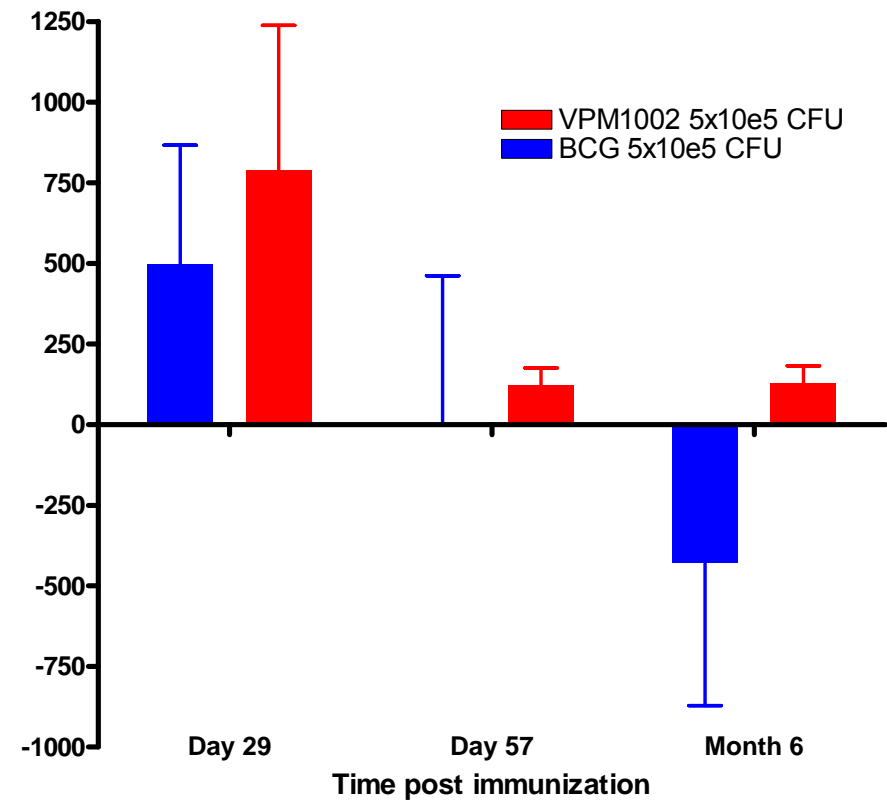
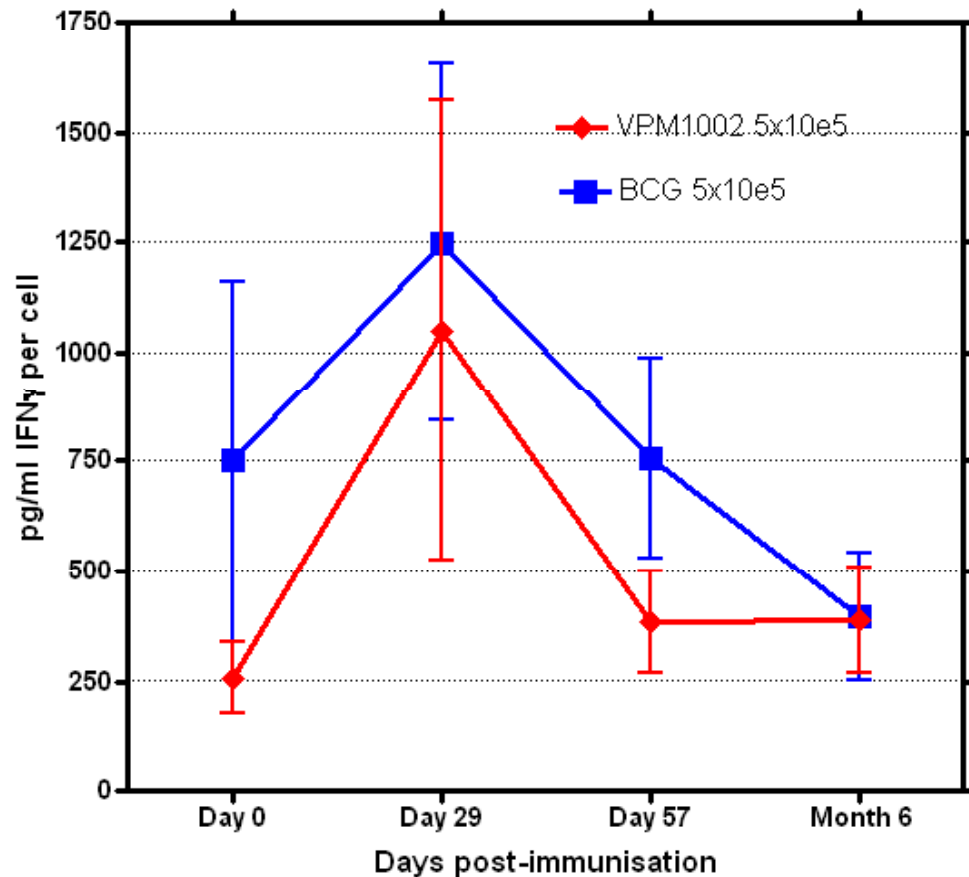
- Naïve Volunteers -

--- marked Increase with VPM1002 after 6 Months ---

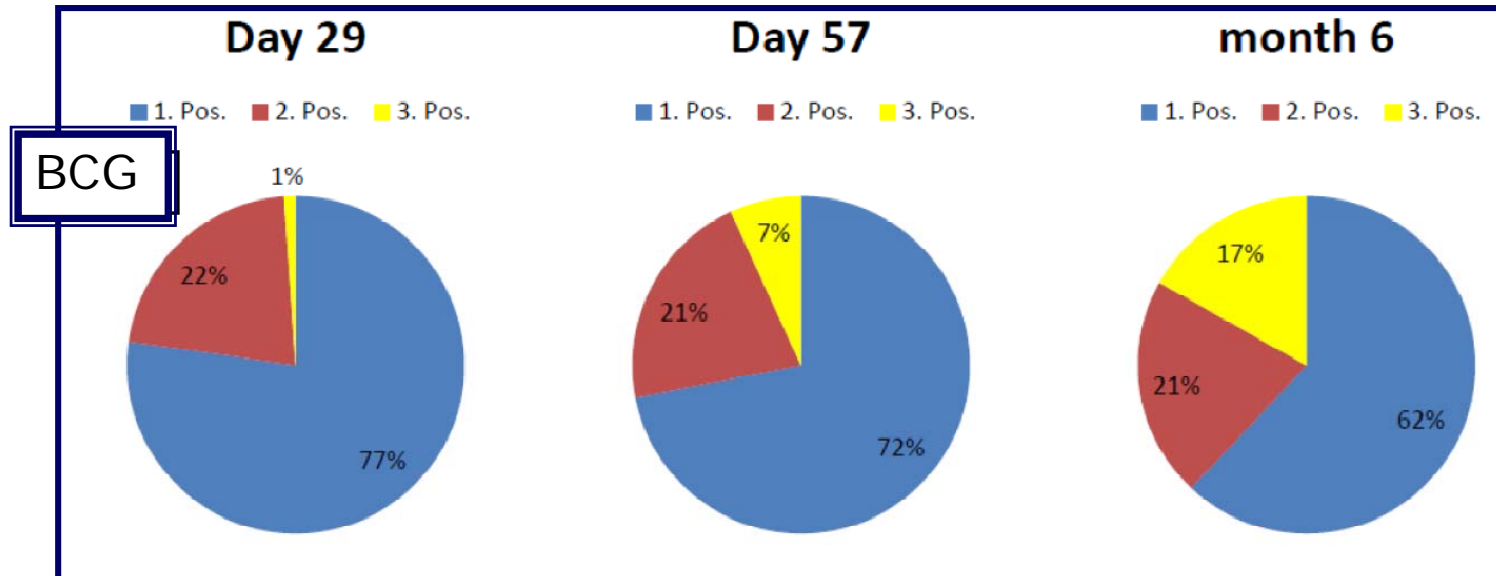


IFN- γ Release by Whole Blood Cells

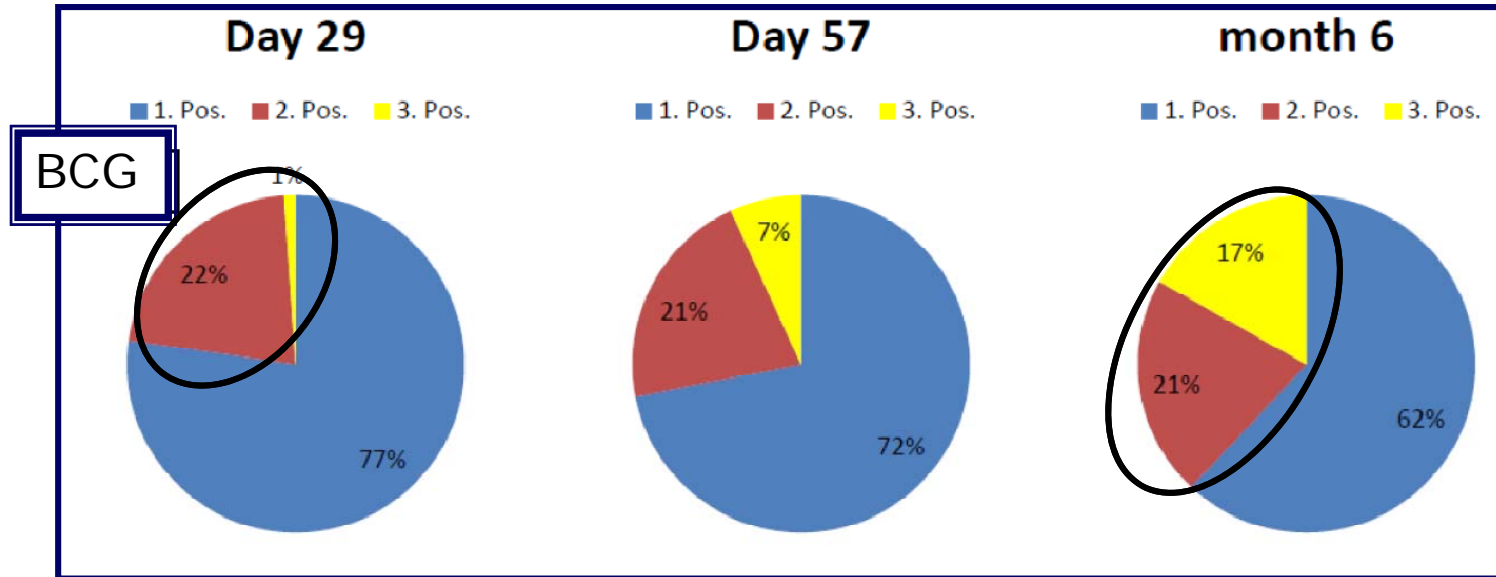
- Naïve Volunteers -



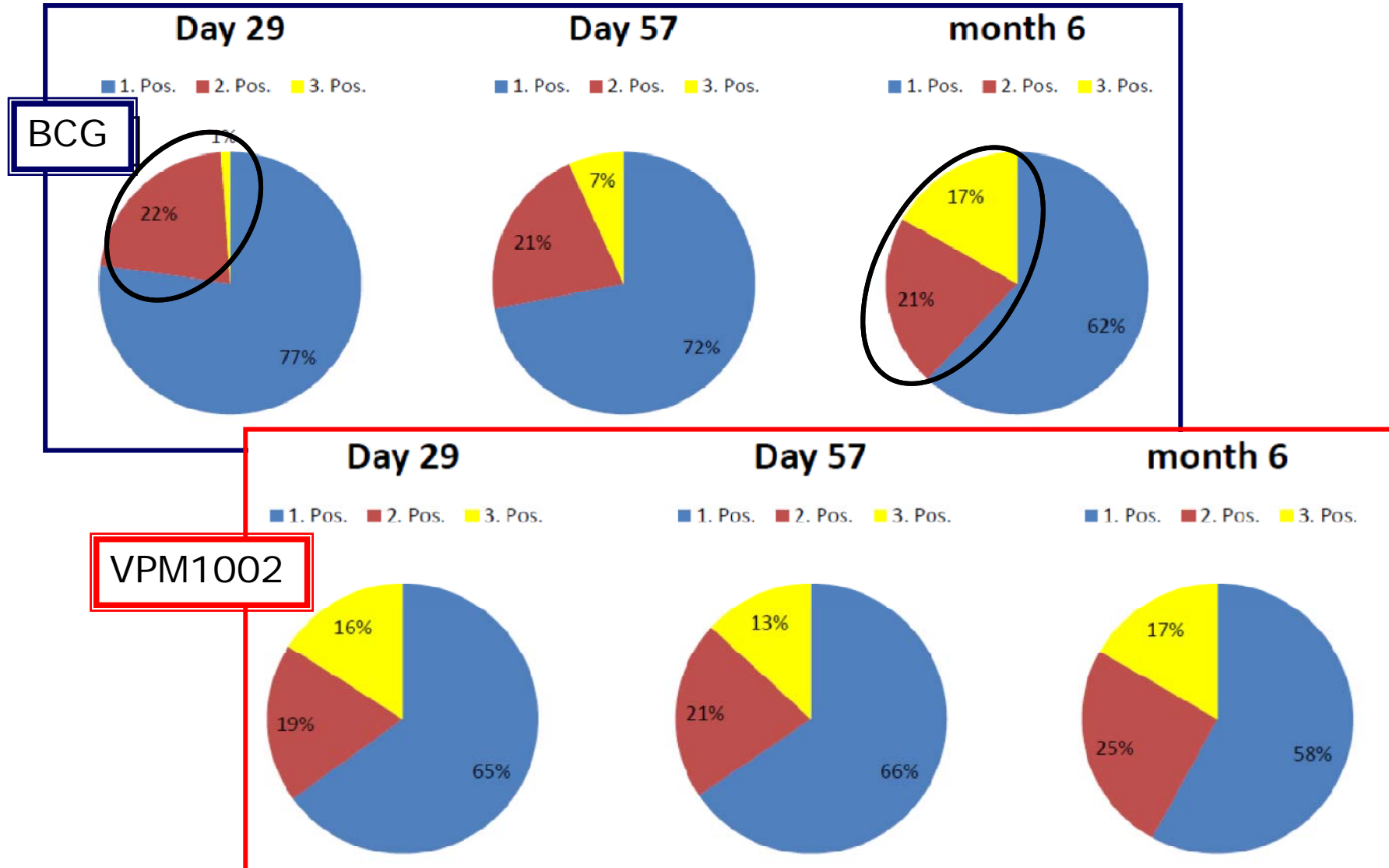
Immune Pattern CD 4+ T-cells - Naïve Volunteers -



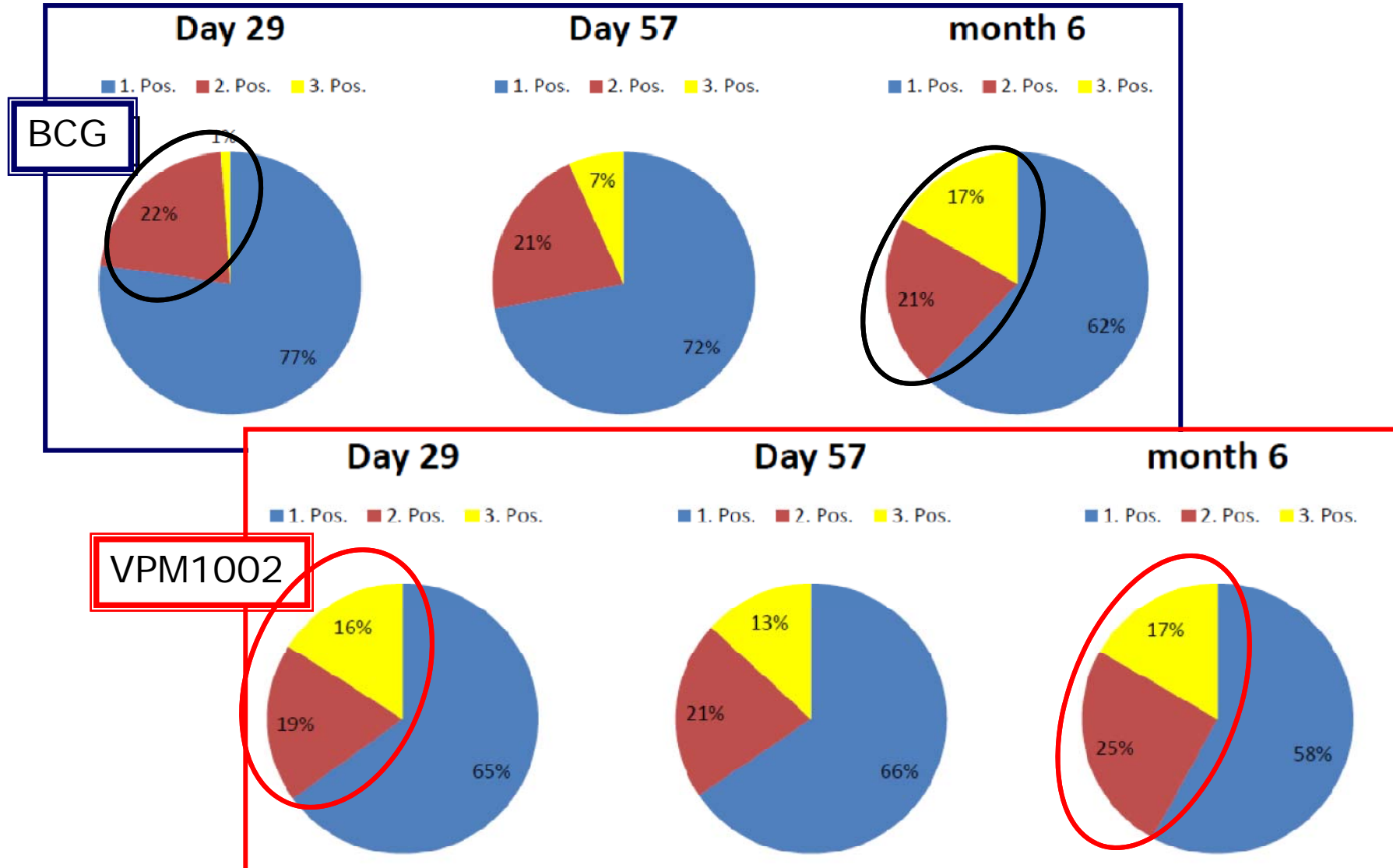
Immune Pattern CD 4+ T-cells - Naïve Volunteers -



Immune Pattern CD 4+ T-cells - Naïve Volunteers -



Immune Pattern CD 4+ T-cells - Naïve Volunteers -

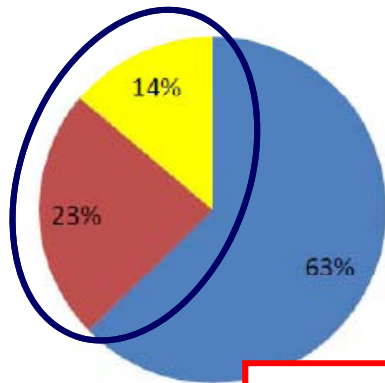


Immune Pattern CD 4+ T-cells - Pre-Immune Volunteers („boost“) -

BCG

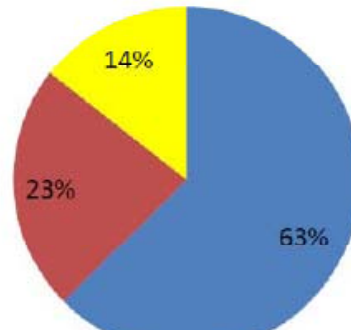
Day 29

■ 1. Pos. ■ 2. Pos. ■ 3. Pos.



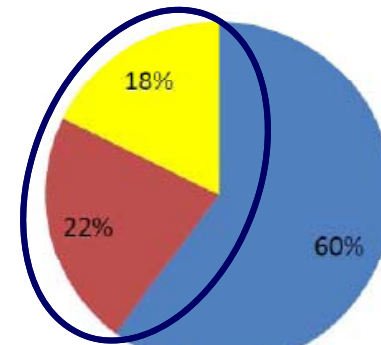
Day 57

■ 1. Pos. ■ 2. Pos. ■ 3. Pos.



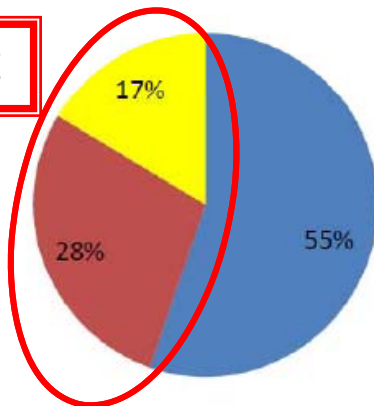
month 6

■ 1. Pos. ■ 2. Pos. ■ 3. Pos.



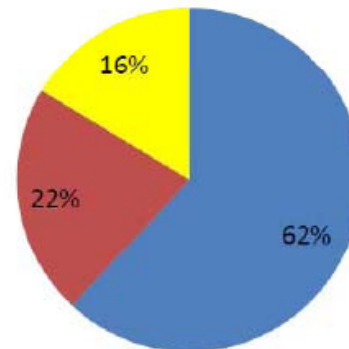
Day 29

■ 1. Pos. ■ 2. Pos. ■ 3. Pos.



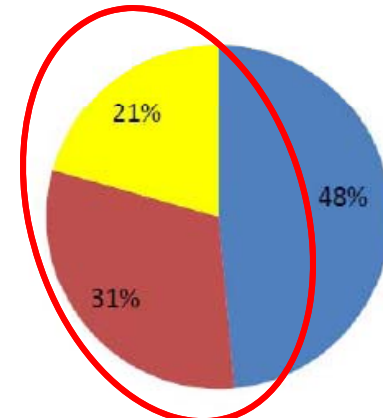
Day 57

■ 1. Pos. ■ 2. Pos. ■ 3. Pos.



month 6

■ 1. Pos. ■ 2. Pos. ■ 3. Pos.



VPM1002

Product Promise of VPM1002

- No interference with Tb diagnostics (→ **unproblematic use**)
- Induction of **CD4+ AND CD8+** Immune response (→ **improved protection**)
- Induction of **Multifunctional T-cells** (IL-2; IFN- γ ; TNF- α) (→ **in children AND adults**)
- **Safer than BCG** in immunocompromised species (→ **usable in high-risk babies**)



VPM1002 Phase Ib: 24 volunteers in S. Africa



Clinical Program Phase Ia-II



- ✓ **Phase Ia:** Evaluation of safety, local and systemic tolerability and immunogenicity of VPM1002 in healthy **adult Caucasians** compared to reference control (BCG)
- **Phase Ib:** Evaluation of safety, local and systemic tolerability and immunogenicity of VPM1002 in healthy **adult Africans** compared to reference control (BCG)

Immunisation completed and immune observation ongoing

- **Phase II:** Double-blind, randomized, BCG controlled Phase II study with VPM1002 vaccination for evaluation of safety, local and systemic tolerability and immunogenicity of VPM1002 in **neonates**.

CTA (IND) in preparation



Contact



Vakzine Projekt Management GmbH

Mellendorfer Str. 9 • D-30625 Hannover • Germany

Tel.: +49 (0) 511 169 908-0, Fax: +49 (0) 511 169 908-29

Info@vakzine-manager.de • www.vakzine-manager.de

