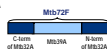


## Rationale for development

- BCG vaccine shows important limitations
- Candidate Tuberculosis (TB) vaccine is being developed to protect against primary TB disease
- Vaccine will be used as a boost to BCG
- Candidate TB vaccine:
  - Recombinant protein Mtb72F
  - Proprietary Adjuvant system AS02A
    - MPL
    - QS21
    - Oil-in-water emulsion



## Study design

- Double-blind, randomised, controlled, single-centre, phase I/II study
- 5th July 2005 - 23th May 2006 (Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland)
- Study population:
  - Healthy adults 18-50 years
  - HIV-1 and -2-negative
  - PPD-positive

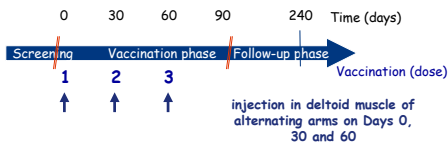
## Study population

- BCG cohort
  - Documented BCG vaccination or BCG scar
  - No history of TB infection or disease
  - No history of therapy or prophylaxis for TB
  - No active, chronic or past TB disease, confirmed by chest X-ray
  - PPD skin test: induration  $\leq 10$  mm
- INFECTIION (INF) cohort
  - Documented history of TB disease or infection
  - History of successful treatment for pulmonary TB or post-exposure chemoprophylaxis (completed at least 2 years prior to vaccination)
  - No history of extrapulmonary TB
  - No active TB disease, confirmed by chest X-ray
  - PPD skin test: induration  $> 10$  mm

## Doses and administration

- Both cohorts received
  - Study vaccine (Mtb72F/AS02A): INF-VAC and BCG-VAC
  - OR
  - Adjuvant only (AS02A): INF-REF and BCG-REF

Groups	Mtb72F	AS02A	N
BCG-VAC	40 $\mu$ g	+	15
BCG-REF	-	+	5
INF-VAC	40 $\mu$ g	+	13
INF-REF	-	+	5



## Safety & Reactogenicity

### Withdrawals and study attrition

Subjects receiving each immunisation			
	Dose 1	Dose 2	Dose 3
BCG-VAC	15	15	14
BCG-REF	5	5	5
INF-VAC	13	10	6
INF-REF	5	4	4

### Reasons for withdrawal from vaccination

- Out of vaccination interval: N=1 (INF-REF)
- Subject's decision: N=2 (INF-VAC), N=1 (BCG-VAC)
- Investigator's decision: N=5 (INF-VAC)

## Reactogenicity: summary

- No SAEs reported
- Haematology & biochemistry:
  - No vaccine-related clinically significant abnormal lab values reported
- Solicited local AEs:
  - Mainly pain at injection site (in all groups - overall and grade 3)
- Solicited general AEs:
  - Mainly fatigue (all groups) and headache (~ more in VAC groups)
  - Headache most commonly reported grade 3 AE
  - No grade 3 AEs reported in REF groups
- Unsolicited AEs:
  - Mainly myalgia (38.6%, INF VAC; 37.9%, BCG-VAC) and chills (18.2%, INF-VAC; 27.6%, BCG-VAC) - all in VAC groups
- Radiological assessments:
  - No change in chest X-rays observed 6 months after vaccination in INF cohort

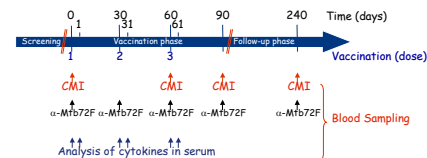
## Conclusions of the study

- The vaccine is highly immunogenic in BCG-primed and Mtb-exposed individuals
- Vaccine is locally reactogenic - mainly transient pain and self-limiting
- Vaccine is safe with acceptable reactogenicity in BCG-primed individuals
- Despite broad assessment of immune markers, no correlation was found between immunogenicity and reactogenicity in vaccinated Mtb-exposed individuals who were withdrawn for AEs

## Immunogenicity

### Laboratory evaluations

- IFN- $\gamma$  ELISPOT
- Intracellular cytokine staining (ICS)
- IFN- $\gamma$  production in serum by ELISA
- Antibody titres to Mtb72F by ELISA



## Mtb72F-specific immune responses: summary

- Vigorous induction of antigen-specific cellular immune responses after 2 immunisations in both cohorts (post-1 not measured)
- No increase in T cell responses observed upon third vaccination
- Limited decrease in T cell responses at month 8
- CD4 T cells pattern of markers expressed: CD40-L = IL-2  $>$  TNF- $\alpha$   $>$  IFN- $\gamma$
- No Mtb72F-specific CD8<sup>+</sup> T cells were detected (data not shown)
- Strong vaccine associated serum INF $\gamma$  secretion
- Vigorous induction of Mtb72F-specific antibodies in both cohorts

## Perspectives

- The study supports the development of the vaccine:
  - Clinical Development in BCG primed infants is planned
  - A dose range study in Mtb exposed individuals is planned
  - A clinical study in HIV positive individuals is planned at CHUV