P27A combined phase Ia/Ib clinical trial : a fast move to the field

An update

F. Spertini, CHUV, Lausanne, CH
S. Shekalaghe, IHI, Bagamoyo, TZ

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ClinicalTrials.gov Identifier: **NCT01949909**
Pan African Clinical Trial Registry number : **PACTR201310000683408**

P27A, a 104 aa long peptide derived from PFF165c

- PFF0165c protein contains intrinsically unstructured protein domains
  - Low in hydrophobic amino acid and high in hydrophilic amino acid content
  - Rapidly obtainable through peptide synthesis
- P27A
  - a 104-residue long peptide was the largest and did not contain long stretches of identical amino acids (poly-Glu or poly-Asn)

Olugbile et al. I&I, 2009

Protein PFF0165c and peptide P27A

Protein PFF0165c

MSNKKRSKNENDESTSLPLENSELLIEYIHNLKSCLNVYRREIQEKNKYISIIKNDLSFHEC
ILTNVNVVWSVFNNDLLNLLCNNEQKEEGEEIIKQRNIGDEINEYNNLTKLQNDENIKNNNM
IKEDLEDDANQNILMKSPYYNIENFLQVFLKYINKKKKKVKVKVKDEGKKEKIEDKKYEQDD
EEENEEEEEEEEEEGEEENKEDEEFFKTFVSFNLYHNNNEKNISYDKNLVKQENDNKDEAR
GNDNMCGNYDIHNERGEMLDKGKSYSGDEKINTSDNAKSCSGDEKVITSDNGKSYDYVKNES
EEQEEKENMLNNKKRSLECNPNEAKKICFSLEEKIGTVQSVKLKEYNELSKENIEKNKHDDN
NICNYLSHNEGENVIEREDKLFNKLNNKNYRNEEEKKKNQINFDYLKKKIKNNQDVFEETIQ
KCFLINLKKTLNLINKIMYLKNVEFRKYNLDYIRKINYEKCFYYKNYIDIKKKISELQKDNE
SLKIQVDRLEKKKATLIYKLNNDNIRKHILDNNIKDYQNGIDNSKVSYFDEGENPYNRNNKN
YRTDNKNSDDNNNNNNYYYNNYNSDDNYNSEDNEYNNGNYRFRNNYKKDSLNEDDVKKNPLK
VCHKINSDSNIFVNFENIITKQNIIHSEPFRNLLKESNELYITLKEKEKENIILKNEILKME
NKKDEEYEHLLNNTIEDKKELTRSIKELEINMMTCNMEKDKISNKVNTLEYEINVLKNIDKN
QTMQLQQKENDILKMKLYIEKLKLSEKNLKDKIILLENEKDKMLSGIHIKDNSFNEESKSEE
GKIQLRDIQNDNDEKYDDEKKRFKELFIENQKLKEELNKKRNVEEELHSLRKNYNIINEEIE
EITKEFEKKQEQVDEMILQIKNKELELLDKFNNKMNKAYVEEKLKELKNTYEEKMKHINNIY
KKHDDFVNIYLNLFFQARKNAILSDSQREEQMNLFIKLKDKYDIIFQKKIELTDILKNVYDC
NKKLIGHCQDLEKENSTLQNKLSNEIKNSKMLSKNLSKNSDDHLLIEENNELRRRLICSVCM
ENFRNYIIIKCGHIYCNNCIFNNLKTRNRKCPQCKVPFDKKDLQKIFLD

Peptide 27A

Peptide 27 (coiled coil)

Schematic Representation

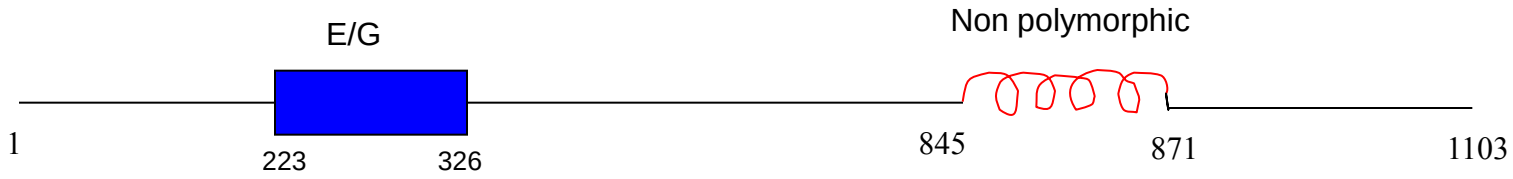
Prevalence of total IgG and cytophilic IgG1/IgG3 among adult donors living in regions where malaria is endemic

Ig class	No. (%) of donors with indicated Ig from Burkina Faso (*n* # 37)	Tanzania (*n* # 42)	Papua New Guinea (*n* # 56)
Total IgG	28 (76)	32 (76)	53 (95)
IgG1	25 (68)	30 (71)	50 (89)
IgG3	28 (76)	31 (73)	52 (93)

Positive samples were those with OD values greater than the average of the OD values of negative controls (Swiss adults with no history of malaria) plus 3 SD

Olugbile et al. 2009

Pre-clinical summary



P27A, unstructured region P27, helical region

P27A

- High prevalence of antibody and T cell responses
- Antibodies with in vitro parasite growth inhibitory activity
- Immunogenic in several strains of mice and rabbits
- Association with protection in endemic area
- Limited polymorphism (E292G)

Safety and Reactogenicity of novel candidate blood-stage malaria vaccine, P27A with Alhydrogel or GLA-SE as Adjuvant in Healthy Malaria Non-Exposed European and Malaria Exposed African Adults aged 18-45 years: A staggered Phase Ia/Ib, Randomised, Single-blind, Antigen and Adjuvant Dose-finding, Multi-Centre trial

- Study design
  - Combined phase Ia/Ib, randomised, single/double-blind, antigen and adjuvant dose-finding, multi-centre trial.
- Primary objective
  - To evaluate **the safety** of P27A
    - with Alhydrogel or GLA-SE
    - in non exposed healthy European adults
    - in healthy African adults previously exposed to the parasite (TZ)
- Secondary objectives
  - To assess the **humoral response** by measuring antigen specific IgG response (ELISA) and its ability to recognise the native protein on merozoites (IFA)
  - To assess the **cellular immune response** by measuring the T cell antigen specific proliferation (CFSE) and cytokine production (supernatant)

Safety and Reactogenicity of novel candidate blood-stage malaria vaccine, P27A…

- Exploratory objectives
  - To assess the quality of the humoral immune response
    - IgG1, IgG2, IgG3, IgG4 subclasses
    - The ability to block parasite growth in vitro by antibody dependent cellular inhibition assay (ADCI)
  - To assess the quality of the cellular immune response
    - Intracellular cytokine staining (ICS) of proliferating T cells (IFN, TNF, IL-2, IL-10)
    - T cell phenotype analysis (memory, effector and regulatory cells)
  - T and B cell epitope mapping according to adjuvant use

Safety and Reactogenicity of novel candidate blood-stage malaria vaccine, P27A…

- Exploratory objectives
  - *Transcriptome analysis* of representative samples to analyse impact of adjuvant on innate immune response at day 0 (vaccination 1), week 8 (vaccination 3) and day 7 after third vaccination (week 9) and at day 84 (week 12)
  - Establish *human hybridoma cell lines*
  - *Impact of intestinal helminthiasis* on vaccine induced immune response (Ib)

Safety and Reactogenicity of novel candidate blood-stage malaria vaccine, P27A…

- ***P27A*** Synthetic Peptide
  - 10 µg and 50 µg
- ***Adjuvant doses***
  - Alhydrogel : 0.85 mg
  - GLA-SE : 2.5µg and 5 µg
- ***Route*** Intramuscular
- **Control Product**
  - Rabies vaccine in African volunteers (Verorab ™)
- **Vaccination Schedule**
  - Day 0, week 4 and week 8
  - **Follow-up duration**
    - At least 26 weeks after the last vaccination

Safety and Reactogenicity of novel candidate blood-stage malaria vaccine, P27A…

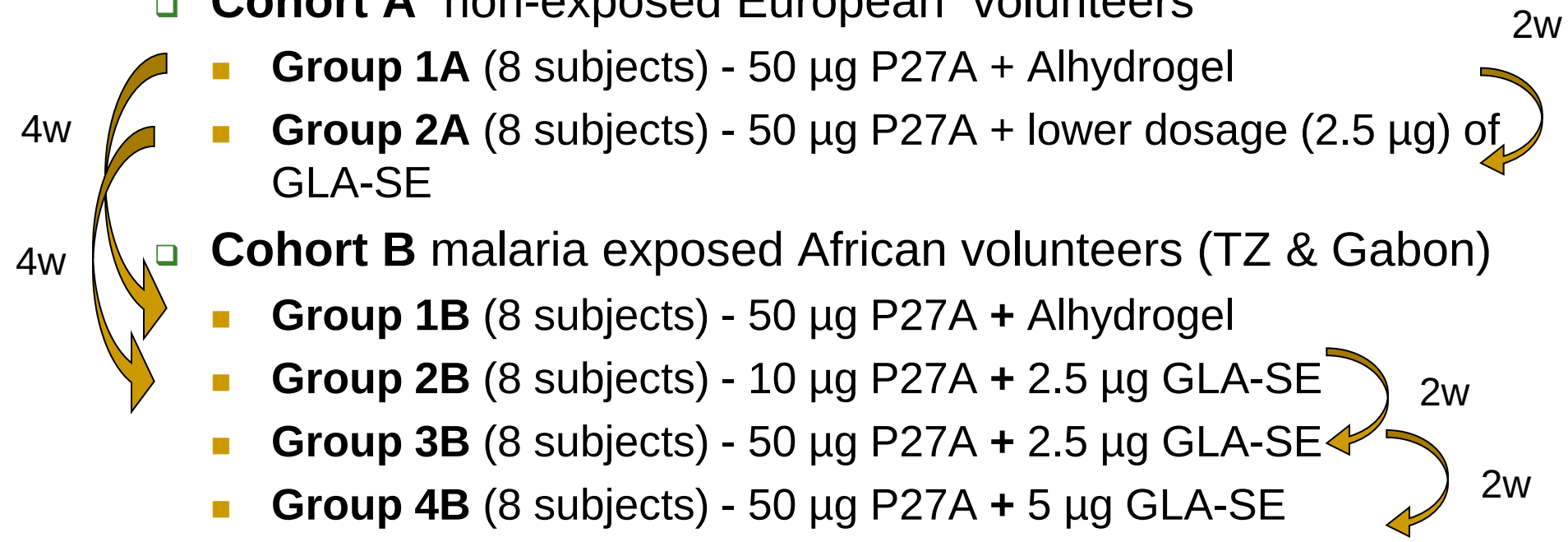
- Inclusion criteria (main ones…)
  - Healthy male and female volunteers aged 18-45 years
  - General good health based on history and clinical examination
- Non inclusion criteria (non malaria exposed vol.)
  - History of malaria or travel in malaria endemic areas within the past twenty-six weeks.
  - Intention to travel to malaria endemic countries during the study period.
  - Positive serology for malaria antigen P27A
  - Positive HIV, HBV or HCV tests…
- Non inclusion criteria (malaria exposed vol.)
  - Previous vaccination with any control vaccine
  - Positive HIV, HCV test or HBVsAg positive…

Safety and Reactogenicity of novel candidate blood-stage malaria vaccine, P27A…***Fast track to the field***

- Fast track strategy
  - The safety of the first immunisation of the non-exposed European volunteers with 50 µg P27A and Alhydrogel is taken as a Go criterion for:
    - the second and third immunisations of the non-exposed European volunteers with the same formulation
    - the first immunisation of the malaria exposed African volunteers with the same formulation
    - the first immunisation of the non-exposed European volunteers with 50µg P27A and GLA-SE lower dosage (2.5µg).

Safety and Reactogenicity of novel candidate blood-stage malaria vaccine, P27A…***Fast track to the field***

- Total number of volunteers : 56
  - **Cohort A** non-exposed European volunteers
    - **Group 1A** (8 subjects) - 50 µg P27A + Alhydrogel
    - **Group 2A** (8 subjects) - 50 µg P27A + lower dosage (2.5 µg) of GLA-SE
  - **Cohort B** malaria exposed African volunteers (TZ & Gabon)
    - **Group 1B** (8 subjects) - 50 µg P27A **+** Alhydrogel
    - **Group 2B** (8 subjects) - 10 µg P27A **+** 2.5 µg GLA-SE
    - **Group 3B** (8 subjects) - 50 µg P27A **+** 2.5 µg GLA-SE
    - **Group 4B** (8 subjects) - 50 µg P27A **+** 5 µg GLA-SE
    - **Group 5B** (8 subject) - Commercial control rabies vaccine



Safety and Reactogenicity of novel candidate blood-stage malaria vaccine, P27A…

- Transition from the European cohort to the African cohort(s) will proceed after the review and approval of the safety data by an Independent **Data Safety Monitoring Board**

- The Go/NoGo criteria for the safety stopping rules
  - Any SAE related to vaccination or 50% subjects had Grade 3 ARs persisting at Grade 3 for > 48 hours during the 14 follow-up days
- There will be a least **a 4-week stagger** between
  - Group 1A of Cohort A and Group 1B of Cohort B
  - Group 2A of Cohort A and Group 2B of Cohort B

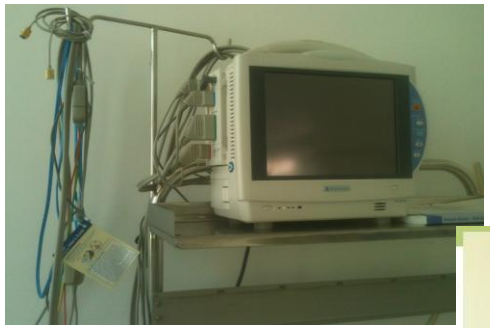
  to allow for evaluation of vaccine safety and reactogenicity and review by the Data Safety Monitoring Board prior to processing with immunisation of Cohort B.

Regulatory steps fullfilled

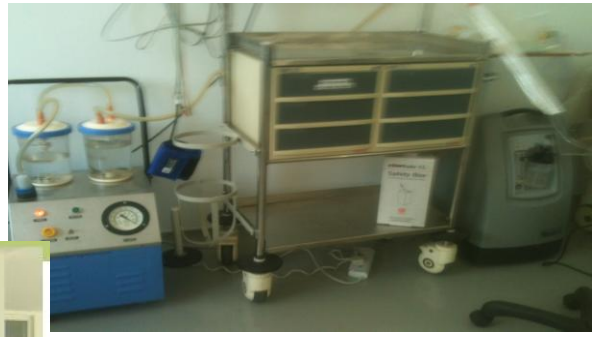
- ERB, University of Lausanne
  - Submission April 30, 2013
  - Conditional acceptance May 27, 2013
  - Accepted July 3, 2013
- Swissmedic, Bern
  - Submission July 26, 2013
  - Preliminary decision Aug. 28, 2013
  - Final decision Nov 6, 2013
- CTP submitted simultaneously in TZ
  - Trial Started on August 2014

Regulatory steps fulfilled

- No major comments from RA
- No major modification of CTP initial version
- Initiation visit in Lausanne
  - Jan. 16, 2014
- First injections in CH
  - From March 5 to April 15, 2014
  - Last visit of last volunteer in Jan 2015



P27A
Phase Ib
Ifakara Health
Bagamoyo, Tanzania



Design

4 Groups (8P27A/2Verorab) = 40 Volunteers

- Group 1B (10 subjects) - 50 µg P27A + Alhydrogel
- Group 2B (10 subjects) - 10 µg P27A + 2.5 µg GLA-SE
- Group 3B (10 subjects) - 50 µg P27A + 2.5 µg GLA-SE
- Group 4B (10 subjects) - 50 µg P27A + 5 µg GLA-SE (1 Vaccination)

Inclusion/Exclusion Criteria

- **Inclusion criteria (main ones…)**
  - Healthy male and female volunteers aged 18-45 years
  - General good health based on history and clinical examination
- **Non inclusion criteria (non malaria exposed vol.)**
  - History of malaria or travel in malaria endemic areas within the past twenty-six weeks.
  - Intention to travel to malaria endemic countries during the study period.
  - Positive serology for malaria antigen P27A
  - Positive HIV, HBV or HCV tests…
- **Exclusion criteria (malaria exposed vol.)**
  - Previous vaccination with vaccine
  - Abnormal Labs…..Clinically significant

Progress

Trial is going on well and on track

- Started August 2014
- Last FU June 2015

Volunteers (All Groups) Enrolled and Immunized

- Group 1B (10 subjects) - 50 µg P27A + Alhydrogel
- Group 2B (10 subjects) - 10 µg P27A + 2.5 µg GLA-SE
- Group 3B (10 subjects) - 50 µg P27A + 2.5 µg GLA-SE
- Group 4B (10 subjects) - 50 µg P27A + 5 µg GLA-SE

Volunteers Compliance

Very cooperative
100% retention
No missed immunizations

Tolerability and Safety

Well Tolerated even with GLA-SE (Low and high dose)
No Reactogenicity
No SAE

Intermediate conclusions

- Very efficient design (saved about 2 yrs)
- Excellent safety with either alum and GLA-SE
  - Cultural/gender differences CH vs TZ?
- Excellent preliminary immunogenicity GLA-SE>Alum (in terms of quantity of IgG)
  - Waiting for functional assays (ADCI), IIF, subclasses
  - T cell studies
- Perspectives
  - Blood-stage challenge?

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