Cochin - Pasteur
Centre d'Investigation Clinique en Vaccinologie

EUROPEAN VACCINE INITIATIVE

Santé publique Inserm
Institut national de la santé et de la recherche médicale

AMA1-DICO

Safety and Immunogenicity of Recombinant Pichia pastoris AMA1-DiCo candidate Malaria vaccine with GLA-SE and Alhydrogel ® as adjuvant in Healthy Malaria Non-Exposed European and Malaria Exposed African Adults : a staggered Phase Ia/Ib, Randomised, Double-blind, Multi-Centre trial.

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EVI RDV, Paris , 03 December 2014

Objective and Evaluation Criteria

➢ Primary Objective:

- To evaluate the safety of 50 µg AMA-1 DiCo candidate malaria vaccine with GLA-SE and Alhydrogel as adjuvant.

➢ Primary Evaluation Criteria:

- Immediate reactogenicity (60 minutes after each vaccination) .
- Local and systemic reactogenicity measured from Day 0 to week 2 after each vaccination.
- Biological safety : Laboratory safety analysis, 1 wk and 4 wks after each vaccination.

Secondary Objectives and Evaluation Criteria

- **The humoral immune response** to the vaccine antigens (DiCo1, DiCo2 and DiCo3) will be assessed by measuring the level of IgG by ELISA on samples obtained at Day 0, Week 1, 4, 5, 8, 26, 27, 30 and 52

- **The cellular immune response** will be assessed by measuring the T cell cytokine IL-5 and IFNγ production by ELISpot following in vitro stimulation with the vaccine antigens on samples obtained at Day 0, Week 26, 30 and 52

Investigational Product

➢ **Investigational Product :** AMA1-DiCo Malaria Vaccin

- Active ingrédient: PfAMA-1 DiCo (Pf=Plasmodium falciparum)
- Form: Lyophilised
- AMA1 DiCo dose: 50 µg
- Route : Intramuscular

➢ **Adjuvants:**

- **GLA-SE 2.5 µg per dose :** stable oil-in-water emulsion containing Glucopyranosyl lipid A (IDRI)(*Infectious Disease Research Institute*)

- **Alhydrogel™ 0.85 mg per dose** : Aluminium hydroxide

Methodology 1/2

- Phase Ia/Ib, Randomised, double -blind, Multicentre trial

- Number of centers: 2 : CIC Cochin Pasteur (France) + CNRFP (Burkina Faso)

- 66 volunteers in 2 cohorts A et B :

  - **Cohort A : 30 European volunteers at CIC Cochin Pasteur (FRANCE)**

    Group 1A : (n=15) 50µg AMA-1DiCo + Alhydrogel
    Group 2A : (n=15) 50 µg AMA-1 DiCo + GLA-SE

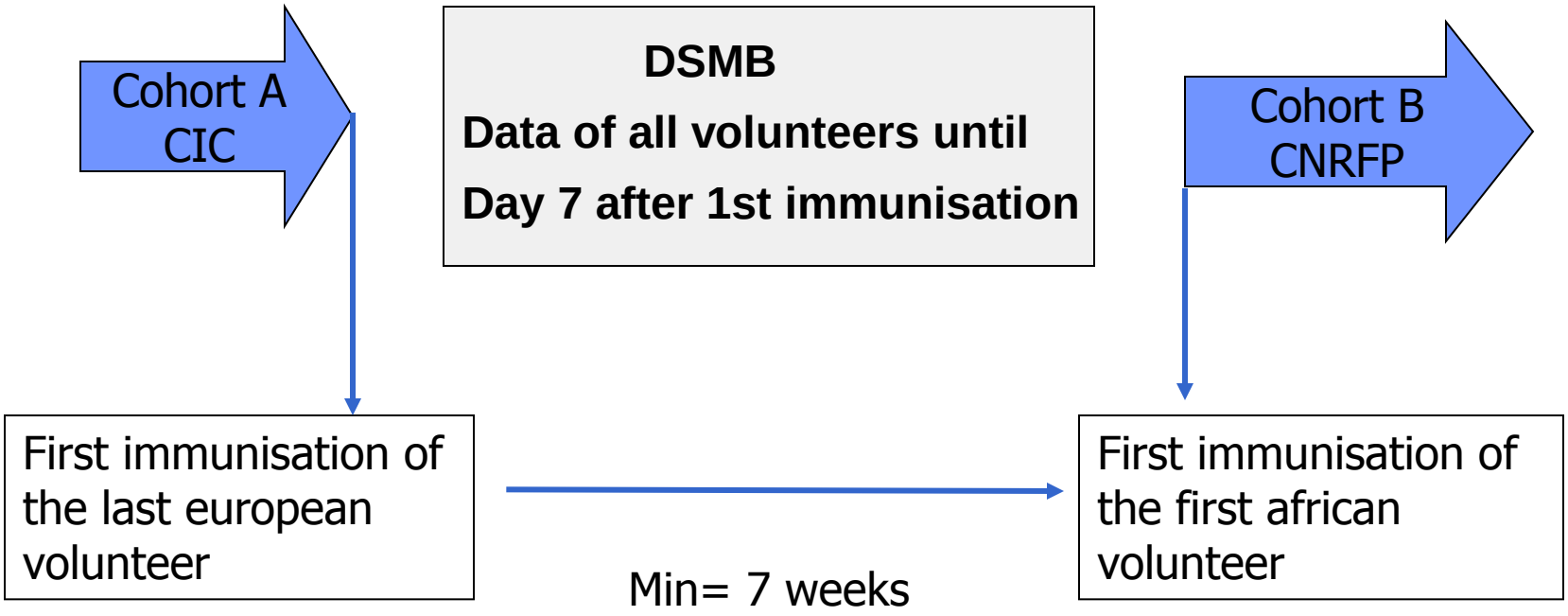
  - **Cohort B : 36 African volunteers at CNRFP (BURKINA FASO)**

    Group 1B : (n=18) 50 µg AMA-1DiCo + GLA-SE
    Group 2B : (n=18) PLACEBO **isotonic** saline solution

- 3 vaccinations IM J0, S4, S26

- Duration of participation: 52 weeks and 10 visits

Methodology 2/2



➢**GO** : **One week after the 1st immunisation of the last volunteer of the European group, if no subject had an SAE related to vaccination and less than 50% subjects had any Grade 3 adverse reaction persisting at Grade 3 for > 48 hours. during the 7 follow-up days**

➢**NO GO: Stopping rule for GLA-SE or Alhydrogel®* Any SAE related to vaccination or 50% of subjects had Grade 3 adverse reaction persisting at Grade 3 for > 48 hours during the 7 follow-up days**

Inclusion Criteria

- **Age ≥ 20 and ≤ 45 years healthy female and male**
- **General good health based on history and clinical examination.**
- **Written informed consent obtained before any trial procedure.**
- **Female and male volunteers practicing contraception before and up to four (4) weeks after the third vaccination.**
- **Available to participate in follow-up for the duration of trial.**

Non-Inclusion Criteria 1/2

- **Positive pregnancy test**
- **Active breast feeding**
- **Previous participation in any malaria vaccine trial**
- **History of blood transfusion within the last 6 months**
- **Symptoms, physical signs or laboratory values suggestive of systemic disorders, including renal, hepatic, cardiovascular, pulmonary, skin, immunodeficiency, psychiatric and other conditions, which could interfere with the interpretation of the trial results or compromise the health of the volunteers.**
- **Any clinically significant laboratory abnormalities on screened blood samples outside the normal range, as defined at the clinical trial site.**
- **Enrolment in any other clinical trial during the whole trial period**
- **Intake of chronic medication, especially immunosuppressive agents (steroids, immunomodulators or immunosuppressive drugs) during the thirteen weeks preceding the screening visit or during the trial period except topical steroid use including intranasal.**

Non-Inclusion Criteria 2/2

- **Any confirmed or suspected immunosuppressive or immunodeficiency condition during the whole trial period**
- **Volunteers unable to be closely followed for social, geographic or psychological reasons.**
- **Previous history of drug or alcohol abuse interfering with normal social function during a period of one year prior to enrolment in the trial.**
- **History of anaphylaxis or Known severe hypersensitivity to any of the vaccine components (adjuvant or antigen or excipient)**
- **Vaccination or gamma globulin: 4 weeks prior and after each vaccination if a vaccination is necessary during this period, the volunteer will be withdrawn from the study.**
- **Positive HIV, HBV (Ag HBS) and HCV tests**

➢ Additional Exclusion Criteria for Malaria non-exposed European volunteers

- **History of malaria or travel in malaria endemic areas within the past twenty-six weeks.**
- **Positive serology for malaria antigen PfAMA-1Intention to travel to malaria endemic countries during the trial period.**

Timelines

- Submission to Cossec* Committee (3 times) :16/05/2012, 26/09/2012, 28/03/2013
- Approval from the Cossec Committee (Requested before the submission to the French Regulatory Autority) : 28/03/2013
- Pre submission procedure to ANSM (French Regulatory Autority) : 26/04/2013
- Response of pre submission procedure : 28/06/2014
- Submission to CPP (French Ethic Committe) : 27/05/2013
- French Ethic Committee approval : 16/09/2013
- Submission to ANSM (French Regulatory Autority) : 09/09/2013
- French Regulatory approval : 08/11/2013
- Initiation visit at CIC Cochin Pasteur France : 06/12/2013
- First inclusion at CIC Cochin Pasteur: 06/01/2014
- First vaccination at CIC Cochin: Pasteur 29/01/2014
- Last vaccination of the last European volunteer : 18/09/2014
- Last visit of the last European volunteer planned : **19/03/2015**

* *Cossec : Comité d'orientation stratégique et de suivi des essais cliniques (INSERM)*

Inclusion (French Site)

- Demographic characteristics of volunteers
  - Number of females : 18/30 (60%)
  - Number of males : 12/30 (40%)
  - Mean age in years : 32 years (range 22 - 44 years)

Date of			Number of volunteers		
Initiation visit	**First inclusion**	**Last inclusion**	**Enrolled**	**Randomised**	**Screen failure**
06/12/2014	**06/01/2014**	**10/03/2014**	**41**	**30**	**11**

Vaccination (French Site)

Number of volunteers who received the first Immunization	Number of volunteers who received the second Immunization	Number of volunteers who received the third Immunization	Number of Withdrawal of the product	Number of Withdrawal of the study	Number of Lost of follow up
30/30	27/30	24/30	3/30	1/30	2/30

Withdrawal of product (French Site)

Subject N°	Reasons of Withdrawal of the product	Number of immunisation received by the volunteer
F07	SAE (Serious Adverse Event) not related Day 7 after first vaccination : Amnesia and disorientation for 6 hours Suspusion of inaugural epileptic crisis	**1** (the second and third immunisation have not been performed)
F23	Local Adverse Event (Grade 3) after the **second immunisation :** Redness> 50mm and pruritus D4/D5 after second injection	**2** (the third vaccination has not be performed)
F41	Local Adverse Event (Grade 3) after the **second immunisation :** Redness> 50mm and pruritus D4/D5 after second injection	**2** (the third vaccination has not been performed)

Withdrawal of Study (French Site)

Subject N°	Reasons of Withdrawal	Number of immunisation received by the volunteer
F28	Following a change of professional status after his first immunisation , the volunteer could not participate in the trial	**1**
F09	Lost of follow up	**1**
F35	Lost of follow up	**2**

DSMB : GO / NO GO to CNRFP (Burkina Faso site) ?

➔ First DSMB meeting : 12/05/2014 based on safety data (Day 7 following the **first vaccination**) of all the European volunteers.

➔ DSMB recommended to have the safety data of Day 7 following the **second vaccination** all the European volunteers before the final decision of Go/No Go to Burkina Faso.

➔ Second DSMB meeting : 16/06/2014. ➔ DSMB recommended : **GO** to start of the recruitment in Burkina Faso with **GLA-SE adjuvant.**

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