

## **Safety, Tolerability, Immunogenicity and Efficacy of PfSPZ Vaccine versus PfSPZ-CVac in Equatoguinean Young Adults.**

*Vicente Urbano<sup>1,2</sup>, Ally Olotu<sup>1,3</sup>, Ali Hamad<sup>1,3</sup>, Ali Mtoro<sup>1,3</sup>, Mwajuma Chemba<sup>1,3</sup>, Stephen R. Manock<sup>1,4</sup>, Maximillian Mpina<sup>1,3</sup>, Elizabeth Nyakarungu<sup>1,3</sup>, Esther Eburu<sup>1,5</sup>, Antonio Enrique Ngua Sama Roca<sup>1,5</sup>, Martin Eka Ondo Mangué<sup>1,2</sup>, Thomas Stabler<sup>1,4</sup>, Yonas Abebe<sup>4</sup>, Carl D. Maas<sup>6</sup>, Mitoha Ondo'o Ayekaba<sup>6</sup>, Salomón Nguema Owono<sup>4</sup>, Matilde Riloha Rivas<sup>4</sup>, Chris Schwabe<sup>5</sup>, Julie Niemczura de Carvalho<sup>5</sup>, Luis Segura<sup>1,5</sup>, Wonder Phiri<sup>1,5</sup>, Tobias Schindler<sup>7</sup>, Elizabeth Saverino<sup>4</sup>, Peter F. Billingsley<sup>4</sup>, B. Kim Lee Sim<sup>4</sup>, Claudia Daubenberger<sup>7,8</sup>, Thomas Richie<sup>4</sup>, Salim Abdulla<sup>3</sup>, Stephen L. Hoffman<sup>4</sup>*

1=Equatorial Guinea Malaria Vaccine Initiative; 2=Ministry of Health and Social Welfare; 3= Ifakara Health Institute; 4=Sanaria Inc.; 5=Medical Care Development International; 6=Marathon EG Production Ltd; 7=Swiss Tropical and Public Health Institute; 8=University of Basel.

PfSPZ Vaccine is a candidate pre-erythrocytic malaria vaccine composed of radiation-attenuated, aseptic, purified, cryopreserved *Plasmodium falciparum* (Pf) NF54 sporozoites (SPZ). In trials in the U.S. and Africa, PfSPZ Vaccine administered by direct venous inoculation (DVI) provided durable protection against heterologous strains and heterogeneous populations of Pf for at least 24 to 33 wks. A second PfSPZ-based vaccine approach – administration of low doses of non-irradiated, infectious NF54 PfSPZ (PfSPZ Challenge) under chloroquine chemoprophylaxis (PfSPZ-CVac) – protected against homologous strains of Pf in the U.S. and Europe for at least 10 wks, but had not been tested in Africa. We conducted a randomized, double blind placebo-controlled trial comparing tolerability, safety, immunogenicity and efficacy against controlled human malaria infection (CHMI) of PfSPZ Vaccine versus PfSPZ-CVac in healthy malaria-exposed Equatoguinean 18 to 35-year-old men and women. We randomized 26 subjects to receive 3 doses of  $2.7 \times 10^6$  PfSPZ (PfSPZ Vaccine) or placebo at 0, 8 and 16 wks, and 24 subjects to receive 3 doses of  $1 \times 10^5$  PfSPZ (PfSPZ Challenge) or placebo at 0, 4 and 8 wks after an oral dose of chloroquine (CQ) 600 mg base then CQ 300 mg base weekly (PfSPZ-CVac), followed in both groups by homologous CHMI at 10-13 wks post final vaccine dose. Adverse events (AEs) were solicited for 7 days and surveillance for unsolicited AEs done for 28 days after each vaccination. Monitoring for serious AEs was done throughout. Hematologic, renal and hepatic tests were done at baseline, 2 and 14 days after each vaccination, and prior to CHMI. Blood samples for humoral and cellular immunology were taken at baseline and 14 days after each vaccination. Both vaccine approaches were well-tolerated, and DVI was typically straightforward with only mild pain associated with injection. Safety, immunogenicity and efficacy data will be presented. This comparison of PfSPZ Vaccine and PfSPZ-CVac will provide more information as to which product could be used in mass vaccination programs aimed at regional elimination of malaria. (ClinicalTrials.gov number, NCT02859350)

# Safety, Tolerability, Immunogenicity and Efficacy of PfSPZ Vaccine versus PfSPZ-CVac in Equatoguinean Young Adults

Vicente Urbano<sup>1</sup>, Ally Olotu<sup>2</sup>, Ali Mtoro<sup>2</sup>, LW Preston Church<sup>3</sup>, Ali Hamad<sup>2</sup>, Mwajuma Chemba<sup>2</sup>, Stephen R. Manock<sup>3</sup>, Maximilian Mpina<sup>2</sup>, Elizabeth Nyakarungu<sup>2</sup>, Esther Eburu<sup>4</sup>, Antonio Enrique Ngua Sama Roca<sup>4</sup>, Martin Eka Ondo Mangue<sup>1</sup>, Thomas Stabler<sup>3</sup>, Yonas Abebe<sup>3</sup>, Carl D. Maas<sup>5</sup>, Mitoha Ondo'o Ayekaba<sup>1</sup>, Salomon Nguema Owono<sup>1</sup>, Matilde Riloha Rivas<sup>1</sup>, Christopher Schwabe<sup>6</sup>, Julie Niemczura<sup>6</sup>, Guillermo Garcia<sup>6</sup>, Luis Segura<sup>4</sup>, Wonder Philip Phiri<sup>4</sup>, Tobias Schindler<sup>7</sup>, Elizabeth Saverino<sup>3</sup>, Peter F. Billingsley<sup>3</sup>, B. Kim Lee Sim<sup>3</sup>, Claudia Daubenberger<sup>7</sup>, Thomas Richie<sup>3</sup>, Salim Abdulla<sup>2</sup>, Stephen L. Hoffman<sup>3</sup>

<sup>1</sup>Ministry of Health and Social Welfare, Malabo, Equatorial Guinea, <sup>2</sup>Ifakara Health Institute, Bagamoyo, Tanzania, United Republic of, <sup>3</sup>Sanaria Inc, Rockville, MD, United States, <sup>4</sup>Medical Care Development International, Malabo, Equatorial Guinea, <sup>5</sup>Marathon EG Production Ltd, Malabo, Equatorial Guinea, <sup>6</sup>Medical Care Development International, Silver Spring, MD, United States, <sup>7</sup>Swiss Tropical and Public Health Institute, Basel, Switzerland

**Abstract:** PfSPZ Vaccine is a candidate pre-erythrocytic malaria vaccine composed of radiation-attenuated, aseptic, purified, cryopreserved *Plasmodium falciparum* (Pf) NF54 sporozoites (SPZ). In trials in the U.S. and Africa, PfSPZ Vaccine administered by direct venous inoculation (DVI) provided durable protection against heterologous strains and heterogeneous populations of Pf for at least 24 to 33 wks. A second PfSPZ-based vaccine approach - administration of low doses of non-irradiated, infectious NF54 PfSPZ (PfSPZ Challenge) under chloroquine chemoprophylaxis (PfSPZ-CVac) - protected against homologous strains of Pf in the U.S. and Europe for at least 10 weeks, but had not been tested in Africa. We conducted a randomized, double blind placebo-controlled trial comparing tolerability, safety, immunogenicity and efficacy against controlled human malaria infection (CHMI) of PfSPZ Vaccine versus PfSPZ-CVac in healthy malaria-exposed Equatoguinean 18 to 35-year-old men and women. We randomized 26 subjects to receive 3 doses of 2.7x10<sup>6</sup> PfSPZ (PfSPZ Vaccine) or placebo at 0, 8 and 16 wks, and 24 subjects to receive 3 doses of 1x10<sup>5</sup> PfSPZ (PfSPZ Challenge) or placebo at 0, 4 and 8 wks after an oral dose of chloroquine (CQ) 600 mg base then CQ 300 mg base weekly (PfSPZ-CVac), followed in both groups by homologous CHMI at 10-13 wks post final vaccine dose. Adverse events (AEs) were solicited for 7 days and surveillance for unsolicited AEs done for 28 days after each vaccination. Monitoring for serious AEs was done throughout. Hematologic, renal and hepatic tests were done at baseline, 2 and 14 days after each vaccination, and prior to CHMI. Blood samples for humoral and cellular immunology were taken at baseline and 14 days after each vaccination. Both vaccine approaches were well-tolerated, and DVI was typically straightforward with only mild pain associated with injection. Safety, immunogenicity and efficacy data will be presented. This comparison of PfSPZ Vaccine and PfSPZ-CVac will provide more information as to which product could be used in mass vaccination programs aimed at regional elimination of malaria. (ClinicalTrials.gov number, NCT02859350)

**Introduction:** Sanaria® PfSPZ Vaccine is composed of aseptic, purified, radiation-attenuated, cryopreserved *P. falciparum* sporozoites (PfSPZ), while Sanaria® PfSPZ-CVac is composed of identical but non-attenuated PfSPZ (called PfSPZ Challenge) that are administered in combination with an antimalarial drug (chloroquine) that kills the parasites *in vivo* (NF54 parasites are highly sensitive to chloroquine). It is as yet unclear which vaccination approach is more protective in African populations

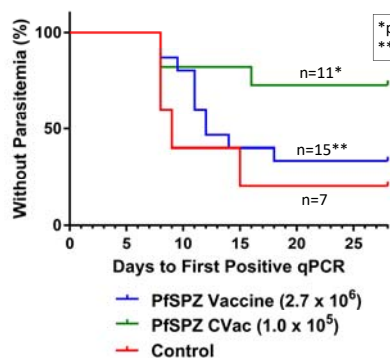
**Objectives:**

- To compare the safety and tolerability of the two vaccines
- To compare the immunogenicity of the two vaccines
- To compare the vaccine efficacy of each vaccine against controlled human malaria infection (CHMI)

**Methods:** 52 Equatoguinean adults age 18-35 were enrolled and allocated as part of a larger study that included infants and children (data in these age groups not presented here); 26 were allocated to PfSPZ Vaccine and 26 to PfSPZ-CVac. Participants in each group were randomized to normal saline placebo (n=6) or vaccine (n=20). PfSPZ Vaccine was administered as 3 doses of 2.7x10<sup>6</sup> PfSPZ by DVI at 0, 8 and 16 weeks. PfSPZ-CVac was administered as 3 doses of 1x10<sup>5</sup> PfSPZ at 0, 4 and 8 weeks. Both PfSPZ-CVac recipients and corresponding controls were also administered chloroquine prophylaxis. All volunteers underwent CHMI using 3,200 PfSPZ of PfSPZ Challenge 12 weeks after the 3<sup>rd</sup> vaccine dose.

**Results – vaccine efficacy**

Results of CHMI average 15 weeks post dose #3

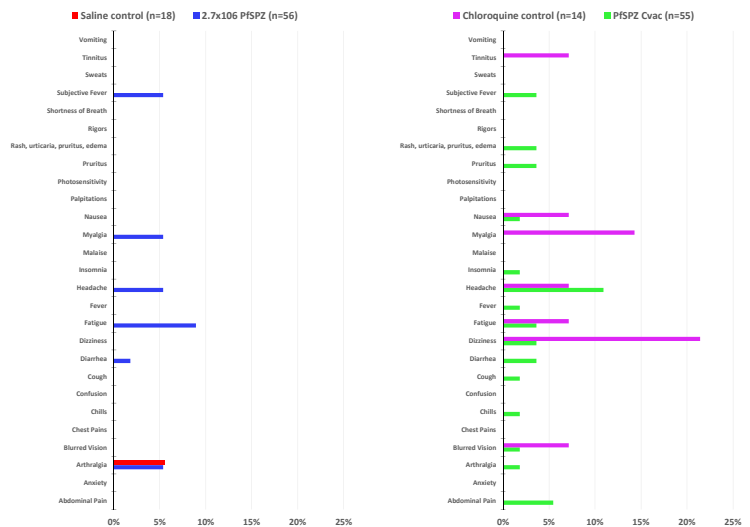


\*p=0.036 vs. control, log-rank test  
\*\*p=0.36 vs. control, log-rank test

**Proportional analyses**  
PfSPZ-CVac – 8 of 11 protected vs. 1 of 7 controls, p=0.02, Barnard's 2-sided test. Vaccine Efficacy = 69%  
PfSPZ Vaccine – 5 of 15 protected vs. 1 of 7 controls, p=0.40, Barnard's 2-sided test. Vaccine Efficacy = 22%

**Solicited Adverse Events**

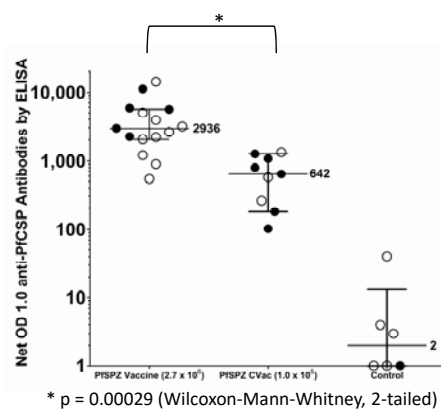
Normal saline controls (red or purple bars) vs. vaccinees (blue or green bars)



**Results - Safety:**

There were no statistically significant differences in local or systemic adverse events between PfSPZ Vaccine and normal saline controls. In participants receiving PfSPZ-CVac, myalgias (p=0.039) and dizziness (p=0.053) were identified more frequently in control patients administered normal saline while taking chloroquine. There were no statistically significant differences in local or systemic adverse events between PfSPZ Vaccine and PfSPZ-CVac + chloroquine.

**Results – Antibodies to circumsporozoite protein (CSP)**



\* p = 0.00029 (Wilcoxon-Mann-Whitney, 2-tailed)

**Conclusions:**

- PfSPZ Vaccine and PfSPZ-CVac were well tolerated in healthy adults. As expected, known side effects of chloroquine were observed in the PfSPZ-CVac group and associated controls. Importantly, symptoms consistent with malaria were minimal during immunization with PfSPZ-CVac.
- The efficacy of the PfSPZ-CVac regimen was similar to efficacy reported for PfSPZ Vaccine at a dose of 9x10<sup>5</sup> administered as 3 doses at 8 week intervals in Tanzania or as 5 doses administered at 0, 2, 4, 6 and 28 days in Tanzania.
- An increased dose of PfSPZ Vaccine at 2.7x10<sup>6</sup> PfSPZ administered as 3 doses at 8 week intervals did not lead to improved efficacy compared with similar trials in sub-Saharan Africa, consistent with a plateau effect.
- Antibody levels by ELISA were significantly less for the PfSPZ-CVac group than for PfSPZ Vaccine and did not correlate with vaccine efficacy.