Safety, Tolerability and Immunogenicity of PfSPZ Vaccine in Equatoguinean Children and Older Adults.

Vicente Urbano[1,2], Ally Olotu[1,3], Ali Hamad[1,3], Ali Mtoro[1,3], Mwajuma Chemba[1,3], Stephen R. Manock[1,4], Maximillian Mpina[1,3], Elizabeth Nyakarungu[1,3], Esther Eburi[1,5], Antonio Enrique Ngua Sama Roca[1,5], Martin Eka Ondo Mangue[1,2], Thomas Stabler[1,4], Yonas Abebe[4], Salomón Nguema Owono[4], Matilde Riloha Rivas[4], Chris Schwabe[5], Julie Niemczura de Carvalho[5], Luis Segura[1,5], Wonder Phiri[1,5], Tobias Schindler[6], Elizabeth Saverino[4], Peter F. Billingsley[4], B. Kim Lee Sim[4], Claudia Daubenberger[6,7], Thomas Richie[4], Salim Abdulla[3], Stephen L. Hoffman[4]

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=Swiss Tropical and Public Health Institute; 7=University of Basel.

PfSPZ Vaccine is a candidate pre-erythrocytic malaria vaccine composed of aseptic, purified, live (metabolically active), radiation-attenuated, cryopreserved *Plasmodium falciparum* (Pf) NF54 sporozoites (SPZ). In trials in the U.S. and Africa, PfSPZ Vaccine administered by direct venous inoculation (DVI) to young adults proved safe and well-tolerated, and provided durable protection against homologous and heterogenous populations of Pf for at least 24 to 33 weeks. PfSPZ Vaccine has undergone limited testing in children in Tanzania and an ongoing trial in Kenya, but has not previously been tested in older adults. Since the eventual goal is to use PfSPZ Vaccine in mass vaccination programs for malaria elimination in specified geographical areas, it is necessary to test the vaccine in all age groups. As part of a larger randomized, double blind placebo-controlled trial, we evaluated the safety, tolerability, and immunogenicity of PfSPZ Vaccine in 62 healthy malaria-exposed Equatoguinean children and older adults. We randomized 15 adults age 36-65 years to receive 3 doses of $2.7x10^6$ PfSPZ of PfSPZ Vaccine, and 16 children age 11-17 years, 16 children age 6-10 years, and 15 children age 1-5 years to receive 3 doses of $1.8x10^6$ PfSPZ, or placebo at 0, 8 and 16 weeks. A sentinel group of 3 subjects was vaccinated one day prior to the rest of each age cohort. Age de-escalation was done sequentially in children, with safety data evaluated by an external data and safety monitoring board before progressing to the youngest group. 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 vaccine dose. Blood samples for immunologic assays were taken prior to and 14 days after each vaccine dose, and at 4 and 20-24 weeks after the final vaccine dose. The vaccine was well-tolerated in all age groups, and DVI was generally straightforward with only mild pain associated with injection. Safety and immunogenicity data will be presented. (ClinicalTrials.gov number, NCT02859350)

Abstract #1151

Safety, Tolerability and Immunogenicity of PfSPZ Vaccine in Equatoguinean Children and Older Adults (EGSPZV2 trial)

Vicente Urbano[1], Ally Olotu[2], Ali Mtoro[2], **LW Preston Church[3]**, Ali Hamad[2], Mwajuma Chemba[2], Stephen R. Manock[3], Maximillian Mpina[2], Elizabeth Nyakarungu[2], Esther Eburi[4], Antonio Enrique Ngua Sama Roca[4], Martin Eka Ondo Mangue[1], Thomas Stabler[3], Yonas Abebe[3], Salomon Nguema Owono[1], Matilde Riloha Rivas[1], Christopher Schwabe[5], Julie Niemczura[5], Guillermo Garcia[5], Wonder Philip Phiri[4], Luis Segura[4], Tobias Schindler[6], Elizabeth Saverino[3], Peter F. Billingsley[3], B. Kim Lee Sim[3], Claudia Daubenberger[6], Thomas L. Richie[3], Salim Abdulla[2], Stephen L. Hoffman[3]

[1]Ministry of Health and Social Welfare, Malabo, Equatorial Guinea, [2]Ifakara Health Institute, Bagamoyo, Tanzania, United Republic of, [3]Sanaria Inc, Rockville, MD, United States, [4]Medical Care Development International, Malabo, Equatorial Guinea, [5]Medical Care Development International, Silver Spring, MD, United States, [6]Swiss Tropical and Public Health Institute, Basel, Switzerland

Abstract: PfSPZ Vaccine is a candidate pre-erythrocytic malaria vaccine composed of aseptic, purified, live (metabolically active), radiation-attenuated, cryopreserved *Plasmodium falciparum* (Pf) NF54 sporozoites (SPZ). In trials in the U.S. and Africa, PfSPZ Vaccine administered by direct venous inoculation (DVI) to young adults proved safe and well-tolerated, and provided durable protection against homologous and heterogenous populations of Pf for at least 24 to 33 weeks. PfSPZ Vaccine has undergone limited testing in children in Tanzania and an ongoing trial in Kenya, but has not previously been tested in older adults. Since the eventual goal is to use PfSPZ Vaccine in mass vaccination programs for malaria elimination in specified geographical areas, it is necessary to test the vaccine in all age groups. As part of a larger randomized, double blind placebo-controlled trial, we evaluated the safety, tolerability, and immunogenicity of PfSPZ Vaccine in 62 healthy malaria-exposed Equatoguinean children and older adults. We randomized 15 adults age 36-65 years to receive 3 doses of $2.7x10^6$ PfSPZ of PfSPZ Vaccine, and 16 children age 11-17 years, 16 children age 6-10 years, and 15 children age 1-5 years to receive 3 doses of $1.8x10^6$ PfSPZ, or placebo at 0, 8 and 16 weeks. A sentinel group of 3 subjects was vaccinated one day prior to the rest of each age cohort. Age de-escalation was done sequentially in children, with safety data evaluated by an external data and safety monitoring board before progressing to the youngest group. 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 vaccine dose. Blood samples for immunologic assays were taken prior to and 14 days after each vaccine dose, and at 4 and 20-24 weeks after the final vaccine dose. The vaccine was well-tolerated in all age groups, and DVI was generally straightforward with only mild pain associated with injection. Safety and immunogenicity data will be presented. (ClinicalTrials.gov number, NCT02859350)

Introduction: Sanaria® PfSPZ Vaccine is composed of aseptic, purified, radiation-attenuated, cryopreserved *P. falciparum* sporozoites (PfSPZ). Safety is established in adults up to age 35 years at doses up to $1.8x10^6$ PfSPZ and in children and infants at doses up to $9x10^5$ PfSPZ.

Objectives:

- Test the safety and tolerability of higher doses in all age groups including adults up to age 65 years
- Assess the feasibility of direct venous inoculation (DVI) in children and infants.

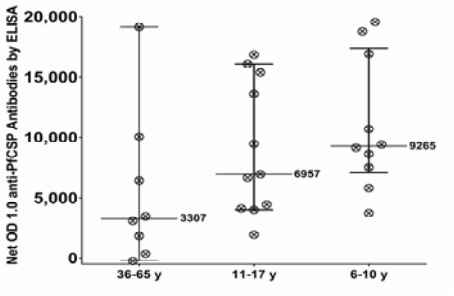
Methods:

We conducted a randomized, double-blind, placebo-controlled trial in Equatorial Guinea. 135 participants in 6 age groups were enrolled and randomized to normal saline placebo or PfSPZ Vaccine, administered as 3 doses at 0, 8 and 16 weeks.

Table 1: TRIAL DESIGN

Study Groups Description				n	PfSPZ dose	Immu-nogen	# dose s	Total SPZ	CHMI
Groups	Age	Subgroups							
Group 1	18 to 35 yrs	1a	Vaccinees	20	$2.7x10^6$	PfSPZ Vaccine	3	$8.1x10^6$	Yes
			NS controls	6	0	-	3	0	Yes
		1b	Vaccinees	20	$1.0x10^5$	PfSPZ-CVac	3	$3.0x10^5$	Yes
			NS controls	6	0	-	3	0	Yes
Group 2	36 to 65 yrs		Vaccinees	12	$1.8x10^6$	PfSPZ Vaccine	3	$5.4x10^6$	No
			NS controls	4	0	-	3	0	No
Group 3	11 to 17 yrs		Vaccinees	12	$1.8x10^6$	PfSPZ Vaccine	3	$5.4x10^6$	No
			NS controls	4	0	-	3	0	No
Group 4	6 to 10 yrs		Vaccinees	12	$1.8x10^6$	PfSPZ Vaccine	3	$5.4x10^6$	No
			NS controls	4	0	-	3	0	No
Group 5	1 to 5 yrs		Vaccinees	12	$1.8x10^6$	PfSPZ Vaccine	3	$5.4x10^6$	No
			NS controls	4	0	-	3	0	No
Group 6	6 to 11 mos	6a	Vaccinees	3	$0.9x10^6$	PfSPZ Vaccine	1	$0.9x10^6$	No
		6b	Vaccinees	12	$1.8x10^6$	PfSPZ Vaccine	3	$5.4x10^6$	No
			NS controls	4	0	-	3	0	No
Total n: 135			NS = normal saline						

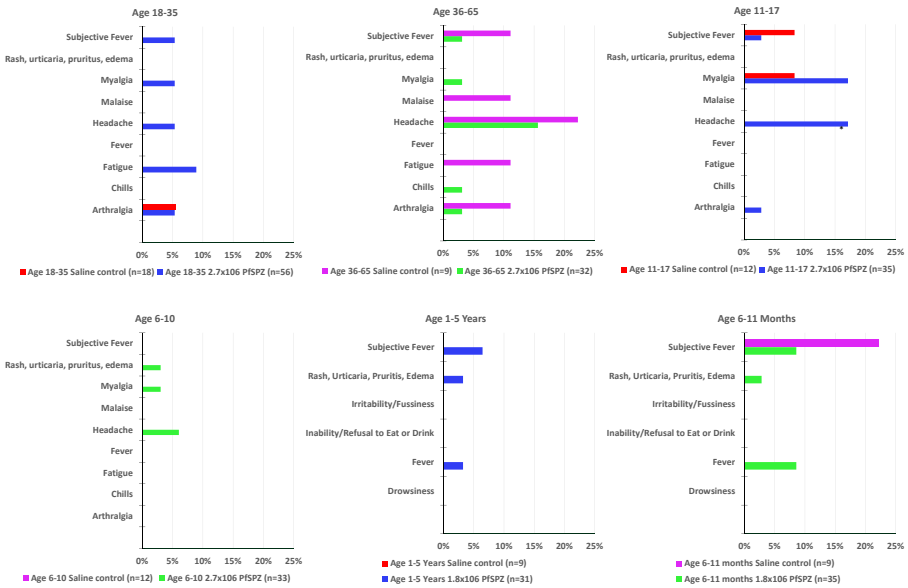
Antibody Levels 2 weeks after the 3rd Dose



Solicited Adverse Events (AEs) by Age Group

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

No AEs were statistically significantly more common in vaccinees



Serious Adverse Events:

Possibly related to vaccination:

- 15 year old male with a solitary seizure after PfSPZ Vaccine - Possibly related to vaccine (biologically plausible explanations)
  - Onset 3.5 hours after 3rd dose 1.8×10^6 PfSPZ
  - No fever, no head trauma, no other known risk factors, but sister with history of epilepsy
  - EEG and neuroimaging "consistent with idiopathic or genetic generalized epilepsy"
- A 19 year old woman with loss of pregnancy at 9 weeks - Possibly related to vaccine
  - Conception estimated to occur about the time of the first dose of $2.7x10^6$ PfSPZ
  - Ultrasound at 9 weeks revealed a 6-week size embryo without spontaneous cardiac activity

Unlikely related to vaccination:

- 44 year old man hospitalized for observation of back pain - $2.7x10^6$ PfSPZ, unlikely related to vaccine
- 15 year old woman with gestational hypertension (34 weeks) and fetus showing intrauterine growth retardation (30 weeks), delivery by cesarean section (34 weeks) – Unlikely related to vaccine.
  - EDC 6 weeks after 3rd dose $1.8x10^6$ PfSPZ.
  - Normal fetal ultrasounds at 16 and 24 weeks
  - 1300 gram male infant - Congenital right inguinal hernia, patent ductus arteriosus , patent foramen ovale
- 29 year old male developed painless swelling in his left neck, subsequently diagnosed as stage IIIB diffuse large B-cell non-Hodgkin's Lymphoma (NHL) - Saline control, unlikely related to vaccine

Unrelated to vaccination:

- 2.5 year old girl with a persistent pneumonia - $1.8x10^6$ PfSPZ, not related to vaccine
  - Diagnostic studies negative for specific pathogens, including TB, non-diagnostic bronchoscopy
  - Multiple courses of oral and intravenous antibiotics → resolution
- 11 month old with a fall and tongue laceration - $9x10^5$ PfSPZ, not related to vaccine
- 9 month old with watery diarrhea and vomiting - $1.8x10^6$ PfSPZ, not related to vaccine
- 2 year old hospitalized for malaria - $1.8x10^6$ PfSPZ, not related to vaccine
- 18 year old woman with hyperemesis gravidarum of moderate severity - not related to vaccine.
  - EDC 2.5 months after 3rd dose $1.8x10^6$ PfSPZ, onset 4.5 months after 3rd dose.
  - She went on to deliver a healthy baby girl at 37 + 4 weeks.

Tolerability: >90% of paticipants reported no or mild pain with injection

Unsolicited adverse events: 106 in the vaccine population (.95/volunteer) vs. 31 unsolicited AE in the saline control population (.97/volunteer)

Lab: Grade 2/3 lab abnormalities were infrequent with similar rates between vaccine and placebo

Conclusions:

- Across all age groups, *including infants and older adults*, PfSPZ Vaccine was safe and well tolerated at the highest doses tested; rates and severity of solicited adverse events were comparable between vaccinees and saline controls.
- Two SAEs, a seizure and fetal loss, were considered possibly related to vaccination but a clear association could not be established.
- Eight SAEs were unrelated or not related to vaccine.
- Lack of compliance with contraception and resulting pregnancies were important challenges to study conduct.
- Antibody responses increased as age decreased to 6 years (antibody assessments in the 6-11 month and 1-5-year-olds are pending).