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

Vicente Urbano1,2, Ally Olotu1,3, Ali Hamad1,3, Ali Mtoro1,3, Mwajuma Chemba1,3, Stephen R. Manock1,4, Maximillian Mpina1,3, Elizabeth Nyakarungu1,3, Esther Ebur1,5, Antonio Enrique Ngua Sama Roca1,5, Martin Eka Ondo Mangue1,2, Thomas Stabler1,4, Yonas Abebe4, Salomon Nguema Owono4, Matilde Riloha Rivas4, Chris Schwabe5, Julie Niemczura de Carvalho5, Luis Segura1,5, Wonder Phiri1,5, Tobias Schindler6, Elizabeth Saverino4, Peter F. Billingsley4, B. Kim Lee Sim4, Claudia Daubenberger6,7, Thomas Richie4, Salim Abdulla3, Stephen L. Hoffman4

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 1.8x10^5 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 Urbano1, Ally Olotu2, Ali Mtoro2, LW Preston Church3, Ali Hamadi4, Mwangi Chebwa3, Stephen R. Manock2, Maximillian Mpina2, Elizabeth Nyakarungu1, Esther Ebur4, Antonio Enrique Ngua Sama Roca4, Martin Eka Ondo Mangue1, Thomas stabler5, Jonas Abebe5, Salomon Ngueuma Owono1, Matilde Riloha Rivas1, Christopher Schwabe5, Julie Niemczura5, Guillermo Garcia5, Wonder Philip Phiri5, Luis Segura5, Tobias Schindler4, Elizabeth Saverino1, Peter F. Billingsley3, B. Kim Lee Sim2, Claudia Daubenberger6, Thomas L. Richie3, Salim Abdulla1, Stephen L. Hoffman3

1Ministry of Health and Social Welfare, Malabo, Equatorial Guinea, 2Ifakara Health Institute, Bagamoyo, Tanzania, United Republic of, 3Sanaria Inc, Rockville, MD, United States, 4Medical Care Development International, Malabo, Equatorial Guinea, 5Medical Care Development International, Silver Spring, MD, United States, 6Swiss 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 (PI) 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 PI 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 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.

Methods:

1. 8x10^6 PfSPZ and in children and infants at doses up to 9x10^5 PfSPZ.

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

Objectives:

- 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

<table>
<thead>
<tr>
<th>Groups</th>
<th>Description</th>
<th>n</th>
<th>PfSPZ dose</th>
<th>Immunogenicity</th>
<th>Total SPZ</th>
<th>SHMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>18 to 35 yrs</td>
<td>26</td>
<td>2.1x10^6</td>
<td>1.8x10^6</td>
<td>2.9x10^6</td>
<td>2.1x10^6</td>
</tr>
<tr>
<td>Group 2</td>
<td>18 to 35 yrs</td>
<td>26</td>
<td>2.1x10^6</td>
<td>1.8x10^6</td>
<td>2.9x10^6</td>
<td>2.1x10^6</td>
</tr>
<tr>
<td>Group 3</td>
<td>18 to 35 yrs</td>
<td>26</td>
<td>2.1x10^6</td>
<td>1.8x10^6</td>
<td>2.9x10^6</td>
<td>2.1x10^6</td>
</tr>
<tr>
<td>Group 4</td>
<td>11 to 17 yrs</td>
<td>26</td>
<td>2.1x10^6</td>
<td>1.8x10^6</td>
<td>2.9x10^6</td>
<td>2.1x10^6</td>
</tr>
<tr>
<td>Group 5</td>
<td>11 to 17 yrs</td>
<td>26</td>
<td>2.1x10^6</td>
<td>1.8x10^6</td>
<td>2.9x10^6</td>
<td>2.1x10^6</td>
</tr>
<tr>
<td>Group 6</td>
<td>11 to 17 yrs</td>
<td>26</td>
<td>2.1x10^6</td>
<td>1.8x10^6</td>
<td>2.9x10^6</td>
<td>2.1x10^6</td>
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<tr>
<td>Group 7</td>
<td>6 to 11 months</td>
<td>35</td>
<td>1.8x10^6</td>
<td>1.8x10^6</td>
<td>3.6x10^6</td>
<td>1.8x10^6</td>
</tr>
<tr>
<td>Group 8</td>
<td>6 to 11 months</td>
<td>35</td>
<td>1.8x10^6</td>
<td>1.8x10^6</td>
<td>3.6x10^6</td>
<td>1.8x10^6</td>
</tr>
<tr>
<td>Total n: 135</td>
<td>Normal saline controls (red or purple bars) vs. vaccinees (blue or green bars)</td>
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</tbody>
</table>

Serious Adverse Events:

- 15 year old male with a solitary seizure after PfSPZ Vaccine - Possibly related to vaccine (biologically plausible explanations)
- 3.5 hours after 3rd dose 1.8x10^6 PfSPZ
- No fever, no headache, no other known risk factors, but sister with history of epilepsy
- EEG and neuroimaging "consistent with idiopathic or genetic generalized epilepsy"
- 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.
- 6 weeks after 3rd dose 1.8x10^6 PfSPZ
- Normal fetal ultrasound 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 full 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 hyperemia gravidarium of moderate severity - not related to vaccine.
- 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 participants reported no or mild pain with injection

Unsolicited adverse events:

- 106 in the vaccine population (0.95/volunteer) vs. 31 unsolicited AE in the saline control population (0.97/volunteer)

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.)