

Challenge (NF54) mimics controlled human malaria infection (CHMI) by mosquito bite. Development of additional strains for CHMI by DVI would facilitate vaccine and therapeutics testing against representative parasitic strains circulating in nature that are heterologous to vaccine strains. Pf7G8 is a Brazilian clone with a divergent genomic sequence from PfNF54. We conducted a double blind, randomized, dose escalation study to assess the infectivity PfSPZ Challenge (7G8) administered by DVI. We randomized 30 malaria-naïve adults to five groups. Four groups received escalating doses of PfSPZ Challenge (7G8) (800, 1600, 3200 and 4800 PfSPZ) and one group received standard dose PfSPZ Challenge (NF54) that infects 100% of malaria-naïve individuals (3200 PfSPZ). We monitored participants daily for symptoms. Daily quantitative polymerase chain reaction (qPCR) testing for parasite RNA and DNA determined malaria patency. Participants tolerated injections well. Only mild local post-injection reactogenicity was recorded (12/30 participants), and only one participant (NF54 group) experienced fever due to malaria before diagnosis and treatment initiation with atovaquone/proguanil. Infectivity of PfSPZ Challenge (7G8) was dose-dependent: 43% (800 PfSPZ; n=7; 95% CI 10-82); 57% (1600 PfSPZ; n=7; 95% CI 18-90); 89% (3200 PfSPZ; n=9; 95% CI 52-100); and 100% (4800 PfSPZ; n=2; 95% CI 48-100); Pearson correlation coefficient = 0.98. All five participants who received PfSPZ Challenge (NF54) developed Pf parasitemia. PfSPZ Challenge (7G8) administered by DVI was well tolerated by malaria-naïve adults. Higher doses of PfSPZ may be required to ensure 100% infectivity of Pf7G8 compared to PfNF54. Additional studies of other Pf strains are needed to confirm the infective dose for each. The availability of multiple Pf strains of diverse geographic origin will greatly aid clinical development of candidate malaria vaccines to inform heterologous efficacy and dose optimization.

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SAFETY AND TOLERABILITY OF A METABOLICALLY ACTIVE, NON-REPLICATING, WHOLE ORGANISM MALARIA VACCINE IN MALARIA-EXPERIENCED ADULTS IN BURKINA FASO

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Plasmodium falciparum sporozoite (PfSPZ) Vaccine is a metabolically active, non-replicating, whole malaria sporozoite vaccine with an extremely favorable safety profile that is protective against *P. falciparum* controlled human malaria infection in malaria-naïve individuals. A recent clinical trial demonstrated 52% protection by time to event and 29% protection by proportional analysis against naturally occurring infection in Malian adults receiving five doses of 2.7 x 10⁵ PfSPZ. We aimed to assess the safety and protective efficacy of higher doses of PfSPZ Vaccine against naturally acquired Pf in malaria-experienced adults in Burkina Faso. We conducted an open-label dose escalation study in four cohorts of eight participants who received two vaccinations at 12-14 week intervals. Vaccine dose increased from 4.5 x 10⁵ to 9 x 10⁵ to 1.8 x 10⁶ to 2.7 x 10⁶ PfSPZ in a step-wise manner after safety and tolerability assessments. Data Safety and Monitoring Board (DSMB) members conducted reviews after the first dose of 2.7 x 10⁶ PfSPZ, and after the first four cohorts received dose two. All 32 participants received two vaccinations except for one participant in the 1.8 x 10⁶ PfSPZ dose group who was lost to follow-up. No participant experienced local solicited symptoms after either vaccination. Only two clinical laboratory abnormalities were noted after vaccination, both deemed related to other causes—mild ALT elevation in one participant and moderate anemia in another. No related grade two or three adverse events were recorded through Day 56 following second vaccination, and only eight mild grade 1 adverse events were noted. The vaccine demonstrated a favorable safety and tolerability profile at all doses tested. At the DSMB's

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recommendation, recruitment and vaccination of a fifth cohort of 80 individuals occurred in early 2017. This double-blinded part of the study randomized participants to receive three doses of either 2.7 x 10⁶ PfSPZ Vaccine or normal saline placebo. We will assess overall and strain-specific efficacy against malaria infection during the malaria transmission seasons in 2017 and 2018.

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HOMOLOGOUS AND HETEROLOGOUS PRIME BOOST VACCINATIONS WITH DISTINCT VARIANTS OF PLASMODIUM VIVAX CIRCUMSPOROZOITE PROTEIN (CSP) PROTECTS MICE AGAINST TRANSGENIC PB/PV SPOOROZOITE CHALLENGE

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Vaccine development against *Plasmodium vivax* malaria lags behind that for *Plasmodium falciparum*. To narrow this gap, we administered recombinant antigens based on *P. vivax* circumsporozoite protein (CSP) to mice. We expressed two novel soluble chimeric proteins by merging the three central repeat regions of different CSP alleles (VK210, VK247, and *P. vivax*-like). The first construct (yPvCSP-AllFL) contained the fused repeat regions flanked by N- and C-terminal regions. The second construct (yPvCSP-AllCT) contained the fused repeat regions and the C-terminal domain only. We generated replication-defective adenovirus vectors expressing CSP of human serotype 5 (AdHu5) and chimpanzee serotype 68 (AdC68). Mice were vaccinated with three doses of yPvCSP in adjuvants Poly (I:C) or Montanide ISA720, or with a regimen of a primary AdHu5 or AdC68 immunization followed by two immunizations with yPvCSP in adjuvant. Regardless of the adjuvant used, mice immunized with yPvCSP-AllFL or yPvCSP-AllCT generated high IgG titres specific to all CSP alleles. After challenge with *P. berghei* ANKA transgenic parasites expressing Pb/PvVK210 or Pb/PvVK247 sporozoites, significant time delays for parasitemia were observed in all vaccinated mice. These vaccine formulations should be clinically tried for their potential as protective universal vaccine against *P. vivax* malaria.

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PFSPZ VACCINE INDUCES T CELL RESPONSES TO SPOOROZOITES AND FOUR MALARIA ANTIGENS

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T cell responses to multiple *Plasmodium falciparum* (Pf) antigens are thought to mediate protection induced by PfSPZ Vaccine. PBMCs from subjects immunized with 3- and 5-doses of PfSPZ Vaccine were tested in a FLUOROSpot assay to measure single IFN- γ , single IL2, and double (IFN- γ + IL2) responses to NF54 Pf sporozoites (PfSPZ) and PfCSP, PfAMA1, PfTRAP/SSP2 and PfCeITOS peptide pools. The 5-dose regimen induced 92% protection against homologous (Pf3D7) controlled human malaria infection (CHMI) and 80% protection against heterologous (Pf7G8) CHMI 3 weeks after final immunization; the 3-dose regimen induced 87% efficacy to homologous CHMI. At 24 weeks after final immunization, the 5-dose regimen induced 70% efficacy against homologous CHMI but only 10% against heterologous CHMI; the 3-dose regimen induced