Presentation Abstract

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Session: Malaria: Vaccines - Clinical Assessment

Abstract Number: 1274

Title: A Phase 1 Trial to Assess the Safety, Attenuation and Immunogenicity of Genetically-attenuated p52-/ p36-/sap1- Plasmodium falciparum Parasites via the Bites of Infected Anopheles stephensi Mosquitoes

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Abstract: Attenuated Plasmodium sporozoite vaccines achieve unprecedented levels of protection against infectious challenge. Both irradiated sporozoites and genetically-attenuated parasites (GAPs) are under consideration for product development. In contrast to genetic heterogeneity observed with irradiated sporozoites, GAPs undergo definitive gene deletion with permanent genetically-defined attenuation and may provide a more rational approach for inducing consistently protective immune responses. Multiple rodent GAPs have been produced, and the cumulative data show that the GAP approach can confer sterile protective immunity. A double gene deletion P. falciparum GAP lacking *p52* and *p36* (GAP2KO, Pf *p52$^-$/p36$^-$*) was generated. A Phase 1 clinical trial of GAP2KO was conducted and at the high 200-bite dose, one of six subjects developed a breakthrough blood-stage infection, indicating conspicuous but incomplete attenuation. To ensure further attenuation, a third deletion was made to the critical liver stage gene encoding Sporozoite Asparagine-rich Protein 1 (GAP3KO, p52$^-$/p36$^-$/sap1$^-$). We conducted a single arm, open-label, phase 1 experimental medicine study designed to evaluate the safety and tolerability of GAP3KO. The study was designed to confirm attenuation of GAP3KO using peripheral blood smears and to evaluate cellular and humoral immune responses. A total of 10 healthy, malaria-naïve adult subjects were enrolled and received GAP3KO via the bites of 150-200 GAP3KO-infected A. stephensi mosquitoes. To confirm attenuation, subjects were evaluated for safety, reactogenicity, and signs and symptoms of malaria infection for 28 days, including monitoring in a hotel setting on Days 8-18 post-GAP3KO administration. All 10 subjects that received GAP3KO did so without incident and completed the 28 day study period. Local and systemic solicited adverse events reported as primary endpoints were classified as Grade 1 (mild) and 2 (moderate). All subjects remained negative for patent parasitemia as demonstrated by evaluation of peripheral blood smears. GAP3KO elicited significant immune responses and will proceed in development.