Safety and Preliminary Efficacy of CS-based Recombinant Adenoviral Serotype 35 and Serotype 26 Malaria Vaccine Candidates in Prime-Boost Vaccination of Healthy Adults Undergoing Subsequent Experimental P. falciparum Sporozoite Challenge

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Study Schema

Materials and Methods

Vaccines: The Ad35.CS.01 and Ad26.CS.01 vaccines are recombinant human adenovirus serotype 35 and serotype 26 vectors carrying the gene encoding the P. falciparum circumsporozoite (CS) surface antigen. Normal saline was used for placebo.

Study Population: A total of 43 healthy, adult volunteers aged 19 to 50 years were enrolled.

Study Design: Three subject cohorts were enrolled in the Vaccination Phase. Cohort 2 vaccine subjects and an (un)infected control subject were enrolled in the Challenge Phase.

Vaccination: Subjects in the low-dose (1x10^10 vp) and high-dose (5x10^10 vp) cohorts received two vaccinations with Ad35.CS.01, followed by Ad26.CS.01 at monthly intervals. Vaccinations between cohorts were staggered by 15 days to allow for adequate review of the safety data. Solicited local and systemic adverse events (AEs) were collected for seven days following each vaccination. Unsolicited AEs were collected throughout the study. All subjects were followed for six months after the last vaccination/infestation and were asked to complete the laboratory and surveillance forms at predetermined time points.

Immunology: Anti-CS antibodies, neutralizing antibodies to Ad26 and Ad35, and CD4 and CD8 T-cell responses against CSP were evaluated at baseline and following each vaccination and during the Challenge Phase. ELISA was used to detect and quantify antibodies against Ad26 and Ad35 and neutralizing antibodies against Ad26 and Ad35, respectively. ELISPOT assays were performed to detect cytokine production by CD4 and CD8 T cells against CS. The incidence of solicited local AEs was similarly assessed after each vaccination.

Results

General: No SAEs were reported during the study period and all subjects completed the study. All Cohort 1 and Cohort 2 subjects received both Ad35.CS.01 vaccinations. All Cohort 1 (10/10) and 18/20 Cohort 2 subjects received the Ad26.CS.01 vaccine.

Infectivity: Of 23 subjects experimentally infected, 6/6 infectivity controls and 16/17 Cohort 2 subjects were protected, remaining blood smear negative throughout the Challenge Phase. The mean pre-patent periods were 9.22 days (range 5-12 days). The duration of parasitemia following diagnosis and treatment ranged from one to three days (mean 1.32 days).

Conclusions

In general, both the Ad35.CS.01 and the Ad26.CS.01 vaccines were well tolerated at the 1x10^10 vp and 5x10^10 vp dose levels. This is the first-in-man study of the Ad26.CS.01 candidate malaria vaccine.

• Vaccine reactogenicity and systemic reactogenicity of the Ad35.CS.01 vaccine were similar to low dose and placebo groups, with slightly higher systemic reactogenicity observed at the higher dose level. Symptoms were more frequent following the third vaccination (Ad26.CS.01).

• One subject out of 17 demonstrated sterile protection against P. falciparum. This subject also showed highest CS antibody titers and T cell response at the time of malaria challenge.

• Up to 6% of subjects developed CD8 T cell responses after vaccination with both vaccines.

• Ad35.CS.01 vaccination elicited modest neutralizing adenoviral vector antibodies, while Ad26.CS.01 vaccination elicited neutralizing anti-vector antibodies in almost all subjects, at higher levels.

• By ELISPOT, T cell responses are consistently higher in vaccine groups compared to placebo.

• ICS detects mainly CD8 responses with very little CD4 responses.

• CD4 TNFα and IFNy responses after vaccination are markedly increased compared to placebo and boosted upon administration of the Ad26.CS.01 boost.

• While Ad35 elicits only few and modest NAb titers, Ad26 elicits NAb titers in most subjects with high levels after just one vaccination.