Recombinant full-length *Plasmodium falciparum* circumsporozoite protein-based vaccine expressed in *Pseudomonas fluorescens* and adjuvanted with GLA-LSQ: results of Phase 1 testing with malaria challenge

Submission Type: Oral or Poster Abstract

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Introduction

The *Plasmodium falciparum* circumsporozoite protein (CSP) is an effective antigen for malaria vaccination. Monoclonal antibodies targeting the junction between the CSP N-terminus and central repeat region provided sterilizing protection in recent clinical trials.[1,2] Full length recombinant CSP (rCSP) vaccines may offer advantage over CSP-based vaccines that do not include the junctional region, including RTS,S and R21.

The central repeat region makes a full-length CSP difficult to produce with good manufacturing practice, but new platforms have been able to overcome this hurdle, one of which expresses a recombinant CSP in a *Pseudomonas fluorescens* platform. CSP on its own is not highly immunogenic until a person has had repeated exposures,[3] so CSP vaccines are generally combined with an adjuvant. Glucopyranosyl Lipid A-liposome *Quillaja saponaria* 21 formulation (GLA-LSQ) combines GLA, a synthetic, homogeneous, nontoxic derivative of Gram-negative bacterial cell wall lipopolysaccharide that functions as a TLR4 agonist, promoting Th1-type responses, and LSQ, a saponin extracted from a South American soapbark tree, which also promotes Th1-type responses and stimulates cytotoxic T cell production.[4,5] Initial pre-clinical studies and first-in-human data showed promising immunogenicity of full-length rCSP vaccine given with GLA-LSQ (AP 10-602).[6,7]

Methods

We performed a Phase 1 clinical trial of a to investigate the safety, immunogenicity and efficacy against controlled human malaria infection (CHMI) of rCSP/GLA-LSQ (AP 10-602). Initial results demonstrated vaccine safety and immunogenicity.[7] For the efficacy portion of the trial, 29 healthy, malaria-naïve Baltimore participants aged 18-45 years old were enrolled into three dosing arms: a high dose (60 µg rCSP + 5 µg GLA-LSQ), delayed 2 dose arm (n = 9), a high dose (60 µg rCSP + 5 µg GLA-LSQ), 3 dose arm (n = 10) and a low dose (10 µg rCSP + 5 µg GLA-LSQ), 3 dose arm (n = 10) given on days 1 and 490 (delayed 2 dose) or 1, 29, and 85 (3 dose) (Figure 1). The delayed high dose, 2-dose group was not initially part of the study design but resulted from COVID-related research shutdowns. Vaccinated participants and six unvaccinated infectivity controls underwent homologous CHMI 28 days after last vaccinations. Study endpoints included anti-CSP IgG antibody by ELISA and time to *P. falciparum* asexual parasitemia after CHMI.

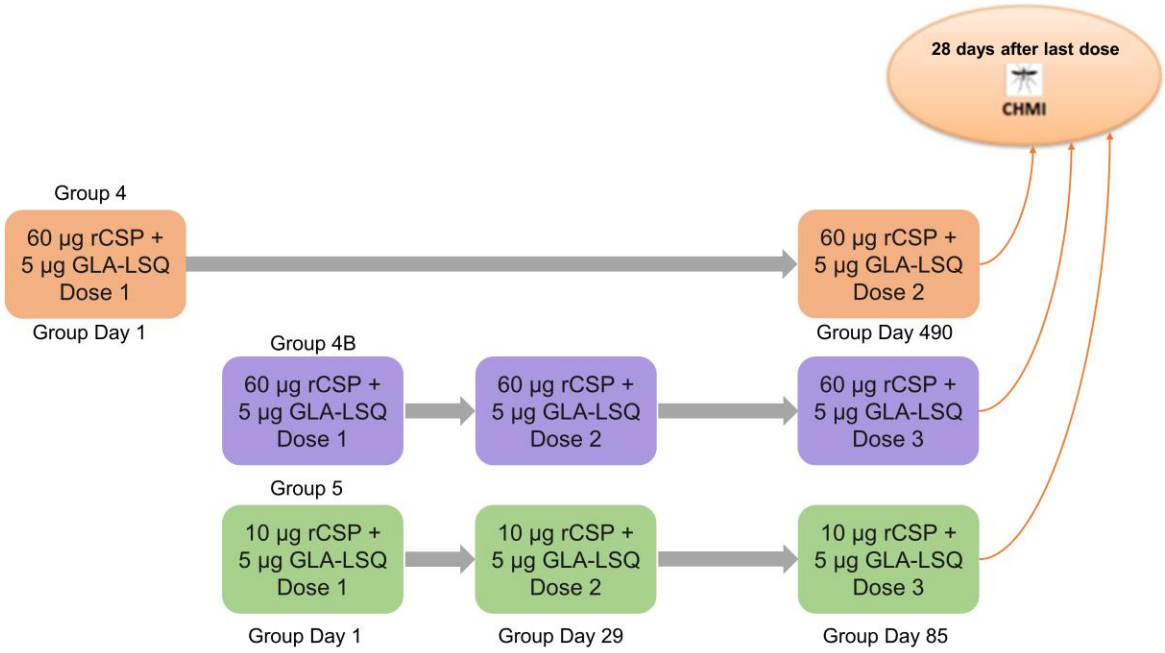

Figure 1: Study schematic

Results

The high dose, 3-dose group achieved the highest geometric mean anti-rCSP IgG fold rise (day of CHMI/baseline): 236.2-fold, 95% CI: 32.4, 1721.1, compared to the low dose group: 55.4-fold, 95% CI: 8.3, 370.0, and the high dose, delayed 2-dose group: 33.3-fold, 95% CI: 1.3, 885.1 (Figure 2).

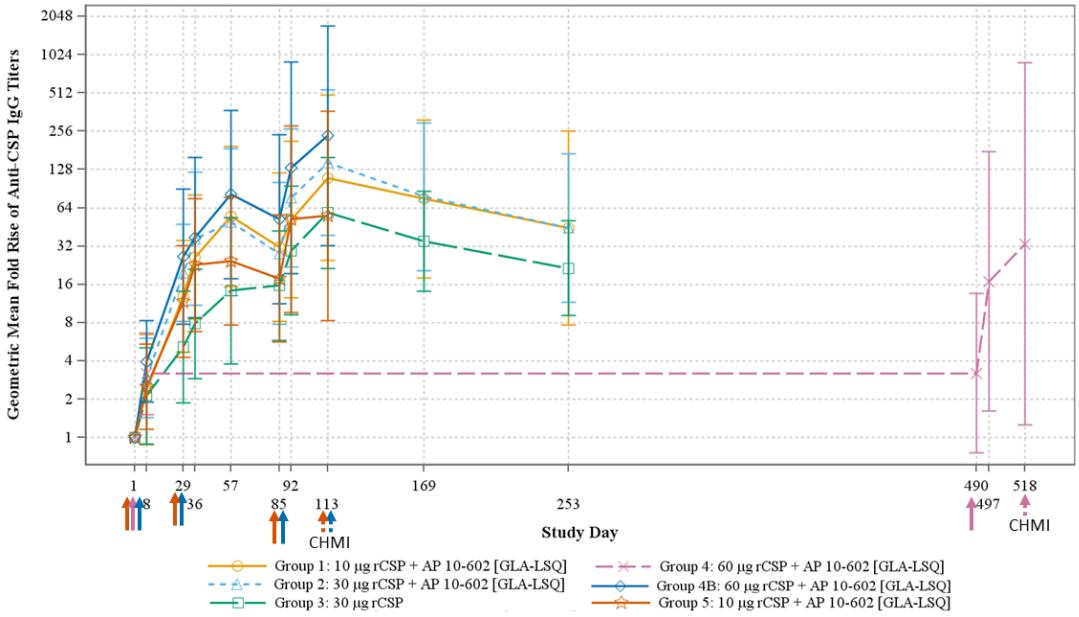

Figure 2: Geometric Mean Fold Rise Time Trends of Anti-CSP IgG Titers by Treatment Group

All vaccinated participants developed *P. falciparum* asexual parasitemia following CHMI (vaccine efficacy: 0%). Median time to parasitemia was eight days after CHMI in all groups and unvaccinated controls (Figure 3).

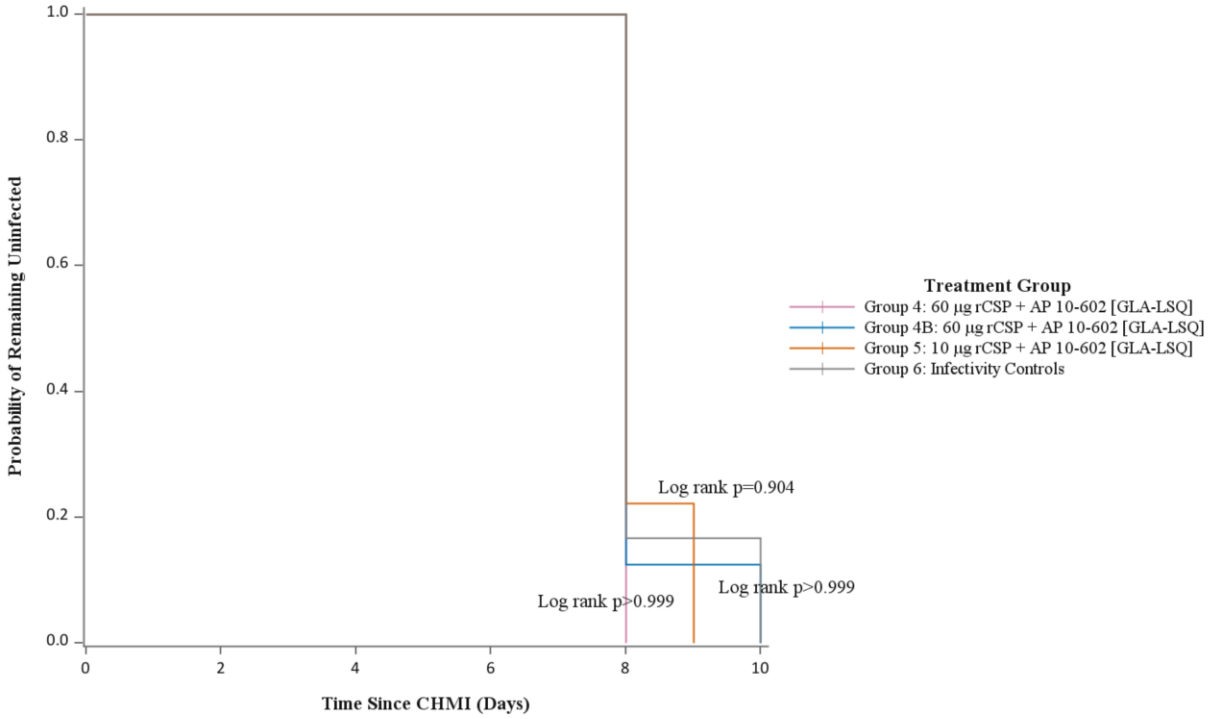

Figure 3: Kaplan-Meier Curves of Time to Malaria Infection after CHMI

Median peak parasite density (parasites per mL) was 58.05 (IQR: 35.65, 224.1) in the high dose, 3 dose group; 147.40 (IQR: 79.9, 409.30) in the high dose, delayed 2 dose group, and 102.80 (IQR: 54.0, 387.20) in the low dose, 3 dose group, and 296.25 (IQR: 129.20, 663.10) in the infectivity controls (Figure 4).

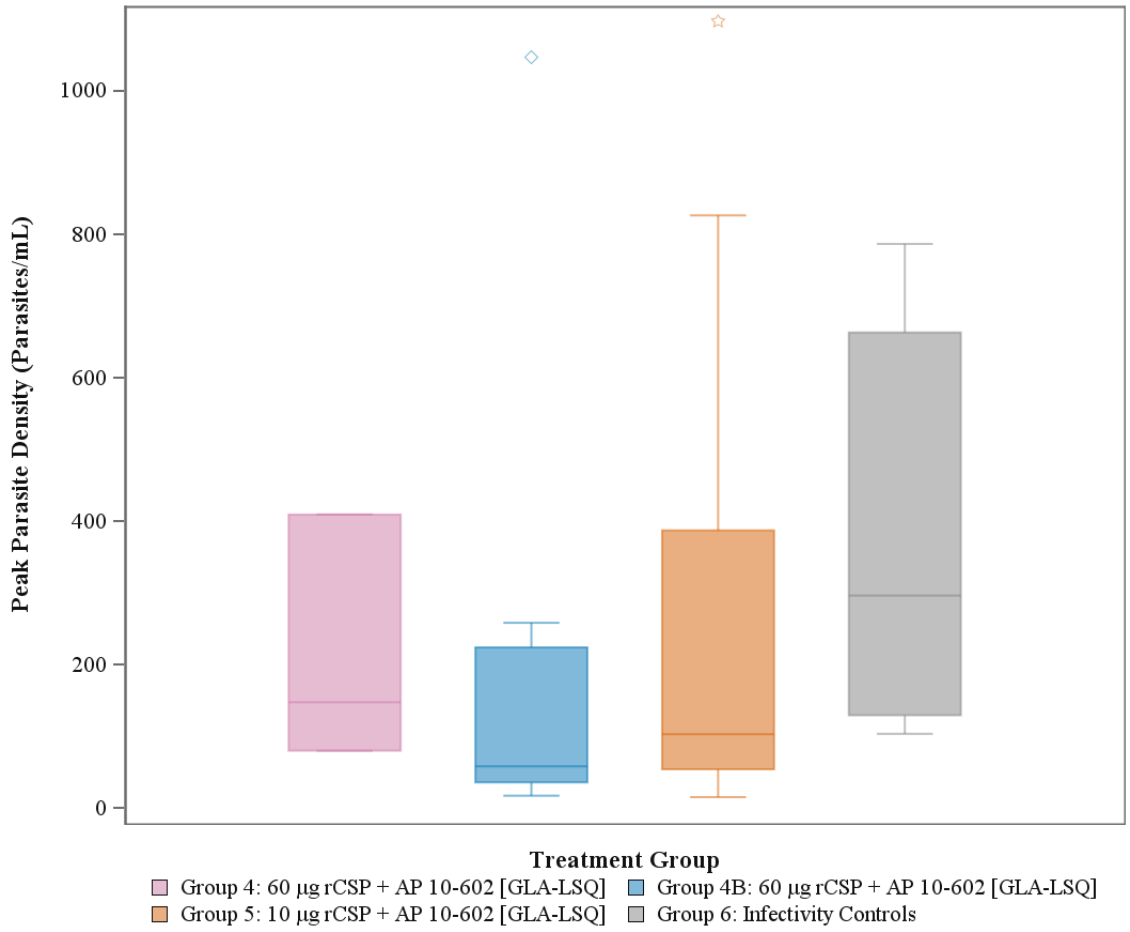

Figure 4: Peak Parasite Density Following CHMI by Treatment Group for Infected Subjects

Discussion/Conclusions

While we saw a dose response relationship between the vaccine dose and IgG levels, the vaccine lacked efficacy. The lack of vaccine efficacy suggests that the vaccine construct and schedules given did not induce functional antibodies that reduce parasitemia or provide sterile protection. Potential explanations include antigen issues such as targeting of immunodominant versus protective epitopes or incorrect folding/presentation of epitopes, adjuvant issues such as suboptimal dose versus targeting the incorrect immune system pathways, or schedule issues such as need for a delayed 3rd dose versus a fractional 3rd dose. It is hoped that dissecting the immune responses to this vaccine will help to define protective responses for future vaccines.

Acknowledgements:

We would like to thank the Baltimore volunteers for graciously consenting to be in this trial, the Division of Microbiology and Infectious Diseases at the NIAID for their invaluable support and advice, The Emmes Company, LLC for statistical support, and the CVD study staff for coordination, oversight and data entry. Funding: NIAID Vaccine and Treatment Evaluation Unit (VTEU) contract number HHSN272201300022I (PI: Karen Kotloff, Protocol PI: Matt Laurens),

NIAID Malaria Vaccine Production Support Services contract number AI-N01-054210, NIAID contracts No. HHSN272201200005I and HHSN272201800009Ild (stability testing), NIAID K23AI155838 (DFK), Burroughs Wellcome Fund/American Society of Tropical Medicine and Hygiene Postdoctoral Fellowship in Tropical Infectious Diseases (DFK). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. Gaudinski MR, Berkowitz NM, Idris AH, et al. A Monoclonal Antibody for Malaria Prevention. *N Engl J Med* 2021; **385**(9): 803-14.
2. Wu RL, Idris AH, Berkowitz NM, et al. Low-Dose Subcutaneous or Intravenous Monoclonal Antibody to Prevent Malaria. *N Engl J Med* 2022; **387**(5): 397-407.
3. Noland GS, Hendel-Paterson B, Min XM, et al. Low prevalence of antibodies to preerythrocytic but not blood-stage Plasmodium falciparum antigens in an area of unstable malaria transmission compared to prevalence in an area of stable malaria transmission. *Infect Immun* 2008; **76**(12): 5721-8.
4. Coler RN, Bertholet S, Moutaftsi M, et al. Development and characterization of synthetic glucopyranosyl lipid adjuvant system as a vaccine adjuvant. *PLoS One* 2011; **6**(1): e16333.
5. Kensil CR, Wu JY, Soltysik S. Structural and immunological characterization of the vaccine adjuvant QS-21. *Pharm Biotechnol* 1995; **6**: 525-41.
6. Noe AR, Espinosa D, Li X, et al. A full-length Plasmodium falciparum recombinant circumsporozoite protein expressed by Pseudomonas fluorescens platform as a malaria vaccine candidate. *PLoS One* 2014; **9**(9): e107764.
7. Friedman-Klabanoff DJ, Berry AA, Travassos MA, et al. Low dose recombinant full-length circumsporozoite protein-based Plasmodium falciparum vaccine is well-tolerated and highly immunogenic in phase 1 first-in-human clinical testing. *Vaccine* 2021; **39**(8): 1195-200.