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Safety, immunogenicity and durability of a novel malaria vaccine candidate, R21 adjuvanted with Matrix-M(TM)

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Background: Plasmodium falciparum malaria remains one of the leading causes of morbidity and mortality worldwide. The search for an effective vaccine has seen unprecedented advances in recent years with one of the leading vaccine candidates, RTS,S/AS01 due to enter pilot deployment trials in Africa in 2018. However, no vaccine to date has demonstrated durable high level efficacy.

Material/methods: R21 has been developed at the Jenner Institute, University of Oxford and is an improved RTS,S like vaccine consisting of the pre-erythrocytic circumsporozoite protein (CSP), which is an abundant coat protein involved in sporozoite development and hepatocyte invasion. R21 is composed of recombinant protein particles formed from a fusion protein comprising of the central repeat and the C-terminus of CSP fused to Hepatitis B surface antigen (HBsAg), but without the excess of unfused HBsAg protein found in RTS,S. GMP manufacture in *Pichia pastoris* was performed at the Clinical Biomanufacturing Facility at Oxford University. We undertook a Phase I, open-label clinical trial to assess the safety and immunogenicity of R21 administered alone at a dose of 50µg (Group 2; n=4) and at two dose levels with the novel saponin-based adjuvant, Matrix-M (Group 1 and 3; n=10 per group).

Results: Preliminary safety and immunogenicity data showed that the vaccines were well-tolerated, that the inclusion of Matrix-M enhanced NANP-specific IgG responses markedly, and that R21 at a 10 μ g or 50 μ g dose level with Matrix-M induced humoral responses comparable to historic data with 50 μ g RTS,S/AS01. NANP antibody responses were durable with titres at 6 months comparable to those reported for RTS,S/AS01. The lower 10 μ g dose induced the more durable response, with significantly higher titres observed at 6 months in the 10 μ g dose group compared to the 50 μ g dose group. We also present preliminary data from an additional group of volunteers who have been given immunisations with a very low dose of 2 μ g R21 with Matrix-M. Reactogenicity was found to be minimal and clearly reduced compared to both 10 μ g and 50 μ g at this very low dose. Initial analysis shows that 2 μ g R21 with Matrix-M induces comparable NANP-specific IgG to the 10 μ g and 50 μ g dose at 28 days after the final vaccination.

Conclusions: These Phase I data have provided the basis to progress this vaccine into an ongoing Phase IIa controlled human malaria infection “challenge” study to evaluate vaccine efficacy.