REPORT ON THE EVALUATION OF R21 MALARIA VACCINE (RECOMBINANT, ADJUVANTED)

1.0 Background Information on the Procedure

1.1 Submission of the Dossier

The local agent – DEK Vaccines Limited – representing Serum Institute of India Pvt Ltd, Off Soli-Poonawalla Road, 212/2 Hadapsar, Pune- 411 028, India, submitted application to the Food and Drugs Authority (FDA) for the registration of R21 Malaria vaccine.

Location address: Serum Institute of India Pvt Ltd, Off Soli-Poonawalla Road, 212/2 Hadapsar, Pune- 411 028, India

An Evaluation Committee[1] chaired by Mr. Seth Seaneke, Deputy Chief Executive (Health Products & Technologies Division) was constituted to evaluate the application.

Receipt of application for pre-submission meeting	24th November 2022
Pre-submission meeting	28th November 2022
Application, including supporting documents received on	16th January, 2023
Documents circulated for preliminary evaluation	9th February 2023
Date of joint evaluation	15 -17th March, 2023
Date of joint peer-review / Registration meeting	17th March, 2023
Date queries were submitted to applicant	20th March 2023
Date responses to queries was received	24th March 2023
Date of joint review of responses to queries	27th March 2023
Date of approval of application	28th March 2023

Evaluation Committee Members

The evaluation committee comprised of the following members – each expert assigned to specific module/section of the application/dossier received from the applicant:

Chairperson/Peer-reviewer (Cross-discipline)

- Seth Seaneke (Deputy Chief Executive Officer (DCEO) –Health Products and Technologies)

Peer-reviewer (Cross-discipline team leader)

- Eric Karikari-Boateng (Director, Centre for Laboratory Services and Research –

Quality reviewers

- Edwin Nkansah – (Director: Vaccines, Vigilance and Clinical Trials Directorate)
- Samuel Asante-Boateng – (Director, Drugs and Nutraceuticals Directorate)
- Nathaniel N.K Nkrumah – (Head, Vaccines and Biological Products Department)

Clinical reviewers

- Yvonne Adu-Boahen (Head, Clinical Trials Department)
- Amma F. Asare (Clinical Trials Department)

Non-Clinical reviewer

- Patrick Owusu-Danso (Head, Drug Laboratory)

Safety reviewer/Risk Management Plan (RMP)

- George Tsey Sabblah (Head, Safety Monitoring Department)
- Adela Ashie – (Safety Monitoring Department)

Administrative part reviewers

- Ernest Kwame-Agyei (Vaccines and Biological Products Department)
- Felix Nabonasi (Vaccines and Biological Products Department)

Legal basis

The legal basis for the receipt, evaluation, and registration of product is provided below:

- Section 118 (1) of the Public Health Act, 2012, Act 851
- Guidelines for registration of vaccines (FDA/SMC/BPD/GL-RVC/2014/05)
- SOP for evaluation and registration of a Biological Product application (FDA/BPD/SOP -01).
- SOP for good review practices - Biological Product dossier evaluation (FDA/BPD/SOP -05)

Registration Pathway

The application was subjected to the FDA's routine product registration pathway. The routine pathway involves full evaluation of submitted product development dossier components (content in the format of the Common Technical Document (CTD) – Modules 1-V. The administrative, quality (Chemistry, Manufacture & Control), non-clinical, Clinical, and post-registration product safety monitoring plan parts were fully and comprehensively evaluated for appropriateness and in compliance with requirements in the guidelines for registration of vaccines (FDA/SMC/BPD/GL-RVC/2014/05).

2.0 Scientific Discussion

2.1 About the Product: <u>General information</u>:

- **Name of vaccine:** R21 Malaria Vaccine (Recombinant, Adjuvanted)
- **Therapeutic indication**: R21 Malaria Vaccine (Recombinant, Adjuvanted) is indicated for active immunization of children aged 5 to 36 months against Malaria caused by *Plasmodium falciparum.*
- **Developer**: Jenner Institute, Oxford University
- **Manufacturer**: Serum Institute of India Pvt. Ltd.
- **Local agent**: DEK Vaccines Limited, Accra
- **Pharmaceutical form:** Clear, colourless to mildly turbid Solution for injection
- **Storage:** The storage temperature of the vaccine is 2-8 °C
- **Shelf-**life: 24 months
- **Product presentation:** Single and multidose vials (co-formulated antigen-adjuvant) in a single vial. FPP filled in a 2mL clear glass vial, stoppered with a 13mm Bromo butyl rubber stopper from Datwyler and crimped with a 13 mm dark blue flip off seal.

2.2 Type of Application and Aspects on Development

Generally, the FDA will register the product when the application has met the minimum registration requirement in compliance with published guidelines. That the assessors/evaluators/experts agree that:

- Based on the totality of scientific evidence available, including data from adequate and well-controlled clinical trials, and a detailed post-registration pharmacovigilance plan, it is reasonable to believe that the product may be effective in the prevention of clinical malaria.
- The known and potential benefits outweigh the known and potential risks of the product when used as part of the interventions to prevent malaria.

2.3 PRODUCT DESCRIPTION

R21 Malaria Vaccine is a Virus-Like Particle (VLP) based circumsporozoite protein (CSP) vaccine called R21. It is formed by the self-assembly of the chimeric VLP of CSP-Hepatitis

B surface antigen (HBsAg) fusion protein and this leads to a vaccine composed of a much higher proportion of CSP, that targets the pre-erythrocytic stage of *Plasmodium falciparum* infection (includes both the sporozoite invasion of the human host and the liver-stage - stage in the disease which is ideal to block progression to clinical malaria). R21 Malaria Vaccine is a pre-erythrocytic vaccine intended to limit the ability of Plasmodium falciparum to infect, mature and multiply in the liver by eliciting predominantly immunity to the circumsporozoite (CS) protein present at the surface of the sporozoite. R21 is produced using a genetically modified organism (GMO) Hansenula polymorpha (yeast cell line).

Qualitative and Quantitative Composition – Each dose of 0.5 mL contains;

a) [1, 2] R21 Malaria Antigen: 5 µg ([1] Portion of P. falciparum circumsporozoite protein fused with hepatitis B surface antigen [2] In the form of non-infectious virus-like particles (VLPs) produced in yeast cells (Hansenula) by recombinant DNA technology),
b) Matrix-M1 (Adjuvant): 50 µg

Posology and method of administration

Vaccination in children from 5 months of age up to 36 months of age (at first dose). Three doses; each of 5 µg R21 and 50 µg Matrix-M1 should be given at monthly intervals. A fourth dose is recommended 12 months after the third dose. Administration of R21 is by IM injection. The deltoid muscle is the preferred site for injection in children aged 5 months and older. If deltoid muscle mass is small, injection can be given in the anterolateral thigh muscle.

3.0 Quality Aspects

3.1 Drug Substance (DS)

General information

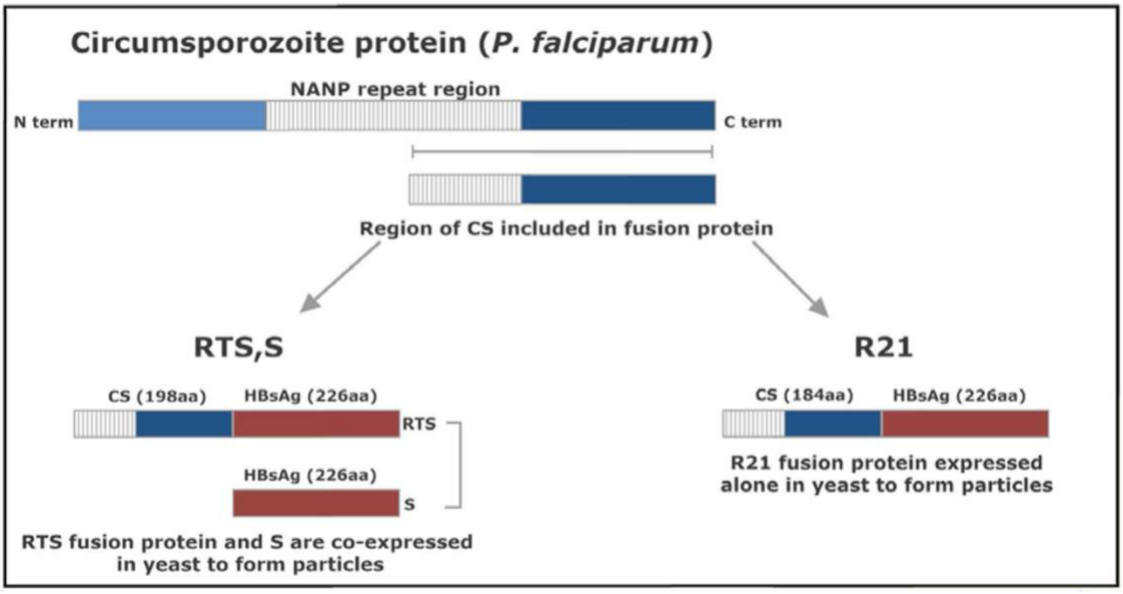
The R21 Drug Substance (DS) is a virus -like particle (VLP) consisting of the circumsporozoite protein (CSP) from *Plasmodium falciparum* expressing the central NANP repeat region fused to the recombinant Hepatitis B Surface Antigen (HBsAg) particles. The monomeric R21 fusion protein has a predicted mass of approximately 45 kDa based on the amino acid sequence derived from the DNA sequence. Multiple copies of the monomeric protein self- assemble into virus like particles (VLPs) with a size and structure, as identified by transmission electron microscopy (TEM), similar to the natural Hepatitis B virus surface particles (between 25 and 40 nm in diameter).

Applicant provided the schematic representation of the R21 fusion protein structure in comparison with RTS,S in Figure 1. Both RTS,S and R21 include the fusion protein of hepatitis B surface antigen to the C-terminus and central repeats of the CSP. These

repeats comprise many copies of the four amino acid sequence NANP i.e. Asparagine, Alanine, Asparagine & Proline.

Applicant intimated that the generation of virus-like particles by both RTS,S and R21 has been shown to be important for allowing induction of high-level antibody responses. However, the R21 DS lacks the excess of HBsAg present in RTS,S and the majority from the C-terminus of CSP.

FIGURE 1



Manufacture, characterization and process controls

The manufacture of R21 is a continuous process and allows no holding of intermediates throughout the process. It involves classical fed batch fermentation of recombinant Hansenula polymorpha strain received from Artes Biotech, followed by harvesting of surface protein and its purification by multiple filtration and chromatographic techniques.

Specification

Submission suggested that no pharmacopoeia monograph is available for Malaria Vaccines, the specifications of R21 DS were documented to have been adopted based on the WHO TRS 980, Annex 3 and ICH Q6B guideline and prior knowledge of batch release testing of Hepatitis B vaccine leveraging on platform knowledge.

The manufacture is adequately controlled via process parameters, in-process test procedures which were found to be within Proven Acceptable Range (PAR). The

specifications included description, total protein content, identity by western blotting using anti-R21 antibody, Endotoxin content, purity by SDS-PAGE & Densitometry, pH, Host cell protein, residual DNA, sterility, antigen to protein ratio, particle size, purity and residual cesium content. Seven (7) batches with batch numbers 9788T001, 9780I002 (clinical batches), 9788T003, 9780001, 9780002, 9780I001 and 9780I003 (commercial batches) analyzed were in compliance with the pre-defined DS specifications and confirmed consistency and uniformity of the DS manufacturer. These batches are executed to support the marketing authorization application as Development/PV and commercial manufacturing.

Nonetheless, the FDA quality assessors requested that applicant should include peptide mapping as a release specification. Subsequently, applicant responded to include peptide mapping as a release specification for the release of batches for DP intended for the Ghana market.

Stability

Stability studies were performed on the batch 9788T003 and on three Process Validation (PV) batches 9780I001, 9780I002 and 9780I003.

The results for all the stability testing parameters were within the set specifications and consistent during stability time points.

The data showed that R21 antigen in polypropylene bottles can be stored for 24 months at 2-8ºC and up to 3 months at (25+/-2ºC; 60+/-5% RH). Due to the change in the primary container closure system from polypropylene to Ultra -Low Density Polyethylene (ULDPE) bags, applicant is requested to submit data under the same conditions mentioned above.

Submission was deemed adequate. Notwithstanding, applicant has committed to continue the long-term stability study on the PV batches and provide all the updated unexpected stability issues in the ongoing studies (out-of-specifications results, etc) and proposed corrective action to the FDA.

3.2 Drug Product (DP)

DP Manufacturer

Serum Institute of India Pvt Ltd, Off Soli-Poonawalla Road, 212/2 Hadapsar, Pune- 411 028, India.

DP Description

R21 Malaria Vaccine is composed of R21 Malaria Antigen as DS, Matrix-M1 as adjuvant and Sucrose, Magnesium Chloride, Tris buffer and PBS used as excipients.

R21 Malaria Vaccine (Recombinant, Adjuvanted) is sterilely produced and presented as ready to use liquid formulation for intramuscular injection stored at 2-8°C.

Pharmaceutical Development

R21 Malaria Vaccine (Recombinant, Adjuvanted) is a formulation of R21 Malaria Antigen and Matrix-M1 adjuvant at 5 µg and 50 µg content respectively. R21 Malaria Vaccine (Recombinant, Adjuvanted) is manufactured as sterile solution filled in 1 dose and 2 dose presentation in vial. Vaccine composition and the quantities of ingredients per dose (0.5mL) was adequately discussed in the dossier. All excipients in the vaccine formulation are of compendial grade.

The adjuvant system, Matrix M1 is prepared from Matrix A and Matrix C. Matrix A and Matrix C were procured from Novavax. The Certificate of Analysis (CoA) was evaluated and found satisfactory.

The manufacturing technology is transferred from Oxford University and was used to manufacture the non-clinical batches, phase-I/II and phase-III CT batches at SIIPL.

The pharmaceutical development adequately discussed dosage form, the formulation, manufacturing process, container-closure system, microbiological attributes, and compatibility of R21 Malaria Vaccine (Recombinant, Adjuvanted).

Adventitious Agents

Results of the characterization of Master Cell Bank (MCB) and Manufacturer's Working Cell Bank (MWCB) suggest that the vaccine is free from adventitious agents. The MCB and MWCB are also stated to be stored at appropriate storage temperatures to prevent later contamination with adventitious agents.

No materials of biological/human or animal origin are used in the manufacturing process of DS and DP of R21 Malaria Vaccine.

Manufacturing Process

The description of manufacturing process and controls is presented in sufficient details and process flow diagram is presented with indications of the critical steps.

Process validation studies were performed on three consecutive batches (both 1 dose (4472Z001, 4472Z002, 4472Z003) and 2 dose (5222Z001, 5222Z002, 5222Z003) with respect to process parameters, in-process testing, batch release testing. Results of tests performed on the R21 malaria vaccine final blend (Batches 13162Z001, 13162Z002 and 13162Z003) has also been submitted.

Results of tested parameters are batch-to batch comparable and are within proposed limits. Comparability between the commercial and clinical batches has been carried out, and result were comparable without any significant deviation. The result verify that the manufacturing process assures adequate batch-to-batch consistency.

Specification and Batch Analysis.

Testing performed on the R21 Malaria Vaccine (Recombinant, Adjuvanted) (Drug Product) included description/appearance, sterility, identity, endotoxin content, purity, pH, extractable volume, container closure integrity test, particulate matter, osmolality, estimation of antigenic ratio, size by DLS, potency, protein content, Matrix A and C identity, Saponin concentration. The list of test parameters was deemed appropriate, protocols for analytical methods appropriate, and results documented to be within acceptance criteria.

Stability

Stability results from three clinical batches (3538H001, 3530H003 and 4471H001) and six PV batches (4472Z001, 4472Z002, 4472Z003, 5222Z001, 5222Z002 and 5222Z003) were submitted. Based on results, applicant proposed that R21 Malaria Vaccine (Recombinant) is stable at long term stability condition (2-8°C) for up to 24 months and at accelerated stability condition (25 ± 2 °C, 60 ± 5% RH) for 6 months when stored siliconized in glass vials. The proposed storage conditions are deemed justifiable relating it to the data provided by the applicant.

Conclusion.

The Chemistry, Manufacturing and Controls part of the application was deemed satisfactory, and in compliance with regulatory requirements set forth for the manufacturing platform. Further, applicant has demonstrated commitment to address all outstanding issues, which were deemed not to significantly impact the manufacture of the DS and DP.

4.0 Non-clinical Aspects

Pharmacology

Immunogenicity studies.

Two immunogenicity studies were undertaken in BALB/C mice both immunized intramuscularly.

First study (study number JI-R21-01). The study included three immunizations, which were given three weeks apart in BALB/C mice at Jenner Institute, Oxford.

The Mosquito Strain Used: ***P Berghei.*** The study was initiated in 2012 and completed in 2013.

- **Study Objectives:** To evaluate the immunogenicity of 0.5 µg R21 alone or in combination with adjuvants (Alhydrogel and Abisco)

A population of 18 study animals were randomized into three groups as follows:

Groups:

R21c alone, R21c + Alhydrogel, R21c+ Abisco

The route of administration used was identical and representative of that intended for clinical administration of the vaccine and this is acceptable.

Route of administration:

Intramuscular

The frequency of dosing was longer as compared to the intended dosing frequency for clinic which is three doses initially at monthly interval and a fourth dose after one year. This is also deemed acceptable.

Dose frequency:

Three immunizations were given three weeks apart. The immunogenicity was assessed by measuring serum antibody titers three weeks after each immunisation and antigen-specific T cell responses in the spleen three weeks after the final immunisation.

- **Evaluation Parameters:** Immunogenicity was assessed by measuring serum antibody titers three weeks after each immunization and antigen-specific T cell responses in the spleen three weeks after the final immunization.

Study Findings

From the study results following a third booster dose given to all groups it was noted that R21c + Abisco-100 induced the highest titers of NANP specific IgG and the response for this group was significantly higher than both R21c + Alhydrogel and R21 alone.

CS-specific IFNγ producing T cells were assayed in a spleen ELISpot after the final immunisation and they were detected in all mice receiving R21c with or without adjuvant. The median response in the R21c+ Abisco-100 group was 700 SFC/106 splenocytes, but

in the R21c + Alhydrogel and R21c alone groups, although the IFNγ producing T cells were detected they were only just above background.

The second study with study number XMM0014 was carried out in BALB/C mice at Jenner Institute, Oxford. Each group received a total of 4 doses each on Day 1, 15, 29 and 43. two weeks apart.

R21 malaria vaccine manufactured by SIIPL with the Matrix-M1 adjuvant also showed potent humoral immunogenicity in mice. The same clinical route was used for the nonclinical studies.

CHALLENGE STUDIES

Challenge study was performed with study number JI-R21-02 at Jenner Institute, Oxford involving the usage of sporozoite challenge to evaluate immunogenicity after prime and prior to challenge and to assess the blood stage parasitemia.

The animal model used for the challenge study was BALB/C mice.

The animal groups used in the challenge studies included:

Naïve mice, Adjuvant control, R21c + Abisco and R21c + Matrix M1.

Five animals were randomized into the adjuvant control group and eight animals were also randomized into each of the intervention groups (Naïve mice, R21c + Abisco and R21c + Matrix M1

The route of administration used was identical and representative of that intended for clinical administration of the vaccine and this was deemed acceptable.

The challenge dose was 1000 sporozoites administered per mouse injected intravenously) using transgenic *Plasmodium berghei* parasite were performed in BALB/C mice. The challenge dose was deemed adequate for evaluation of vaccine efficacy in the animal model.

R21c + adjuvant was administered twice, eight weeks apart and mice were challenged three weeks after the second dose.

Thin blood films looking for parasitaemia were performed daily from Day 5 post-challenge. Sterile protection was defined as remaining slide negative at Day 14.

Study Findings and Discussion

From the study results it was noted that R21c + Abisco provided sterile protection in 100% of the challenged mice with a p value of p=< 0.0001) while R21c + Matrix-M1 provided sterile protection in 87.5% of the challenged mice (p=0.0002) and this was confirmed in

a second independent challenge (p = < 0.0001). There was no significant difference between the two adjuvants.

PHARMACOKINETICS

No pharmacokinetic data was provided.

TOXICOLOGY STUDIES

Single-Dose Toxicity

No Single-Dose Toxicity studies have been performed on R21 Malaria Vaccine (Recombinant, Adjuvanted).

Repeat-Dose Toxicity Studies

Two repeat dose toxicity studies were performed in BALB/C mice.The first study with study number XMM0014 was performed in BALB/c mice at Envigo CRS Limited under GLP environment.

The second study with study number CM25FF was also performed in BALB/C mice at Covance Laboratories Limited, UK in a GLP environment. Signed and dated GLP statements of compliance were submitted for both study sites.

1st Repeat-Dose Toxicity (Envigo study XMM0014)

Report of repeat dose toxicity study (study number XMM0014) with intramuscular administration to BALB/C mice was submitted. The study was conducted to investigate the potential toxicity of R21c either alone or combined with AS01B or Matrix M1 adjuvant to BALB/C mice (Mus musculus) when administered on four occasions each with a 14-day interval followed by a 3- or 21-day observation period.

The study was designed with animal groups consisting of four study groups as follows:

Group 1: PBS **Group 2**: 5 µg R21c +5 µg Matrix M1 **Group 3**: 5 µg R21c +50 µg AS01B and **Group 4**: 5 µg R21c

A total of 72 BALB/C Mice were allocated to the four study groups as follows:

Group 1 (n=12): PBS (6 Male + 6 Female)

Group 2 (n=20): 5 µg R21c +5 µg Matrix M1 (10 Male + 10Female)

Group 3 (n=20): 5 µg R21c +50 µg AS01B (10 Male + 10Female)

Group 4 (n=20): 5 µg R21c (10 Male + 10 Female)

Study design was deemed acceptable by the assessor.

The study was initiated on the 18th March 2015 and the experimental completion date (last day of data recording) was 14th July 2015.

Study Findings and discussion

From the study results it was noted that the administration of R21c alone or combined with AS01B or Matrix-M1 adjuvant was well tolerated and was not associated with any systemic toxicological change. All test article related changes were consistent with the expected immune stimulation associated with the administration of a vaccine with or without adjuvant or with minimal inflammatory changes in the muscle injection sites. There was no histopathological correlate for the slightly increased red cell distribution width, the slightly higher reticulocyte counts, lower platelet counts, lower alkaline phosphatase activity or higher aspartate aminotransferase activity. None of these minor variations are considered adverse.

2nd Repeat-Dose Toxicity (Covance Laboratories Limited, UK study CM25FF)

The toxicity of R21 manufactured at the Serum Institute India (SII) mixed with Matrix-M1 was tested in BALB/C mice to investigate the potential toxicity of R21, a malarial vaccine, with Matrix M1 adjuvant in Buffer A, and R21 with Matrix M adjuvant in Buffer B to BALB/C mice when administered on four occasions each with a 14-day interval followed by a 3 day or 21-day observation period.

Two formulations of R21 were tested: R21 in formulation buffer A or formulation buffer B.

The study was designed with animal groups consisting of three study groups as follows:

Group 1: PBS

Group 2: 5 µg R21 (A) + 5 µg Matrix-M1 (Buffer A: 20mM TrispH 7.4, 15% Sucrose, and 30 mM MgCl2)

Group 3: 5 µg R21 (B) + 5 µg Matrix-M1 (Buffer B: 20mM Tris Buffer pH 7.4 and 150 mM NaCl)

A total of 52 BALB/C Mice were allocated into the four study groups as follows:

Group 1 (n=12): PBS (6 Male + 6 Female)

Group 2 (n=20): 5 µg R21 (A) + 5 µg Matrix-M1 (10 Male + 10Female)

Group 3 (n=20): 5 µg R21 (B) + 5 µg Matrix-M1 (10 Male + 10Female)

The study was initiated on the 5th July 2018 and completed on 19th October 2018

The dosing frequency: Animals received the control phosphate buffered saline (PBS), or the test substance, R21 either alone or in combination with Matrix M by intramuscular injection on four occasions (Days 1, 15, 29 and 43) over 64 days, with half the number of animals being Euthanized/sacrificed on Day 46 and the remaining animals being euthanized/sacrificed on Day 64. The age animals used for the 54 to 60 days old.

Study Findings

There were no unscheduled deaths recorded in the study. There were no clinical signs considered related to treatment and there was no apparent reaction to treatment at the dose site. It was concluded that the administration of R21 combined with Matrix M adjuvant was well tolerated and was not associated with any systemic toxicological changes.

R21(A)/Matrix M

It was noted that changes at the intramuscular injection sites and surrounding subcutaneous tissue (inflammatory cell infiltrates) were observed in all males and females treated with R21 (A)/Matrix M (Group 2) euthanized/sacrificed on Day 46. Minimal changes in the subcutaneous tissue surrounding the muscle of the left intramuscular injection site (inflammatory cell infiltrates) were see in some previously treated males and one previously treated female euthanized/sacrificed on Day 64.

Enlargement of the spleen and increased spleen weight were observed on Day 46 for most males and females treated with R21(A)/Matrix M, correlating microscopically with increased extramedullary hematopoiesis; recovery was apparent at the Day 64 examinations.

Increased germinal centre development of the inguinal lymph nodes correlated macroscopically with enlargement, was observed in most treated males and females euthanized/sacrificed on Day 46. A full recovery was seen in all treated males and apartial recovery in females. On Day 64, one previously treated female was observed with minimal increased germinal centre development. Increased germinal centre development of the axillary lymph nodes correlated macroscopically with enlargement and was observed in some treated females euthanized/sacrificed on Day 46.

There was a full recovery of the lesions observed in the inguinal lymph nodes in treated males and a partial recovery in treated females by Day 64. A full recovery was also observed in axillary lymph nodes of treated females by Day 64. Slight to moderate increased cellularity was observed in the sternal bone of all treated females and some treated males euthanized/sacrificed on Day 46; recovery from this was apparent at the Day 64 examinations.

On Day 46, hematology investigations revealed slightly higher than control group mean circulating large unstained cell counts for males and females. On Day 64, large unstained cell counts for treated males and females were similar to control. Slightly higher circulating white blood cell numbers were observed in treated males and females euthanized/sacrificed on Day 64, however these differences did show a high degree of individual variability.

On Day 46, blood chemistry investigations revealed slightly lower albumin and higher globulin concentration in both sexes. On Day 64 only a higher globulin concentration was seen. A lower glucose and triglyceride concentration was observed for treated males. This was not apparent on Day 64. A slightly higher potassium and phosphorus concentration was observed for males on Day 46, by Day 64 only the higher phosphorus concentration was observed.

R21(B)/Matrix M

Changes at the intramuscular injection sites (inflammatory cell infiltrates) and surrounding subcutaneous tissue were observed in all males and females treated with 5 µg R21 (B)/5 µg.

Matrix M (Group 3) euthanized/sacrificed on Day 46. Minimal changes in the subcutaneous tissue

surrounding the muscle of the left intramuscular injection site (inflammatory cell infiltrates) were see in some previously treated males euthanized/sacrificed on Day 64.

Enlargement of the spleen and increased spleen weight were observed on Day 46 for the majority of males and females treated with R21(B)/Matrix M, correlating microscopically with increased extramedullary hematopoiesis; recovery was apparent at the Day 64 examinations.

Increased germinal centre development of the inguinal lymph nodes correlated macroscopically with enlargement, was observed in most treated males and all treated females euthanized/sacrificed on Day 46. A full recovery was seen in all treated females and a partial recovery in males. On Day 64, two previously treated males were observed with minimal increased germinal centre development. Increased germinal centre development of the axillary lymph nodes correlated macroscopically with enlargement and was observed in most treated females euthanized/sacrificed on Day 46. A full recovery was observed for this lesion in axillary lymph nodes of treated animals by Day 64.

Slight to moderate increased cellularity was observed in the sternal bone of all treated females and the majority of treated males euthanized/sacrificed on Day 46; recovery of this lesion was apparent at the Day 64 examinations.

Slightly higher circulating neutrophil, lymphocyte, eosinophil and large unstained cell numbers were observed on Day 46 for the majority of treated males and females when compared with control, with recovery apparent in treated males by Day 64. Investigations performed on Day 64 revealed slightly higher group mean circulating neutrophil and lymphocyte counts for females. However, these differences did show a high degree of individual variability.

Slightly higher than control group mean circulating white blood cell numbers were observed in treated males and females euthanized/sacrificed on Day 46 and previously treated males and females euthanized/sacrificed on Day 64 mainly due to a high degree of individual variability.

On Day 46, blood chemistry investigations revealed slightly lower albumin and higher globulin concentration in males. On Day 64 only a higher globulin concentration was observed but this time in males and females. On Day 46, a slightly higher triglyceride concentration was observed for treated males which was also apparent for treated males on Day 64. A slightly higher potassium and phosphorus concentration was observed for males on Day 46 which was not apparent on Day 64.

CONCLUDING REMARKS

The treatment by intra-muscular administration of R21 with Matrix M adjuvant in Buffer A (5 µg R21 (A)/5 µg Matrix M) or R21 with Matrix M adjuvant in Buffer B (5 µg R21 (B)/5 µg Matrix M) to BALB/C mice on four occasions each with a 14 day interval followed by a 3 day observation period was associated with findings in the muscular injection sites (mixed inflammatory cell infiltrates), inguinal and axillary lymph nodes (increased germinal center development), sternal bone marrow (increased cellularity) and spleen (increased extramedullary hematopoiesis).

Following a 21-day observation period full recovery was observed in the right muscular injection site, axillary lymph nodes and bone marrow of previously treated animals. Partial recovery was observed in the left muscular injection site, inguinal lymph nodes and spleen. These findings are commonly observed in vaccine component studies. The incidence and/or severity of findings in the inguinal/axillary lymph nodes, bone marrow and spleen appeared slightly higher in females and in animals treated with 5 µg R21 (B)/5 µg Matrix M (Group 3).

Supportive Toxicity Studies Evaluating Matrix-M1 Adjuvant

Multiple repeat-dose toxicity studies have been conducted by Novavax in rats and rabbits with Matrix-M1 adjuvant alone or with other nanoparticle antigens.

Reports 499514, 37348 TSR, 2088-12408, 2088-12925, 2088-13549, and 161014)

Consistent results have been observed across all toxicology studies with no evidence of overt systemic or organ-specific toxicity. Matrix-M1 adjuvant has been well-tolerated with no evidence of toxicity suggestive of any unusual risk or target organ toxicity. Non-adverse findings, including local injection site inflammation, reversible enlargement of the lymph nodes draining the injection sites (but not elsewhere), and chemical markers of inflammation (ie, CRP, fibrinogen, and globulin) were transient. These studies provide adequate nonclinical safety for the novel Matrix-M1 adjuvant in 2 different animal species.

Genotoxicity

Applicant did not conduct their own genotoxicity studies but provided available literature information to support the absence of genotoxic potential of Adjuvant. Since the adjuvant has been used in other vaccines it is not novel, as a result additional genotoxicity studies will not be further pursued.

Reproductive Toxicity

Reproductive toxicity studies have not been conducted with R21/Matrix-M1.

Local Tolerance and Other Studies

No Local Tolerance Toxicity Studies are performed on R21 Malaria Vaccine (Recombinant, Adjuvanted). This study shall not be further pursued since it was embedded in the chronic toxicity study and no major issues with reactogenicity at injection sites were observed.

CONCLUSION

The nonclinical data provided is sufficient to support safety of the vaccine.

5.0 CLINICAL ASPECTS

Good Clinical Practice (GCP)

The study reports summaries presented below contained statements that the studies were conducted in compliance with the World Medical Association Declaration of Helsinki and ICH Topic E6 (R2), guidelines for GCP, including archiving of essential documents.

The phase I/IIa, took place in the UK, phase Ib took place in Kilifi (Kenya) with Ib/IIb study taking place in Nanoro, Burkina Faso. The phase III study took place at Bougouni (Mali), Nanoro (Burkina Faso), Dande (Burkina Faso), Bagamoyo (Tanzania) and Kilifi (Kenya).

For phase III, the report indicated site initiation visits were conducted prior to study start. Monitoring visits by a professional representative of the sponsor were scheduled at specific times and carried out to ensure the study's compliance with the protocol. The sponsor also contracted an external auditor to perform an audit of each trial site from June to August 2022. The objective of the audits was to assess whether the study participants' safety and well-being were adequately protected, whether the collected data as complete and reliable, and to ensure that the study was being conducted in compliance with ICH-GCP and applicable regulations. The audit at each site included a tour of facilities, review of Investigator Site Files and a sample of study participants' records (paper source documents and eCRF), and interviews of key personnel.

Again, from the report, following inspections at the sites, there were documented corrective and preventative action plans put in place to address any findings. Records of such inspections may be made available by the Sponsor on request by any ethics committee or regulatory authorities.

OVERVIEWS OF SUBMITTED AND EVALUATED CLINICAL STUDIES

Clinical Efficacy

Generally, the cumulative efficacy data from the clinical efficacy studies presented below appeared well-maintained at 73% efficacy after the primary vaccination series of 0, 1, 2 months after 12 months before booster. Although data from the booster dose from the pivotal study (VAC078) was not available at the time of the evaluation, it was noted from the phase IIb trial which had been followed up for three years that the vaccine efficacy appeared well-maintained at 73 % over this time period with a single booster dose at the end of the first year.

Phase I/IIa Study (VAC072)

One safety and efficacy trial (phase I/IIa), was undertaken of the R21 Malaria Vaccine/Matrix M1 in the United Kingdom using a well-studied human challenge protocol with infectious mosquito bites in 77 healthy malaria naïve participants (https://clinicaltrials.gov/ct2/show/NCT03970993). The study was to assess safety, immunogenicity, and protective efficacy of R21/Matrix-M, administered in different dose schedules (10µg R21/50µg MM and 50µg R21/50µg MM). The study reported no Suspected Unexpected Serious Adverse Reactions (SUSARs) or Serious Adverse Events (SAEs) related to vaccination. For the standard dose of 10µg R21/50µg Matrix-M, the majority of Adverse Events (AEs) were mild with very few AEs graded as severe. In total, there were only 6 participants who experienced fever. For the higher dose of 50µg R21/50µg Matrix-M, the majority of AEs were also mild.

The vaccine was well tolerated and immunogenic at a range of dose levels and particularly high efficacy was observed, of 75%, using a low dose regimen of 10 µg R21 in 50 µg of Matrix-M1 adjuvant.

Phase Ib Study (VAC073)

The first trial in Africa of the R21 Malaria Vaccine/Matrix M1 (phase Ib) took place in Kilifi, Kenya assessing the safety and immunogenicity of several R21 Malaria Vaccine/Matrix M1 dosing regimens in 91 subjects, was an age de-escalation dose escalation trial to evaluate the safety and tolerability of R21 with adjuvant Matrix-M in healthy adults (18 – 45 years) then children (1 – 5 years) and finally infants (5 months – 12 months (https://clinicaltrials.gov/ct2/show/NCT03580824). Doses used were 10µg R21/50µg Matrix-M, 5µg R21/25µg Matrix-M and 5µg R21/50µg Matrix-M.

The vaccine was well tolerated and immunogenic in all age groups, and most immunogenic in infants administered the 5 µg R21 with 50 µg Matrix M1 formulation later used in the phase III trial.

Phase Ib/IIb Study (VAC076)

This ongoing single-site phase Ib/IIb trial involving 450 children (5-17 months old) in Nanoro, Burkina Faso is to assess the protective efficacy against clinical malaria of R21 adjuvanted with Matrix-M in 5-17-month-old children living in a malaria-endemic area, for 6 months after the third vaccination using 5µg R21/25µg Matrix-M, 5µg R21/50µg Matrix-M and a control Rabies vaccine. Those who received 5µg R21/50µg Matrix-M had a higher vaccine efficacy (VE) after three primary series doses plus a booster dose at 12 months was observed to be 76%, 77% and 73% efficacy over one, two and three years of follow-up, respectively. This dose was therefore carried on to the phase III study.

According to the interim analysis, so far, thirteen (13) SAEs have been recorded in this trial and all were assessed as unrelated to vaccination, including 2 fatalities. Pain, redness and swelling were experienced across all groups after the primary series of vaccinations but generally, the proportion of participants who experienced AEs were low. No specific trends in laboratory AEs have been noted following vaccinations. The SAEs were fairly distributed across the 3 groups (5µg R21/25µg Matrix-M, 5µg R21/50µg Matrix-M and a control Rabies vaccine).

Pivotal Phase III Study (VAC078)

In an ongoing phase III randomized controlled double-blind study (commenced on 29th April, 2021), conducted at 5 sites in 4 sub-Saharan African countries, Burkina Faso, Mali, Tanzania and Kenya with a wide range of transmission intensities, more than 4,800

children from 5-36 months of age were enrolled to evaluate efficacy and safety of R21 Malaria Vaccine/Matrix-M1 when given according to a 0, 1, 2-month schedule. In addition, these children receive per protocol a fourth dose, administered 12 months after the third dose. The study's primary objective was efficacy against the first or only episode of clinical malaria over a follow-up period of 12 months after three doses of 5µg R21/50µg Matrix-M compared with a control Rabies vaccine in each age group. Vaccine efficacy after three primary series doses plus a booster dose at 12 months was observed to be over 70%, similar to what was observed in phase IIb trial (VAC076). There was a significant difference in vaccine efficacy between 5–17-month-olds and 18-36-month-olds. This 5-17-month-old age group also allows a more direct comparison with the approved RTS,S/AS01 vaccine which has been evaluated also in this age group. In 5–17-months-olds, the efficacy of R21/Matrix-M was 79% (73-84) at seasonal sites and 75% (65-83) at standard sites. Across all sites, the overall efficacy over 12 months is 78% (73-82).

So far, 15 AESIs (febrile convulsions, meningitis, and cerebral malaria) have been reported in the interim analysis up to the data cut-off date of 16th Jan-2023. These included 11 events of febrile convulsion [4 events at the Seasonal Regime Sites and 7 events at the Standard Regime sites], 2 events of bacterial meningitis [1 at the Seasonal Regime Site and 1 at the Standard Regime site] and 2 events of cerebral malaria [1 at the Seasonal Regime Site and 1 at the Standard Regime site]. The AESI events were reported as SAEs. Of the 11 febrile convulsions, 9 were reported by participants from the R21/Matrix-M vaccine arm and 2 were reported by participants from the Rabies vaccine arm. In the 7 days following vaccination, there was no imbalance in the incidence of febrile convulsions between rabies and malaria vaccinees. Statistical power in any comparison is, however, reduced due to the very small numbers in each group. Out of the 11 events of febrile convulsions, 6 were unrelated to the study vaccine, 3 were assessed as possibly related to the study vaccine, 1 event each was assessed as probably and 1 was definitely related to the study vaccine. Also, the events of bacterial meningitis and cerebral malaria were assessed as not related to the study vaccine.

Efficacy against severe malaria

It was observed that the statement, *"Efficacy against severe malaria across all sites was 74% (12 – 93, P = 0.03) in a time to event analysis"* was made in section 5.1 of the SmPC. However, based on the clinical information provided in support of the application (per the interim analysis in the clinical report), there is not enough data and sufficient power to support this indication. As a result, assessor proposed that the claim could not be supported with the evidence available and should be deleted to which the applicant has complied.

Phase Ib Study (VAC088)

This double-blind randomized controlled trial being conducted in Bougouni, Mali, is designed to evaluate the safety and immunogenicity of a new single-vial formulation of R21 mixed with Matrix-M compared to the previously used two-vial formulation of R21

and Matrix-M presented in separate vials and mixed before administration. The groups “a” (two vial) and “b” (single vial) totalling 123 subjects were stratified by age into 5–11-month-olds (Group 1), 12-23-month-olds (Group 2) and 24-36-month-olds (Group 3) age categories.

There was no indication of reduced immunogenicity in response to vaccination with the single-vial (‘b’ groups) compared with the two-vial (‘a’ groups) formulation after vaccination with 2 doses or 3 dose.

Pain at the injection site and fever, particularly after dose 2, were the most frequent AEs for both two- and single-vial presentation groups. There were no significant differences in rates or grades of solicited adverse events between groups a and b in any age group after any vaccination dose. Analysis of the combined age groups also revealed no differences in adverse events rate between groups a and b. There was one fatal SAE, a case of septic shock, reported for a subject in Group 1a (5–11-month-olds administered with two vial vaccine) occurring 7 days after dose 3. This was considered unrelated to vaccination. For laboratory safety assessment, bilirubin, ALT, creatinine, red blood cell count, haemoglobin level, platelets, lymphocytes and neutrophils were measured at day 0 (first vaccination), 7, 30, 60 and 90 days during the trial, and no differences were observed between groups a and b and between the three age groups.

Clinical Safety

Safety findings have been acceptable with no vaccine-related serious adverse events and a well-tolerated safety profile. This includes local pain at the injection site and fever as the only very common (>10%) adverse events.

In summary, R21 Malaria Vaccine/Matrix M1 has shown an acceptable safety profile in four trials enrolling over 5,350 subjects in five countries. The efficacy of the vaccine reached 75% in a phase IIa, a phase IIb and a recent phase III trial in the first year of follow-up.

<u>Phase I/IIa Study (VAC072)</u>

For solicited AEs, pain at the injection site was the most common local AE. Myalgia and fatigue were the most systemic solicited AEs recorded. Most of the AEs were mild to moderate and resolved in a few days.

There was one serious adverse event (SAE) which was a left wrist fracture that occurred in a participant two months following their third vaccination after a sports injury and required surgical intervention. This was deemed as not related to vaccination. Also, no

serious adverse reactions (SARs) or suspected unexpected serious adverse reactions (SUSARs) occurred.

Phase Ib Study (VAC073)

For the children and infants in this study, common local AEs were pain, swelling and warmth at the vaccination site which often resolved without intervention and were transient. Fever was the predominant systemic AE in this group but mostly settled within 72 hours of immunization and was most common after 2nd, 3rd, and 4th vaccinations. The most frequent systemic solicited AEs seen in adults were chills, headache, and fatigue (3 each out of 11 participants), with most AEs occurring after 1st vaccination and none after 4th vaccination.

Changes in safety laboratory blood samples were mostly transient and self-resolving except for a participant who was withdrawn due to disclosure of excess alcohol consumption and associated liver function anomalies.

2 SAEs were reported in the trial in the infant cohort (both participants 13 months old). 1 diagnosed with a lower respiratory tract infection and gastroenteritis with features of septicemia in the complete blood count results. The other diagnosed with a lower respiratory tract infection with features of iron deficiency anaemia in the complete blood count results. Both were treated, recovered and discharged. The SAEs were determined not to be related to the IMP.

Phase Ib/IIb Study (VAC076)

For local AEs, pain, redness and swelling were experienced across all groups after the primary series of vaccinations but overall, the number of participants experiencing each AE was low. The highest proportion of participants experiencing a local AE after any given vaccine dose was 15.6%. Swelling was the most common AE across all groups and experienced in more participants after their second dose of vaccine. There were no severe local adverse events reported.

For systemic AEs, the most common across the primary series of vaccinations and following the booster dose was fever which were generally mild. Following each dose of vaccine, there were significantly more fevers in the active arm with a higher adjuvant dose of the malaria vaccine

For laboratory AEs, anaemia was noted across all 3 arms and leucocytosis in one participant in one of the active arms None of these abnormalities were assessed as related to vaccination. Severe anaemia was also noted in relation to SAEs. No specific trends in laboratory AEs have been noted following vaccinations.

Thirteen (13) SAEs have been reported to date and all were assessed to be not related to the IMP. Of these, 2 were fatal (malaria and acute lymphocytic leukaemia).

Phase III Study (VAC078)

Overall, 5,375 AEs [1,211 solicited AEs in 734 participants and 4,164 unsolicited AEs in 2,014 participants] were reported by those who received the R21/Matrix-M vaccine and 2,396 AEs [345 solicited AEs in 254 participants and 2,051 unsolicited AEs in 1,013 participants] were reported by participants in the Rabies vaccine as control. Injection site pain was the most frequently reported local solicited AE whereas fever was the most frequently reported systemic solicited AE in the R21/Matrix M vaccine arm following the primary series vaccination. Most of the unsolicited AEs were not related to the study vaccine and recovered without sequalae. Upper respiratory tract infection was the most common unsolicited AE reported across both the vaccination arms (control and investigational) following the primary series of vaccinations and the booster vaccinations.

As of the data cut-off date of 16-Jan-2023, there have been 133 SAEs (87 SAEs in 81 of 3,252 participants in the R21/Matrix-M vaccine arm as compared to 46 SAEs in 40 of 1,626 participants in the Rabies vaccine arm). Of these 133 SAEs recorded 15 were AESIs (febrile convulsions, meningitis and cerebral malaria). Of the AESIs, 11 were febrile convulsions; 6 were not related to the study vaccine, 3 were assessed as possibly related to the study vaccine and 1 event each was assessed as probably and definitely related to the study vaccine. Of the 133 SAEs, 106 SAEs recovered/resolved without sequelae, 2 recovered with sequelae, 5 reported as recovering/resolving, 3 reported as not recovered / not resolved and 16 deaths (none of which were considered as related to the study vaccine).

For laboratory safety parameters, there were no significant changes in the haematology and biochemistry from baseline to Day 84 following primary vaccination and from baseline to Day 28 following the booster vaccination.

So far, AEs recorded in the phase III study are no different from the early phase studies with fever and injection site pain being the most common. Most of the SAEs have been assessed as having no relation to the study IP. There are no peculiar trends in laboratory safety analyses either.

6.0 Safety aspects

Safety considerations for non-clinical, clinical studies were provided and reviewed accordingly. Generally, safety report was considered adequate to assure the safety of the

vaccine when administered. Additional requirements are however requested such as an updated to summary of product characteristics.

Risk Management Plan (RMP)

Evaluation of the Risk Management Plan (RMP) was satisfactory. As per requirements of the FDA, the Qualified Person for Pharmacovigilance (QPPV) for Serum Institute of India Pvt Ltd is required to submit signed declaration form for implementation of RMP in Ghana.

Nonetheless, the applicant is requested to submit protocol for the study of the vaccine in children with HIV, as well as any study.

7.0 Conclusions on the chemical, pharmaceutical and biological aspects

Though the non-clinical data in the initial submission was found adequate, quality, and clinical data of the vaccine was inadequate to grant an authorization, however, applicant's responses to the FDA query letter was considered acceptable and satisfactory to justify granting a conditional registration of 1 year, and subsequently extended by an additional two years upon satisfactory evaluation outcome of the pending queries.

The physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in an acceptable way. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that from a quality perspective the product should have a satisfactory and uniform clinical performance.

The submitted information suggest that currently manufactured product batches are of a quality that is appropriate and comparable to that of clinical development batches.

However, to ensure that the quality of future batches will also remain appropriate and comparable to that of clinical development batches over the life cycle of the R21 Malaria Vaccine (recombinant, adjuvanted), the following regulatory issues are proposed to be addressed.

8.0. RECOMMENDATION

Balancing the identified inadequacies in the product development dossier submitted with the need for a safe and efficacious additional intervention for Malaria control , as well as the commitment demonstrated by the manufacturer/applicant to address all pending regulatory issues, the evaluation committee recommend that R21 Malaria Vaccine

(Recombinant, Adjuvanted) be registered, granted a 1 -year registration validity, and subsequently extended upon a satisfactory evaluation outcome of all pending queries. Generally, the registration of R21 Malaria Vaccine was recommended by the committee.

- based on a satisfactory evaluation outcome of the quality, safety and efficacy data submitted to the FDA, as well as a detailed post-registration product safety monitoring plan.
- Because the evaluation of the application concluded that the benefit of the vaccine significantly outweighs the risk associated with the use of the vaccine
- The vaccine has a potential to reduce mortality caused by clinical malaria in children under 5 years of age in Ghana.