Clinical trial results:
A Phase I/IIa Sporozoite Challenge Study to assess the safety, immunogenicity and protective efficacy of adjuvanted R21, administered in different dose schedules in healthy UK volunteers.

Summary

EudraCT number	2018-004391-34
Trial protocol	GB
Global end of trial date	24 August 2021

Results information

Result version number	v1 (current)
This version publication date	10 September 2022
First version publication date	10 September 2022

Trial information

Trial identification

Sponsor protocol code	VAC072

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03970993
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	Churchill Hospital, Old road, Headington, Oxford, United Kingdom, OX3 7LE
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 August 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 August 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and tolerability of adjuvanted R21 using different immunisation schedules in healthy malaria-naïve volunteers, and the efficacy (prevention of occurrence of P. falciparum parasitemia, assessed by PCR) of adjuvanted R21 against malaria sporozoite challenge, in healthy malaria-naïve volunteers using two immunisation regimes.

Secondary Objectives:
To assess humoral immunogenicity generated in malaria-naïve individuals by adjuvanted R21 using different immunisation schedules in healthy malaria-naïve volunteers and to assess the safety and tolerability of adjuvanted R21 using different vaccination regimes and compared to R21c against malaria sporozoite challenge, in healthy malaria-naïve volunteers.

Protection of trial subjects:

Volunteers given at least 24 hours to read VIS before being seen and then given plenty of opportunity to ask questions prior to agreeing to take part in a study.
- Screening visit including full medical history, physical examination and baseline blood tests to ensure volunteers are healthy prior to enrolment.
- Vaccination carried out in clinical environment with staff trained in resuscitation in case of allergic reaction.
- Safety review prior to dose escalation (LSM)
- Total blood volume taken during study kept to a volume that should not compromise healthy volunteers
(i.e. less than regular donation to blood transfusion service).
- Volunteers observed for 1-2 hours after vaccination to monitor for any
immediate adverse effects.
- Volunteers seen within 3 days of vaccination for safety review and provided with 24/7 contact number for trial clinician and emergency contact card for the department.
-Volunteers phoned daily by the clinic team prior to first in-person follow up after CHMI

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 June 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 76
Worldwide total number of subjects	76
EEA total number of subjects	0

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	76
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Volunteers were first recruited to Group 1a in June 2019. Volunteers were recruited and vaccinated at the CCVTM, Oxford and the NIHR WTCRF Southampton, Imperial College London and GSTT, London. Vaccine efficacy were assessed using Controlled Human Malaria Infection (CHMI). CHMI was conducted at Imperial College, London, and the follow up in Oxford

Pre-assignment

Screening details:

Screening details:
Inclusion / Exclusion criteria
Informed consent
Medical History
Physical Examination
Biochemistry
Haematology
Urinalysis
Serum B-HCG (women only)
Coagulation profile
Review contraindications
HBV,HCV,HIV serology
Biochemistry
Haematology

Period 1

Period 1 title	Week 0
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Laboratory investigators processing samples for PCR analysis were blinded to group allocation. No other blinding was used.

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1a

Arm description:

10 µg R21 in 50 µg Matrix-M1 adjuvant administered at week 0, 4, 8 and 60 (4-dose regimen) with no CHMI.

Arm type	Experimental
Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

R21 10 µg / Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at week 0

Arm title	Group 1b

Arm description:

10µg R21 in 50µg Matrix M-1 adjuvant administered at weeks 0, 4, 8 and 60 with no CHMI (4-dose regimen).

Arm type	Experimental

Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

R21 10 µg / Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at week 0

Arm title	Group 2a

Arm description:

10 µg R21 in 50 µg Matrix-M1 adjuvant administered at weeks 0, 4, 24 and 56-80 with sporozoite CHMI (mosquito bites) at day 28 and 60-84.
4 dose regimen with 2 CHMI

Arm type	Experimental
Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

R21 10 µg / Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at week 0

Arm title	Group 2b

Arm description:

10ug R21 in 20ug Matrix -M1 adjuvant administered at weeks 0, 4 and 24 with no CHMI

Arm type	Experimental
Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

R21 10 µg / Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at week 0

Arm title	Group 3a

Arm description:

10 µg R21 in 50 µg Matrix-M1 adjuvant administered at weeks 0, 4, 8 and 40-64. A sporozoite CHMI took place at week 12 with a repeat CHMI at week 44-64.

Arm type	Experimental
Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

R21 10 µg / Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at week 0

Arm title	Group 3b

Arm description:

10 µg R21 in 50 µg Matrix M adjuvant administered at weeks 0, 4 and 8 with no CHMI

Arm type	Experimental

Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

R21 10 µg / Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at week 0

Arm title	Group 4a and b

Arm description:

50 µg of R21 in 50 µg Matrix-M1 adjuvant administered at weeks 0, and 4 followed by 10 µg R21 in 50 µg Matrix-M1 adjuvant at week 24 with a sporozoite CHMI at week 28.

Arm type	Experimental
Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

50 µg R21/ Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at weeks 0 and 4 and 10 µg R21/ Matrix-M1 50 µg at week 24

Arm title	Group 5

Arm description:

10 µg R21/ Matrix-M1 50 µg administered at weeks 0 and 4 followed by receiving a dose of 2 µg R21/ Matrix-M1 50 µg at week 24. This group then underwent a sporozoite CHMI at week 28.

Arm type	Experimental
Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

R21 10 µg / Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at week 0 and 4 followed by R21 2 µg / Matrix-M1 50 µg at week 28.

Arm title	Group 6 and 7

Arm description:

Sporozoite (mosquito bite) CHMI groups serving as infectivity controls. No IMPs were administered in groups 6 and 7.

Arm type	CHMI

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Group 1a	Group 1b	Group 2a
Started	3	7	13
Completed	3	7	13
Not completed	0	0	0
Consent withdrawn by subject	-	-	-

Number of subjects in period 1	Group 2b	Group 3a	Group 3b
Started	3	16	2

Completed	3	15	1
Not completed	0	1	1
Consent withdrawn by subject	-	1	1

Number of subjects in period 1	Group 4a and b	Group 5	Group 6 and 7
Started	11	9	12
Completed	10	7	12
Not completed	1	2	0
Consent withdrawn by subject	1	2	-

Period 2

Period 2 title	Week 4
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1a

Arm description:

4 vaccinations of R21 10 µg / Matrix-M1 50 µg at weeks 0, 4, 8 and 60 with no CHMI

Arm type	Experimental
Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

R21 10 µg / Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at week 4

Arm title	Group 1b

Arm description:

4 vaccinations with 10 µg / Matrix-M1 50 µg at weeks 0, 4, 8 and 60. No CHMI.

Arm type	Experimental
Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

R21 10 µg / Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at week 4

Arm title	Group 2a

Arm description:

4 vaccinations of R21 10 µg / Matrix-M1 50 µg administered at weeks 0, 4, 24 and 56-80 with a sporozoite CHMI at week 28 followed by a repeat CHMI at 60-84 weeks.

Arm type	Experimental

Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

R21 10 µg / Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at week 4

Arm title	Group 2b

Arm description:

3 vaccinations of R21 10 µg / Matrix-M1 50 µg administered at weeks 0, 4 and 24. No CHMI.

Arm type	Experimental
Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

R21 10 µg / Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at week 4

Arm title	Group 3a

Arm description:

10 µg R21 in 50 µg Matrix-M1 adjuvant administered at weeks 0, 4, 8 and 40-64. A sporozoite CHMI took place at week 12 with a repeat CHMI at week 44-68.

Arm type	Experimental
Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

R21 10 µg / Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at week 4

Arm title	Group 3b

Arm description:

10 µg R21 in 50 µg Matrix M adjuvant administered at weeks 0, 4 and 8 with no CHMI

Arm type	Experimental
Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

R21 10 µg / Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at week 4

Arm title	Group 4a & b

Arm description:

50 µg of R21 in 50 µg Matrix-M1 adjuvant administered at weeks 0, and 4 followed by 10 µg R21 in 50 µg Matrix-M1 adjuvant at week 24 with a sporozoite CHMI at week 28.

Arm type	Experimental
Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

R21 50 µg / Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at week 4

Arm title	Group 5

Arm description:

10 µg R21/ Matrix-M1 50 µg administered at weeks 0 and 4 followed by receiving a dose of 2 µg R21/ Matrix-M1 50 µg at week 24. This group then underwent a sporozoite CHMI at week 28.

Arm type	Experimental
Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

R21 10 µg / Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at week 4

Number of subjects in period 2[1]	Group 1a	Group 1b	Group 2a
Started	3	7	13
Completed	3	7	13

Number of subjects in period 2[1]	Group 2b	Group 3a	Group 3b
Started	3	15	1
Completed	3	15	1

Number of subjects in period 2[1]	Group 4a & b	Group 5
Started	10	7
Completed	10	7

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Some time points at CHMI only

Period 3

Period 3 title	Week 8
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes

Arm title	Group 1a

Arm description:

4 vaccinations of R21 10 µg / Matrix-M1 50 µg at weeks 0, 4, 8 and 60 with no CHMI

Arm type	Experimental
Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

R21 10 µg / Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at week 0

Arm title	Group 1b

Arm description:

10µg R21 in 50µg Matrix M-1 adjuvant administered at weeks 0, 4, 8 and 60 with no CHMI (4-dose regimen).

Arm type	Experimental
Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

R21 10 µg / Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at week 8

Arm title	Group 3a

Arm description:

10 µg R21 in 50 µg Matrix-M1 adjuvant administered at weeks 0, 4, 8 and 40-64. A sporozoite CHMI took place at week 12 with a repeat CHMI at week 44-64.

Arm type	Experimental
Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

R21 10 µg / Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at week 8

Arm title	Group 3b

Arm description:

10 µg R21 in 50 µg Matrix-M1 adjuvant administered at weeks 0, 4, 8 and 40-64. A sporozoite CHMI took place at week 12 with a repeat CHMI at week 44-68.

Arm type	Experimental
Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

R21 10 µg / Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at week 0

Number of subjects in period 3[2]	Group 1a	Group 1b	Group 3a
Started	3	7	15
Completed	3	7	15

Number of subjects in period 3[2]	Group 3b
Started	1
Completed	1

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Some time points are CHMI only

Period 4

Period 4 title	Week 12
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Group 3a

Arm description:

10 µg R21 in 50 µg Matrix-M1 adjuvant administered at weeks 0, 4, 8 and 40-64. A sporozoite CHMI took place at week 12 with a repeat CHMI at week 44-64.

Arm type	Experimental
Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

R21 10 µg / Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at week 0, 4, 8 4--64

Number of subjects in period 4[3]	Group 3a
Started	15
Completed	15

Notes:

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Some time points are CHMI only

Period 5

Period 5 title	Week 24
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Group 2a

Arm description:

10 µg R21 in 50 µg Matrix-M1 adjuvant administered at weeks 0, 4, 24 and 56-80 with sporozoite CHMI (mosquito bites) at day 28 and 60-84. 4 dose regimen with 2 CHMI

Arm type	Experimental
Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

R21 10 µg / Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at week 24

Arm title	Group 2b

Arm description:

3 vaccinations of R21 10 µg / Matrix-M1 50 µg administered at weeks 0, 4 and 24. No CHMI.

Arm type	Experimental
Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

R21 10 µg / Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at week 24

Arm title	Group 4a & b

Arm description:

50 µg of R21 in 50 µg Matrix-M1 adjuvant administered at weeks 0, and 4 followed by 10 µg R21 in 50 µg Matrix-M1 adjuvant at week 24 with a sporozoite CHMI at week 28.

Arm type	Experimental
Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

R21 10 µg / Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at week 0

Arm title	Group 5

Arm description:

10 µg R21/ Matrix-M1 50 µg administered at weeks 0 and 4 followed by receiving a dose of 2 µg R21/ Matrix-M1 50 µg at week 24. This group then underwent a sporozoite CHMI at week 28

Arm type	Experimental

Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

R21 10 µg / Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at week 24

Number of subjects in period 5	Group 2a	Group 2b	Group 4a & b
Started	13	3	10
Completed	13	3	10

Number of subjects in period 5	Group 5
Started	7
Completed	7

Period 6

Period 6 title	Week 28
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 4a and 4b

Arm description:

50 µg of R21 in 50 µg Matrix-M1 adjuvant administered at weeks 0, and 4 followed by 10 µg R21 in 50 µg Matrix-M1 adjuvant at week 24 with a sporozoite CHMI at week 28.

Arm type	Experimental
Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

R21 10 µg / Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at week 0

Arm title	Group 2a

Arm description:

10 µg R21 in 50 µg Matrix-M1 adjuvant administered at weeks 0, 4, 24 and 56-80 with sporozoite CHMI (mosquito bites) at day 28 and 60-84. 4 dose regimen with 2 CHMI

Arm type	Experimental

Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

R21 10 µg / Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at week 0, 4, 24 and 56-80

Arm title	Group 5

Arm description:

10 µg R21/ Matrix-M1 50 µg administered at weeks 0 and 4 followed by receiving a dose of 2 µg R21/ Matrix-M1 50 µg at week 24. This group then underwent a sporozoite CHMI at week 28.

Arm type	Experimental
Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

R21 10 µg / Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at weeks 0, 4, 24.

Number of subjects in period 6	Group 4a and 4b	Group 2a	Group 5
Started	10	13	7
Completed	10	13	7

Period 7

Period 7 title	Week 60
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Group 1a

Arm description:

10 µg R21 in 50 µg Matrix-M1 adjuvant administered at week 0, 4, 8 and 60 (4-dose regimen) with no CHMI.

Arm type	Experimental

Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

R21 10 µg / Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at week 60

Arm title	Group 1b

Arm description:

10µg R21 in 50µg Matrix M-1 adjuvant administered at weeks 0, 4, 8 and 60 with no CHMI (4-dose regimen).

Arm type	Experimental
Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

R21 10 µg / Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at week 60

Number of subjects in period 7	Group 1a	Group 1b
Started	3	7
Completed	3	7

Period 8

Period 8 title	Week 40-64
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Group 3a

Arm description:

10 µg R21 in 50 µg Matrix-M1 adjuvant administered at weeks 0, 4, 8 and 40-64. A sporozoite CHMI took place at week 12 with a repeat CHMI at week 44-64. less

Arm type	Experimental
Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

R21 10 µg / Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at week 40-64

Number of subjects in period 8	Group 3a
Started	15
Completed	15

Period 9

Period 9 title	Week 44-68
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Group 3a

Arm description:

Repeat CHMI at week 44-64: 10 µg R21 in 50 µg Matrix-M1 adjuvant administered at weeks 0, 4, 8 and 40-64. A sporozoite CHMI took place at week 12 with the repeat CHMI at week 44-64.

Arm type	Experimental
Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

R21 10 µg / Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at week 44-64

Number of subjects in period 9	Group 3a
Started	15
Completed	15

Period 10

Period 10 title	Week 56-80
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Group 2a

Arm description:

10 µg R21 in 50 µg Matrix-M1 adjuvant administered at weeks 0, 4, 24 and 56-80 with sporozoite CHMI (mosquito bites) at day 28 and 60-84. 4 dose regimen with 2 CHMI

Arm type	Experimental
Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

R21 10 µg / Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at week 0

Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

R21 10 µg / Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at week 56-80

Number of subjects in period 10[4]	Group 2a
Started	13
Completed	13

Notes:

[4] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Some of the time points are CHMI

Period 11

Period 11 title	Week 64-84
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Group 2a

Arm description:

10 µg R21 in 50 µg Matrix-M1 adjuvant administered at weeks 0, 4, 24 and 56-80 with sporozoite CHMI (mosquito bites) at day 28 and 60-84. 4 dose regimen with 2 CHMI.

Arm type	Experimental
Investigational medicinal product name	R21 in adjuvant Matrix-M1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Repeat CHMI for Gp 3 at week 60-84. R21 10 µg / Matrix-M1 50 µg injected intramuscularly into the deltoid muscle of the arm at weeks 0, 4, 24 and 56-80.

Number of subjects in period 11	Group 2a
Started	13
Completed	13

Baseline characteristics

Reporting groups	
Reporting group title	Week 0

Reporting group description: -

Reporting group values	Week 0	Total	
Number of subjects	76	76	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	76	76	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	38	38	
Male	38	38	

End points

End points reporting groups

Reporting group title	Group 1a
Reporting group description:	
10 µg R21 in 50 µg Matrix-M1 adjuvant administered at week 0, 4, 8 and 60 (4-dose regimen) with no CHMI.	
Reporting group title	Group 1b
Reporting group description:	
10µg R21 in 50µg Matrix M-1 adjuvant administered at weeks 0, 4, 8 and 60 with no CHMI (4-dose regimen).	
Reporting group title	Group 2a
Reporting group description:	
10 µg R21 in 50 µg Matrix-M1 adjuvant administered at weeks 0, 4, 24 and 56-80 with sporozoite CHMI (mosquito bites) at day 28 and 60-84. 4 dose regimen with 2 CHMI	
Reporting group title	Group 2b
Reporting group description:	
10ug R21 in 20ug Matrix -M1 adjuvant administered at weeks 0, 4 and 24 with no CHMI	
Reporting group title	Group 3a
Reporting group description:	
10 µg R21 in 50 µg Matrix-M1 adjuvant administered at weeks 0, 4, 8 and 40-64. A sporozoite CHMI took place at week 12 with a repeat CHMI at week 44-64.	
Reporting group title	Group 3b
Reporting group description:	
10 µg R21 in 50 µg Matrix M adjuvant administered at weeks 0, 4 and 8 with no CHMI	
Reporting group title	Group 4a and b
Reporting group description:	
50 µg of R21 in 50 µg Matrix-M1 adjuvant administered at weeks 0, and 4 followed by 10 µg R21 in 50 µg Matrix-M1 adjuvant at week 24 with a sporozoite CHMI at week 28.	
Reporting group title	Group 5
Reporting group description:	
10 µg R21/ Matrix-M1 50 µg administered at weeks 0 and 4 followed by receiving a dose of 2 µg R21/ Matrix-M1 50 µg at week 24. This group then underwent a sporozoite CHMI at week 28.	
Reporting group title	Group 6 and 7
Reporting group description:	
Sporozoite (mosquito bite) CHMI groups serving as infectivity controls. No IMPs were administered in groups 6 and 7.	
Reporting group title	Group 1a
Reporting group description:	
4 vaccinations of R21 10 µg / Matrix-M1 50 µg at weeks 0, 4, 8 and 60 with no CHMI	
Reporting group title	Group 1b
Reporting group description:	
4 vaccinations with 10 µg / Matrix-M1 50 µg at weeks 0, 4, 8 and 60. No CHMI.	
Reporting group title	Group 2a
Reporting group description:	
4 vaccinations of R21 10 µg / Matrix-M1 50 µg administered at weeks 0, 4, 24 and 56-80 with a sporozoite CHMI at week 28 followed by a repeat CHMI at 60-84 weeks.	
Reporting group title	Group 2b
Reporting group description:	
3 vaccinations of R21 10 µg / Matrix-M1 50 µg administered at weeks 0, 4 and 24. No CHMI.	
Reporting group title	Group 3a

Reporting group description:

10 µg R21 in 50 µg Matrix-M1 adjuvant administered at weeks 0, 4, 8 and 40-64. A sporozoite CHMI took place at week 12 with a repeat CHMI at week 44-68.

Reporting group title	Group 3b

Reporting group description:

10 µg R21 in 50 µg Matrix M adjuvant administered at weeks 0, 4 and 8 with no CHMI

Reporting group title	Group 4a & b

Reporting group description:

50 µg of R21 in 50 µg Matrix-M1 adjuvant administered at weeks 0, and 4 followed by 10 µg R21 in 50 µg Matrix-M1 adjuvant at week 24 with a sporozoite CHMI at week 28.

Reporting group title	Group 5

Reporting group description:

10 µg R21/ Matrix-M1 50 µg administered at weeks 0 and 4 followed by receiving a dose of 2 µg R21/ Matrix-M1 50 µg at week 24. This group then underwent a sporozoite CHMI at week 28.

Reporting group title	Group 1a

Reporting group description:

4 vaccinations of R21 10 µg / Matrix-M1 50 µg at weeks 0, 4, 8 and 60 with no CHMI

Reporting group title	Group 1b

Reporting group description:

10µg R21 in 50µg Matrix M-1 adjuvant administered at weeks 0, 4, 8 and 60 with no CHMI (4-dose regimen).

Reporting group title	Group 3a

Reporting group description:

10 µg R21 in 50 µg Matrix-M1 adjuvant administered at weeks 0, 4, 8 and 40-64. A sporozoite CHMI took place at week 12 with a repeat CHMI at week 44-64.

Reporting group title	Group 3b

Reporting group description:

10 µg R21 in 50 µg Matrix-M1 adjuvant administered at weeks 0, 4, 8 and 40-64. A sporozoite CHMI took place at week 12 with a repeat CHMI at week 44-68.

Reporting group title	Group 3a

Reporting group description:

10 µg R21 in 50 µg Matrix-M1 adjuvant administered at weeks 0, 4, 8 and 40-64. A sporozoite CHMI took place at week 12 with a repeat CHMI at week 44-64.

Reporting group title	Group 2a

Reporting group description:

10 µg R21 in 50 µg Matrix-M1 adjuvant administered at weeks 0, 4, 24 and 56-80 with sporozoite CHMI (mosquito bites) at day 28 and 60-84. 4 dose regimen with 2 CHMI

Reporting group title	Group 2b

Reporting group description:

3 vaccinations of R21 10 µg / Matrix-M1 50 µg administered at weeks 0, 4 and 24. No CHMI.

Reporting group title	Group 4a & b

Reporting group description:

50 µg of R21 in 50 µg Matrix-M1 adjuvant administered at weeks 0, and 4 followed by 10 µg R21 in 50 µg Matrix-M1 adjuvant at week 24 with a sporozoite CHMI at week 28.

Reporting group title	Group 5

Reporting group description:

10 µg R21/ Matrix-M1 50 µg administered at weeks 0 and 4 followed by receiving a dose of 2 µg R21/ Matrix-M1 50 µg at week 24. This group then underwent a sporozoite CHMI at week 28

Reporting group title	Group 4a and 4b

Reporting group description:

50 µg of R21 in 50 µg Matrix-M1 adjuvant administered at weeks 0, and 4 followed by 10 µg R21 in 50 µg Matrix-M1 adjuvant at week 24 with a sporozoite CHMI at week 28.

Reporting group title	Group 2a

Reporting group description:

10 µg R21 in 50 µg Matrix-M1 adjuvant administered at weeks 0, 4, 24 and 56-80 with sporozoite CHMI (mosquito bites) at day 28 and 60-84. 4 dose regimen with 2 CHMI

Reporting group title	Group 5

Reporting group description:

10 µg R21/ Matrix-M1 50 µg administered at weeks 0 and 4 followed by receiving a dose of 2 µg R21/ Matrix-M1 50 µg at week 24. This group then underwent a sporozoite CHMI at week 28.

Reporting group title	Group 1a

Reporting group description:

10 µg R21 in 50 µg Matrix-M1 adjuvant administered at week 0, 4, 8 and 60 (4-dose regimen) with no CHMI.

Reporting group title	Group 1b

Reporting group description:

10µg R21 in 50µg Matrix M-1 adjuvant administered at weeks 0, 4, 8 and 60 with no CHMI (4-dose regimen).

Reporting group title	Group 3a

Reporting group description:

10 µg R21 in 50 µg Matrix-M1 adjuvant administered at weeks 0, 4, 8 and 40-64. A sporozoite CHMI took place at week 12 with a repeat CHMI at week 44-64. less

Reporting group title	Group 3a

Reporting group description:

Repeat CHMI at week 44-64: 10 µg R21 in 50 µg Matrix-M1 adjuvant administered at weeks 0, 4, 8 and 40-64. A sporozoite CHMI took place at week 12 with the repeat CHMI at week 44-64.

Reporting group title	Group 2a

Reporting group description:

10 µg R21 in 50 µg Matrix-M1 adjuvant administered at weeks 0, 4, 24 and 56-80 with sporozoite CHMI (mosquito bites) at day 28 and 60-84. 4 dose regimen with 2 CHMI

Reporting group title	Group 2a

Reporting group description:

10 µg R21 in 50 µg Matrix-M1 adjuvant administered at weeks 0, 4, 24 and 56-80 with sporozoite CHMI (mosquito bites) at day 28 and 60-84. 4 dose regimen with 2 CHMI.

Primary: To assess the safety and tolerability of adjuvanted R21 using different immunisation schedules in healthy malaria-naïve volunteers

End point title	To assess the safety and tolerability of adjuvanted R21 using different immunisation schedules in healthy malaria-naïve volunteers[1]

End point description:

Due to the confidential nature of this data, we have not provided this analysis at this time. The scientific paper can be uploaded following publication, if required.

End point type	Primary

End point timeframe:

All solicited local & systemic reactogenicity signs and symptoms for 7 days after vaccination. All unsolicited AEs for 28 days after vaccination. Change from day 0 (baseline) to day 28 for safety laboratory measures. SAEs were collected during whole study

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the confidential nature of this information, we have not provided this analysis at this time. The scientific paper containing the final analysis can be uploaded following publication if required.

End point values	Group 1a	Group 1b	Group 2a	Group 2b
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	7	13	3
Units: number of participants	3	7	13	3

End point values	Group 3a	Group 3b	Group 4a and b	Group 5
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	2	11	9
Units: number of participants	16	2	11	9

End point values	Group 6 and 7			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: number of participants	12			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

All AEs occurring in the 28 days following each vaccination collected from diary cards, clinical review, clinical examination, laboratory results, or reported by the volunteer, whether or not attributed to study medication.

Adverse event reporting additional description:

All AEs occurring in the 28 days following each vaccination observed by the Investigator or reported by the volunteer, whether or not attributed to study medication, are recorded. Recording and reporting of all AEs will take place as detailed in SOP VC027. SAEs are collected throughout the entire trial period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

Reporting groups

Reporting group title	Group 3a

Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Due to the confidential nature of this information, we have not provided this analysis at this time. The scientific paper containing the final analysis of all of the endpoints can be uploaded following publication if required.

Serious adverse events	Group 3a		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 16 (6.25%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Musculoskeletal and connective tissue disorders			
Wrist fracture injury	Additional description: There was one serious adverse event (SAE) deemed as not related to vaccination (Gp 3a). This was a left wrist fracture that occurred in a participant two months following their third vaccination after a sports injury, requiring surgical intervention		
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Group 3a		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 August 2019	Request to extend the shelf life of R21 to 18 months
06 September 2019	Change of conduct/management of the trial: 1. Groups are now sub-divided with a new naming scheme for clarity in understanding and documentation during the trial. 2. Vaccination time point intervals have been shortened and windows have also been increased due to further scientific consideration of optimum dosing intervals. 3. Compensation amounts updated to reflect the new visit schedules. 4. Advertising materials have been updated 5. Collection of GP records has been clarified. 6. R21 storage details have been updated in the trial protocol following recommendations from the manufacturer. 7. Blood films are no longer required for diagnosis following validation of qPCR 8. Text has been added to the protocol clarifying university of oxford intellectual property terms. 9. R21 IB has been updated (reference safety information now refers exclusively to SARs, formulation and storage of R21 has been updated). 10. Consent form amended to a generic version that can be used at sites other than Oxford 11. Wording changed in PIS regarding malaria diagnosis from "two negative malaria tests" to "malaria tests showing a significant decrease in parasites" for increased clarity 12. To avoid the possibility of discrepancies: one original consent form will now be signed by volunteers and investigators, with this then being subsequently photocopied and provided to the volunteer, rather than two originals. 13. For harmonisation purposes, screening windows have now been shortened to 3 months from 6 months 14. The local safety committee chairman will be re-designated as the local safety monitor “LSM”. 15a. Various changes to visits have been made throughout the protocol. 17. Safety section of the protocol has been updated to remove reference to adverse events of special interest. We are collecting the usual AEs that we always collect in our vaccine trials at the Jenner institute and for the same duration of time.

01 November 2019	Change in conduct of trial: 1. The window of vaccination 3 for Group 2a and 2b has been increased. It now has a -35 day window. This is because from recent research presented, showing better immunogenicity and efficacy with a delayed third vaccine dose, time points used by the 2 research groups have varied between 4.5 months and 7 months after first vaccination (NCT03906474). Therefore it is unknown when exactly the best time to give the third dose is. By extending this window and reducing the time between 2nd and 3rd dose, we are giving a wider range for the time he third dose can be given and falls in to the range of 4.5-7 months. This also helps facilitate timelines with CHMI. We have not changed the PIS to reflect this as no windows on vaccinations are mentioned in the PIS and also, at the time of screening, consent and enrolment, the volunteers were informed about this research and the possibility of the window on vaccination 3 changing. 2. In the procedures table, 'diary card completed' row has been amended so that in every group, this check is done 28 days post each vaccination. 3. In section 7.1.4, a correction has been made. There has been no change to dosing regimen. The groups mentioned for vaccination were Groups 1-3 when it should have been Groups 1-5. 4. In section 9.4.9, clarification if volunteer has extra clinical review, qPCR will be performed. This will be performed instead of thick film microscopy in view of qPCR now being a validated assay and our experience in other CHMI trials where qPCR has diagnosed malaria earlier than microscopy. 5. The diary given to volunteers post CHMI has now been converted to an electronic format. While the paper diary will still be there as a back-up, in the first instance, volunteers will be asked to record these details electronically now, similar to what they do post vaccinations.
16 December 2019	Change in conduct of trial and change of PI: 1) In the last 3 CHMI trials conducted at the Jenner Institute (VAC 065a, VAC 065b and VAC 066), 1 control volunteer in each trial who underwent CHMI did not become infected with malaria. However, when looking at biting and infectivity records, these do not seem to differ from other volunteers who have undergone CHMI and have become infected. In view of this, we leave open now the option to increase the number of volunteers, should suitable volunteers be available, from 6 to 8 subjects in Groups 6 and 7 to gain more power in showing adequate malaria infection in control volunteers to be able to make suitable comparisons to vaccination groups when determining efficacy. 2) We have increased the group number sizes for Groups 4b and 5. These groups are testing the safety and immunogenicity of delayed, fractional dosing and with Group 4b, a higher dose of R21 compared to the rest of the trial. We feel it would be beneficial to have larger numbers in these groups to gain more data on these dosing regimes to help us decide if these regimes are justified to proceed into efficacy trials against CHMI. 3) The PI at NIHR Imperial College has changed from Prof David Lewis to Dr Katrina Pollock as Prof Lewis is retiring.

17 June 2020	1. Group 1: optional booster vaccine approximately 60 weeks after the first vaccination with immunology follow up. During RTS,S/AS01B efficacy trials, increased efficacy was seen following a fourth vaccine. Given this finding, we plan to assess the immunological effect of a booster vaccine. 2. Group 2a and 3a: For volunteers demonstrating sterile protection in the first challenge a) optional booster vaccine (rationale as above) AND/OR b) long term immunology follow up to assess durability of immunogenicity. As per previous protocol, all protected volunteers will be invited back for a re-challenge. The booster vaccination will be timed to occur prior to the re-challenge. Volunteers will have the choice if they want a booster vaccination or not or if they just want to have the re-challenge. 3. Group 4 and 5: optional CHMI To test efficacy (protection from P. falciparum) of delayed dose regimes and compare efficacy between regimes. The window on this third, delayed fractional dose has been increased. This is because from the unpublished studies but recent research presented, showing better immunogenicity and efficacy with a delayed third vaccine dose, time points used by the 2 research groups have varied between 4.5 months and 7 months after first vaccination (NCT03906474). Therefore, it is unknown when exactly the best time to give the third dose is. By extending this window and reducing the time between 2nd and 3rd dose, we are giving a wider range for the time the third dose can be given, and falls in to the range of 4-9 months. 4. Clarification of challenge arrangements 5.Timing of re-challenge and booster vaccinations for protected volunteers in Groups 2a and 3a
04 September 2020	1. Additional measures taking place in view of COVID-19. These include social distancing practises in clinical areas/use of PPE/adhering to PHE guidance for isolation rules and testing/what will happen in the event of a fever post vaccination or malaria challenge. 2. Windows on vaccinations for all groups have been increased. These include booster vaccinations for Groups 1/2/3, or 3rd vaccination for Groups 4/5, and all follow-up visits. This is in view of participants potentially self- isolating or if they are unable to travel to us. Telephone assessments will still take place over this period to ensure safety. • When ECGs will be performed for Groups 4/5 have been clarified in these tables also as these are needed prior to malaria challenge and can occur at any vaccination visit. • COVID-19 swab necessary at the day before the challenge to ensure that the participant does not have COVID-19 when we are giving them malaria. 3. Change of malaria diagnosis endpoint. This is to ensure diagnosis as early as possible to reduce number of clinic visits. 4. Change in follow up time post malaria challenge. This again is reduced to ensure there are less clinic visits. This will still be safe as we are diagnosing malaria at a lower parasite threshold and everyone is treated with antimalarials at the end of follow-up, regardless of if they are protected or not. 5. Clarification of treatment of malaria so Riamet and Malarone are both first-line options. 6. Compensation and blood volumes adjusted to reflect these changes. 7. Reporting of positive SARS-CoV-2 test results, as required by law.• In this case, the result and personal data (including volunteer name, contact details, and postcode) will be shared in a secure manner with Public Health England for referral to the NHS Test and Trace system.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported