



Clinical trial results:

A Phase I/IIa clinical trial to assess the safety, immunogenicity and efficacy of the blood-stage Plasmodium vivax malaria vaccine candidate PvDBPII in Matrix M1 in healthy adults living in the UK

Summary

EudraCT number	2019-002872-14
Trial protocol	GB
Global end of trial date	14 July 2022

Results information

Result version number	v1 (current)
This version publication date	11 October 2022
First version publication date	11 October 2022
Summary attachment (see zip file)	Impact of a blood-stage vaccine on Plasmodium vivax malaria (Hou et al vivax paper.pdf)

Trial information

Trial identification

Sponsor protocol code	VAC079
-----------------------	--------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04201431
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	Old Road, Oxford , United Kingdom, OX3 7LE
Public contact	Angela Minassian, University of Oxford, +44 01865611425, angela.minassian@ndm.ox.ac.uk
Scientific contact	Angela Minassian, University of Oxford, +44 01865611425, angela.minassian@ndm.ox.ac.uk

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	02 September 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 July 2022
Global end of trial reached?	Yes
Global end of trial date	14 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and efficacy of the PvDBPII in Matrix M1 vaccine

Protection of trial subjects:

Volunteers given at least 24 hours to read PIS before being seen and then given plenty of opportunity to ask questions prior to agreeing to take part in a study.

Volunteers completed a questionnaire testing their understanding of the trial as part of the consent process to ensure that individuals understand the trial sufficiently to give informed consent.

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.

Volunteers observed for 1 hour after vaccination to monitor for any immediate adverse effects.

Inclusion of AE related safety stopping/holding rules at both a group and individual level in the protocol.

Volunteers given emergency contact card detailing that they have been infected with malaria.

Volunteers seen once to twice daily during malaria challenge with measurement of parasitaemia at which visit

Malaria treated promptly when diagnosed with highly efficacious medication and at least half of doses directly observed.

Volunteers provided with symptomatic treatment (antipyretic/analgesic and antiemetic) in case of malaria symptoms.

Volunteers who remained undiagnosed with malaria at Day 21 given a treatment course of anti-malarials.

Volunteers followed up until at least 2 consecutive qPCR results with substantial reduction in genome copies/mL.

Total blood volume taken during study kept to volume that should not compromise healthy volunteers.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 October 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: 16
Worldwide total number of subjects	16
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)	16
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Volunteers were recruited by use of advertisements, formally approved by the ethics committee, distributed or posted in public places (including newspapers, social media, stalls at fairs and public transport) or via email distribution, including to individuals who have registered an interest in taking part in clinical trials at the study sites.

Pre-assignment

Screening details:

Screening visit consisted of Informed Consent, Informed Consent Questionnaire, Medical History, Physical Observations, Physical Examination, Urinalysis, Electrocardiogram, beta-HCG urine (women only), blood tests (HBV, HCV, HIV, EBV, CMV, Haematology, Biochemistry, DARC, G6PD). Review of screening visit results against inclusion/exclusion criteria.

Period 1

Period 1 title	Vaccinations and primary CHMI
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1

Arm description:

Three doses of candidate vaccine 50ug PvDBPII in 50ug Matrix-M adjuvant at 0, 1 and 12-18 months prior to blood-stage CHMI 2-4 weeks after the third vaccination.

Arm type	Experimental
Investigational medicinal product name	PvDBPII vaccine with Matrix-M adjuvant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Three doses of 50ug PvDBPII mixed with 50ug Matrix-M adjuvant given intramuscularly at 0, 1 and 12-18 months

Arm title	Group 2
-----------	---------

Arm description:

Three doses of candidate vaccine 50ug PvDBPII in 50ug Matrix-M adjuvant at 0, 1 and 2 months prior to blood-stage CHMI 2-4 weeks after the third vaccination.

Arm type	Experimental
Investigational medicinal product name	PvDBPII vaccine with Matrix-M adjuvant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Three doses of 50ug PvDBPII mixed with 50ug Matrix-M adjuvant given intramuscularly at 0, 1 and 2 months

Number of subjects in period 1	Group 1	Group 2
Started	12	4
Primary CHMI	6	4
Completed	6	4
Not completed	6	0
Consent withdrawn by subject	6	-

Period 2

Period 2 title	4th vaccination and secondary CHMI
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Group 3
Arm description:	
Subset of Group 1 volunteers who received a fourth dose of PvDBPII 50ug/Matrix M 50ug, at 5 months post the third dose, prior to a second CHMI 2-4 weeks later.	
Arm type	Experimental
Investigational medicinal product name	PvDBPII vaccine with Matrix-M adjuvant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Fourth dose of 50ug PvDBPII mixed with 50ug Matrix-M adjuvant given intramuscularly 19 months (5 months after third vaccination)

Number of subjects in period 2 ^[1]	Group 3
Started	5
Completed	5

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: This period applies to Group 3 volunteers only, who are a subset of Group 1 volunteers. Group 1 volunteers who complete 3 vaccinations and primary CHMI and subsequently consented to receive a 4th vaccination and secondary CHMI were reassigned to Group 3.

Baseline characteristics

Reporting groups

Reporting group title	Group 1
-----------------------	---------

Reporting group description:

Three doses of candidate vaccine 50ug PvDBPII in 50ug Matrix-M adjuvant at 0, 1 and 12-18 months prior to blood-stage CHMI 2-4 weeks after the third vaccination.

Reporting group title	Group 2
-----------------------	---------

Reporting group description:

Three doses of candidate vaccine 50ug PvDBPII in 50ug Matrix-M adjuvant at 0, 1 and 2 months prior to blood-stage CHMI 2-4 weeks after the third vaccination.

Reporting group values	Group 1	Group 2	Total
Number of subjects	12	4	16
Age categorical			
Units: Subjects			
Adults (18-64 years)	12	4	16
Age continuous			
Units: years			
arithmetic mean	30	34	
full range (min-max)	19 to 44	27 to 39	-
Gender categorical			
Units: Subjects			
Female	10	2	12
Male	2	2	4

End points

End points reporting groups

Reporting group title	Group 1
Reporting group description: Three doses of candidate vaccine 50ug PvDBPII in 50ug Matrix-M adjuvant at 0, 1 and 12-18 months prior to blood-stage CHMI 2-4 weeks after the third vaccination.	
Reporting group title	Group 2
Reporting group description: Three doses of candidate vaccine 50ug PvDBPII in 50ug Matrix-M adjuvant at 0, 1 and 2 months prior to blood-stage CHMI 2-4 weeks after the third vaccination.	
Reporting group title	Group 3
Reporting group description: Subset of Group 1 volunteers who received a fourth dose of PvDBPII 50ug/Matrix M 50ug, at 5 months post the third dose, prior to a second CHMI 2-4 weeks later.	

Primary: To assess the safety and tolerability of the PvDBPII vaccine formulated in Matrix M1

End point title	To assess the safety and tolerability of the PvDBPII vaccine formulated in Matrix M1 ^[1]
End point description: Occurrence of solicited local and systemic reactogenicity for 7 days following each vaccination; unsolicited adverse events and laboratory adverse events for 28 days following each vaccination; serious adverse events during the whole study duration	
End point type	Primary
End point timeframe: Study duration	
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: No statistical analyses were specified in the protocol for the safety data and no comparisons are made. Analysis of safety data is descriptive only.	

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	4	5	
Units: Number of participants				
Serious adverse events	0	0	0	
Grade 3 adverse event	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: To establish whether the PvDBPII-Matrix M1 vaccine can demonstrate a reduced parasite multiplication rate in vaccinated subjects compared to infectivity controls in a blood-stage controlled human malaria infection model

End point title	To establish whether the PvDBPII-Matrix M1 vaccine can demonstrate a reduced parasite multiplication rate in
-----------------	--

vaccinated subjects compared to infectivity controls in a blood-stage controlled human malaria infection model
--

End point description:

Assessed by quantitative PCR-derived parasite multiplication rate (PMR). The PMR of the volunteers vaccinated with PvDBPII-Matrix M1 will be compared to the PMR of the malaria-naïve controls partaking in parallel CHMI.

End point type	Primary
----------------	---------

End point timeframe:

From day of controlled human malaria infection up to commencement of antimalarial treatment

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	4	5	
Units: parasite multiplication rate per 48hr				
median (full range (min-max))	3.2 (2.3 to 4.3)	6.3 (5.1 to 7.9)	4.3 (3.7 to 5.5)	

Statistical analyses

Statistical analysis title	Comparison of PMR between vaccinees and controls
-----------------------------------	--

Statistical analysis description:

Comparison of parasite multiplication rate in vaccinated subjects compared to infectivity controls in a blood-stage controlled human malaria infection model

Comparison groups	Group 1 v Group 2
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	other ^[2]
P-value	= 0.01 ^[3]
Method	Wilcoxon (Mann-Whitney)

Notes:

[2] - Comparison of pooled data from Groups 1 and 2 volunteers who completed primary CHMI with pooled data of infectivity controls from CHMI study running in parallel (VAC069 study, n=13 participants, median PMR 6.8 fold per 48hr)

[3] - Two tailed p value reported for Mann-Whitney test comparing infectivity controls with vaccinees

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Data on solicited adverse events were collected for 7 days after vaccinated and unsolicited adverse events for 28 days post-vaccination. Serious adverse events were collected for the study duration.

Adverse event reporting additional description:

Following each vaccination, volunteers completed an electronic diary card for 28 days with adverse event data. Solicited AEs, collected for 7 days, included local AEs (pain, erythema, warmth, swelling and itching) and systemic AEs (headache, malaise, myalgia, arthralgia, feverishness, nausea, fatigue, and measured fever

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Group 1
-----------------------	---------

Reporting group description:

Three doses of candidate vaccine 50ug PvDBPII in 50ug Matrix-M adjuvant at 0, 1 and 12-18 months prior to blood-stage CHMI 2-4 weeks after the third vaccination.

Reporting group title	Group 2
-----------------------	---------

Reporting group description:

Three doses of candidate vaccine 50ug PvDBPII in 50ug Matrix-M adjuvant at 0, 1 and 2 months prior to blood-stage CHMI 2-4 weeks after the third vaccination.

Serious adverse events	Group 1	Group 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 4 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Group 1	Group 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 12 (66.67%)	3 / 4 (75.00%)	
Nervous system disorders			
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 12 (41.67%)	2 / 4 (50.00%)	
occurrences (all)	5	2	
General disorders and administration			

site conditions Fatigue alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	3 / 12 (25.00%) 3	2 / 4 (50.00%) 2	
Musculoskeletal and connective tissue disorders Back pain alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	3 / 12 (25.00%) 3	0 / 4 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 November 2019	Revision of accepted methods of contraception for women of child bearing potential to include highly effective methods only. Clarification of requirement for female participants using hormonal contraceptive methods to use an additional form of contraceptive until the next menstrual period, following initiation of treatment with artemether/lumefantrine
02 March 2020	Exclusion criteria relating to prior immunoglobulin exposure amended. Removal of thick blood film as diagnostic measure during CHMI. Updates and corrections to schedule of visits and bleed volumes, including reduction of maximal blood draw. Addition of timing windows for recording physical observations on day of challenge. Clarifications to collection of adverse event data. Potential for use of alternative antiemetic to cyclizine. Change to group sizes (target range now specified) and removal of back up volunteers. Clarification regarding timing of screening visits and for re-screening procedures for participants screened >90 days prior to enrolment. CRP added as an exploratory measure. Local safety monitor takes on role previously taken by local safety committee. Additional wording in the protocol and PIS to clarify the repeat screening for blood-borne infection at day 96 post challenge.
25 November 2020	Change of vaccination schedule for group 1 - delay of 3rd vaccination due to temporary trial halt. Addition of Group 2, to be recruited if fewer than 6 participants complete the study in Group 1. Addition of serum bhCG to C+28/day of malaria diagnosis. Clarification that G6PD, DARC and haemoglobinopathy screen are only done at NHS labs. Extension of time window for study visits. Changes to trial procedures to account for possibility of COVID-19 infection during CHMI. Addition of COVID-19 PCR swab test prior to challenge and on day of malaria diagnosis. Guidance on testing for COVID-19 if fever post vaccination and post challenge. Added option of using Malarone as first line anti-malaria treatment. Correction of typographical errors. Removal of measurement of T cell responses to PvDBPII by ELISpot from Secondary Immunological Outcome Measures. Correction of error in calculation of total blood volumes in schedule of attendance table. Addition of retrospective COVID-19 serology testing for exploratory analysis of effects of COVID serostatus on vaccine immunogenicity.
25 January 2021	Clarification of exclusion criteria regarding concomitant vaccinations and addition of specific criteria relating to licensed COVID-19 vaccination. Addition of section on administration of concomitant COVID-19 vaccination. Extension of time window for 2nd and 3rd vaccinations. Threshold at which new participants are recruited into Group 2 amended to if less than 8 participants complete study in Group 1 (previously less than 6 participants).
11 March 2021	Addition of exclusion criteria on concomitant COVID-19 vaccination around time of CHMI. Shortened time window of when COVID-19 vaccination can be given following malaria vaccination to aid scheduling of COVID-19 vaccinations. Updated section on Conduct of CHMI in the context of COVID-19 pandemic. Removal of specific timeframe during which baseline observations are taken pre-challenge. Correction of blood volume taken for HLA and total blood volumes.

26 July 2021	Addition of Group 3, comprising a subset of volunteers originally in Group 1, who consent to undergo a 4th vaccination and secondary CHMI. Addition of secondary objective to assess vaccine efficacy in Group 3. For Groups 2 and 3 - post-challenge follow-up visits changed to once a day until parasite count reaches >1000 genome copies/ml, then to continue twice a day visits until diagnosis. Latest day of treatment reduced to C+21. For Groups 2 and 3 - change of post malaria treatment visit from T+2 to T+3. Reduction in number of observed doses of antimalarial medication to two observed doses. For Group 2 – addition of immunology bleed at D42. Updated compensation table. Correction of error in lumefantrine dose in section 8.5.5. Addition of reticulocyte count to FBC taken at C-2 visit. Removal of need to collect unused medications after completion of challenge. Correction under C+56 visit – no collection of any diaries occur at this timepoint. Correction of errors in protocol – only weight taken at C-2 visit. No CRPs are taken during post-challenge followup. Changed Senior Laboratory Investigator address. Addition of New Biochemistry Building as location for processing of research bloods.
21 June 2022	Samples will now be stored long term under University of Oxford's HTA license at Department of Biochemistry instead of Oxford Vaccine Centre Biobank.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
27 March 2020	Temporary trial halt due to Covid-19 pandemic.	21 January 2021

Notes:

Limitations and caveats

None reported