



Clinical trial results:

A Phase IIa challenge study to assess efficacy of the Plasmodium vivax malaria vaccine candidates ChAd63 PvDBP and MVA PvDBP in healthy adults living in the UK

Summary

EudraCT number	2019-000643-27
Trial protocol	GB
Global end of trial date	07 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	VAC071
-----------------------	--------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04009096
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 01865611338, angela.minassian@ndm.ox.ac.uk
Scientific contact	Angela Minassian, University of Oxford, +44 01865611338, 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	Interim
Date of interim/final analysis	02 September 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 July 2022
Global end of trial reached?	Yes
Global end of trial date	07 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess efficacy of the ChAd63 and MVA PvDBP vaccines, administered in a heterologous prime-boost regimen, as assessed by a reduced parasite multiplication rate in vaccinated subjects following a blood-stage parasite inoculum

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	01 May 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	0

wk	
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	Overall trial (overall period)
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:

Volunteers receiving 5×10^{10} vp ChAd63 PvDBP and 2×10^8 pfu MVA PvDBP 8 weeks later, in a heterologous prime-boost regimen, followed by blood-stage CHMI 2-4 weeks later.

Arm type	Experimental
Investigational medicinal product name	ChAd63 PvDBP
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

5×10^{10} vp ChAd63 PvDBP given at day 0

Investigational medicinal product name	MVA PvDBP
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

2×10^8 pfu MVA PvDBP given at 8 weeks after ChAd63 PvDBP

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

Arm description:

Volunteers receiving one dose of 5×10^{10} vp ChAd63 PvDBP, 12-18 months later receiving a second dose of 5×10^{10} vp ChAd63 PvDBP and 8 weeks later 2×10^8 pfu MVA PvDBP, followed by blood-stage CHMI 2-4 weeks later.

Arm type	Experimental
Investigational medicinal product name	ChAd63 PvDBP
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:	
5 x 10 ¹⁰ vp ChAd63 PvDBP given at day 0, second dose of 5 x 10 ¹⁰ vp ChAd63 PvDBP given at 12-18 months	
Investigational medicinal product name	MVA PvDBP
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
2 x 10 ⁸ pfu MVA PvDBP given 8 weeks after the second dose of ChAd63 PvDBP	
Arm title	Group 3
Arm description:	
Volunteers receiving 5 x 10 ¹⁰ vp ChAd63 PvDBP and 2 x10 ⁸ pfu MVA PvDBP 8 weeks later, in a heterologous prime-boost regimen, followed by blood-stage CHMI 2-4 weeks later.	
Arm type	Experimental
Investigational medicinal product name	ChAd63 PvDBP
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
5 x 10 ¹⁰ vp ChAd63 PvDBP given at day 0	
Investigational medicinal product name	MVA PvDBP
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
2 x 10 ⁸ pfu MVA PvDBP given at 8 weeks after ChAd63 PvDBP	

Number of subjects in period 1	Group 1	Group 2	Group 3
Started	3	10	3
Primary CHMI	3	2	3
Completed	3	2	3
Not completed	0	8	0
Consent withdrawn by subject	-	7	-
Physician decision	-	1	-

Baseline characteristics

Reporting groups

Reporting group title	Group 1
Reporting group description: Volunteers receiving 5 x 10 ¹⁰ vp ChAd63 PvDBP and 2 x 10 ⁸ pfu MVA PvDBP 8 weeks later, in a heterologous prime-boost regimen, followed by blood-stage CHMI 2-4 weeks later.	
Reporting group title	Group 2
Reporting group description: Volunteers receiving one dose of 5 x 10 ¹⁰ vp ChAd63 PvDBP, 12-18 months later receiving a second dose of 5 x 10 ¹⁰ vp ChAd63 PvDBP and 8 weeks later 2 x 10 ⁸ pfu MVA PvDBP, followed by blood-stage CHMI 2-4 weeks later.	
Reporting group title	Group 3
Reporting group description: Volunteers receiving 5 x 10 ¹⁰ vp ChAd63 PvDBP and 2 x 10 ⁸ pfu MVA PvDBP 8 weeks later, in a heterologous prime-boost regimen, followed by blood-stage CHMI 2-4 weeks later.	

Reporting group values	Group 1	Group 2	Group 3
Number of subjects	3	10	3
Age categorical Units: Subjects			
Adults (18-64 years)	3	10	3
Age continuous Units: years arithmetic mean full range (min-max)	32 29 to 38	28 20 to 44	25 21 to 29
Gender categorical Units: Subjects			
Female	2	4	1
Male	1	6	2

Reporting group values	Total		
Number of subjects	16		
Age categorical Units: Subjects			
Adults (18-64 years)	16		
Age continuous Units: years arithmetic mean full range (min-max)	-		
Gender categorical Units: Subjects			
Female	7		
Male	9		

End points

End points reporting groups

Reporting group title	Group 1
Reporting group description: Volunteers receiving 5×10^{10} vp ChAd63 PvDBP and 2×10^8 pfu MVA PvDBP 8 weeks later, in a heterologous prime-boost regimen, followed by blood-stage CHMI 2-4 weeks later.	
Reporting group title	Group 2
Reporting group description: Volunteers receiving one dose of 5×10^{10} vp ChAd63 PvDBP, 12-18 months later receiving a second dose of 5×10^{10} vp ChAd63 PvDBP and 8 weeks later 2×10^8 pfu MVA PvDBP, followed by blood-stage CHMI 2-4 weeks later.	
Reporting group title	Group 3
Reporting group description: Volunteers receiving 5×10^{10} vp ChAd63 PvDBP and 2×10^8 pfu MVA PvDBP 8 weeks later, in a heterologous prime-boost regimen, followed by blood-stage CHMI 2-4 weeks later.	
Subject analysis set title	Groups 1, 2 and 3
Subject analysis set type	Full analysis
Subject analysis set description: Pooled data of all Group 1, 2 and 3 volunteers	
Subject analysis set title	Controls
Subject analysis set type	Full analysis
Subject analysis set description: Infectivity controls from VAC069 study	

Primary: Efficacy of the ChAd63 and MVA PvDBP vaccines, administered in a heterologous prime-boost regimen, assessed by a reduced parasite multiplication rate in vaccinated subjects

End point title	Efficacy of the ChAd63 and MVA PvDBP vaccines, administered in a heterologous prime-boost regimen, assessed by a reduced parasite multiplication rate in vaccinated subjects
End point description: Quantitative PCR-derived parasite multiplication rate (PMR) will be the primary efficacy endpoint and a comparison of the endpoint between vaccinees and malaria-naïve controls partaking in simultaneous CHMI, under identical conditions, will constitute the primary analysis for efficacy.	
End point type	Primary
End point timeframe: From day of controlled human malaria infection up to commencement of antimalarial treatment	

End point values	Groups 1, 2 and 3	Controls		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8 ^[1]	13		
Units: parasite multiplication rate per 48hr				
median (full range (min-max))	5.4 (4.0 to 7.3)	6.8 (4.0 to 11.1)		

Notes:

[1] - Only volunteers who underwent CHMI are included in this analysis

Statistical analyses

Statistical analysis title	Comparison of PMR between vaccinees and controls
Statistical analysis description: Comparison of pooled data from Groups 1, 2 and 3 volunteers who completed CHMI with pooled data of infectivity controls (unvaccinated) from CHMI study running in parallel (VAC069 study)	
Comparison groups	Controls v Groups 1, 2 and 3
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other ^[2]
P-value	= 0.14 ^[3]
Method	Wilcoxon (Mann-Whitney)

Notes:

[2] - Test for significant difference between vaccinees and controls

[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	Following ChAd63 PvDBP vaccination
-----------------------	------------------------------------

Reporting group description:

Volunteers who received at least one dose of ChAd63 PvDBP

Reporting group title	Following MVA PvDBP vaccination
-----------------------	---------------------------------

Reporting group description:

Volunteers who received vaccination with MVA PvDBP

Serious adverse events	Following ChAd63 PvDBP vaccination	Following MVA PvDBP vaccination	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 8 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Following ChAd63 PvDBP vaccination	Following MVA PvDBP vaccination	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 16 (12.50%)	0 / 8 (0.00%)	
Reproductive system and breast disorders			
Dysmenorrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 16 (12.50%)	0 / 8 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 April 2019	Addition of safety data from the VAC069 study. Addition of stopping and holding rules. Removal of barrier methods of contraception as an acceptable form of effective contraception, where used as the sole contraceptive. Addition of information relating to concomitant medications. Addition of exclusion criterion regarding receipt of licensed vaccines. Clarification of the definition of SARs and SUSARs
14 February 2020	Changes to exclusion criteria relating to haemoglobin levels at screening and prior exposure to immunoglobulins. Exclusion criteria relating to prior immunoglobulin exposure amended. Removal of thick blood film as diagnostic measure during CHMI for Group 2. Addition of repeat blood-borne viral screen at C+96. Updates and corrections to schedule of visits and bleed volumes, including reduction of maximal blood draw for Group 2. 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. Removal of AEs of special interest. Change to group sizes (target range now specified). 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.
26 November 2020	Trial restart. Change of vaccination schedule for group 2 due to temporary trial halt. Justification for addition of second dose of ChAd63 PvDBP. Addition of Group 3, to be recruited if fewer than 6 participants complete the study in Group 2. C-1 visit changed to C-2. 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 antimalaria treatment. Addition of serum bhCG to C+28/day of malaria diagnosis. Clarification that G6PD, DARC and haemoglobinopathy screen are only done at NHS labs. Correction of typographical errors. 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. Extension of time window for MVA PvDBP vaccinations. Addition of section on administration of concomitant COVID-19 vaccination
21 April 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. Addition of safety information on risk of blood clots with viral vectored COVID-19 vaccines in sections 4.5 and 8.5.2
28 July 2021	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. Addition of section 11.5.4 on initial follow-up visits post antimalarial treatment. For Groups 2 and 3 - change of post malaria treatment visit from T+2 to T+3. Correction of error in lumefantrine dose in section 8.5.5. Addition of reticulocyte count to FBC taken at C-2 visit. Correction of errors in protocol – only weight taken at C-2 visit. Changed Senior Laboratory Investigator address. Addition of New Biochemistry Building as location for processing of research bloods. Updated compensation table

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 during Covid-19 pandemic	21 January 2021

Notes:

Limitations and caveats

None reported