Clinical trial results:
A Phase I/IIa Sporozoite Challenge Study to Assess the Safety and Protective Efficacy of Concomitant Administration of the Combination Malaria Vaccine Candidate Regimen of RTS,S/AS01¬B + ChAd63 and MVA encoding ME-TRAP and also RTS,S/AS01B alone

Summary

EudraCT number	2014-001301-40
Trial protocol	GB
Global end of trial date	16 October 2015

Results information

Result version number	v1 (current)
This version publication date	30 October 2016
First version publication date	30 October 2016

Trial information

Trial identification

Sponsor protocol code	VAC059

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02252640
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	CTRG, Old Road, Oxford, United Kingdom, OX3 7LE
Public contact	Professor Adrian Hill, University of Oxford, 01865 617610, adrian.hill@ndm.ox.ac.uk
Scientific contact	Professor Adrian Hill, University of Oxford, 01865 617610, adrian.hill@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	16 October 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 October 2015
Global end of trial reached?	Yes
Global end of trial date	16 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To establish whether the combination immunization regimen with ChAd63/MVA ME-TRAP given concomitantly with two different dosing regimens of RTS,S/AS01B, and of RTS,S/AS01B alone at either full standard dose or with a reduced third dose can demonstrate safety and efficacy against malaria sporozite challenge, in healthy malaria naive 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 escalations (LSM)
- Total blood volume taken during study kept to volume that should not compromise healthy volunteers (i.e. less than regular donation to blood transfusion service).
- Volunteers observed for 30 mins - 2 hours (depending on trial) after vaccination to monitor for any immediate adverse effects.
- Volunteers seen within 1 – 3 days of vaccination (most trials) for safety review and provided with 24/7 contact number for trial clinician and emergency contact card for the department.
- ECG and cholesterol checked prior to enrolment to aid cardiac risk assessment
- Age range 18 – 45 years (tighter than for Phase I)
- Volunteers given emergency contact card detailing that they have been infected with malaria.
- Volunteers seen twice daily once blood stage malaria is possible with twice daily malaria films and PCR
- 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 followed up until at least 2 consecutive negative blood films seen.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 January 2015
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: 45
Worldwide total number of subjects	45
EEA total number of subjects	45

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)	45
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The planned trial period is 11 to 13 months from the first study visit, provided if any group 1-4 volunteers are sterilely protected at first challenge, and undergo re-challenge. Without re-challenge, the planned trial period is 8 months from first vaccination.

Pre-assignment

Screening details:

Inclusion / Exclusion criteria
Informed consent
Medical History
Physical Examination
Urinalysis
B-HCG urine test (women only)
Review contraindications
Physical observations
HBV,HCV,HIV
Haematology
Biochemistry

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1

Arm description:

This arm received RTS,S/AS01B (Standard dose) in week 0 followed by the same dose in week 4 and 8 and malaria challenge in week 11

Arm type	Experimental
Investigational medicinal product name	RTS,S/AS01B
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

The standard dose of RTS,S/AS01B will contain 50mcg of RTS,S and standard adult dose of AS01.

Arm title	Group 2

Arm description:

This arm received RTS,S/AS01B (Standard dose) in weeks 0 and 4 followed by the 1/5th of the standard dose in week 8 and malaria challenge in week 11

Arm type	Experimental
Investigational medicinal product name	RTS,S/AS01B
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

The standard dose of RTS,S/AS01B will contain 50mcg of RTS,S and standard adult dose of AS01.

Arm title	Group 3
Arm description:	
This arm received RTS,S/AS01B (Standard dose) & ChAd63 ME-TRAP in week 0 followed by RTS,S/AS01B (Standard dose) & MVA ME-TRAP in week 4 and 8 & malaria challenge in week 11	
Arm type	Experimental
Investigational medicinal product name	RTS,S/AS01B
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
The standard dose of RTS,S/AS01B will contain 50mcg of RTS,S and standard adult dose of AS01.	

Arm title	Group 4
Arm description:	
This arm received RTS,S/AS01B (Standard dose) & ChAd63 ME-TRAP in week 0 followed by RTS,S/AS01B (Standard dose) & MVA ME-TRAP in week 4 and RTS,S/AS01B (1/5 Standard dose) & MVA ME-TRAP in week 8. The malaria sporozite challenge to take place in week 11.	
Arm type	Experimental
Investigational medicinal product name	RTS,S/AS01B
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use
Dosage and administration details:	
The standard dose of RTS,S/AS01B will contain 50mcg of RTS,S and standard adult dose of AS01.	

Arm title	Group 5
Arm description:	
The arm was the control arm and the volunteers in this arm did not receive any experimental medication.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Group 1	Group 2	Group 3
Started	10	10	10
Completed	8	9	10
Not completed	2	1	0
Consent withdrawn by subject	2	1	-

Number of subjects in period 1	Group 4	Group 5
Started	11	4
Completed	9	4
Not completed	2	0
Consent withdrawn by subject	2	-

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 2

Arm description:

This arm received RTS,S/AS01B (Standard dose) in weeks 0 and 4 followed by the 1/5th of the standard dose in week 8 and malaria challenge in week 11

Arm type	Experimental
Investigational medicinal product name	RTS,S/AS01B
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

The standard dose of RTS,S/AS01B will contain 50mcg of RTS,S and standard adult dose of AS01, 1/5th standard dose of RTS,S/AS01B will contain 10mcg of RTS,S and one fifth of the standard dose of AS01

Arm title	Group 3

Arm description:

This arm received RTS,S/AS01B (Standard dose) & ChAd63 ME-TRAP in week 0 followed by RTS,S/AS01B (Standard dose) & MVA ME-TRAP in week 4 and 8 & malaria challenge in week 11 less

Arm type	Experimental
Investigational medicinal product name	RTS,S/AS01B
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

The standard dose of RTS,S/AS01B will contain 50mcg of RTS,S and standard adult dose of AS01.

Investigational medicinal product name	RTS,S/AS01B
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

The standard dose of RTS,S/AS01B will contain 50mcg of RTS,S and standard adult dose of AS01.

Arm title	Group 4

Arm description:

This arm received RTS,S/AS01B (Standard dose) & ChAd63 ME-TRAP in week 0 followed by RTS,S/AS01B (Standard dose) & MVA ME-TRAP in week 4 and RTS,S/AS01B (1/5 Standard dose) & MVA ME-TRAP in week 8. The malaria sporozite challenge to take place in week 11.

Arm type	Experimental

Investigational medicinal product name	RTS,S/AS01B
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

The standard dose of RTS,S/AS01B will contain 50mcg of RTS,S and standard adult dose of AS01.

Number of subjects in period 2[1]	Group 2	Group 3	Group 4
Started	10	10	11
Completed	9	10	10
Not completed	1	0	1
Consent withdrawn by subject	1	-	1

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: Subject numbers completing each period differes from previous due to inclusion of control arm which received challenge agent but no IMP.

Period 3

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 3

Arm description:

This arm received RTS,S/AS01B (Standard dose) & ChAd63 ME-TRAP in week 0 followed by RTS,S/AS01B (Standard dose) & MVA ME-TRAP in week 4 and 8 & malaria challenge in week 11

Arm type	Experimental
Investigational medicinal product name	RTS,S/AS01B
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

The standard dose of RTS,S/AS01B will contain 50mcg of RTS,S and standard adult dose of AS01, ChAd63 ME-TRAP will be given intramuscularly at a dose of 5 x 1010 vp
MVA ME-TRAP will be given intramuscularly at a dose of 2 x 108 pfu

Arm title	Group 4

Arm description:

This arm received RTS,S/AS01B (Standard dose) & ChAd63 ME-TRAP in week 0 followed by RTS,S/AS01B (Standard dose) & MVA ME-TRAP in week 4 and RTS,S/AS01B (1/5 Standard dose) & MVA ME-TRAP in week 8. The malaria sporozite challenge to take place in week 11.

Arm type	Experimental

Investigational medicinal product name	RTS,S/AS01B
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

The standard dose of RTS,S/AS01B will contain 50mcg of RTS,S and standard adult dose of AS01.

Number of subjects in period 3[2]	Group 3	Group 4
Started	10	10
Completed	10	10

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: Subject numbers completing each period differes from previous due to inclusion of control arm which received challenge agent but no IMP.

Period 4

Period 4 title	Week 11
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Group 4

Arm description:

This arm received RTS,S/AS01B (Standard dose) & ChAd63 ME-TRAP in week 0 followed by RTS,S/AS01B (Standard dose) & MVA ME-TRAP in week 4 and RTS,S/AS01B (1/5 Standard dose) & MVA ME-TRAP in week 8. The malaria sporozite challenge to take place in week 11.

Arm type	Experimental
Investigational medicinal product name	RTS,S/AS01B
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

The standard dose of RTS,S/AS01B will contain 50mcg of RTS,S and standard adult dose of AS01,
ChAd63 ME-TRAP will be given intramuscularly at a dose of 5 x 1010 vp
MVA ME-TRAP will be given intramuscularly at a dose of 2 x 108 pfu

Number of subjects in period 4[3]	Group 4
Started	11
Completed	9
Not completed	2
Consent withdrawn by subject	2

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: Subject numbers completing each period differes from previous due to inclusion of control arm which received challenge agent but no IMP.

Baseline characteristics

Reporting groups	
Reporting group title	Group 1
Reporting group description:	
This arm received RTS,S/AS01B (Standard dose) in week 0 followed by the same dose in week 4 and 8 and malaria challenge in week 11	
Reporting group title	Group 2
Reporting group description:	
This arm received RTS,S/AS01B (Standard dose) in weeks 0 and 4 followed by the 1/5th of the standard dose in week 8 and malaria challenge in week 11	
Reporting group title	Group 3
Reporting group description:	
This arm received RTS,S/AS01B (Standard dose) & ChAd63 ME-TRAP in week 0 followed by RTS,S/AS01B (Standard dose) & MVA ME-TRAP in week 4 and 8 & malaria challenge in week 11	
Reporting group title	Group 4
Reporting group description:	
This arm received RTS,S/AS01B (Standard dose) & ChAd63 ME-TRAP in week 0 followed by RTS,S/AS01B (Standard dose) & MVA ME-TRAP in week 4 and RTS,S/AS01B (1/5 Standard dose) & MVA ME-TRAP in week 8. The malaria sporozite challenge to take place in week 11.	
Reporting group title	Group 5
Reporting group description:	
The arm was the control arm and the volunteers in this arm did not receive any experimental medication.	

Reporting group values	Group 1	Group 2	Group 3
Number of subjects	10	10	10
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	10	10	10
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	4	7	3
Male	6	3	7

Reporting group values	Group 4	Group 5	Total
Number of subjects	11	4	45
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0

Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	11	4	45
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	6	3	23
Male	5	1	22

End points

End points reporting groups

Reporting group title	Group 1
Reporting group description:	
This arm received RTS,S/AS01B (Standard dose) in week 0 followed by the same dose in week 4 and 8 and malaria challenge in week 11	
Reporting group title	Group 2
Reporting group description:	
This arm received RTS,S/AS01B (Standard dose) in weeks 0 and 4 followed by the 1/5th of the standard dose in week 8 and malaria challenge in week 11	
Reporting group title	Group 3
Reporting group description:	
This arm received RTS,S/AS01B (Standard dose) & ChAd63 ME-TRAP in week 0 followed by RTS,S/AS01B (Standard dose) & MVA ME-TRAP in week 4 and 8 & malaria challenge in week 11	
Reporting group title	Group 4
Reporting group description:	
This arm received RTS,S/AS01B (Standard dose) & ChAd63 ME-TRAP in week 0 followed by RTS,S/AS01B (Standard dose) & MVA ME-TRAP in week 4 and RTS,S/AS01B (1/5 Standard dose) & MVA ME-TRAP in week 8. The malaria sporozite challenge to take place in week 11.	
Reporting group title	Group 5
Reporting group description:	
The arm was the control arm and the volunteers in this arm did not receive any experimental medication.	
Reporting group title	Group 2
Reporting group description:	
This arm received RTS,S/AS01B (Standard dose) in weeks 0 and 4 followed by the 1/5th of the standard dose in week 8 and malaria challenge in week 11	
Reporting group title	Group 3
Reporting group description:	
This arm received RTS,S/AS01B (Standard dose) & ChAd63 ME-TRAP in week 0 followed by RTS,S/AS01B (Standard dose) & MVA ME-TRAP in week 4 and 8 & malaria challenge in week 11 less	
Reporting group title	Group 4
Reporting group description:	
This arm received RTS,S/AS01B (Standard dose) & ChAd63 ME-TRAP in week 0 followed by RTS,S/AS01B (Standard dose) & MVA ME-TRAP in week 4 and RTS,S/AS01B (1/5 Standard dose) & MVA ME-TRAP in week 8. The malaria sporozite challenge to take place in week 11.	
Reporting group title	Group 3
Reporting group description:	
This arm received RTS,S/AS01B (Standard dose) & ChAd63 ME-TRAP in week 0 followed by RTS,S/AS01B (Standard dose) & MVA ME-TRAP in week 4 and 8 & malaria challenge in week 11	
Reporting group title	Group 4
Reporting group description:	
This arm received RTS,S/AS01B (Standard dose) & ChAd63 ME-TRAP in week 0 followed by RTS,S/AS01B (Standard dose) & MVA ME-TRAP in week 4 and RTS,S/AS01B (1/5 Standard dose) & MVA ME-TRAP in week 8. The malaria sporozite challenge to take place in week 11.	
Reporting group title	Group 4
Reporting group description:	
This arm received RTS,S/AS01B (Standard dose) & ChAd63 ME-TRAP in week 0 followed by RTS,S/AS01B (Standard dose) & MVA ME-TRAP in week 4 and RTS,S/AS01B (1/5 Standard dose) & MVA ME-TRAP in week 8. The malaria sporozite challenge to take place in week 11.	

Primary: Efficacy assessed by Controlled Human Malaria Infection (CHMI) with P. falciparum by mosquito bite

End point title	Efficacy assessed by Controlled Human Malaria Infection (CHMI) with P. falciparum by mosquito bite[1][2]

End point description:

End point type	Primary

End point timeframe:

Completely protected individuals are those who do not, by Day 23 following sporozoite challenge, develop blood stage infection

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 publication will be uploaded at a later date.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Due to the confidential nature of this information, we have not provided this analysis at this time. The publication will be uploaded at a later date.

End point values	Group 1	Group 2	Group 3	Group 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	9	10	9
Units: Number	8	9	10	9

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

AEs collected and reviewed from day of vaccination to 90 days post malaria challenge.
SAEs reported to the sponsor within 24 hours of awareness.
SUSARs reported within 15 days of awareness (7 days for fatal or life threatening events)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

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

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 data at this time. The publication will be uploaded at a later date.

There were a total of 2 SAEs, none of which were realted to any of the IMPs or challenge procedures.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 November 2014	To extend the shelf life of RTS,S lot for use in clinical trial
12 November 2014	To extend the shelf life of ChAd63 ME-TRAP for use in trial
22 December 2014	Change has been made to the window period for the second and third vaccination-extended from +2 days to +7 days to decrease the loss to follow-up
09 February 2015	To extend the shelf life of MVA ME-TRAP lot for a further year

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes: