Clinical trial results:
A Phase I/IIb randomized, double-blind, controlled study of the safety, immunogenicity and proof-of-concept of RTS,S/AS02D, a candidate malaria vaccine in infants living in a malaria-endemic region.

Summary

EudraCT number	2015-001538-25
Trial protocol	Outside EU/EEA
Global end of trial date	27 December 2007

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	17 July 2015

Trial information

Trial identification

Sponsor protocol code	103967

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00197028
WHO universal trial number (UTN)	-
Other trial identifiers	IND number: 10514

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline Biologicals
Sponsor organisation address	Rue de l'Institut 89, Rixensart, Belgium, B-1330
Public contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, 044 2089-904466, GSKClinicalSupportHD@gsk.com
Scientific contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, 044 2089-904466, GSKClinicalSupportHD@gsk.com

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 July 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 December 2007
Global end of trial reached?	Yes
Global end of trial date	27 December 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To describe the safety and reactogenicity of RTS,S/AS02D administered as 3 doses intramuscularly in the left thigh to infants at 10, 14 and 18 weeks of age, staggered with the administration of 3 doses of TETRActHib (vaccine against diphteria, tetanus, pertussis and Haemophilus influenzae type B) intramuscularly in the right thigh at 8, 12 and 16 weeks of age.

Protection of trial subjects:

The vaccines were observed closely for at least 60 minutes, with appropriate medical treatment readily available in case of an anaphylactic reaction following the administration of vaccines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 August 2005
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	11 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Mozambique: 220
Worldwide total number of subjects	220
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)	220
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

220 subjects were enrolled in the study out of which 214 were vaccinated and 6 were not withdrawn from the study by removal of consent by their parents/guardians.

Pre-assignment

Screening details:

The study comprised 2 phases, a double-blind vaccination phase from Month 0 to Month 6, and a single-blind phase (Month 7 to Month 14).

Pre-assignment period milestones

Number of subjects started	220
Number of subjects completed	214

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 6

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

'Double blinded (observer blinded)' means that the vaccinees and their parent(s)/guardian(s) and those responsible for the evaluation of safety, immunogenicity and efficacy endpoints were all unaware which treatment, RTS,S/AS02D or Engerix-B, was administered to a particular subject. The only study staff aware of the vaccine assignment for RTS,S/AS02D or Engerix-B will be those responsible for the preparation and administration of vaccines; these staff will play no other role in the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	RTS,S/AS02D Group

Arm description:

Subjects aged between 6 and 12 weeks at the time of first vaccination received by intramuscular injection a 3-dose vaccination course of RTS,S/AS02D at days 14, 44 and 74 and a 3-dose vaccination course of TETRActHib™ vaccine at days 0, 30 and 60. The RTS,S/AS02D vaccine was administered in the left anterolateral thigh, and the TETRActHib™ vaccine in the right anterolateral thigh.

Arm type	Experimental
Investigational medicinal product name	Candidate Plasmodium falciparum malaria vaccine
Investigational medicinal product code	RTS,S/AS02D
Other name	
Pharmaceutical forms	Powder and suspension for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

3-dose intramuscular injection in the thigh

Investigational medicinal product name	TETRAct-HIB
Investigational medicinal product code	
Other name	TETRActHib™
Pharmaceutical forms	Powder and suspension for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

3-dose intramuscular injection in the thigh.

Arm title	Engerix-B Group

Arm description:

Subjects aged between 6 and 12 weeks at the time of first vaccination received by intramuscular injection a 3-dose vaccination course of Engerix-B® vaccine at days 14, 44 and 74 and a 3-dose of TETRActHib™ vaccine at days 0, 30 and 60. The Engerix-B® vaccine was administered in the left anterolateral thigh, and the TETRActHib™ vaccine in the right anterolateral thigh.

Arm type	Active comparator
Investigational medicinal product name	TETRAct-HIB
Investigational medicinal product code	
Other name	TETRActHib™
Pharmaceutical forms	Powder and suspension for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

3-dose intramuscular injection in the thigh.

Investigational medicinal product name	Engerix-B Junior
Investigational medicinal product code	HBV Paediatric 10
Other name	Engerix-B®, Engerix-B
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

3-dose intramuscular injection in the thigh.

Number of subjects in period 1[1]	RTS,S/AS02D Group	Engerix-B Group
Started	107	107
Completed	91	86
Not completed	16	21
Consent withdrawn by subject	8	12
Adverse event, non-fatal	2	2
Unspecified	3	6
Lost to follow-up	1	-
Protocol deviation	2	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 220 subjects were enrolled in the study out of which 214 were vaccinated and 6 were not withdrawn from the study by removal of consent by their parents/guardians.

Baseline characteristics

Reporting groups	
Reporting group title	RTS,S/AS02D Group
Reporting group description:	
Subjects aged between 6 and 12 weeks at the time of first vaccination received by intramuscular injection a 3-dose vaccination course of RTS,S/AS02D at days 14, 44 and 74 and a 3-dose vaccination course of TETRActHib™ vaccine at days 0, 30 and 60. The RTS,S/AS02D vaccine was administered in the left anterolateral thigh, and the TETRActHib™ vaccine in the right anterolateral thigh.	
Reporting group title	Engerix-B Group
Reporting group description:	
Subjects aged between 6 and 12 weeks at the time of first vaccination received by intramuscular injection a 3-dose vaccination course of Engerix-B® vaccine at days 14, 44 and 74 and a 3-dose of TETRActHib™ vaccine at days 0, 30 and 60. The Engerix-B® vaccine was administered in the left anterolateral thigh, and the TETRActHib™ vaccine in the right anterolateral thigh.	

Reporting group values	RTS,S/AS02D Group	Engerix-B Group	Total
Number of subjects	107	107	214
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: weeks			
arithmetic mean	8.3	8.3	
standard deviation	± 1.42	± 1.08	-
Gender categorical			
Units: Subjects			
Female	48	59	107
Male	59	48	107

End points

End points reporting groups

Reporting group title	RTS,S/AS02D Group

Reporting group description:

Subjects aged between 6 and 12 weeks at the time of first vaccination received by intramuscular injection a 3-dose vaccination course of RTS,S/AS02D at days 14, 44 and 74 and a 3-dose vaccination course of TETRActHib™ vaccine at days 0, 30 and 60. The RTS,S/AS02D vaccine was administered in the left anterolateral thigh, and the TETRActHib™ vaccine in the right anterolateral thigh.

Reporting group title	Engerix-B Group

Reporting group description:

Subjects aged between 6 and 12 weeks at the time of first vaccination received by intramuscular injection a 3-dose vaccination course of Engerix-B® vaccine at days 14, 44 and 74 and a 3-dose of TETRActHib™ vaccine at days 0, 30 and 60. The Engerix-B® vaccine was administered in the left anterolateral thigh, and the TETRActHib™ vaccine in the right anterolateral thigh.

Primary: Number of subjects with serious adverse events (SAEs).

End point title	Number of subjects with serious adverse events (SAEs).[1]

End point description:

SAEs were defined as medical occurrences that resulted in death, were life threatening, required hospitalization or prolongation of hospitalization or resulted in disability/incapacity.

End point type	Primary

End point timeframe:

From Month 0 to Month 6.

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: The analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

End point values	RTS,S/AS02D Group	Engerix-B Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	107		
Units: Subjects				
Subjects with any SAEs	17	17		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with serious adverse events (SAEs).

End point title	Number of subjects with serious adverse events (SAEs).

End point description:

SAEs were defined as medical occurrences that resulted in death, were life threatening, required hospitalization or prolongation of hospitalization or resulted in disability/incapacity.

End point type	Secondary

End point timeframe:

Throughout the entire study period (from Month 0 to Month 14).

End point values	RTS,S/AS02D Group	Engerix-B Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	107		
Units: Subjects				
Subjects with any SAEs	35	34		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of antibodies against hepatitis B (Anti-HB).

End point title	Concentrations of antibodies against hepatitis B (Anti-HB).

End point description:

Concentrations were expressed as geometric mean concentrations (GMCs) in milli-international unit per milliliter (mIU/mL). The seroprotection cut-off of the assay was 10 mIU/mL.

End point type	Secondary

End point timeframe:

Prior to vaccination at Month 0 (PRE) and 1 month post Dose 3 of Engerix-B® or RTS,S/AS02D vaccine (Day 104).

End point values	RTS,S/AS02D Group	Engerix-B Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	70		
Units: mIU/mL				
geometric mean (confidence interval 95%)				
Anti-HB, PRE [N=72;70]	14 (9.6 to 20.5)	16.6 (11 to 25)		
Anti-HB, Day 104 [N=68;64]	10081.6 (7394.9 to 13744.4)	392.4 (297 to 518.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of anti-circumsporozoite protein (anti-CS) antibodies.

End point title	Concentrations of anti-circumsporozoite protein (anti-CS) antibodies.

End point description:

Antibodies were measured by Enzyme-linked immunosorbent assay (ELISA). Concentrations are expressed as geometric mean concentrations (GMCs) in ELISA unit per milliliter (EL.U/mL). The seropositivity cut-off of the assay was 0.5 EL.U/mL.

End point type	Secondary

End point timeframe:

Prior to vaccination at Month 0 (PRE), 1 month post Dose 3 of Engerix-B® or RTS,S/AS02D vaccine (Day 104) and 3½ months post Dose 3 of Engerix-B® or RTS,S/AS02D vaccine (Day 180).

End point values	RTS,S/AS02D Group	Engerix-B Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	77		
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Anti-CS, PRE [N=76;77]	0.4 (0.3 to 0.5)	0.4 (0.3 to 0.4)		
Anti-CS, Day 104 [N=71;68]	199.9 (150.9 to 264.7)	0.3 (0.2 to 0.3)		
Anti-CS, Day 180 [N=53;61]	58.8 (41.8 to 82.8)	0.4 (0.3 to 0.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of antibodies against anti-diphtheria (Anti-D).

End point title	Concentrations of antibodies against anti-diphtheria (Anti-D).

End point description:

Antibodies were measured by Enzyme-linked immunosorbent assay (ELISA). Concentrations were expressed as geometric mean concentrations (GMCs) in international unit per milliliter (IU/mL). The seroprotection cut-off of the assay was 0.1 IU/mL.

End point type	Secondary

End point timeframe:

At Day 90 (1 month post Dose 3 of TETRActHib™ vaccine).

End point values	RTS,S/AS02D Group	Engerix-B Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	72		
Units: IU/mL				
geometric mean (confidence interval 95%)				
Anti-D	1.4 (1.1 to 1.7)	1.4 (1.2 to 1.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of antibodies against tetanus (Anti-T).

End point title	Concentrations of antibodies against tetanus (Anti-T).

End point description:

Antibodies were measured by Enzyme-linked immunosorbent assay (ELISA). Concentrations were expressed as geometric mean concentrations (GMCs) in international unit per milliliter (IU/mL). The seroprotection cut-off of the assay was 0.1 IU/mL.

End point type	Secondary

End point timeframe:

At Day 90 (1 month post Dose 3 of TETRActHib™ vaccine).

End point values	RTS,S/AS02D Group	Engerix-B Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	72		
Units: IU/mL				
geometric mean (confidence interval 95%)				
Anti-T	6.2 (5 to 7.7)	5.1 (4.2 to 6.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of anti-Bordetella pertussis toxin antibodies (Anti-BPT).

End point title	Concentrations of anti-Bordetella pertussis toxin antibodies (Anti-BPT).

End point description:

Antibodies were measured by Enzyme-linked immunosorbent assay (ELISA). Concentrations were expressed as geometric mean concentrations (GMCs) in ELISA unit per milliliter (EL.U/mL). The seropositivity cut-off of the assay was 15 EL.U/mL.

End point type	Secondary

End point timeframe:

At Day 90 (1 month post Dose 3 of TETRActHib™ vaccine).

End point values	RTS,S/AS02D Group	Engerix-B Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	70		
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Anti-BPT	104.4 (89.1 to 122.4)	106.8 (93.3 to 122.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of anti-polyribosyl ribitol phosphate antibodies (Anti-PRP).

End point title	Concentrations of anti-polyribosyl ribitol phosphate antibodies (Anti-PRP).

End point description:

Antibodies were measured by Enzyme-linked immunosorbent assay (ELISA). Concentrations were expressed as geometric mean concentrations (GMCs) in microgram per milliliter (µg/mL). The seroprotection cut-off of the assay was 0.15 µg/mL.

End point type	Secondary

End point timeframe:

At Day 90 (1 month post Dose 3 of TETRActHib™ vaccine).

End point values	RTS,S/AS02D Group	Engerix-B Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	72		
Units: µg/mL				
geometric mean (confidence interval 95%)				
Anti-PRP	22.1 (16.3 to 29.9)	17.9 (13.5 to 23.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first malaria infection.

End point title	Time to first malaria infection.

End point description:

Malaria infection by Plasmodium falciparum (P. falciparum) was detected by active detection of infection (ADI) and passive case detection (PCD), and was defined as the presence of P. falciparum asexual parasitemia above 0 per microliter (µL) on Giemsa stained thick blood films. The time to first malaria infection is expressed in terms of rate of first malaria infection, that is, the number of malaria infection events reported (n) over the period elapsed until the event occurred (i.e. events per Persons Year at

Risk [PYAR]) for each group.

End point type	Secondary

End point timeframe:

Over the period starting 14 days after Dose 3 of RTS,S/AS02D or Engerix-B® vaccine and extending for 12 weeks thereafter (from Month 2.5 to Month 6).

End point values	RTS,S/AS02D Group	Engerix-B Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	92		
Units: n/PYAR				
number (not applicable)				
Rate of first malaria infection	1.01	2.67		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects prevalent for Plasmodium falciparum (P. falciparum).

End point title	Number of subjects prevalent for Plasmodium falciparum (P. falciparum).

End point description:

Subjects prevalent for P. falciparum parasitemia were defined as subjects with the presence of P. falciparum asexual parasitemia above 0 per microliter (µL) on Giemsa stained thick blood films.

End point type	Secondary

End point timeframe:

At Month 6 (3½ months post Dose 3 of RTS,S/AS02D or Engerix-B® vaccine).

End point values	RTS,S/AS02D Group	Engerix-B Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	90		
Units: Subjects				
Subjects prevalent for P. falciparum parasitemia	4	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasmodium falciparum (P. falciparum) parasite density in subjects prevalent for parasitemia.

End point title	Plasmodium falciparum (P. falciparum) parasite density in subjects prevalent for parasitemia.

End point description:

The parasite density in subjects prevalent for P. falciparum parasitemia (subjects with the presence of P. falciparum asexual parasitemia above 0 per microliter (µL) on Giemsa stained thick blood films), was detected at a cross sectional time point 3 ½ months after administration of Dose 3 of RTS,S/AS02D or Engerix-B® vaccine (Month 6). Parasite density is expressed as mean, minimum and maximum density in parasite per µL.

End point type	Secondary

End point timeframe:

At Month 6 (3½ months post Dose 3 of RTS,S/AS02D or Engerix-B® vaccine).

End point values	RTS,S/AS02D Group	Engerix-B Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	7		
Units: Parasites per µL				
geometric mean (confidence interval 95%)				
P. falciparum Parasite density	11573 (131 to 33471)	10612 (89 to 31993)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with solicited local symptoms.

End point title	Number of subjects with solicited local symptoms.

End point description:

Assessed solicited local symptoms were pain and swelling at injection site.

End point type	Secondary

End point timeframe:

During the 7 day (Days 0-6) follow-up period after any vaccination with TETRActHib™ vaccine.

End point values	RTS,S/AS02D Group	Engerix-B Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	107		
Units: Subjects				
Pain	107	107		
Swelling	39	47		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with solicited local symptoms.

End point title	Number of subjects with solicited local symptoms.

End point description:

Assessed solicited local symptoms were pain and swelling at injection site.

End point type	Secondary

End point timeframe:

During the 7 day (Days 0-6) follow-up period after any vaccination with Engerix-B® or RTS,S/AS02D vaccine.

End point values	RTS,S/AS02D Group	Engerix-B Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	106		
Units: Subjects				
Pain	105	105		
Swelling	26	23		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with solicited general symptoms.

End point title	Number of subjects with solicited general symptoms.

End point description:

Assessed solicited general symptoms were drowsiness, fever, irritability and loss of appetite. Fever was defined as axillary temperature equal or above (≥) to 37.5 degrees Celsius (C).

End point type	Secondary

End point timeframe:

During the 7 day (Days 0-6) follow-up period after any vaccination with TETRActHib™ vaccine

End point values	RTS,S/AS02D Group	Engerix-B Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	107		
Units: Subjects				
Dorwsiness	64	58		
Fever ≥ 37.5°C	24	25		
Irritability	89	88		
Loss of appetite	58	49		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with solicited general symptoms.

End point title	Number of subjects with solicited general symptoms.

End point description:

Assessed solicited general symptoms were drowsiness, fever, irritability and loss of appetite. Fever was defined as axillary temperature equal or above (≥) to 37.5 degrees Celsius (C).

End point type	Secondary

End point timeframe:

During the 7 day (Days 0-6) follow-up period after any vaccination with Engerix-B® or RTS,S/AS02D vaccine.

End point values	RTS,S/AS02D Group	Engerix-B Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	106		
Units: Subjects				
Drowsiness	60	69		
Fever ≥ 37.5°C	25	23		
Irritability	81	81		
Loss of appetite	53	62		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with unsolicited Adverse Events (AEs).

End point title	Number of subjects with unsolicited Adverse Events (AEs).

End point description:

An unsolicited AE is any AE (i.e. any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with use of a medicinal product, whether or not considered related to the medicinal product) reported in addition to those solicited during the clinical study and any solicited symptom with onset outside the specified period of follow-up for solicited symptoms.

End point type	Secondary

End point timeframe:

During the 14 day (Days 0-13) follow-up period after any vaccination with of TETRActHib™ vaccine.

End point values	RTS,S/AS02D Group	Engerix-B Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	107		
Units: Subjects				
Subjects with any AE(s)	64	51		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with unsolicited Adverse Events (AEs).

End point title	Number of subjects with unsolicited Adverse Events (AEs).

End point description:

An unsolicited AE is any AE (i.e. any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with use of a medicinal product, whether or not considered related to the medicinal product) reported in addition to those solicited during the clinical study and any solicited symptom with onset outside the specified period of follow-up for solicited symptoms.

End point type	Secondary

End point timeframe:

During the 14 day (Days 0-13) follow-up period after vaccination with any among Doses 1 and 2 of Engerix-B® or RTS,S/AS02D vaccine.

End point values	RTS,S/AS02D Group	Engerix-B Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	106		
Units: Subjects				
Subjects with any AE(s)	50	47		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with unsolicited Adverse Events (AEs).

End point title	Number of subjects with unsolicited Adverse Events (AEs).

End point description:

An unsolicited AE is any AE (i.e. any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with use of a medicinal product, whether or not considered related to the medicinal product) reported in addition to those solicited during the clinical study and any solicited symptom with onset outside the specified period of follow-up for solicited symptoms.

End point type	Secondary

End point timeframe:

During the 30 day (Days 0-29) follow-up period after vaccination with Dose 3 of Engerix-B® or RTS,S/AS02D vaccine.

End point values	RTS,S/AS02D Group	Engerix-B Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	97		
Units: Subjects				
Subjects with any AE(s)	32	39		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs: entire study period (Months 0-14); Unsolicited AEs: Days 0-13 or 0-29 periods (as specified in notes); Solicited local/general symptoms: 7 day (Days 0-6) follow-up period after any vaccination.

Adverse event reporting additional description:

For solicited symptoms and unsolicited AEs assessed following vaccination, the number of participants at risk included those vaccinated subjects from the Total Vaccinated cohort who had the symptom sheet completed. The occurrence of reported AEs (all/related) was not available and is encoded as equal to the number of subjects affected.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups

Reporting group title	RTS,S/AS02D Group

Reporting group description:

Subjects aged between 6 and 12 weeks at the time of first vaccination received by intramuscular injection a 3-dose vaccination course of RTS,S/AS02D at days 14, 44 and 74 and a 3-dose vaccination course of TETRActHib™ vaccine at days 0, 30 and 60. The RTS,S/AS02D vaccine was administered in the left anterolateral thigh, and the TETRActHib™ vaccine in the right anterolateral thigh.

Reporting group title	Engerix-B Group

Reporting group description:

Subjects aged between 6 and 12 weeks at the time of first vaccination received by intramuscular injection a 3-dose vaccination course of Engerix-B® vaccine at days 14, 44 and 74 and a 3-dose of TETRActHib™ vaccine at days 0, 30 and 60. The Engerix-B® vaccine was administered in the left anterolateral thigh, and the TETRActHib™ vaccine in the right anterolateral thigh.

Serious adverse events	RTS,S/AS02D Group	Engerix-B Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 107 (32.71%)	34 / 107 (31.78%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Thermal burn			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Febrile convulsion			
subjects affected / exposed	1 / 107 (0.93%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	17 / 107 (15.89%)	13 / 107 (12.15%)	
occurrences causally related to treatment / all	0 / 17	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 107 (0.00%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 107 (0.00%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial hyper reactivity			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Gastroenteritis			
subjects affected / exposed	13 / 107 (12.15%)	18 / 107 (16.82%)	
occurrences causally related to treatment / all	0 / 13	0 / 18	
deaths causally related to treatment / all	0 / 1	0 / 2	
Plasmodium falciparum infection			
subjects affected / exposed	15 / 107 (14.02%)	13 / 107 (12.15%)	
occurrences causally related to treatment / all	0 / 15	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	4 / 107 (3.74%)	5 / 107 (4.67%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	3 / 107 (2.80%)	4 / 107 (3.74%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 107 (3.74%)	3 / 107 (2.80%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	2 / 107 (1.87%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	1 / 107 (0.93%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 107 (0.93%)	3 / 107 (2.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyoderma			

subjects affected / exposed	1 / 107 (0.93%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascariasis			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Furuncle			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaria			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastoiditis			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal sepsis			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Staphylococcal sepsis			

subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tinea capitis			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	4 / 107 (3.74%)	3 / 107 (2.80%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Marasmus			
subjects affected / exposed	2 / 107 (1.87%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	RTS,S/AS02D Group	Engerix-B Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	107 / 107 (100.00%)	107 / 107 (100.00%)	
Blood and lymphatic system disorders			
Anaemia (14-day FU after TETRAct/Hib vaccination)	Additional description: During the 14-day follow-up period after vaccination with TETRAct/Hib vaccine		
subjects affected / exposed	11 / 107 (10.28%)	4 / 107 (3.74%)	
occurrences (all)	11	4	
General disorders and administration site conditions			
Pain (7-day after vaccination with TETRAct/Hib)	Additional description: During the 7-day follow-up period after vaccination with TETRAct/Hib vaccine		
alternative assessment type: Systematic			

subjects affected / exposed	107 / 107 (100.00%)	107 / 107 (100.00%)	
occurrences (all)	107	107	
Swelling (7-day after vaccination with TETRAct/Hib)	Additional description: During the 7-day follow-up period after vaccination with TETRAct/Hib vaccine		
alternative assessment type: Systematic			
subjects affected / exposed[1]	39 / 105 (37.14%)	47 / 106 (44.34%)	
occurrences (all)	39	47	
Drowsiness (14-day FU after TETRAct/Hib vaccination)	Additional description: During the 14-day follow-up period after vaccination with TETRAct/Hib vaccine		
alternative assessment type: Systematic			
subjects affected / exposed	64 / 107 (59.81%)	58 / 107 (54.21%)	
occurrences (all)	64	58	
Fever (14-day FU after TETRAct/Hib vaccination)	Additional description: During the 14-day follow-up period after vaccination with TETRAct/Hib vaccine		
alternative assessment type: Systematic			
subjects affected / exposed	24 / 107 (22.43%)	25 / 107 (23.36%)	
occurrences (all)	24	25	
Irritability (14-day after vaccination with TETRAct/Hib)	Additional description: During the 14-day follow-up period after vaccination with TETRAct/Hib vaccine		
alternative assessment type: Systematic			
subjects affected / exposed	89 / 107 (83.18%)	88 / 107 (82.24%)	
occurrences (all)	89	88	
Loss of appetite (14 day after vaccination with TETRAct/Hib)	Additional description: During the 14-day follow-up period after vaccination with TETRAct/Hib vaccine		
alternative assessment type: Systematic			
subjects affected / exposed	58 / 107 (54.21%)	49 / 107 (45.79%)	
occurrences (all)	58	49	
Pyrexia (29-day after vaccination with Dose 3 of RTS,S/AS02D or Engerix-B)	Additional description: During the 29-day follow-up period after vaccination with Dose 3 of RTS,S/AS02D or Engerix-B® vaccine		
subjects affected / exposed[2]	5 / 97 (5.15%)	3 / 97 (3.09%)	
occurrences (all)	5	3	
Pain (7-day after vaccination with RTS,S/AS02D or Engerix-B)	Additional description: During the 7-day follow-up period after vaccination with RTS,S/AS02D or Engerix-B® vaccine		
alternative assessment type: Systematic			
subjects affected / exposed[3]	105 / 105 (100.00%)	105 / 106 (99.06%)	
occurrences (all)	105	105	
Swelling (7-day after vaccination with RTS,S/AS02D or Engerix-B)	Additional description: During the 7-day follow-up period after vaccination with RTS,S/AS02D or Engerix-B® vaccine		

alternative assessment type: Systematic			
subjects affected / exposed[4]	23 / 106 (21.70%)	26 / 105 (24.76%)	
occurrences (all)	23	26	
Drowsiness (7-day after vaccination with RTS,S/AS02D or Engerix-B)	Additional description: During the 7-day follow-up period after vaccination with RTS,S/AS02D or Engerix-B® vaccine		
alternative assessment type: Systematic			
subjects affected / exposed[5]	60 / 105 (57.14%)	69 / 106 (65.09%)	
occurrences (all)	60	69	
Fever (7-day after vaccination with RTS,S/AS02D or Engerix-B)	Additional description: During the 7-day follow-up period after vaccination with RTS,S/AS02D or Engerix-B® vaccine		
alternative assessment type: Systematic			
subjects affected / exposed[6]	25 / 105 (23.81%)	23 / 106 (21.70%)	
occurrences (all)	25	23	
Irritability (7-day after vaccination with RTS,S/AS02D or Engerix-B)	Additional description: During the 7-day follow-up period after vaccination with RTS,S/AS02D or Engerix-B® vaccine		
alternative assessment type: Systematic			
subjects affected / exposed[7]	81 / 105 (77.14%)	81 / 106 (76.42%)	
occurrences (all)	81	81	
Loss of appetite (7-day after vaccination with RTS,S/AS02D or Engerix-B)	Additional description: During the 7-day follow-up period after vaccination with RTS,S/AS02D or Engerix-B® vaccine		
alternative assessment type: Systematic			
subjects affected / exposed[8]	53 / 105 (50.48%)	62 / 106 (58.49%)	
occurrences (all)	53	62	
Eye disorders			
Conjunctivitis (14-day after RTS, S/AS02D or Engerix-B vaccination)	Additional description: During the 14-day follow-up period after vaccination with RTS,S/AS02D or Engerix-B® vaccine		
subjects affected / exposed	7 / 107 (6.54%)	2 / 107 (1.87%)	
occurrences (all)	7	2	
Gastrointestinal disorders			
Diarrhea (14-day FU after TETRAct/Hib vaccination)	Additional description: During the 14-day follow-up period after vaccination with TETRAct/Hib vaccine		
subjects affected / exposed	17 / 107 (15.89%)	6 / 107 (5.61%)	
occurrences (all)	17	6	
Diarrhea (14-day after vaccination with Doses 1 and 2 of RTS,S/AS02D or Engerix-B)	Additional description: During the 14-day follow-up period after vaccination with Doses 1 and 2 of RTS,S/AS02D or Engerix-B® vaccine		
subjects affected / exposed[9]	8 / 105 (7.62%)	8 / 106 (7.55%)	
occurrences (all)	8	8	
Diarrhea (29-day after vaccination with Dose 3 of RTS,S/AS02D or	Additional description: During the 29-day follow-up period after vaccination with Dose 3 of RTS,S/AS02D or Engerix-B® vaccine		

Engerix-B)			
subjects affected / exposed[10]	6 / 97 (6.19%)	6 / 97 (6.19%)	
occurrences (all)	6	6	
Respiratory, thoracic and mediastinal disorders			
Cough (14-day FU after TETRAct/Hib vaccination)	Additional description: During the 14-day follow-up period after vaccination with TETRAct/Hib vaccine		
subjects affected / exposed	13 / 107 (12.15%)	10 / 107 (9.35%)	
occurrences (all)	13	10	
Infections and infestations			
Upper respiratory tract infection (14 day FU after TETRAct/Hib vaccination)	Additional description: During the 14-day follow-up period after vaccination with TETRAct/Hib vaccine		
subjects affected / exposed	26 / 107 (24.30%)	18 / 107 (16.82%)	
occurrences (all)	26	18	
Malaria (14 day FU after TETRAct/Hib vaccination)	Additional description: During the 14-day follow-up period after vaccination with TETRAct/Hib vaccine		
subjects affected / exposed	14 / 107 (13.08%)	7 / 107 (6.54%)	
occurrences (all)	14	7	
Bronchitis (14 day FU after TETRAct/Hib vaccination)	Additional description: During the 14-day follow-up period after vaccination with TETRAct/Hib vaccine		
subjects affected / exposed	7 / 107 (6.54%)	5 / 107 (4.67%)	
occurrences (all)	7	5	
Upper respiratory tract infection (14-day after Doses 1 and 2 of RTS, S/AS02Dor Engerix-B)	Additional description: During the 14-day follow-up period after vaccination with Doses 1 and 2 of RTS,S/AS02D or Engerix-B vaccine		
subjects affected / exposed[11]	21 / 105 (20.00%)	24 / 106 (22.64%)	
occurrences (all)	21	24	
Upper respiratory tract infection (29-day FU after Dose 3 of RTS,S/AS02D or Engerix-B)	Additional description: During the 29-day follow-up period after vaccination with Dose 3 of RTS,S/AS02D or Engerix-B vaccine		
subjects affected / exposed[12]	7 / 97 (7.22%)	15 / 97 (15.46%)	
occurrences (all)	7	15	
Malaria (30-day after vaccination with RTS,S/AS02D or Engerix-B)	Additional description: During the 30-day follow-up period after vaccination with RTS,S/AS02D or Engerix-B® vaccine		
subjects affected / exposed[13]	0 / 97 (0.00%)	7 / 97 (7.22%)	
occurrences (all)	0	7	
Ear infection (14-day FU after TETRAct/Hib vaccination)	Additional description: During the 14-day follow-up period after vaccination with TETRAct/Hib vaccine		
subjects affected / exposed	3 / 107 (2.80%)	6 / 107 (5.61%)	
occurrences (all)	3	6	
Malaria (14-day after Doses 1 and 2 of RTS,S/AS02D or Engerix-B)	Additional description: During the 14-day follow-up period after vaccination with Doses 1 and 2 of RTS,S/AS02D or Engerix-B® vaccine		

subjects affected / exposed[14] occurrences (all)	3 / 105 (2.86%) 3	7 / 106 (6.60%) 7	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Results are for subjects with available results for the indicated vaccinations received and/or period of safety follow-up specified.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Results are for subjects with available results for the indicated vaccinations received and/or period of safety follow-up specified.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Results are for subjects with available results for the indicated vaccinations received and/or period of safety follow-up specified.

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Results are for subjects with available results for the indicated vaccinations received and/or period of safety follow-up specified.

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Results are for subjects with available results for the indicated vaccinations received and/or period of safety follow-up specified.

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Results are for subjects with available results for the indicated vaccinations received and/or period of safety follow-up specified.

[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Results are for subjects with available results for the indicated vaccinations received and/or period of safety follow-up specified.

[8] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Results are for subjects with available results for the indicated vaccinations received and/or period of safety follow-up specified.

[9] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Results are for subjects with available results for the indicated vaccinations received and/or period of safety follow-up specified.

[10] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Results are for subjects with available results for the indicated vaccinations received and/or period of safety follow-up specified.

[11] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Results are for subjects with available results for the indicated vaccinations received and/or period of safety follow-up specified.

[12] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Results are for subjects with available results for the indicated vaccinations received and/or period of safety follow-up specified.

[13] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Results are for subjects with available results for the indicated vaccinations received and/or period of safety follow-up specified.

[14] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: Results are for subjects with available results for the indicated vaccinations received and/or period of safety follow-up specified.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 January 2005	The exclusion criterion relating to weight of children at screening was updated to reflect the average birth weights of the local community. The minimum weight for children at screening in the trial was now expressed as a weight for age z-score. This corresponds to a weight of 3.9 kg for 2 month old boys and 3.6 kg for 2 month old girls. In order to help study personnel carrying out the screening visit, the suitable kg weights for 2 month old boys and girls were also cited in the exclusion criteria.
12 April 2005	The Centro de Investigação em Saude da Manhiça (CISM), GSK Biologicals and Malaria Vaccine Initiative (MVI) teams decided to remove assessments of candidate genes specific for malaria vaccination responses from this study. All references to the assessments were removed throughout the protocol. The volume of collected blood was increased from 1 mL to 2 mL for cell-mediated immunity (CMI) assessment. In order to assess the pertussis response it was necessary to account for maternally acquired immunity. Assessment of antibodies to pertussis at screening was omitted in previous versions of the protocol. This was corrected in this amendment.
05 July 2005	In order to expedite the recruitment for this trial, a second health centre was used to recruit mothers and vaccinate infants in addition to the health centre at Ilha Josina. This second health centre, Taninga, was similar to that at Ilha Josina. All facilities available at Ilha Josina were also available at Taninga and all staff was trained to the same standard. It was proposed to carry out all procedures in exactly the same manner as for those mothers and infants recruited at Ilha Josina. A detailed description of the facilities available at the Taninga Health Center was added to the protocol with this amendment. At the request of the Food and Drug Administration, a rationale for the proposed interim analysis at 1 month post final dose of vaccine was added. It was clarified that the Data Safety Monitoring Board (DSMB) may suspend the trial temporarily. However should it be necessary to stop the trial permanently, the responsibility remained with the Sponsor, GSK Biologicals. Treatment options for women who were HIV positive and the infants they give birth to were updated to be in line with the current recommendations of the Mozambican Ministry of Health.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported