



Clinical trial results:

A Phase IIb randomized, double-blind, controlled study of the safety, immunogenicity and proof-of-concept of RTS,S/AS02D, a candidate malaria vaccine, when incorporated into an Expanded Program on Immunization (EPI) regimen that includes DTPw/Hib in infants living in a malaria-endemic region.

Summary

EudraCT number	2015-001539-19
Trial protocol	Outside EU/EEA
Global end of trial date	15 January 2009

Results information

Result version number	v1
This version publication date	11 May 2016
First version publication date	08 July 2015

Trial information

Trial identification

Sponsor protocol code	104298
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00289185
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, 44 2089904466, GSKClinicalSupportHD@gsk.com
Scientific contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, 44 2089904466, 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	11 December 2009
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	15 January 2009
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 + TETRActHib (vaccine against diphtheria, tetanus, pertussis and Haemophilus influenzae type B) co-administered as 3 doses intramuscularly in separate thighs to infants at 8, 12 and 16 weeks of age.
-To demonstrate the non-inferiority of antibody responses to antigens D (diphtheria), T (tetanus), Pw (whole-cell pertussis), Hib (Haemophilus influenzae type B) and HBs (hepatitis B), when administered as 3 doses of RTS,S/AS02D + TETRActHib at 8, 12 and 16 weeks of age compared to a regimen of 3 doses of Engerix-B (hepatitis B vaccine) + TETRActHib at the same age when assessed at 1 month post Dose 3.

Protection of trial subjects:

Vaccinations took place the expanded program of immunization (EPI) clinic of the Bagamoyo District Hospital (BDH). All subjects were supervised closely for at least one hour following vaccination with appropriate medical treatment readily available to evaluate and treat any acute adverse events. Vaccines were administered by qualified and trained personnel. Vaccines were administered only to eligible subjects that had no contraindications to any components of the vaccines. Subjects were followed-up for one month (minimum 30 days) following administration of the last dose of study vaccines. Subjects who could not be vaccinated on the originally scheduled were vaccinated within 7 days and undergo all study procedures for the visit on the same day as vaccination. In the particular case of any child found to be febrile (axillary temperature $\geq 37.5^{\circ}\text{C}$), a blood slide was taken to investigate for malaria. Children were treated as appropriate for their condition and were followed up until resolution of any symptoms and vaccinated if their clinical symptoms resolved within 7 days. Those who could not be re-vaccinated within 7 days of their scheduled date continued all study procedures apart from receiving further study vaccinations. The parent(s)/guardian(s) of infants who are withdrawn from the study will be advised on an appropriate method of completing the infants' vaccination regimen. In addition to above, subjects were followed-up for post-vaccination adverse events (AEs) and serious AEs (SAEs) according to the following timeframes: 7-day (Days 0-6) and 21-day (Days 0-20) periods post vaccination for solicited symptoms and unsolicited AEs, respectively; SAEs were assessed throughout the entire study period, from Week 0 to Month 20.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 September 2006
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
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	Tanzania, United Republic of: 340
Worldwide total number of subjects	340
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)	340
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:

A total of 340 subjects were enrolled for this study. The study comprised 2 phases, a double-blind phase, from Week 0 to Month 9 (2 months after the administration of the last vaccine dose), followed by a single-blind safety phase, from Month 9 to study end at Month 20.

Pre-assignment

Screening details:

Screening included the following: routine antenatal care to counsel/test for HIV infection in pregnancy, check for inclusion/exclusion criteria, vaccination contraindications/precautions & subjects' medical history, & signing informed consent forms.

Period 1

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

Blinding implementation details:

The study was run as a double blind to Month 9, then as a single blind to Month 20. To Month 9, data pertaining to RTS,S/AS02D or Engerix-B were collected in a double blinded manner and data relating to TETRActHib in an open fashion. 'Double blinded' meant that the vaccine recipient and their parent(s)/guardian(s) as well as those responsible for the evaluation of safety, immunogenicity and efficacy endpoints were unaware which treatment, RTS,S/AS02D or Engerix-B, was administered to a

Arms

Are arms mutually exclusive?	Yes
Arm title	Engerix-B Group

Arm description:

Subjects aged between 6 and 10 weeks at the time of first vaccination received by intramuscular injection a 3-dose vaccination course of Engerix-B® vaccine co-administered with the TETRActHib™ vaccine at Week 0, Week 4 (Month 1) and Week 8 (Month 2). 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	Engerix-B Junior
Investigational medicinal product code	HBV Paediatric 10
Other name	HBV, Engerix-B
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

3-dose intramuscular injection in the thigh.

Investigational medicinal product name	TETRActHib
Investigational medicinal product code	DTPw+Hib
Other name	DTPw/Hib
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	RTS,S/AS02D Group
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Arm description:

Subjects aged between 6 and 10 weeks at the time of first vaccination received by intramuscular injection a 3-dose vaccination course of the RTS,S/AS02D vaccine co-administered with the TETRActHib™ vaccine at Week 0, Week 4 (Month 1) and Week 8 (Month 2). 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	TETRActHib
Investigational medicinal product code	DTPw+Hib
Other name	DTPw/Hib
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	Candidate Plasmodium falciparum Malaria vaccines
Investigational medicinal product code	RTS,S/AS02D
Other name	GSK 257146; RTS,S/AS02D
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

Number of subjects in period 1	Engerix-B Group	RTS,S/AS02D Group
Started	170	170
Completed	142	144
Not completed	28	26
Physician decision	4	-
Consent withdrawn by subject	-	8
Death	1	1
Lost to follow-up	23	17

Baseline characteristics

Reporting groups

Reporting group title	Engerix-B Group
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Reporting group description:

Subjects aged between 6 and 10 weeks at the time of first vaccination received by intramuscular injection a 3-dose vaccination course of Engerix-B® vaccine co-administered with the TETRActHib™ vaccine at Week 0, Week 4 (Month 1) and Week 8 (Month 2). The Engerix-B® vaccine was administered in the left anterolateral thigh, and the TETRActHib™ vaccine in the right anterolateral thigh..

Reporting group title	RTS,S/AS02D Group
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Reporting group description:

Subjects aged between 6 and 10 weeks at the time of first vaccination received by intramuscular injection a 3-dose vaccination course of the RTS,S/AS02D vaccine co-administered with the TETRActHib™ vaccine at Week 0, Week 4 (Month 1) and Week 8 (Month 2). The RTS,S/AS02D vaccine was administered in the left anterolateral thigh, and the TETRActHib™ vaccine in the right anterolateral thigh.

Reporting group values	Engerix-B Group	RTS,S/AS02D Group	Total
Number of subjects	170	170	340
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	7.87	7.82	
standard deviation	± 0.83	± 0.77	-
Gender categorical			
Units: Subjects			
Female	85	91	176
Male	85	79	164

End points

End points reporting groups

Reporting group title	Engerix-B Group
Reporting group description:	
Subjects aged between 6 and 10 weeks at the time of first vaccination received by intramuscular injection a 3-dose vaccination course of Engerix-B® vaccine co-administered with the TETRActHib™ vaccine at Week 0, Week 4 (Month 1) and Week 8 (Month 2). The Engerix-B® vaccine was administered in the left anterolateral thigh, and the TETRActHib™ vaccine in the right anterolateral thigh..	
Reporting group title	RTS,S/AS02D Group
Reporting group description:	
Subjects aged between 6 and 10 weeks at the time of first vaccination received by intramuscular injection a 3-dose vaccination course of the RTS,S/AS02D vaccine co-administered with the TETRActHib™ vaccine at Week 0, Week 4 (Month 1) and Week 8 (Month 2). The RTS,S/AS02D vaccine was administered in the left anterolateral thigh, and the TETRActHib™ vaccine in the right anterolateral thigh.	

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

End point title	Concentrations of antibodies against hepatitis B (Anti-HB) ^[1]
End point description:	
Concentrations were expressed as geometric mean concentrations (GMCs) in milli-international unit per milliliter (mIU/mL). The cut-off of the assay was the seroprotection cut-off of 10 mIU/mL. Month 3 results are the specific results for this primary outcome measure.	
End point type	Primary
End point timeframe:	
Prior to vaccination at Week 0 (PRE), at Month 2 and at Month 3.	
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	Engerix-B Group	RTS,S/AS02D Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	165		
Units: mIU/mL				
geometric mean (confidence interval 95%)				
Anti-HB – PRE (N=134;116)	13 (9.8 to 17.2)	14.3 (10.8 to 19)		
Anti-HB – Month 2 (N=148;149)	16.9 (13.5 to 21.2)	111.8 (89.9 to 139)		
Anti-HB – Month 3 (N=141;141)	113.8 (91.3 to 141.8)	667.4 (533.8 to 834.4)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of subjects with serious adverse events (SAEs) ^[2]
End point description: SAEs assessed include medical occurrences that result in death, are life threatening, require hospitalization or prolongation of hospitalization or result in disability/incapacity.	
End point type	Primary
End point timeframe: From Week 0 to Month 9.	

Notes:

[2] - 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	Engerix-B Group	RTS,S/AS02D Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	170		
Units: Subject	42	31		

Statistical analyses

No statistical analyses for this end point

Primary: Concentrations of antibodies against diphtheria (Anti-D)

End point title	Concentrations of antibodies against diphtheria (Anti-D) ^[3]
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 cut-off of the assay was the seroprotection cut-off of 0.1 IU/mL. Month 3 results are the specific results for this primary outcome measure.	
End point type	Primary
End point timeframe: Prior to vaccination at Week 0 (PRE), and at Month 3.	

Notes:

[3] - 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	Engerix-B Group	RTS,S/AS02D Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	162		
Units: IU/mL				
geometric mean (confidence interval 95%)				
Anti-D – PRE (N=165;162)	0.1 (0.1 to 0.1)	0.1 (0.1 to 0.1)		
Anti-D – Month 3 (N=151;149)	1.3 (1.1 to 1.5)	1.1 (1 to 1.3)		

Statistical analyses

No statistical analyses for this end point

Primary: Concentrations of antibodies against tetanus (Anti-T)

End point title	Concentrations of antibodies against tetanus (Anti-T) ^[4]
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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 cut-off of the assay was the seroprotection cut-off of 0.1 IU/mL. Month 3 results are the specific results for this primary outcome measure.

End point type	Primary
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End point timeframe:

Prior to vaccination at Week 0 (PRE), and at Month 3.

Notes:

[4] - 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	Engerix-B Group	RTS,S/AS02D Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	162		
Units: IU/mL				
geometric mean (confidence interval 95%)				
Anti-T – PRE (N=165;162)	1.1 (0.9 to 1.4)	1.2 (1 to 1.6)		
Anti-T – Month 3 (N=151;149)	4.2 (3.6 to 4.8)	3 (2.6 to 3.4)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Concentrations of anti-polyribosyl ribitol phosphate antibodies (Anti-PRP). ^[5]
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End point description:

Concentrations were expressed as geometric mean concentrations (GMCs) in microgram per milliliter (µg/mL). The cut-off of the assay is the seroprotection cut-off value of 0.15 µg/mL. Month 3 results are the specific results for this primary outcome measure.

End point type	Primary
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End point timeframe:

Prior to vaccination at Week 0 (PRE), and at Month 3.

Notes:

[5] - 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	Engerix-B Group	RTS,S/AS02D Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	162		
Units: µg/mL				
geometric mean (confidence interval 95%)				
Anti-PRP – PRE (N=165;162)	0.2 (0.2 to 0.2)	0.2 (0.2 to 0.2)		
Anti-PRP – Month 3 (N=151;148)	19.3 (15.6 to 24)	14.3 (11.5 to 17.9)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of subjects with serious adverse events (SAEs) ^[6]
End point description: SAEs assessed include medical occurrences that result in death, are life threatening, require hospitalization or prolongation of hospitalization or result in disability/incapacity.	
End point type	Primary
End point timeframe: From Month 9 to Month 20.	
Notes: [6] - 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	Engerix-B Group	RTS,S/AS02D Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	170		
Units: Subjects	34	34		

Statistical analyses

No statistical analyses for this end point

Primary: 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 cut-off of the assay was the seropositivity cut-off of 15 EL.U/mL. Month 3 results are the specific results for this primary outcome measure.	
End point type	Primary
End point timeframe: Prior to vaccination at Week 0 (PRE), and at Month 3.	

End point values	Engerix-B Group	RTS,S/AS02D Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162	165		
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Anti-BPT – PRE (N=165;162)	7.6 (7.4 to 7.8)	7.6 (7.4 to 7.7)		
Anti-BPT – Month 3 (N=144;148)	101.4 (92.5 to 111.2)	82.3 (75.4 to 89.9)		

Statistical analyses

Statistical analysis title	Non-inferiority - Anti-BPT immune response
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Statistical analysis description:

The aim was to test the non-inferiority (NI) of 3 doses of RTS,S/AS02D vs 3 doses of HBV, both co-administered with DTPw/Hib, as regards antigens for HBs, D, T, PRP and BPT. NI was demonstrated if - ALL criteria to be met: 1) difference between groups in percent of seroprotection (SPR) < 10% for anti-HB, -D, -T and PRP antibodies AND 2) geometric mean concentration (GMC) ratio between groups < 1.5 for anti-BPT antibodies.

Comparison groups	Engerix-B Group v RTS,S/AS02D Group
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[7]
Parameter estimate	GMC ratio
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.08
upper limit	1.4

Notes:

[7] - This analysis concerns the NI assessment for anti-PBT immune response. GMC ratio between groups (Engerix-B over RTS,S/AS02D) as anti BPT antibody concentrations (expressed in %) was calculated as well as the 95% CI (standardized asymptotic) (criteria for success = lower limit of 95% CI of GMC ratio between groups < 1.5). Results from this analysis are to be combined with those for NI assessment for antigens for HB, D, T, PRP and BPT to obtain an overall assessment of NI.

Primary: Number of subjects with hepatitis B antibody (Anti-HB) concentrations equal to or above (>=) the seroprotection cut-off value

End point title	Number of subjects with hepatitis B antibody (Anti-HB) concentrations equal to or above (>=) the seroprotection cut-off value
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End point description:

The seroprotection cut-off value was 10 milli-international units per milliliter (mIU/mL). Blood samples were collected prior to vaccination at Week 0 (PRE), at Month 2 and at Month 3. Month 3 results are the specific results for this primary outcome measure.

End point type	Primary
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End point timeframe:

Prior to vaccination at Week 0 (PRE), at Month 2 and at Month 3.

End point values	Engerix-B Group	RTS,S/AS02D Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	149		
Units: Subjects				
Anti-HB \geq 10 mIU/mL – PRE (N=134;116)	45	44		
Anti-HB \geq 10 mIU/mL – Month 2 (N=148;149)	82	141		
Anti-HB \geq 10 mIU/mL – Month 3 (N=141;141)	133	141		

Statistical analyses

Statistical analysis title	Non-inferiority - Anti-HB SPR immune response
Statistical analysis description:	
The aim was to test the non-inferiority (NI) of 3 doses of RTS,S/AS02D vs 3 doses of HBV, both co-administered with DTPw/Hib, as regards antigens for HB, D, T, PRP and BPT as assessed at Month 3. NI was demonstrated if - ALL criteria to be met: 1) difference between groups in percent of seroprotection (SPR) < 10% for anti-HB, -D, -T and PRP antibodies AND 2) geometric mean concentration (GMC) ratio between groups < 1.5 for anti-BPT antibodies.	
Comparison groups	Engerix-B Group v RTS,S/AS02D Group
Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[8]
Parameter estimate	Difference in %
Point estimate	-5.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.8
upper limit	2.9

Notes:

[8] - This analysis assesses NI as regards anti-HB immune response. The difference between groups (Engerix-B minus RTS,S/AS02D) as regards SPR (expressed in %) was calculated as well as the 95% CI (standardized asymptotic) around this difference (criteria for success = lower limit of 95% CI of difference between groups in percent of SPR < 10%). Results from this analysis are to be combined with those for NI assessment for antigens for HB, D, T, PRP and BPT to obtain an overall assessment of NI.

Primary: Number of subjects with anti-diphtheria antibody (Anti-D) concentrations equal to or above (\geq) the seroprotection cut-off value

End point title	Number of subjects with anti-diphtheria antibody (Anti-D) concentrations equal to or above (\geq) the seroprotection cut-off value
End point description:	
Antibodies were measured by Enzyme-linked immunosorbent assay (ELISA). The seroprotection cut-off value was 0.1 international unit per milliliter (IU/mL). Blood samples were collected prior to vaccination at Week 0 (PRE), and at Month 3. Month 3 results are the specific results for this primary outcome measure.	
End point type	Primary

End point timeframe:

Prior to vaccination at Week 0 (PRE), and at Month 3.

End point values	Engerix-B Group	RTS,S/AS02D Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	162		
Units: Subjects				
Anti-D \geq 0.1 IU/mL – PRE (N=165;162)	27	24		
Anti-D \geq 0.1 IU/mL – Month 3 (N=151;149)	148	148		

Statistical analyses

Statistical analysis title	Non-inferiority - Anti-D SPR immune response
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Statistical analysis description:

The aim was to test the non-inferiority (NI) of 3 doses of RTS,S/AS02D vs 3 doses of HBV, both co-administered with DTPw/Hib, as regards antigens for HB, D, T, PRP and BPT as assessed at Month 3. NI was demonstrated if - ALL criteria to be met: 1) difference between groups in percent of seroprotection (SPR) < 10% for anti-HB, -D, -T and PRP antibodies AND 2) geometric mean concentration (GMC) ratio between groups < 1.5 for anti-BPT antibodies.

Comparison groups	Engerix-B Group v RTS,S/AS02D Group
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[9]
Parameter estimate	Difference in %
Point estimate	-1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.09
upper limit	1.9

Notes:

[9] - This analysis assesses NI as regards anti-D immune response. The difference between groups (Engerix-B minus RTS,S/AS02D) as regards SPR (expressed in %) was calculated as well as the 95% CI (standardized asymptotic) around this difference (criteria for success = lower limit of 95% CI of difference between groups in percent of SPR < 10%). Results from this analysis are to be combined with those for NI assessment for antigens for HB, D, T, PRP and BPT to obtain an overall assessment of NI.

Primary: Number of subjects with anti-tetanus antibody (Anti-T) concentrations equal to or above (\geq) the seroprotection cut-off value

End point title	Number of subjects with anti-tetanus antibody (Anti-T) concentrations equal to or above (\geq) the seroprotection cut-off value
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End point description:

Antibodies were measured by Enzyme-linked immunosorbent assay (ELISA). The seroprotection cut-off value was 0.1 international unit per milliliter (IU/mL). Blood samples were collected prior to vaccination at Week 0 (PRE), and at Month 3. Month 3 results are the specific results for this primary outcome measure.

End point type	Primary
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End point timeframe:

Prior to vaccination at Week 0 (PRE), and at Month 3.

End point values	Engerix-B Group	RTS,S/AS02D Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	162		
Units: Subjects				
Anti-T \geq 0.1 IU/mL – PRE (N=165;162)	156	155		
Anti-T \geq 0.1 IU/mL – Month 3 (N=151;149)	151	149		

Statistical analyses

Statistical analysis title	Non-inferiority - Anti-T SPR immune response
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Statistical analysis description:

The aim was to test the non-inferiority (NI) of 3 doses of RTS,S/AS02D vs 3 doses of HBV, both co-administered with DTPw/Hib, as regards antigens for HB, D, T, PRP and BPT as assessed at Month 3. NI was demonstrated if - ALL criteria to be met: 1) difference between groups in percent of seroprotection (SPR) < 10% for anti-HB, -D, -T and PRP antibodies AND 2) geometric mean concentration (GMC) ratio between groups < 1.5 for anti-BPT antibodies.

Comparison groups	Engerix-B Group v RTS,S/AS02D Group
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[10]
Parameter estimate	Difference in %
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.48
upper limit	2.51

Notes:

[10] - This analysis assesses NI as regards anti-T immune response. The difference between groups (Engerix-B minus RTS,S/AS02D) as regards SPR (expressed in %) was calculated as well as the 95% CI (standardized asymptotic) around this difference (criteria for success = lower limit of 95% CI of difference between groups in percent of SPR < 10%). Results from this analysis are to be combined with those for NI assessment for antigens for HB, D, T, PRP and BPT to obtain an overall assessment of NI.

Primary: Number of subjects with anti-polyribosyl ribitol phosphate antibody (Anti-PRP) concentrations equal to or above (\geq) the seroprotection cut-off value

End point title	Number of subjects with anti-polyribosyl ribitol phosphate antibody (Anti-PRP) concentrations equal to or above (\geq) the seroprotection cut-off value
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End point description:

Antibodies were measured by Enzyme-linked immunosorbent assay (ELISA). The seroprotection cut-off value was 0.15 microgram per milliliter (μ g/mL). Blood samples were collected prior to vaccination at Week 0 (PRE), and at Month 3. Month 3 results are the specific results for this primary outcome measure.

End point type	Primary
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End point timeframe:

Prior to vaccination at Week 0 (PRE), and at Month 3.

End point values	Engerix-B Group	RTS,S/AS02D Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	162		
Units: Subjects				
Anti-PRP $\geq 0.15 \mu\text{g/mL}$ - PRE (N=165;162)	86	78		
Anti-PRP $\geq 0.15 \mu\text{g/mL}$ - Month 3 (N=151;148)	150	147		

Statistical analyses

Statistical analysis title	Non-inferiority - Anti-PRP SPR immune response
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Statistical analysis description:

The aim was to test the non-inferiority (NI) of 3 doses of RTS,S/AS02D vs 3 doses of HBV, both co-administered with DTPw/Hib, as regards antigens for HB, D, T, PRP and BPT as assessed at Month 3. NI was demonstrated if - ALL criteria to be met: 1) difference between groups in percent of seroprotection (SPR) $< 10\%$ for anti-HB, -D, -T and PRP antibodies AND 2) geometric mean concentration (GMC) ratio between groups < 1.5 for anti-BPT antibodies.

Comparison groups	Engerix-B Group v RTS,S/AS02D Group
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[11]
Parameter estimate	Difference in %
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.04
upper limit	3.12

Notes:

[11] - This analysis assesses NI as regards anti-PRP immune response. The difference between groups (Engerix-B minus RTS,S/AS02D) as regards SPR (expressed in %) was calculated as well as the 95% CI (standardized asymptotic) around this difference (criteria for success = lower limit of 95% CI of difference between groups in percent of SPR $< 10\%$). Results from this analysis are to be combined with those for NI assessment for antigens for HB, D, T, PRP and BPT to obtain an overall assessment of NI.

Primary: Number of subjects with anti-Bordetella pertussis toxin antibody (Anti-BPT) concentrations equal to or above (\geq) the seropositivity cut-off value

End point title	Number of subjects with anti-Bordetella pertussis toxin antibody (Anti-BPT) concentrations equal to or above (\geq) the seropositivity cut-off value ^[12]
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End point description:

Antibodies were measured by Enzyme-linked immunosorbent assay (ELISA). The seropositivity cut-off value was 15 ELISA units per milliliter (EL.U/mL). Blood samples were collected prior to vaccination at Week 0 (PRE), and at Month 3. Month 3 results are the specific results for this primary outcome measure.

End point type	Primary
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End point timeframe:

Prior to vaccination at Week 0 (PRE), and at Month 3.

Notes:

[12] - 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	Engerix-B Group	RTS,S/AS02D Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	162		
Units: Subjects				
Anti-BPT \geq 15 EL.U/mL - PRE (N=165;162)	2	1		
Anti-BPT \geq 15 EL.U/mL - Month 3 (N=144;148)	142	148		

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
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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 cut-off of the assay was the seropositivity cut-off value of 0.5 EL.U/mL.

End point type	Secondary
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End point timeframe:

Prior to vaccination at Week 0 (PRE), at Month 2, at Month 3 and at Month 9.

End point values	Engerix-B Group	RTS,S/AS02D Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156	151		
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Anti-CS - PRE (N=152;141)	0.4 (0.3 to 0.4)	0.3 (0.3 to 0.4)		
Anti-CS - Month 2 (N=156;151)	0.3 (0.3 to 0.3)	28.9 (22.4 to 37.3)		
Anti-CS - Month 3 (N=144;143)	0.3 (0.2 to 0.3)	69.5 (53.9 to 89.6)		
Anti-CS - Month 9 (N=147;143)	0.3 (0.3 to 0.3)	6.2 (4.6 to 8.3)		

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.
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End point description:

Assessed solicited local symptoms were pain and swelling following vaccination with the RTS,S/AS02D or Engerix-B vaccine.

End point type	Secondary
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End point timeframe:

Within 7 days (Days 0-6) after vaccination with the RTS,S/AS02D or Engerix-B vaccine.

End point values	Engerix-B Group	RTS,S/AS02D Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	170		
Units: Subjects				
Pain	167	161		
Swelling	17	19		

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.
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End point description:

Assessed solicited local symptoms were pain and swelling following vaccination with the TETRActHib vaccine.

End point type	Secondary
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End point timeframe:

Within 7 days (Days 0-6) after vaccination with the TETRActHib vaccine.

End point values	Engerix-B Group	RTS,S/AS02D Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	170		
Units: Subjects				
Pain	169	168		
Swelling	68	67		

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.
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End point description:

Assessed solicited general symptoms were drowsiness, fever, irritability, and loss of appetite. Fever was defined as axillary temperature above or equal to (\geq) 37.5 degrees Celsius ($^{\circ}\text{C}$).

End point type	Secondary
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End point timeframe:

Within 7 days (Days 0-6) after vaccination

End point values	Engerix-B Group	RTS,S/AS02D Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	170		
Units: Subjects				
Drowsiness	4	3		
Fever (Temperature $\geq 37.5^{\circ}\text{C}$)	52	103		
Irritability	71	81		
Loss of Appetite	5	5		

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).
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End point description:

An unsolicited adverse event is any adverse event (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
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End point timeframe:

Within 30 days (Days 0-29) after vaccination

End point values	Engerix-B Group	RTS,S/AS02D Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	170		
Units: Subjects	141	137		

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)
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End point description:

SAEs assessed include medical occurrences that result in death, are life threatening, require hospitalization or prolongation of hospitalization or result in disability/incapacity.

End point type	Secondary
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End point timeframe:

Throughout the entire study, from Week 0 to Month 20.

End point values	Engerix-B Group	RTS,S/AS02D Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	170		
Units: Subjects	62	57		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first malaria infection

End point title	Time to first malaria infection
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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
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End point timeframe:

Over the period starting 14 days after Dose 3 of RTS,S or HBV vaccine and extending for 6 months thereafter (from Month 2.5 up to Month 9).

End point values	Engerix-B Group	RTS,S/AS02D Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	146		
Units: n/PYAR				
number (not applicable)	0.12	0.29		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects prevalent for parasitemia

End point title	Number of subjects prevalent for parasitemia
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 9	

End point values	Engerix-B Group	RTS,S/AS02D Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	137		
Units: Subjects	1	0		

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 ^[13]
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 7 months after administration of Dose 3 of RTS,S or HBV vaccine (Month 9). Parasite density is expressed as mean, minimum and maximum density in parasite per µL. This outcome for solely assessed in the Engerix-B Group, as no subject in the RTS,S/AS02D Group was assessed as prevalent for parasitemia.	
End point type	Secondary
End point timeframe: At Month 9	

Notes:

[13] - 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: This outcome for solely assessed in the Engerix-B Group, as no subject in the RTS, S/AS02D Group was assessed as prevalent for parasitemia.

End point values	Engerix-B Group			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: parasite/ μ L				
arithmetic mean (full range (min-max))	23276 (23276 to 23276)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Time frames for adverse events (AEs) reporting were the 7-day (Days 0-6) and 30-day (Days 0-29) periods post vaccination for solicited symptoms and unsolicited AES, respectively. Serious adverse events were assessed throughout, from Week 0 to Month 20.

Adverse event reporting additional description:

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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	12.1
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Reporting groups

Reporting group title	Engerix-B Group
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Reporting group description:

Subjects aged between 6 and 10 weeks at the time of first vaccination received by intramuscular injection a 3-dose vaccination course of Engerix-B® vaccine co-administered with the TETRActHib™ vaccine at Week 0, Week 4 (Month 1) and Week 8 (Month 2). The Engerix-B® vaccine was administered in the left anterolateral thigh, and the TETRActHib™ vaccine in the right anterolateral thigh.

Reporting group title	RTS,S/AS02D Group
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Reporting group description:

Subjects aged between 6 and 10 weeks at the time of first vaccination received by intramuscular injection a 3-dose vaccination course of the RTS,S/AS02D vaccine co-administered with the TETRActHib vaccine at Week 0, Week 4 (Month 1) and Week 8 (Month 2). The RTS,S/AS02D vaccine was administered in left anterolateral thigh, and the TETRActHib vaccine in the right anterolateral thigh.

Serious adverse events	Engerix-B Group	RTS,S/AS02D Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	62 / 170 (36.47%)	57 / 170 (33.53%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Poisoning			
subjects affected / exposed	1 / 170 (0.59%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Convulsion			
subjects affected / exposed	2 / 170 (1.18%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile convulsion			
subjects affected / exposed	2 / 170 (1.18%)	5 / 170 (2.94%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	16 / 170 (9.41%)	16 / 170 (9.41%)	
occurrences causally related to treatment / all	0 / 16	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis			
subjects affected / exposed	0 / 170 (0.00%)	3 / 170 (1.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis toxic			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	
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			
Asthma			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial hyperreactivity			

subjects affected / exposed	3 / 170 (1.76%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loeffler's syndrome			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary pneumatocele			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess			
subjects affected / exposed	2 / 170 (1.18%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess neck			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acarodermatitis			
subjects affected / exposed	2 / 170 (1.18%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			

subjects affected / exposed	1 / 170 (0.59%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral malaria			
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysentery			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	12 / 170 (7.06%)	16 / 170 (9.41%)	
occurrences causally related to treatment / all	0 / 12	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaria			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Measles			
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis viral			
subjects affected / exposed	1 / 170 (0.59%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasmodium falciparum infection			

subjects affected / exposed	25 / 170 (14.71%)	19 / 170 (11.18%)
occurrences causally related to treatment / all	0 / 25	0 / 19
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia		
subjects affected / exposed	36 / 170 (21.18%)	25 / 170 (14.71%)
occurrences causally related to treatment / all	0 / 36	0 / 25
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia viral		
subjects affected / exposed	2 / 170 (1.18%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pyoderma		
subjects affected / exposed	1 / 170 (0.59%)	0 / 170 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Sepsis		
subjects affected / exposed	2 / 170 (1.18%)	2 / 170 (1.18%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Upper respiratory tract infection		
subjects affected / exposed	3 / 170 (1.76%)	2 / 170 (1.18%)
occurrences causally related to treatment / all	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Urinary tract infection		
subjects affected / exposed	3 / 170 (1.76%)	4 / 170 (2.35%)
occurrences causally related to treatment / all	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Viral infection		
subjects affected / exposed	0 / 170 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

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

Non-serious adverse events	Engerix-B Group	RTS,S/AS02D Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	169 / 170 (99.41%)	168 / 170 (98.82%)	
General disorders and administration site conditions			
Pain			
alternative assessment type: Systematic			
subjects affected / exposed	169 / 170 (99.41%)	168 / 170 (98.82%)	
occurrences (all)	169	168	
Swelling			
alternative assessment type: Systematic			
subjects affected / exposed	68 / 170 (40.00%)	67 / 170 (39.41%)	
occurrences (all)	68	67	
Fever			
alternative assessment type: Systematic			
subjects affected / exposed	53 / 170 (31.18%)	103 / 170 (60.59%)	
occurrences (all)	53	103	
Irritability			
alternative assessment type: Systematic			
subjects affected / exposed	71 / 170 (41.76%)	81 / 170 (47.65%)	
occurrences (all)	71	81	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	6 / 170 (3.53%)	12 / 170 (7.06%)	
occurrences (all)	6	12	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	80 / 170 (47.06%)	80 / 170 (47.06%)	
occurrences (all)	80	80	
Rhinorrhoea			
subjects affected / exposed	73 / 170 (42.94%)	56 / 170 (32.94%)	
occurrences (all)	73	56	
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	1 / 170 (0.59%)	12 / 170 (7.06%)	
occurrences (all)	1	12	
Infections and infestations			
Acarodermatitis			
subjects affected / exposed	4 / 170 (2.35%)	13 / 170 (7.65%)	
occurrences (all)	4	13	
Pneumonia			
subjects affected / exposed	54 / 170 (31.76%)	49 / 170 (28.82%)	
occurrences (all)	54	49	
Skin infection			
subjects affected / exposed	3 / 170 (1.76%)	11 / 170 (6.47%)	
occurrences (all)	3	11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 May 2006	At the request of National Institute of Medical Research (NIMR) and Malaria Vaccine Initiative (MVI) at Program for Appropriate Technology in Health (PATH), a number of operational and administrative details were made to the protocol. A number of errors in the final version of the protocol were corrected.
15 September 2006	Capillary puncture for obtaining blood samples was added as an alternative method to venous extraction with a needle and syringe in order to increase compliance with obtaining blood samples at the required visits. The minimum volume of blood to be obtained at each visit was also reviewed and decreased where appropriate.
20 August 2007	The study protocol was amended due to the low transmission rates observed in the community which would have resulted in an under-powered study to reach the efficacy objective. Efficacy data will be collected to 18 months post Dose 3 (Month 20) by passive case detection. It was proposed not to prolong active detection of infection visits given their intrusive nature for the families. Assessment of SAEs will be conducted for the duration of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported