



Clinical trial results:

Evaluation of the Effectiveness of Two Vaccination Strategies Using GlaxoSmithKline Biologicals' HPV Vaccine GSK580299 (Cervarix TM) Administered in Healthy Adolescents

Summary

EudraCT number	2007-001731-55
Trial protocol	FI
Global end of trial date	17 December 2014

Results information

Result version number	v1
This version publication date	13 April 2016
First version publication date	22 May 2015

Trial information

Trial identification

Sponsor protocol code	106636
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00534638
WHO universal trial number (UTN)	-

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	Interim
Date of interim/final analysis	25 October 2012
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	17 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

CO-PRIMARY OBJECTIVES

- To demonstrate the overall (direct and indirect) effectiveness of GSK Biologicals' HPV-16/18 vaccine in reducing the prevalence of HPV-16/18 genital infection in females approximately 18.5 years of age following community-based vaccination of 12 - 15 year old females only (Arm B versus Arm C).
- To demonstrate the overall (direct and indirect) effectiveness of GSK Biologicals' HPV-16/18 vaccine in reducing the prevalence of HPV-16/18 genital infection in females approximately 18.5 years of age, following community-based vaccination of 12 - 15 year old females and males (Arm A versus Arm C).

Protection of trial subjects:

All subjects were supervised closely for at least 30 minutes following vaccination with appropriate medical treatment readily available. Vaccines were administered by qualified and trained personnel. Vaccines/products were administered only to eligible subjects that had no contraindications to any components of the vaccines. Subjects were followed-up from the time the subject consents to participate in the study until she/he is discharged.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 October 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Finland: 32176
Worldwide total number of subjects	32176
EEA total number of subjects	32176

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	32176
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Immunisation phase (Visit 1 at Day 0 to Phone contact at Month 12) = adolescents (birth cohorts 1992-95) were vaccinated with Cervarix™ or Engerix™-B vaccine. Effectiveness evaluation phase (Visit 5) = the impact of the vaccine intervention was assessed on female subjects of approximately 18.5 years of age.

Pre-assignment

Screening details:

At the time when the study was initiated, the Cervarix™ vaccine was not licensed for use in boys; therefore, male adolescents from communities who received Cervarix™ vaccine were considered to be part of a Phase III trial.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

All subjects knew of the intervention Arm their community had been assigned to (Arm A, B or C – see Treatment Section

below). Blinding was as follows:

- Study participants in Arm A communities and female study participants in Arm B communities were blinded to their treatment allocation (HPV or HBV vaccine).

- Study participants (males and females) in Arm C communities and male study participants in Arm B communities were aware of their treatment allocation as they all received HBV vaccine.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cervarix pooled Group

Arm description:

Male and female subjects receiving Cervarix™ vaccine. The vaccine was administered intramuscularly in the deltoid region of the non-dominant arm according to a 0, 1, 6-month schedule.

Arm type	Experimental
Investigational medicinal product name	Cervarix™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

3 doses by intramuscular injection in the deltoid region of the non-dominant arm

Arm title	Engerix-B pooled Group
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Arm description:

Male and female subjects receiving Engerix™-B vaccine. The vaccine was administered intramuscularly in the deltoid region of the non-dominant arm according to a 0, 1, 6-month schedule.

Arm type	Experimental
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Investigational medicinal product name	Engerix™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

3 doses by intramuscular injection in the deltoid region of the non-dominant arm

Number of subjects in period 1	Cervarix pooled Group	Engerix-B pooled Group
Started	14838	17338
Completed	14713	17188
Not completed	125	150
Consent withdrawn by subject	17	36
Lost to follow-up (subjects with complete vaccinat	22	24
Other - ae:urticaria	2	1
Adverse event, non-fatal	3	3
Other - lost to follow-up	2	-
Non-Serious Adverse Event/ Protocol violation	2	8
Migrated/moved from study area	2	7
Other - consent withdrawal / did not want to come,	46	30
Other – other	6	9
Lost to follow-up	-	2
Lost to follow-up (subjects with incomplete vaccin	22	29
Other - ae/allergic reaction after vaccination	1	1

Baseline characteristics

Reporting groups

Reporting group title	Cervarix pooled Group
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Reporting group description:

Male and female subjects receiving Cervarix™ vaccine. The vaccine was administered intramuscularly in the deltoid region of the non-dominant arm according to a 0, 1, 6-month schedule.

Reporting group title	Engerix-B pooled Group
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Reporting group description:

Male and female subjects receiving Engerix™-B vaccine. The vaccine was administered intramuscularly in the deltoid region of the non-dominant arm according to a 0, 1, 6-month schedule.

Reporting group values	Cervarix pooled Group	Engerix-B pooled Group	Total
Number of subjects	14838	17338	32176
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: years			
arithmetic mean	14.1	14.1	
standard deviation	± 0.75	± 0.76	-
Gender categorical Units: Subjects			
Female	12398	8117	20515
Male	2440	9221	11661

End points

End points reporting groups

Reporting group title	Cervarix pooled Group
Reporting group description: Male and female subjects receiving Cervarix™ vaccine. The vaccine was administered intramuscularly in the deltoid region of the non-dominant arm according to a 0, 1, 6-month schedule.	
Reporting group title	Engerix-B pooled Group
Reporting group description: Male and female subjects receiving Engerix™-B vaccine. The vaccine was administered intramuscularly in the deltoid region of the non-dominant arm according to a 0, 1, 6-month schedule.	

Primary: Genital Human papillomavirus 16 and/or 18 (HPV-16 and/or HPV-18) deoxyribonucleic acid (DNA) positivity (by polymerase chain reaction [PCR])

End point title	Genital Human papillomavirus 16 and/or 18 (HPV-16 and/or HPV-18) deoxyribonucleic acid (DNA) positivity (by polymerase chain reaction [PCR])[¹]
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End point description:

End point type	Primary
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End point timeframe:

At the time of visit 5 (at 18.5 years of age)

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	Cervarix pooled Group	Engerix-B pooled Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[2]	0 ^[3]		
Units: Subjects				

Notes:

[2] - Results were not available at the time of this assessment.

[3] - Results were not available at the time of this assessment.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting any and severe (Grade 3) solicited local symptoms, in a subset of subjects.

End point title	Number of subjects reporting any and severe (Grade 3) solicited local symptoms, in a subset of subjects.
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End point description:

End point type	Secondary
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End point timeframe:

Within 7 days (Days 0 - 6) after any vaccination

End point values	Cervarix pooled Group	Engerix-B pooled Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	603	1028		
Units: Subjects				
Pain, Any	506	251		
Pain, Grade 3	26	2		
Redness, Any	169	1331		
Redness, Grade 3	4	0		
Swelling, Any	131	46		
Swelling, Grade 3	8	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting any, severe (Grade 3) and related to vaccination solicited general symptoms, in a subset of subjects.

End point title	Number of subjects reporting any, severe (Grade 3) and related to vaccination solicited general symptoms, in a subset of subjects.
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End point description:

End point type	Secondary
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End point timeframe:

Within 7 days (Days 0 - 6) after any vaccination

End point values	Cervarix pooled Group	Engerix-B pooled Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	604	1028		
Units: Subjects				
Arthralgia, Any	107	97		
Arthralgia, Grade 3	1	4		
Arthralgia, Related	87	81		
Fatigue, Any	291	411		
Fatigue, Grade 3	7	21		
Fatigue, Related	233	351		
Fever (axillary), Any	48	85		
Fever (axillary), Grade 3	6	9		
Fever (axillary), Related	28	53		
Gastrointestinal, Any	106	163		
Gastrointestinal, Grade 3	11	13		
Gastrointestinal, Related	70	128		

Headache, Any	261	371		
Headache, Grade 3	15	14		
Headache, Related	176	280		
Myalgia, Any	321	250		
Myalgia, Grade 3	12	3		
Myalgia, Related	291	211		
Rash, Any	29	33		
Rash, Grade 3	0	0		
Rash, Related	14	23		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting any, severe (Grade 3) and related to vaccination unsolicited adverse events (AEs), in a subset of subjects.

End point title	Number of subjects reporting any, severe (Grade 3) and related to vaccination unsolicited adverse events (AEs), in a subset of subjects.
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End point description:

End point type	Secondary
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End point timeframe:

Within 30 days (Days 0 - 29) after any vaccination

End point values	Cervarix pooled Group	Engerix-B pooled Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	643	1047		
Units: Subjects				
Subjects with any AEs	157	202		
Subjects with Grade 3 AEs	31	46		
Subjects with related AEs	12	19		
Nasopharyngitis	33	17		
Oropharyngeal pain	15	32		
Headache	23	16		
Influenza	0	23		
Cough	6	14		
Rhinitis	7	9		
Tonsillitis	6	10		
Upper Respiratory Tract Infection	13	0		
Sinusitis	0	9		
Back pain	0	6		
Pain in extremities	6	0		
Dizziness	5	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting rash and urticaria, in a subset of subjects.

End point title	Number of subjects reporting rash and urticaria, in a subset of subjects.
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End point description:

End point type	Secondary
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End point timeframe:

Within 30 minutes following vaccination

End point values	Cervarix pooled Group	Engerix-B pooled Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	643	1047		
Units: Subjects				
Confirmed after Dose 1 (n=643, 1047)	0	0		
Infirmed after Dose 1 (n=643, 1047)	643	1047		
Confirmed after Dose 2 (n=634, 1042)	0	0		
Infirmed after Dose 2 (n=634, 1042)	634	1042		
Confirmed after Dose 3 (n=631, 1039)	0	0		
Infirmed after Dose 3 (n=631,1039)	630	1039		
Missing Confirmed after Dose 3 (n=631, 1039)	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting medically significant conditions (MSCs), in a subset of subjects.

End point title	Number of subjects reporting medically significant conditions (MSCs), in a subset of subjects.
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End point description:

MSCs are defined as AEs prompting emergency room or physician visits that are not (1) related to common diseases or (2) routine visits for physical examination or vaccination, or SAEs that are not related to common diseases. Common diseases include: upper respiratory infections sinusitis, pharyngitis, gastroenteritis, urinary tract infections and injury.

End point type	Secondary
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End point timeframe:
From Dose 1 (at Day 0) until Month 12 (phone contact)

End point values	Cervarix pooled Group	Engerix-B pooled Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	643	1047		
Units: Subjects				
Subjects with any MSC	47	76		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting any serious adverse events (SAEs) and SAEs causally related to vaccination, in a subset of subjects

End point title	Number of subjects reporting any serious adverse events (SAEs) and SAEs causally related to vaccination, in a subset of subjects
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End point description:

An SAE is any untoward medical occurrence that: a.results in death, b.is life-threatening, c.requires hospitalisation or prolongation of existing hospitalisation, d.results in disability/incapacity, or e.is a congenital anomaly/birth defect in the offspring of a study participant.

End point type	Secondary
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End point timeframe:

From Dose 1 (at Day 0) until Month 12

End point values	Cervarix pooled Group	Engerix-B pooled Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2436	1267		
Units: Subjects				
Subjects with any SAEs	58	25		
Subjects with SAEs assessed as related to vaccine	4	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting SAEs assessed by the investigator as possibly related to vaccination.

End point title	Number of subjects reporting SAEs assessed by the investigator as possibly related to vaccination.
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End point description:

End point type	Secondary
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End point timeframe:

During the entire study period up to the Visit 5 (18.5 years of age)

End point values	Cervarix pooled Group	Engerix-B pooled Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14838	17338		
Units: Subjects				
Subjects with any related SAE(s)	22	30		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting new onset of autoimmune diseases (NOADs).

End point title	Number of subjects reporting new onset of autoimmune diseases (NOADs).
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End point description:

NOADs include colitis ulcerative, juvenile arthritis, type 1 diabetes mellitus, coeliac disease and Chron's disease, Basedow's disease, erythema nodosum VIIth nerve paralysis and psoriasis.

End point type	Secondary
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End point timeframe:

Between Visit 1 (at Day 0) and Visit 5 (at 18.5 years of age)

End point values	Cervarix pooled Group	Engerix-B pooled Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2436	1267		
Units: Subjects				
Subjects with any NOAD(s)	72	101		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting pregnancies with onset and their outcomes.

End point title	Number of subjects reporting pregnancies with onset and their outcomes.
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End point description:

End point type	Secondary
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End point timeframe:

Between Visit 1 (at Day 0) and Visit 5 (at 18.5 years of age)

End point values	Cervarix pooled Group	Engerix-B pooled Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	74		
Units: Subjects				
Live infant no apparent anomaly	29	16		
Elective termination no apparent anomaly	29	52		
Spontaneous abortion no apparent anomaly	7	2		
Molar pregnancy	1	0		
Pregnancy ongoing	3	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Unsolicited AEs occurring within the 30-day (Days 0-29) post-vaccination period. SAEs up to Month 12

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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Reporting groups

Reporting group title	Cervarix Pooled Group
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Reporting group description:

Male and female subjects receiving Cervarix™ vaccine. The vaccine was administered intramuscularly in the deltoid region of the non-dominant arm according to a 0, 1, 6-month schedule.

Reporting group title	Engerix-B Pooled Group
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Reporting group description:

Male and female subjects receiving Engerix™-B vaccine. The vaccine was administered intramuscularly in the deltoid region of the non-dominant arm according to a 0, 1, 6-month schedule.

Serious adverse events	Cervarix Pooled Group	Engerix-B Pooled Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	58 / 2436 (2.38%)	25 / 1267 (1.97%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Astrocytoma, low grade			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Testicular torsion			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disturbance in social behaviour			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emotional disorder of childhood			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic disorder			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Alcohol poisoning			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 2436 (0.12%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 2436 (0.16%)	4 / 1267 (0.32%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand Fracture			
alternative assessment type: Systematic			

subjects affected / exposed	2 / 2436 (0.08%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 2436 (0.08%)	2 / 1267 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot Fracture			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 2436 (0.08%)	2 / 1267 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forearm Fracture			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 2436 (0.08%)	2 / 1267 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 2436 (0.08%)	2 / 1267 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Joint dislocation alternative assessment type: Systematic			
subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury alternative assessment type: Systematic			
subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture alternative assessment type: Systematic			
subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle rupture alternative assessment type: Systematic			
subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck injury alternative assessment type: Systematic			
subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic rupture alternative assessment type: Systematic			
subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture alternative assessment type: Systematic			

subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic renal injury			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Vitello-intestinal duct remnant			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 2436 (0.08%)	2 / 1267 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Splenomegaly			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain			
alternative assessment type: Systematic			

subjects affected / exposed	2 / 2436 (0.08%)	2 / 1267 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Acne			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Exostosis			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Juvenile arthritis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 2436 (0.21%)	3 / 1267 (0.24%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious mononucleosis			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 2436 (0.16%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 2436 (0.16%)	4 / 1267 (0.32%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar abscess			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 2436 (0.08%)	2 / 1267 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis bacterial			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sinusitis bacterial alternative assessment type: Systematic subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders Type 1 diabetes mellitus alternative assessment type: Systematic subjects affected / exposed	1 / 2436 (0.04%)	1 / 1267 (0.08%)	
occurrences causally related to treatment / all	0 / 1	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	Cervarix Pooled Group	Engerix-B Pooled Group	
Total subjects affected by non-serious adverse events subjects affected / exposed	506 / 2436 (20.77%)	411 / 1267 (32.44%)	
General disorders and administration site conditions Pain alternative assessment type: Systematic subjects affected / exposed ^[1] occurrences (all)	506 / 603 (83.91%) 506	251 / 1028 (24.42%) 251	
Redness alternative assessment type: Systematic subjects affected / exposed ^[2] occurrences (all)	131 / 603 (21.72%) 131	169 / 1028 (16.44%) 169	
Swelling alternative assessment type: Systematic subjects affected / exposed ^[3] occurrences (all)	131 / 603 (21.72%) 131	46 / 1028 (4.47%) 46	
Arthralgia alternative assessment type: Systematic			

<p>subjects affected / exposed^[4]</p> <p>occurrences (all)</p>	<p>107 / 604 (17.72%)</p> <p>107</p>	<p>97 / 1028 (9.44%)</p> <p>97</p>	
<p>Fatigue</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed^[5]</p> <p>occurrences (all)</p>	<p>291 / 604 (48.18%)</p> <p>291</p>	<p>411 / 1028 (39.98%)</p> <p>411</p>	
<p>Fever (Axillary)</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed^[6]</p> <p>occurrences (all)</p>	<p>48 / 604 (7.95%)</p> <p>48</p>	<p>85 / 1028 (8.27%)</p> <p>85</p>	
<p>Gastrointestinal</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed^[7]</p> <p>occurrences (all)</p>	<p>106 / 604 (17.55%)</p> <p>106</p>	<p>163 / 1028 (15.86%)</p> <p>163</p>	
<p>Headache</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed^[8]</p> <p>occurrences (all)</p>	<p>261 / 604 (43.21%)</p> <p>261</p>	<p>371 / 1028 (36.09%)</p> <p>371</p>	
<p>Myalgia</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed^[9]</p> <p>occurrences (all)</p>	<p>321 / 604 (53.15%)</p> <p>321</p>	<p>250 / 1028 (24.32%)</p> <p>250</p>	
<p>Rash</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed^[10]</p> <p>occurrences (all)</p>	<p>29 / 604 (4.80%)</p> <p>29</p>	<p>33 / 1028 (3.21%)</p> <p>33</p>	
<p>Urticaria</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed^[11]</p> <p>occurrences (all)</p>	<p>4 / 604 (0.66%)</p> <p>4</p>	<p>15 / 1267 (1.18%)</p> <p>15</p>	
<p>Infections and infestations</p> <p>Nasopharyngitis</p> <p>subjects affected / exposed^[12]</p> <p>occurrences (all)</p>	<p>33 / 643 (5.13%)</p> <p>33</p>	<p>17 / 1047 (1.62%)</p> <p>17</p>	

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: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed

[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: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed

[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: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed

[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: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed

[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: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed

[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: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed

[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: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed

[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: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed

[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: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed

[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: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed

[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: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed

[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: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 March 2014	Oropharyngeal samples are being collected from female subjects born in 1992 to maximize the chance of detecting vaccine effect against oropharyngeal infection. Additional study objectives and endpoints to evaluate vaccine effectiveness against oropharyngeal infection were added. The end-of-study analysis plan was clarified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported