Clinical trial results:
A phase III/IV, community-randomised, controlled study to evaluate the effectiveness of two vaccination strategies using GlaxoSmithKline Biologicals' HPV-16/18 L1 VLP AS04 vaccine in reducing the prevalence of HPV-16/18 infection when administered intramuscularly according to a 0, 1, 6-month schedule in healthy female and male study participants aged 12 - 15 years.

Summary

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

Results information

Result version number	v3 (current)
This version publication date	15 November 2019
First version publication date	22 May 2015
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	106636

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	Final
Date of interim/final analysis	14 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 December 2014
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:

• To demonstrate the overall (direct and indirect) effectiveness of HPV 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 HPV 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 consented to participate in the study until she/he was discharged.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 October 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	7 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Finland: 34412
Worldwide total number of subjects	34412
EEA total number of subjects	34412

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)	2236
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Immunization phase (Day 0 to Month 12) = adolescents (birth cohorts '92-'95) were vaccinated with Cervarix/Engerix-B. Effectiveness evaluation phase (Visit 5) = the vaccine's impact was assessed on female subjects aged 18.5. At Day 0, Cervarix was not licensed for males;male subjects receiving the vaccine were considered part of a Phase III trial.

Pre-assignment

Screening details:

34412 subjects were enrolled in the study, out of which 2236 subjects had a subject number allocated, but did not receive a vaccine dose, and 1 subject was excluded due to non-eligibility criteria, hence 32175 subjects were vaccinated and started the study.

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:

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 vaccinated with 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	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

3 doses administered by intramuscular injection into the deltoid region of the non-dominant arm according to a 0, 1, 6-month schedule.

Arm title	Engerix-B Pooled Group

Arm description:

Male and female subjects vaccinated with 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
Investigational medicinal product name	Engerix-B
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

3 doses administered by intramuscular injection into the deltoid region of the non-dominant arm according to a 0, 1, 6-month schedule.

Number of subjects in period 1[1]	Cervarix Pooled Group	Engerix-B Pooled Group
Started	14837	17338
Completed	8346	5547
Not completed	6491	11791
Consent withdrawn by subject	3	4
Migrated/moved from study area	13	11
Lost to follow-up,incomplete vaccination	83	117
Unspecified	1685	902
Lost to follow-up, complete vaccination	4707	10757

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Although 34412 subjects were enrolled, only 32175 subjects were vaccinated and started the study.

Baseline characteristics

Reporting groups	
Reporting group title	Cervarix Pooled Group
Reporting group description:	
Male and female subjects vaccinated with 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 vaccinated with 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	14837	17338	32175
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age Continuous			
Out of the 2236 subjects included in the Adults (18-64 years) category in Population of trial subjects section, for 554 subjects the age categorical data were missing.			
Units: years			
arithmetic mean	14.1	14.1	
standard deviation	± 0.8	± 0.8	-
Sex: Female, Male			
After the database freeze, discrepancies in the gender of 10 subjects were detected, this leading to 12401 female and 2436 male subjects in the Cervarix Pooled Group, and 8111 female and 9227 male subjects in the Engerix-B Pooled Group. These 10 subjects were not part of the Immunogenicity subset, the Diary Card subset or included in the active safety follow-up up to Month 12 for SAEs. These 10 subjects did not report any AEs and did not have any sample results. The impact on the AEs and overall effectiveness analysis was limited to the number of subjects exposed and considered minor.			
Units: Subjects			
Female	12399	8119	20518
Male	2438	9219	11657
Race/Ethnicity, Customized			
Units: Subjects			
African heritage/African American	9	8	17
Asian - Central/South Asian heritage	3	4	7
Asian - East Asian heritage	8	0	8
Asian - Japanese heritage	1	1	2
Asian - South East Asian heritage	13	4	17

White - Arabic/North African heritage	31	39	70
White - Caucasian/European heritage	14669	17190	31859
Mixed origin	103	92	195

End points

End points reporting groups

Reporting group title	Cervarix Pooled Group

Reporting group description:

Male and female subjects vaccinated with 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 vaccinated with 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.

Subject analysis set title	Cervarix/Engerix-B A Group
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The A group includes subjects from communities where 70% of male and female adolescents were to be vaccinated with Cervarix vaccine. To achieve a Cervarix vaccination coverage of 70%, a 9:1 ratio was used to allocate study participants to receive Cervarix vaccine versus control Engerix-B vaccine (meaning 90% of vaccinated subjects were randomized to Cervarix). Finally, subjects from A group were either vaccinated with Cervarix, Engerix-B (control vaccine), or not vaccinated (enrolled control without vaccination). Vaccines were administered intramuscularly in the deltoid region of the non-dominant arm according to a 0, 1, 6-month schedule.

Subject analysis set title	Cervarix/Engerix-B B Group
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The B group includes subjects from communities where 70% of female adolescents were to be vaccinated with Cervarix vaccine. To achieve a Cervarix vaccination coverage of 70%, a 9:1 ratio was used to allocate female participants to receive Cervarix vaccine versus control Engerix-B vaccine (meaning 90% of vaccinated females were randomized to Cervarix). In this group, all male adolescents were to be vaccinated with Engerix-B control vaccine. Finally, subjects from B group were either vaccinated with Cervarix (females) or Engerix-B/not vaccinated (males and females). Vaccines were administered intramuscularly in the deltoid region of the non-dominant arm according to a 0, 1, 6-month schedule.

Subject analysis set title	Engerix-B Group
Subject analysis set type	Sub-group analysis

Subject analysis set description:

In this control group, all adolescents were to be vaccinated with Engerix-B control vaccine. Finally, subjects from this group were either vaccinated with Engerix-B or not vaccinated. The vaccine was administered intramuscularly in the deltoid region of the non-dominant arm according to a 0, 1, 6-month schedule.

Subject analysis set title	Cervarix/Engerix-B Pooled Group
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Pooled A and B group: This pooled group includes subjects from communities where 70% of male and female adolescents (A group) or 70% of female adolescents (B group) were to be vaccinated with Cervarix vaccine. To achieve a Cervarix vaccination coverage of 70%, a 9:1 ratio was used to allocate study participants (A group) or female participants (B group) to receive Cervarix vaccine versus control Engerix-B vaccine (meaning 90% of vaccinated subjects (A group) or vaccinated females (B group) were randomized to Cervarix). Finally, subjects from this pooled group were either vaccinated with Cervarix, Engerix-B (control vaccine), or not vaccinated (enrolled control without vaccination). Vaccines were administered intramuscularly in the deltoid region of the non-dominant arm according to a 0, 1, 6-month schedule.

Primary: Number of female subjects with overall vaccine effectiveness against genital infection with Human Papilloma Virus (HPV)-16/18 types in Cervarix/Engerix-B B Group versus Engerix-B Group and in Cervarix/Engerix-B A Group versus Engerix-B Group

End point title	Number of female subjects with overall vaccine effectiveness against genital infection with Human Papilloma Virus (HPV)-16/18 types in Cervarix/Engerix-B B Group versus Engerix-B

	Group and in Cervarix/Engerix-B A Group versus Engerix-B Group

End point description:

The analysis of overall effectiveness of Cervarix vaccine against genital infection with HPV-16/18 types was based on stratified Mantel-Haenszel adjusted for clustering. The overall vaccine effectiveness was computed as 1- the prevalence odd ratio in all subjects from the investigated group (prevalence rate in all subjects from the investigated group/prevalence rate in all subjects from Engerix-B Group).
The analysis was performed on female study participants from the Total Enrolled cohort on effectiveness, which included all study participants who were previously enrolled in the immunization phase, and those who joined the trial at Visit 5, for whom results were available.

End point type	Primary

End point timeframe:

At the time of Visit 5 (i.e. at 18.5 years of age)

End point values	Cervarix/Engerix-B A Group	Cervarix/Engerix-B B Group	Engerix-B Group	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3629	4029	3168	
Units: Participants	139	117	329	

Statistical analyses

Statistical analysis title	Overall efectiveness against HPV-16/18

Statistical analysis description:

The analysis of the overall effectiveness of GSK's HPV-16/18 vaccine against HPV-16/18 genital infection in Cervarix/Engerix-B B Group versus Engerix-B Group was based on stratified Mantel-Haenszel adjusted for clustering.

Comparison groups	Cervarix/Engerix-B B Group v Engerix-B Group
Number of subjects included in analysis	7197
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.004 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Vaccine effectiveness percentage
Point estimate	49.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	20.1
upper limit	68.2

Notes:

[1] - An objective was reached if the 2-sided p-value associated to the objective was below 5%.

Statistical analysis title	Overall efectiveness against HPV-16/18

Statistical analysis description:

The analysis of the overall effectiveness of GSK's HPV-16/18 vaccine against HPV-16/18 genital infection in Cervarix/Engerix-B A Group versus Engerix-B Group was based on stratified Mantel-Haenszel adjusted for clustering.

Comparison groups	Cervarix/Engerix-B A Group v Engerix-B Group

Number of subjects included in analysis	6797
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.232 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Vaccine effectiveness percentage
Point estimate	23.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19
upper limit	51.1

Notes:

[2] - An objective was reached if the 2-sided p-value associated to the objective was below 5%.

Secondary: Number of female subjects with overall vaccine effectiveness against genital infection with HPV-16/18 types in Cervarix/Engerix-B A Group versus Cervarix/Engerix-B B Group

End point title	Number of female subjects with overall vaccine effectiveness against genital infection with HPV-16/18 types in Cervarix/Engerix-B A Group versus Cervarix/Engerix-B B Group

End point description:

The analysis of overall effectiveness of Cervarix vaccine against genital infection with HPV-16/18 types was based on stratified Mantel-Haenszel adjusted for clustering. The overall vaccine effectiveness was computed as 1- the prevalence odd ratio in all subjects from the investigated group (prevalence rate in all subjects from the Cervarix/Engerix-B A Group/prevalence rate in all subjects from Engerix-B Group).
Note: As per Protocol and as the confirmatory objectives were not met, only exploratory interpretation could be performed for what concerns this secondary outcome measure.
The analysis was performed on female study participants from the Total Enrolled cohort on effectiveness, which included all study participants who were previously enrolled in the immunization phase, and those who joined the trial at Visit 5, for whom results were available.

End point type	Secondary

End point timeframe:

At the time of Visit 5 (i.e. at 18.5 years of age)

End point values	Cervarix/Engerix-B A Group	Cervarix/Engerix-B B Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3629	4029		
Units: Participants	139	117		

Statistical analyses

Statistical analysis title	Overall efectiveness against HPV-16/18

Statistical analysis description:

The analysis of the overall effectiveness of GSK's HPV-16/18 vaccine against HPV-16/18 genital infection in Cervarix/Engerix-B A Group versus Cervarix/Engerix-B B was based on stratified Mantel-Haenszel adjusted for clustering.

Comparison groups	Cervarix/Engerix-B A Group v Cervarix/Engerix-B B Group

Number of subjects included in analysis	7658
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.069 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Vaccine effectiveness percentage
Point estimate	-52.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-139.4
upper limit	3.3

Notes:

[3] - An objective was reached if the 2-sided p-value associated to the objective was below 5%.

Secondary: Number of female subjects with overall vaccine effectiveness against genital oncogenic infection with specific HPV types

End point title	Number of female subjects with overall vaccine effectiveness against genital oncogenic infection with specific HPV types

End point description:

The analysis of overall effectiveness of Cervarix vaccine against genital infection with specific HPV types (16, 18, 31/45, 31/33/45, 31/33/45/51, 31/33/45/51/52, 31/33/35/39/45/51/52/56/58/59/66/68, 16/18/31/33/35/39/45/51/52/56/58/59/66/68, 6, 11, 6/11, 6/11/53/74) was based on stratified Mantel-Haenszel adjusted for clustering. The effectiveness was computed as 1- the prevalence odd ratio in all subjects from the investigated group (prevalence rate in all subjects from the investigated group/prevalence rate in all subjects from Engerix-B Group).
The analysis was performed on female study participants from the Total Enrolled cohort on effectiveness, which included all study participants who were previously enrolled in the immunization phase, and those who joined the trial at Visit 5, for whom results were available.

End point type	Secondary

End point timeframe:

At the time of Visit 5 (i.e. at 18.5 years of age)

End point values	Cervarix/Engerix-B A Group	Cervarix/Engerix-B B Group	Engerix-B Group	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3629	4029	3168	
Units: Participants				
HPV-16	88	85	227	
HPV-18	62	41	134	
HPV-31/45	97	93	182	
HPV-31/33/45	175	173	271	
HPV-31/33/45/51	449	450	441	
HPV-31/33/45/51/52	563	585	532	
HPV-31/33/35/39/45/51/52/56/58/59/66/68	923	961	776	
HPV-16/18/31/33/35/39/45/51/52/56/58/59/66/68	965	999	883	
HPV-6	192	183	139	
HPV-11	39	32	34	
HPV-6/11	221	204	165	

HPV-6/11/53/74	403	381	307	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of female subjects with total vaccine effectiveness against oropharyngeal infection with HPV-16/18 types

End point title	Number of female subjects with total vaccine effectiveness against oropharyngeal infection with HPV-16/18 types

End point description:

The analysis of total effectiveness of Cervarix vaccine against oropharyngeal infection with HPV-16/18 types was based on stratified Mantel-Haenszel adjusted for clustering. The effectiveness was computed as 1- the prevalence odd ratio in Cervarix vaccinated subjects from the investigated group (prevalence rate in Cervarix vaccinated subjects from the investigated group/prevalence rate in all subjects from Engerix-B Group).
The analysis was performed on female study participants from the Total Enrolled cohort on effectiveness, which included all study participants who were previously enrolled in the immunization phase, and those who joined the trial at Visit 5, for whom results were available.

End point type	Secondary

End point timeframe:

At the time of Visit 5 (i.e. at 18.5 years of age)

End point values	Engerix-B Group	Cervarix/Engerix-B Pooled Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1679	3192		
Units: Participants	27	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of female subjects with total vaccine effectiveness against oropharyngeal oncogenic infection with specific HPV types

End point title	Number of female subjects with total vaccine effectiveness against oropharyngeal oncogenic infection with specific HPV types

End point description:

The analysis of total effectiveness of Cervarix vaccine against oropharyngeal infection with specific HPV types (16, 18, 31/45, 31/33/45, 31/33/45/51, 31/33/45/51/52, 31/33/35/39/45/51/52/56/58/59/66/68, 16/18/31/33/35/39/45/51/52/56/58/59/66/68, 6, 11, 6/11, 6/11/53/74) was based on stratified Mantel-Haenszel adjusted for clustering. The effectiveness was computed as 1- the prevalence odd ratio in all Cervarix vaccinated subjects from the investigated group (prevalence rate in all Cervarix vaccinated subjects from the investigated group/prevalence rate in all subjects from Engerix-B Group).

The analysis was performed on female study participants from the Total Enrolled cohort on effectiveness, which included all study participants who were previously enrolled in the immunization phase, and those who joined the trial at Visit 5, for whom results were available.

End point type	Secondary

End point timeframe:

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

End point values	Engerix-B Group	Cervarix/Engerix-B Pooled Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1679	3192		
Units: Participants				
HPV-16	19	6		
HPV-18	10	4		
HPV-31/45	9	3		
HPV-31/33/45	16	9		
HPV-31/33/45/51	42	53		
HPV-31/33/45/51/52	49	63		
HPV-31/33/35/39/45/51/52/56/58/59/66/68	79	129		
HPV-16/18/31/33/35/39/45/51/52/56/58/59/66/68	95	136		
HPV-6	27	36		
HPV-11	5	5		
HPV-6/11	29	41		
HPV-6/11/53/74	45	72		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of male subjects reporting any and Grade 3 solicited local symptoms, in a subset of subjects

End point title	Number of male subjects reporting any and Grade 3 solicited local symptoms, in a subset of subjects

End point description:

Assessed solicited local symptoms were pain, redness and swelling. Any = occurrence of the symptom regardless of intensity grade. Grade 3 pain = pain that prevented normal activity. Grade 3 redness/swelling = redness/swelling spreading beyond 50 millimeters (mm) of injection site.
The analysis was performed on the Total vaccinated cohort (TVC) - the Diary card subset, which included a subset of male adolescents from Cervarix/Engerix-B A Group and Engerix-B Group, with at least one study vaccine administration documented, who were selected for active assessment of safety using diary cards and for whom data were available.

End point type	Secondary

End point timeframe:

During the 7-day post-vaccination period following each dose and across doses

End point values	Cervarix Pooled Group	Engerix-B Pooled Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	603	1028		
Units: Participants				
Any Pain, Dose 1 (N=590;1021)	463	157		
Grade 3 Pain, Dose 1 (N=590;1021)	12	1		
Any Redness, Dose 1 (N=590;1021)	99	90		
Grade 3 Redness, Dose 1 (N=590;1021)	1	0		
Any Swelling, Dose 1 (N=590;1021)	61	29		
Grade 3 Swelling, Dose 1 (N=590;1021)	4	0		
Any Pain, Dose 2 (N=509;935)	331	123		
Grade 3 Pain, Dose 2 (N=509;935)	9	1		
Any Redness, Dose 2 (N=509;935)	88	59		
Grade 3 Redness, Dose 2 (N=509;935)	1	0		
Any Swelling, Dose 2 (N=509;935)	66	16		
Grade 3 Swelling, Dose 2 (N=509;935)	3	0		
Any Pain, Dose 3 (N=491;812)	326	108		
Grade 3 Pain, Dose 3 (N=491;812)	11	0		
Any Redness, Dose 3 (N=491;812)	100	50		
Grade 3 Redness, Dose 3 (N=491;812)	2	0		
Any Swelling, Dose 3 (N=491;812)	69	18		
Grade 3 Swelling, Dose 3 (N=491;812)	3	0		
Any Pain, Across doses (N=603;1028)	506	251		
Grade 3 Pain, Across doses (N=603;1028)	26	2		
Any Redness, Across doses (N=603;1028)	169	131		
Grade 3 Redness, Across doses (N=603;1028)	4	0		
Any Swelling, Across doses (N=603;1028)	131	46		
Grade 3 Swelling, Across doses (N=603;1028)	8	0		

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of male subjects reporting any, Grade 3 and related to vaccination solicited general symptoms, in a subset of subjects

End point description:

Assessed solicited general symptoms were arthralgia, fatigue, fever [defined as axillary temperature equal to or above 37.5 degrees Celsius (°C)], gastrointestinal symptoms (including nausea, vomiting, diarrhoea and/or abdominal pain), headache, myalgia, rash and urticaria. Any = occurrence of the symptom regardless of intensity grade. Grade 3 symptom = symptom that prevented normal activity. Grade 3 fever = fever > 39.0 °C. Related = symptom assessed by the investigator as related to the

vaccination.
The analysis was performed on the TVC - the Diary card subset, which included a subset of male adolescents from Cervarix/Engerix-B A Group and Engerix-B Group, with at least one study vaccine administration documented, who were selected for active assessment of safety using diary cards and for whom data were available.

End point type	Secondary

End point timeframe:

During the 7-day post-vaccination period following each dose and across doses

End point values	Cervarix Pooled Group	Engerix-B Pooled Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	604	1028		
Units: Participants				
Any Arthralgia, Dose 1 (N=590;1021)	58	58		
Grade 3 Arthralgia, Dose 1 (N=590;1021)	0	1		
Related Arthralgia, Dose 1 (N=590;1021)	37	45		
Any Fatigue, Dose 1 (N=590;1021)	224	301		
Grade 3 Fatigue, Dose 1 (N=590;1021)	3	9		
Related Fatigue, Dose 1 (N=590;1021)	156	246		
Any Fever (axillary), Dose 1 (N=590;1021)	15	35		
Grade 3 Fever (axillary), Dose 1 (N=590;1021)	3	4		
Related Fever (axillary), Dose 1 (N=590;1021)	7	23		
Any Gastrointestinal, Dose 1 (N=590;1021)	73	101		
Grade 3 Gastrointestinal, Dose 1 (N=590;1021)	7	6		
Related Gastrointestinal, Dose 1 (N=590;1021)	45	84		
Any Headache, Dose 1 (N=590;1021)	178	255		
Grade 3 Headache, Dose 1 (N=590;1021)	10	7		
Related Headache, Dose 1 (N=590;1021)	108	181		
Any Myalgia, Dose 1 (N=590;1021)	229	169		
Grade 3 Myalgia, Dose 1 (N=590;1021)	6	2		
Related Myalgia, Dose 1 (N=590;1021)	196	138		
Any Rash, Dose 1 (N=590;1021)	13	17		
Grade 3 Rash, Dose 1 (N=590;1021)	0	0		
Related Rash, Dose 1 (N=590;1021)	5	12		
Any Urticaria, Dose 1 (N=590;1021)	3	12		
Grade 3 Urticaria, Dose 1 (N=590;1021)	0	0		
Related Urticaria, Dose 1 (N=590;1021)	2	11		
Any Arthralgia, Dose 2 (N=511;936)	41	38		
Grade 3 Arthralgia, Dose 2 (N=511;936)	0	3		
Related Arthralgia, Dose 2 (N=511;936)	36	33		
Any Fatigue, Dose 2 (N=511;936)	136	155		
Grade 3 Fatigue, Dose 2 (N=511;936)	2	7		

Related Fatigue, Dose 2 (N=511;936)	100	123		
Any Fever, Dose 2 (N=511;936)	19	28		
Grade 3 Fever, Dose 2 (N=511;936)	1	2		
Related Fever, Dose 2 (N=511;936)	11	10		
Any Gastrointestinal, Dose 2 (N=511;936)	45	50		
Grade 3 Gastrointestinal, Dose 2 (N=511;936)	4	5		
Related Gastrointestinal, Dose 2 (N=511;936)	27	38		
Any Headache, Dose 2 (N=511;936)	101	144		
Grade 3 Headache, Dose 2 (N=511;936)	5	4		
Related Headache, Dose 2 (N=511;936)	55	104		
Any Myalgia, Dose 2 (N=511;936)	151	97		
Grade 3 Myalgia, Dose 2 (N=511;936)	1	1		
Related Myalgia, Dose 2 (N=511;936)	143	77		
Any Rash, Dose 2 (N=511;936)	9	14		
Grade 3 Rash, Dose 2 (N=511;936)	0	0		
Related Rash, Dose 2 (N=511;936)	4	9		
Any Urticaria, Dose 2 (N=511;936)	1	2		
Grade 3 Urticaria, Dose 2 (N=511;936)	0	0		
Related Urticaria, Dose 2 (N=511;936)	1	1		
Any Arthralgia, Dose 3 (N=492;814)	53	33		
Grade 3 Arthralgia, Dose 3 (N=492;814)	1	0		
Related Arthralgia, Dose 3 (N=492;814)	41	29		
Any Fatigue, Dose 3 (N=492;814)	135	141		
Grade 3 Fatigue, Dose 3 (N=492;814)	4	6		
Related Fatigue, Dose 3 (N=492;814)	100	116		
Any Fever, Dose 3 (N=492;814)	15	27		
Grade 3 Fever, Dose 3 (N=492;814)	2	3		
Related Fever, Dose 3 (N=492;814)	10	24		
Any Gastrointestinal, Dose 3 (N=492;814)	19	50		
Grade 3 Gastrointestinal, Dose 3 (N=492;814)	0	2		
Related Gastrointestinal, Dose 3 (N=492;814)	12	39		
Any Headache, Dose 3 (N=492;814)	101	123		
Grade 3 Headache, Dose 3 (N=492;814)	2	3		
Related Headache, Dose 3 (N=492;814)	69	97		
Any Myalgia, Dose 3 (N=492;814)	158	80		
Grade 3 Myalgia, Dose 3 (N=492;814)	5	0		
Related Myalgia, Dose 3 (N=492;814)	137	69		
Any Rash, Dose 3 (N=492;814)	11	9		
Grade 3 Rash, Dose 3 (N=492;814)	0	0		
Related Rash, Dose 3 (N=492;814)	5	8		
Any Urticaria, Dose 3 (N=492;814)	0	3		
Grade 3 Urticaria, Dose 3 (N=492;814)	0	0		
Related Urticaria, Dose 3 (N=492;814)	0	3		
Any Arthralgia, Across doses (N=604;1028)	107	97		

Grade 3 Arthralgia, Across doses (N=604;1028)	1	4		
Related Arthralgia, Across doses (N=604;1028)	87	81		
Any Fatigue, Across doses (N=604;1028)	291	411		
Grade 3 Fatigue, Across doses (N=604;1028)	7	21		
Related Fatigue, Across doses (N=604;1028)	233	351		
Any Fever, Across doses (N=604;1028)	48	85		
Grade 3 Fever, Across doses (N=604;1028)	6	9		
Related Fever, Across doses (N=604;1028)	28	53		
Any Gastrointestinal, Across doses (N=604;1028)	106	163		
Grade 3 Gastrointestinal, Across doses(N=604;1028)	11	13		
Related Gastrointestinal,Across doses(N=604;1028)	70	128		
Any Headache, Across doses (N=604;1028)	261	371		
Grade 3 Headache, Across doses (N=604;1028)	15	14		
Related Headache, Across doses (N=604;1028)	176	280		
Any Myalgia, Across doses (N=604;1028)	321	250		
Grade 3 Myalgia, Across doses (N=604;1028)	12	3		
Related Myalgia, Across doses (N=604;1028)	291	211		
Any Rash, Across doses (N=604;1028)	29	33		
Grade 3 Rash, Across doses (N=604;1028)	0	0		
Related Rash, Across doses (N=604;1028)	14	23		
Any Urticaria, Across doses (N=604;1028)	4	15		
Grade 3 Urticaria, Across doses (N=604;1028)	0	0		
Related Urticaria, Across doses (N=604;1028)	3	13		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

An unsolicited AE covers any untoward medical occurrence in a clinical investigation subject temporally associated with the use of a medicinal product, whether or not considered related to the medicinal

product and 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. Any was defined as the occurrence of any unsolicited AE regardless of intensity grade or relation to vaccination. Grade 3 AE = an AE which prevented normal, everyday activities. Related = AE assessed by the investigator as related to the vaccination.
This analysis was performed on the TVC - the Diary Card subset, which included a subset of male adolescents from Cervarix/Engerix-B A Group and Engerix-B Group who were selected for active assessment of safety using diary cards and for whom data were available.

End point type	Secondary

End point timeframe:

Within the 30-day post-vaccination period

End point values	Cervarix Pooled Group	Engerix-B Pooled Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	643	1047		
Units: Participants				
Any AEs	157	202		
Grade 3 AEs	31	46		
Related AEs	12	19		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of male subjects with urticaria/rash within 30 minutes after each vaccination dose, in a subset of subjects

End point title	Number of male subjects with urticaria/rash within 30 minutes after each vaccination dose, in a subset of subjects

End point description:

The number of subjects with urticaria/rash assessed within 30 minutes following each vaccine dose are reported. Confirmed urticaria/rash = subjects who reported urticaria/rash within the specified time frame. Not confirmed urticaria/rash = number of subjects who did not report urticaria/rash within the specified time frame.
This analysis was performed on the TVC - the Diary Card subset, which included a subset of male adolescents from Cervarix/Engerix-B A Group and Engerix-B Group who were selected for active assessment of safety using diary cards and for whom data were available.

End point type	Secondary

End point timeframe:

Within 30 minutes following each vaccination dose

End point values	Cervarix Pooled Group	Engerix-B Pooled Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	643	1047		
Units: Participants				
Not confirmed urticaria/rash, Dose 1 (N=643;1047)	643	1047		

Confirmed urticaria/rash, Dose 1 (N=643;1047)	0	0		
Not confirmed urticaria/rash, Dose 2 (N=634;1042)	634	1042		
Confirmed urticaria/rash, Dose 2 (N=634;1042)	0	0		
Not confirmed urticaria/rash, Dose 3 (N=631;1039)	630	1039		
Confirmed urticaria/rash, Dose 3 (N=631;1039)	0	0		
Missing urticaria/rash, Dose 3 (N=631;1039)	1	0		

Statistical analyses

No statistical analyses for this end point

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

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

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. This analysis was performed on the TVC - the Diary Card subset, which included a subset of male adolescents from Cervarix/Engerix-B A Group and Engerix-B Group who were selected for active assessment of safety using diary cards and for whom data were available.

End point type	Secondary

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	643	1047		
Units: Participants	47	76		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Serious adverse events (SAEs) assessed include medical occurrences that resulted in death, were life-threatening, required hospitalization or prolongation of hospitalization or resulted in disability/incapacity. The analysis was performed on the TVC - subset of male subjects with active follow-up Month 0-Month 12 for SAEs, which included the male subjects in the Diary Card subset and the remaining Cervarix/Engerix-B A Group male subjects for whom data were available.

End point type	Secondary

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: Participants				
Any SAEs	58	25		
Related SAEs	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

End point description:

Serious adverse events (SAEs) assessed include medical occurrences that resulted in death, were life-threatening, required hospitalization or prolongation of hospitalization or resulted in disability/incapacity. The analysis was performed on the Total Vaccinated Cohort, which included all vaccinated subjects for whom data were available.

End point type	Secondary

End point timeframe:

During the entire study period (from Day 0 up to Visit 5 [18.5 years of age] or up to the day before 19 years of age for subjects who did not attend Visit 5)

End point values	Cervarix Pooled Group	Engerix-B Pooled Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14837	17338		
Units: Participants	25	30		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with new onset of autoimmune diseases (NOADs), retrieved from Care Register for Social Welfare and Health Care (HILMO)

End point title	Number of subjects with new onset of autoimmune diseases (NOADs), retrieved from Care Register for Social Welfare and Health Care (HILMO)

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.
The analysis was performed on the Total Vaccinated cohort, which included all vaccinated subjects for whom data were available.

End point type	Secondary

End point timeframe:

During the entire study period (from day 0 up to Visit 5 [at 18.5 years of age] or up to the day before 19 years of age for subjects who did not attend Visit 5)

End point values	Cervarix Pooled Group	Engerix-B Pooled Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14837	17338		
Units: Participants	149	180		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting pregnancies and outcomes of reported pregnancies with onset during the study period, retrieved from Medical Birth Registry and HILMO

End point title	Number of subjects reporting pregnancies and outcomes of reported pregnancies with onset during the study period, retrieved from Medical Birth Registry and HILMO

End point description:

Pregnancies with onset during the study were classified by their outcome. Outcomes included live infant with no apparent congenital anomaly, elective termination with no apparent congenital anomaly, spontaneous abortion with no apparent congenital anomaly, ectopic pregnancy, stillbirth with no apparent congenital anomaly and molar pregnancy. Note: The analysis was performed based on the corrected demographical data. Please refer to the rationale provided in the Baseline characteristics section.
The analysis was performed on the total number of pregnant subjects reported, part of the Total Vaccinated cohort, which included all vaccinated subjects for whom data were available.

End point type	Secondary

End point timeframe:

During the entire study period (from Day 0 up to Visit 5 [at 18.5 years of age] or up to the day before 19 years of age for subjects who did not attend Visit 5)

End point values	Cervarix Pooled Group	Engerix-B Pooled Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	777	567		
Units: Participants				
Live infant with no apparent anomaly	254	183		
Elective termination with no apparent anomaly	454	332		
Ectopic pregnancy	5	5		
Spontaneous abortion with no apparent anomaly	62	45		
Stillbirth with no apparent congenital anomaly	0	1		
Molar pregnancy	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with HPV-16 and HPV-18 antibody concentrations equal to or above the cut-off values, by gender, in a subset of subjects

End point title	Number of subjects with HPV-16 and HPV-18 antibody concentrations equal to or above the cut-off values, by gender, in a subset of subjects[4]

End point description:

The antibody concentrations against HPV-16 and HPV-18 were determined by Enzyme-linked immunosorbent assay (ELISA). The cut-off of the assay was 8 ELISA units per milliliter (EL.U/mL) for anti-HPV-16 and 7 EL.U/mL for anti-HPV-18 at Visits 1 and 4 and 19 EL.U/mL for HPV-16 and 18 EL.U/mL for HPV-18 at Visit 5.
The analysis was performed on the ATP cohort for immunogenicity-Immunogenicity subset, which comprised the same male study subjects from the Cervarix/Engerix-B A Group included in the Diary Card subset, plus approximately 1500 female study subjects from the same Cervarix/Engerix-B A Group, with assay results available at the considered time point.

End point type	Secondary

End point timeframe:

At the time of Visit 1 (at Day 0), Visit 4 (at Month 7) and Visit 5 (at 18.5 years of age)

Notes:

[4] - 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: The results were only assessed in a subset of subjects.

End point values	Cervarix Pooled Group			
Subject group type	Reporting group			
Number of subjects analysed	1163			
Units: Participants				
anti-HPV-16 ≥ 8 EL.U/mL, males (Day 0) (N=536)	40			
anti-HPV-16 ≥ 8 EL.U/mL, males (Month 7) (N=536)	536			
anti-HPV-16 ≥ 19 EL.U/mL, males (18.5Y) (N=217)	217			
anti-HPV-16 ≥ 8 EL.U/mL, females (Day 0) (N=1163)	86			

anti-HPV-16 ≥ 8 EL.U/mL,females (Month 7) (N=1163)	1163			
anti-HPV-16 ≥ 19 EL.U/mL, females (18.5Y) (N=688)	688			
anti-HPV-18 ≥ 7 EL.U/mL, males (Day 0) (N=535)	31			
anti-HPV-18 ≥ 7 EL.U/mL, males (Month 7) (N=535)	535			
anti-HPV-18 ≥ 18 EL.U/mL, males (18.5Y) (N=217)	217			
anti-HPV-18 ≥ 7 EL.U/mL, females (Day 0) (N=1160)	84			
anti-HPV-18 ≥ 7 EL.U/mL,females (Month 7) (N=1160)	1160			
anti-HPV-18 ≥ 18 EL.U/mL, females (18.5Y) (N=686)	685			

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HPV-16 and anti-HPV-18 antibody concentrations, by gender, in a subset of subjects

End point title	Anti-HPV-16 and anti-HPV-18 antibody concentrations, by gender, in a subset of subjects[5]

End point description:

The antibody concentrations against HPV-16 and HPV-18 were determined by Enzyme-linked immunosorbent assay (ELISA). The cut-off of the assay was 8 ELISA units per milliliter (EL.U/mL) for anti-HPV-16 and 7 EL.U/mL for anti-HPV-18 at Visits 1 and 4 and 19 EL.U/mL for HPV-16 and 18 EL.U/mL for HPV-18 at Visit 5.
The analysis was performed on the ATP cohort for immunogenicity-Immunogenicity subset, which comprised the same male study subjects from the Cervarix/Engerix-B A Group included in the Diary Card subset, plus approximately 1500 female study subjects from the same Cervarix/Engerix-B A Group, with assay results available at the considered time point.

End point type	Secondary

End point timeframe:

At the time of Visit 1 (Day 0), Visit 4 (at Month 7) and at the time of Visit 5 (18.5 years of age)

Notes:

[5] - 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: The results were only assessed in a subset of subjects.

End point values	Cervarix Pooled Group			
Subject group type	Reporting group			
Number of subjects analysed	1163			
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
anti-HPV-16 ≥ 8 EL.U/mL, males (Day 0) (N=536)	4.5 (4.3 to 4.6)			
anti-HPV-16 ≥ 8 EL.U/mL, males (Month 7) (N=536)	23959.1 (22301.0 to 25740.4)			
anti-HPV-16 ≥ 19 EL.U/mL, males (18.5Y) (N=217)	2759.5 (2432.1 to 3130.9)			

anti-HPV-16 ≥ 8 EL.U/mL, females (Day 0) (N=1163)	4.5 (4.4 to 4.6)			
anti-HPV-16 ≥ 8 EL.U/mL,females (Month 7) (N=1163)	21327.2 (20338.9 to 22363.5)			
anti-HPV-16 ≥ 19 EL.U/mL, females (18.5Y) (N=688)	2609.6 (2444.4 to 2785.9)			
anti-HPV-18 ≥ 7 EL.U/mL, males (Day 0) (N=535)	3.8 (3.7 to 4.0)			
anti-HPV-18 ≥ 7 EL.U/mL, males (Month 7) (N=535)	8583.9 (7974.7 to 9239.5)			
anti-HPV-18 ≥ 18 EL.U/mL, males (18.5Y) (N=217)	837.7 (727.3 to 964.9)			
anti-HPV-18 ≥ 7 EL.U/mL, females (Day 0) (N=1160)	3.9 (3.8 to 4.0)			
anti-HPV-18 ≥ 7 EL.U/mL,females (Month 7) (N=1160)	8227.3 (7847.7 to 8625.4)			
anti-HPV-18 ≥ 18 EL.U/mL, females (18.5Y) (N=686)	890.0 (826.2 to 958.7)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited AEs:within 7 days post-vaccination. Unsolicited AEs:within 30 days post-vaccination. SAEs: during the entire study (from Day 0 up to Visit 5 [at 18.5 years of age] or up to the day before 19 years of age for subjects who did not attend Visit 5).

Adverse event reporting additional description:

AEs were collected in the TVC-Diary Card subset. The Total Number of Participants Affected in Other AEs Table is populated with the highest value within the Other AEs table since consolidated analysis was not technically possible for solicited/unsolicited AEs. Moreover, the N of affected subjects is equal to N of events for the Other AEs section.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Engerix-B Pooled Group

Reporting group description:

Male and female subjects vaccinated with 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 title	Cervarix Pooled Group

Reporting group description:

Male and female subjects vaccinated with Cervarix 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	Engerix-B Pooled Group	Cervarix Pooled Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	152 / 17338 (0.88%)	188 / 14837 (1.27%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Astrocytoma, low grade			
subjects affected / exposed	1 / 17338 (0.01%)	0 / 14837 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenoma benign			
subjects affected / exposed	1 / 17338 (0.01%)	0 / 14837 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign hydatidiform mole			

subjects affected / exposed	1 / 17338 (0.01%)	2 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Behcet's syndrome			
subjects affected / exposed	1 / 17338 (0.01%)	0 / 14837 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion missed			
subjects affected / exposed	15 / 17338 (0.09%)	10 / 14837 (0.07%)	
occurrences causally related to treatment / all	0 / 15	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion spontaneous			
subjects affected / exposed	18 / 17338 (0.10%)	32 / 14837 (0.22%)	
occurrences causally related to treatment / all	0 / 20	0 / 32	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion spontaneous complete			
subjects affected / exposed	2 / 17338 (0.01%)	4 / 14837 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion spontaneous incomplete			
subjects affected / exposed	3 / 17338 (0.02%)	10 / 14837 (0.07%)	
occurrences causally related to treatment / all	0 / 3	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ectopic pregnancy			
subjects affected / exposed	5 / 17338 (0.03%)	5 / 14837 (0.03%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripartum haemorrhage			
subjects affected / exposed	1 / 17338 (0.01%)	0 / 14837 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pre-eclampsia			
subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Premature baby			
subjects affected / exposed	6 / 17338 (0.03%)	11 / 14837 (0.07%)	
occurrences causally related to treatment / all	0 / 6	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small for dates baby			
subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stillbirth			
subjects affected / exposed	1 / 17338 (0.01%)	0 / 14837 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 17338 (0.00%)	2 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 17338 (0.00%)	2 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Reproductive system and breast disorders			
Testicular torsion			
subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
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			
Dyspnoea			
subjects affected / exposed	1 / 17338 (0.01%)	0 / 14837 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperventilation			
subjects affected / exposed	1 / 17338 (0.01%)	0 / 14837 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neonatal asphyxia			
subjects affected / exposed	0 / 17338 (0.00%)	2 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumomediastinum			
subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 17338 (0.01%)	0 / 14837 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disturbance in social behaviour			

subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emotional disorder of childhood			
subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic disorder			
subjects affected / exposed	1 / 17338 (0.01%)	0 / 14837 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	1 / 17338 (0.01%)	0 / 14837 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination			
subjects affected / exposed	1 / 17338 (0.01%)	0 / 14837 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypnagogic hallucination			
subjects affected / exposed	1 / 17338 (0.01%)	0 / 14837 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep attacks			
subjects affected / exposed	1 / 17338 (0.01%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Alcohol poisoning			

subjects affected / exposed	1 / 17338 (0.01%)	3 / 14837 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	0 / 17338 (0.00%)	4 / 14837 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 17338 (0.00%)	2 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 17338 (0.00%)	2 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 17338 (0.00%)	2 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			
subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 17338 (0.01%)	0 / 14837 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			

subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck injury			
subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle rupture			
subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic rupture			
subjects affected / exposed	1 / 17338 (0.01%)	0 / 14837 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 17338 (0.01%)	0 / 14837 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic renal injury			
subjects affected / exposed	1 / 17338 (0.01%)	0 / 14837 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	2 / 17338 (0.01%)	0 / 14837 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forearm fracture			
subjects affected / exposed	1 / 17338 (0.01%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			

subjects affected / exposed	1 / 17338 (0.01%)	2 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Vitello-intestinal duct remnant			
subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 17338 (0.01%)	2 / 14837 (0.01%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataplexy			
subjects affected / exposed	1 / 17338 (0.01%)	2 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	2 / 17338 (0.01%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillain-barre syndrome			
subjects affected / exposed	1 / 17338 (0.01%)	0 / 14837 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 17338 (0.01%)	0 / 14837 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Multiple sclerosis			
subjects affected / exposed	1 / 17338 (0.01%)	2 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Narcolepsy			
subjects affected / exposed	1 / 17338 (0.01%)	2 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic neuritis			
subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Splenomegaly			
subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune thrombocytopenic purpura			
subjects affected / exposed	2 / 17338 (0.01%)	2 / 14837 (0.01%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	14 / 17338 (0.08%)	12 / 14837 (0.08%)	
occurrences causally related to treatment / all	3 / 14	5 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abdominal pain			
subjects affected / exposed	0 / 17338 (0.00%)	2 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	15 / 17338 (0.09%)	7 / 14837 (0.05%)	
occurrences causally related to treatment / all	5 / 15	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis ulcerative			
subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis			
subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Henoch-schonlein purpura			
subjects affected / exposed	1 / 17338 (0.01%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stevens-johnson syndrome			
subjects affected / exposed	1 / 17338 (0.01%)	0 / 14837 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urticaria			
subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Tubulointerstitial nephritis and uveitis syndrome			
subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Thyroiditis			
subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basedow's disease			
subjects affected / exposed	1 / 17338 (0.01%)	0 / 14837 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Exostosis			
subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	1 / 17338 (0.01%)	0 / 14837 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis reactive			
subjects affected / exposed	2 / 17338 (0.01%)	0 / 14837 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Juvenile idiopathic arthritis			

subjects affected / exposed	4 / 17338 (0.02%)	3 / 14837 (0.02%)	
occurrences causally related to treatment / all	0 / 4	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sacroiliitis			
subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sjogren's syndrome			
subjects affected / exposed	1 / 17338 (0.01%)	0 / 14837 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	3 / 17338 (0.02%)	5 / 14837 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious mononucleosis			
subjects affected / exposed	1 / 17338 (0.01%)	4 / 14837 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	1 / 17338 (0.01%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar abscess			
subjects affected / exposed	1 / 17338 (0.01%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	0 / 17338 (0.00%)	2 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 17338 (0.01%)	0 / 14837 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis bacterial			
subjects affected / exposed	1 / 17338 (0.01%)	0 / 14837 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis bacterial			
subjects affected / exposed	1 / 17338 (0.01%)	0 / 14837 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 17338 (0.01%)	0 / 14837 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	2 / 17338 (0.01%)	0 / 14837 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital infection			

subjects affected / exposed	1 / 17338 (0.01%)	0 / 14837 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle abscess			
subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic infection			
subjects affected / exposed	1 / 17338 (0.01%)	0 / 14837 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 17338 (0.00%)	1 / 14837 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 17338 (0.00%)	4 / 14837 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Type 1 diabetes mellitus			
subjects affected / exposed	25 / 17338 (0.14%)	13 / 14837 (0.09%)	
occurrences causally related to treatment / all	9 / 25	3 / 13	
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 Pooled Group	Cervarix Pooled Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	411 / 17338 (2.37%)	506 / 14837 (3.41%)	
General disorders and administration site conditions			
Arthralgia	Additional description: Solicited symptom during the 7-day post-vaccination period (across doses).		
subjects affected / exposed[1]	97 / 1028 (9.44%)	107 / 604 (17.72%)	
occurrences (all)	97	107	
Fatigue	Additional description: Solicited symptom during the 7-day post-vaccination period (across doses).		
subjects affected / exposed[2]	411 / 1028 (39.98%)	291 / 604 (48.18%)	
occurrences (all)	411	291	
Headache	Additional description: Solicited symptom during the 7-day post-vaccination period (across doses).		
subjects affected / exposed[3]	371 / 1028 (36.09%)	261 / 604 (43.21%)	
occurrences (all)	371	261	
Pain	Additional description: Solicited symptom during the 7-day post-vaccination period (across doses).		
subjects affected / exposed[4]	251 / 1028 (24.42%)	506 / 603 (83.91%)	
occurrences (all)	251	506	
Redness	Additional description: Solicited symptom during the 7-day post-vaccination period (across doses).		
subjects affected / exposed[5]	131 / 1028 (12.74%)	169 / 603 (28.03%)	
occurrences (all)	131	169	
Fever (Axillary)	Additional description: Solicited symptom during the 7-day post-vaccination period (across doses).		
subjects affected / exposed[6]	85 / 1028 (8.27%)	48 / 604 (7.95%)	
occurrences (all)	85	48	
Gastrointestinal	Additional description: Solicited symptom during the 7-day post-vaccination period (across doses).		
subjects affected / exposed[7]	163 / 1028 (15.86%)	106 / 604 (17.55%)	
occurrences (all)	163	106	
Swelling	Additional description: Solicited symptom during the 7-day post-vaccination period (across doses).		
subjects affected / exposed[8]	46 / 1028 (4.47%)	131 / 603 (21.72%)	
occurrences (all)	46	131	
Myalgia	Additional description: Solicited symptom during the 7-day post-vaccination period (across doses).		
subjects affected / exposed[9]	250 / 1028 (24.32%)	321 / 604 (53.15%)	
occurrences (all)	250	321	

Infections and infestations			
Nasopharyngitis	Additional description: Unsolicited symptom during the 30-day post-vaccination period (across doses).		
subjects affected / exposed[10]	17 / 1047 (1.62%)	33 / 643 (5.13%)	
occurrences (all)	17	33	

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.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 October 2007	•As the HPV-16/18 L1 VLP AS04 vaccine has been licensed in Europe in September 2007, the introduction was updated accordingly. In addition, reference to recently published efficacy results from the phase III study HPV-008 and to the current Investigator Brochure was made. •The indication of the HPV-16/18 L1 VLP AS04 vaccine has been updated in accordance with the current Summary of Product Characteristics. •The list of common diseases that are not to be recorded as medically significant conditions has been updated to include injury. •Instructions for the reporting of NOADs retrieved from the Hospital Discharge Registry, pregnancies retrieved from the Medical Birth Registry, and new neoplastic diseases (CIN3 and ICC) retrieved from the Finnish Cancer Registry have been clarified throughout the protocol. •The length of study visit intervals has been changed to allow for maximum attendance of study participants at the study visits. •The study procedures for study participants who become pregnant during the effectiveness evaluation phase have been clarified to allow for continuation of blood sampling (if applicable) and completion of the behavioural questionnaire. •Section 7.5 was updated to clarify that AEs not previously documented in the study need to be recorded in the Adverse Event section in the study participant's eCRF only for subjects included in the Diary Card subset. In addition, subheadings were added in this section to further clarify the reporting of AEs and SAEs. •The enrolment period has been extended to facilitate recruitment of the prespecified number of subjects.
04 March 2008	•A note has been added regarding the timing of the baseline behavioural questionnaire at Visit 3. This was completed at Visit 3 for study participants aged 15 years. The other study participants received it by mail after they have reached their 15th birthday. •A note to the Visit 1 (vaccination visit) has been added to mention that randomization may be done before the Visit 1 date, provided that written informed consent/assent has been obtained. •The recruitment period has been extended until May 2008 for subjects born in 1992, until December 2008 for subjects born in 1993 and until December 2009 for subjects born in 1994 and 1995. Taking this change into account, the recruitment period lasted approximately 2 years starting from the time the first birth cohort started to be enrolled. •The list of autoimmune diseases (checked during the passive safety surveillance) has been updated.

10 February 2009	The HPV-040 protocol was amended for the following reasons: •Update of the introduction in order to include the results of the first immunogenicity and safety study of GSK Biologicals' HPV vaccine in males 10-18 years of age and update of the introduction and rationale in order to reflect changes in the marketing and licensure status of the vaccine. •Amendment of Arm A and Arm C males in the Diary Card subset descriptions with regards to subject vaccination status. •The enrolment of female subjects in the immunological subset (IS) was stopped according to the recommendation of the Steering Committee. The number of female subjects in the immunological subset has been changed from approximately 3000 subjects to 1500 subjects. •Replacement of the term "medical examination" by the term "clinical examination" in the context of Study Visit 1. •The history directed clinical examination at Study Visit 1 was not mandatory, but performed only if needed. The protocol has been updated accordingly. •The Hospital Discharge Registry which allows retrieval of NOADs was updated once a year, not four times a year. The protocol has been updated accordingly. •Update of the instructions for vaccine storage. •Instructions for pregnancy and SAE reporting have been amended to clarify that any pregnancy outcome meets the criteria of serious adverse events, it should be reported as an SAE irrespective of its relationship to vaccination. •The National Public Health Institute (KTL) and the Research and Development Centre for Social Welfare and Health (STAKES) merged in 2009. The new acronym is THL and the official name in English is National Institute for Health and Welfare. The protocol has been updated accordingly. •Change of the title "List of autoimmune diseases" to "List of immune-mediated diseases" (with no change in content).
02 April 2010	The HPV-040 protocol was amended for the following reasons: •Only subjects born between 1992-1995, approximately 18.5 years of age at Visit 5, were eligible for the effectiveness evaluation phase of the study. •The primary endpoint of HPV-16/-18 DNA positivity (by PCR) in all 18-19-year old female study participants has been replaced by two co-primary endpoints. •Tertiary objectives and endpoints have been added. •The list of communities has been amended for a discrepancy in the number of females and males. •The enrolment description has been updated to reflect that the enrolment period was extended from 2 years to 2.5 years. •Male and female vaccinated subjects, enrolled in the immunization phase who did not return at Visit 5, were unblinded once they reached 19 years of age. •Amendment of the description of the passive safety follow-up. •Qualitative monitoring of the occurrence of NOADs and cervical neoplastic diseases (CIN3+). •Calculation of the standardized incidence ratios of CIN3+. •Update of the study contact information and the contact information for the back-up study contact for reporting SAEs. •Addition of information on emergency unblinding/code breaking study contact. •Information regarding the Effectiveness evaluation phase (e.g., invitation to the effectiveness evaluation phase, clinical management algorithm) was subjected to changes. •Modification of the instructions for vaccine immunogenicity and immunological read-outs. •Urine and/or a self-obtained cervical sample were not provided as part of the study, but as part of the Finnish National Chlamydia Screening Programme. •The gene expression profile of HPV viruses was not evaluated. •All laboratory assays were performed by GSK Biologicals/a validated laboratory designated by GSK Biologicals. • Only one safety/immunogenicity interim analysis was performed. •Amendment of the description of the interim analysis for effectiveness. •Other miscellaneous updates.

16 February 2012	The HPV-040 protocol was amended for the following reasons: •The interim analysis for effectiveness was not performed in order to reserve maximal study power for end of study analyses. •Oropharyngeal samples for HPV DNA testing were collected at Visit 5 from female subjects born in 1993, 1994 and 1995, who joined the effectiveness evaluation phase of the study. •Tertiary objectives and endpoints have been added. •HPV infection has been specified as "genital" or "oropharyngeal" for all objectives/endpoints. •The Multiplex Type-specific (MPTS) PCR assay HPV PCR Luminex was performed in parallel with the SPF-10 PCR-DEIA/LiPA assay already described in the protocol, in order to align laboratory data from the HPV-040 PRI study with other studies in the project. •Any pIMDs reported to the investigator were reported to GSK Biologicals using SAE screens and were not time-expedited. •Standardized incidence rate ratios of CIN3+ and of NOADs in the cohort (RVI) of HPV vaccinated study participants versus the 1992-1995 born HPV unvaccinated population in the cohort (RVI) in the study communities were calculated at the final analysis. •A registry of vaccinated individuals (RVI) containing personal identifiers has been established at the National Institute for Health and Welfare (THL) at study enrolment. •The number of study participants has been updated with the number of study participants enrolled in immunization phase. •Study procedures at Visit 5 have been clarified. •Clarifications regarding the Engerix formulation. •Update of the introduction. Addition of recent references to literature. •Update of the sponsor information, the list of contributing authors, the list of abbreviations and the list of references.
22 June 2012	As the investigators had immediate and direct access to the individual treatment codes via the SBIR system, Section 7.13 "Emergency unblinding" was not applicable and was removed from the protocol.
09 May 2013	The HPV-040 protocol was amended to: •Further substantiate the rationale behind including long-term follow-up for pregnancy and pregnancy outcomes via Finnish health registries in this study. •Allow usage of the Care Register for Social Welfare and Health Care for passive surveillance of pregnancy and pregnancy outcomes in this study.
28 November 2013	The HPV-040 protocol was amended for the following reason: The assay used to measure anti-HPV-16/-18 antibody concentrations at the designated laboratory was improved to increase the assay precision by changing the assay cut-off value from 8 EL.U/mL to 19 EL.U/mL for HPV-16 and from 7 EL.U/mL to 18 EL.U/mL for HPV-18. This change in the assay was implemented for the testing of samples from Visit 5 onwards.
24 March 2014	The HPV-040 protocol was amended for the following reasons: •Oropharyngeal samples were 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