Clinical trial results:
Estudio en fase III, doble ciego, aleatorizado, controlado, multicéntrico para evaluar la eficacia de la vacuna HPV-16/18 VLP/AS04 de GlaxoSmithKline Biologicals comparada con la vacuna antihepatitis A como control en la prevención de la infección cervical persistente por el HPV-16 o HPV-18 y del cáncer de cérvix, administrada por vía intramuscular conforme a la pauta de vacunación 0, 1 y 6 meses, en mujeres sanas entre 15 y 25 años
A phase III, double-blind, randomized, controlled study to evaluate the efficacy of GlaxoSmithKline Biologicals' HPV-16/18 VLP/AS04 vaccine compared to hepatitis A vaccines as control in prevention of persistent HPV-16 or HPV-18 cervical infection and cervical neoplasia, administered intramuscularly according to a 0, 1, 6 month schedule in healthy female subjects aged 15 – 25 years or age.

Summary

EudraCT number	2004-001325-14
Trial protocol	ES
Global end of trial date	26 November 2009
Results information	
Result version number	v2
This version publication date	29 April 2016
First version publication date	25 October 2014
Version creation reason	• New data added to full data set • Correction of full data set Data for primary endpoints have been added. Data for secondary endpoints have been added. Data (typos) were corrected.

Trial information

Trial identification	
Sponsor protocol code	580299/008
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00122681
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	GlaxoSmithKline Biologicals
Sponsor organisation address	Rue de l'Institut 89, Rixensart, Belgium,
Public contact	Clinical Trials Call Center , GlaxoSmithKline Biologicals , 044 2089904466, GSKClinicalSupportHD@gsk.com
Scientific contact	Clinical Trials Call Center

, GlaxoSmithKline Biologicals , 044 2089904466, GSKClinicalSupportHD@gsk.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 September 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 November 2006
Global end of trial reached?	Yes
Global end of trial date	26 November 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

primary objectives:
- To demonstrate efficacy of the candidate vaccine compared with control in the prevention of histopathologically confirmed CIN2+ associated with HPV-16 or HPV-18 cervical infection detected in the preceding cytological specimen (by PCR) post dose 3 (after Month 6 to Month 48) in adolescent and young adult women who are negative for HPV DNA (by PCR) at Months 0 and 6 for the corresponding HPV type

The principal analysis will be performed on subjects who are seronegative (by ELISA) prior to vaccination for the corresponding HPV type present in the sample.

Protection of trial subjects:

As with all injectable vaccines, appropriate medical treatment was always readily available in case of anaphylactic reactions following the administration of the vaccine.
For this reason, the vaccinee remained under medical supervision for 30 minutes after vaccination.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 May 2004
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	Australia: 548
Country: Number of subjects enrolled	Belgium: 173
Country: Number of subjects enrolled	Brazil: 1803
Country: Number of subjects enrolled	Canada: 506
Country: Number of subjects enrolled	Finland: 4808
Country: Number of subjects enrolled	Germany: 772
Country: Number of subjects enrolled	Italy: 37
Country: Number of subjects enrolled	Mexico: 971
Country: Number of subjects enrolled	Philippines: 2467
Country: Number of subjects enrolled	Spain: 387
Country: Number of subjects enrolled	Taiwan: 1485
Country: Number of subjects enrolled	Thailand: 1852
Country: Number of subjects enrolled	United Kingdom: 271
Country: Number of subjects enrolled	United States: 2564
Worldwide total number of subjects	18644
EEA total number of subjects	6448

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	18644
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of the 18729 subjects enrolled in the study, 64 subjects were not vaccinated. Within the 18665 subjects vaccinated, 21 subjects from 1 center were excluded from all analyses because of potential data discrepancies identified at this center. As a result, a total of 18644 subjects are reported as started in the participant flow.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Havrix Group

Arm description:

Subjects received 3 doses of GSK Biologicals' hepatitis A vaccine [HAV] (Havrix™-based investigational formulation) at Months 0, 1 and 6.

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:

Intramuscular injection, 3 doses

Arm title	Cervarix Group

Arm description:

Subjects received 3 doses of Cervarix™ (GSK Biologicals' human papillomavirus [HPV] vaccine) at Months 0, 1 and 6.

Arm type	Active comparator
Investigational medicinal product name	Havrix™-based investigational formulation
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Intramuscular injection, 3 doses

Number of subjects in period 1	Havrix Group	Cervarix Group
Started	9325	9319
Completed	7811	7798
Not completed	1514	1521
Consent withdrawn by subject	257	251
Personal reasons	150	147
Adverse event, non-fatal	20	16
Lost to follow-up	1080	1097
Protocol deviation	7	10

Baseline characteristics

Reporting groups	
Reporting group title	Havrix Group
Reporting group description:	
Subjects received 3 doses of GSK Biologicals' hepatitis A vaccine [HAV] (Havrix™-based investigational formulation) at Months 0, 1 and 6.	
Reporting group title	Cervarix Group
Reporting group description:	
Subjects received 3 doses of Cervarix™ (GSK Biologicals' human papillomavirus [HPV] vaccine) at Months 0, 1 and 6.	

Reporting group values	Havrix Group	Cervarix Group	Total
Number of subjects	9325	9319	18644
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			
median	20	20	
standard deviation	± 3.12	± 3.1	-
Gender categorical			
Units: Subjects			
Female	9325	9319	18644
Male	0	0	0

End points

End points reporting groups

Reporting group title	Havrix Group
Reporting group description:	
Subjects received 3 doses of GSK Biologicals' hepatitis A vaccine [HAV] (Havrix™-based investigational formulation) at Months 0, 1 and 6.	
Reporting group title	Cervarix Group
Reporting group description:	
Subjects received 3 doses of Cervarix™ (GSK Biologicals' human papillomavirus [HPV] vaccine) at Months 0, 1 and 6.	

Primary: Number of subjects with histopathologically-confirmed cervical intraepithelial neoplasia (CIN)2+ associated with HPV-16 and/or -18 cervical infection

End point title	Number of subjects with histopathologically-confirmed cervical intraepithelial neoplasia (CIN)2+ associated with HPV-16 and/or -18 cervical infection
End point description:	
CIN2+ was defined as CIN grades 2 and 3, endocervical adenocarcinoma in situ (AIS) and invasive cervical cancer. Detection was done in: 1. DNA- and sero-: subjects HPV deoxyribonucleic acid (DNA) negative (DNA-) at Month 0 and Month 6 for the corresponding HPV-type and seronegative (sero-) for HPV-16 and/or HPV-18 by Enzyme-linked Immunosorbent Assay (ELISA) at baseline (Month 0). 2. Overall: subjects DNA- at Month 0 and Month 6 for the corresponding HPV-type and regardless of initial serostatus at baseline.	
End point type	Primary
End point timeframe:	
Up to the moment when 36 cases of CIN2+ lesions associated with HPV-16 or HPV-18 infection had been detected, including at least 15 cases of CIN2+ associated with HPV-18 infection. Mean follow-up was 34.9 months post-dose 3	

End point values	Havrix Group	Cervarix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7767	7814		
Units: Subjests				
HPV-16/18, DNA- & sero- subjects (n= 7312, 7344)	56	4		
HPV-16, DNA- & sero- subjects (n= 6165, 6303)	46	2		
HPV-18, DNA- & sero- subjects (n= 6746, 6794)	15	2		
HPV-16/18, overall (n= 7767, 7814)	65	6		
HPV-16, overall (n= 7276, 7372)	54	4		
HPV-18, overall (n= 7583, 7645)	16	2		

Statistical analyses

Statistical analysis title	Vaccine efficacy against CIN2+ analysis 1

Statistical analysis description:

Vaccine efficacy against CIN2+ associated with HPV-16 or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline, using conditional exact method. The VE was defined as follows: VE = 1-Rate Ratio (RR), where RR = incidence rate in HPV Group (vaccine)/ incidence rate in HAV Group (control); Incidence rate = n/T(per 100); n= number of subjects reporting at least one event in each group and T(years) = sum of follow-up period (censored at the first occurrence of an event) expressed.

Comparison groups	Havrix Group v Cervarix Group
Number of subjects included in analysis	15581
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	1-Rate Ratio
Point estimate	87.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	57.2
upper limit	97.5

Notes:

[1] - Efficacy

Statistical analysis title	Vaccine efficacy against CIN2+ analysis 2

Statistical analysis description:

Vaccine efficacy against CIN2+ associated with HPV-16 (by PCR) in HPV DNA negative and seronegative subjects at baseline, using conditional exact method. The VE was defined as follows: VE = 1-Rate Ratio (RR), where RR = incidence rate in HPV Group (vaccine)/ incidence rate in HAV Group (control); Incidence rate = n/T(per 100); n= number of subjects reporting at least one event in each group and T(years) = sum of follow-up period (censored at the first occurrence of an event) expressed.

Comparison groups	Havrix Group v Cervarix Group
Number of subjects included in analysis	15581
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	1-Rate Ratio
Point estimate	95.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	82.9
upper limit	99.6

Notes:

[2] - Efficacy

Statistical analysis title	Vaccine efficacy against CIN2+ analysis 3

Statistical analysis description:

Vaccine efficacy against CIN2+ associated with HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline, using conditional exact method. The VE was defined as follows: VE = 1-Rate Ratio (RR), where RR = incidence rate in HPV Group (vaccine)/ incidence rate in HAV Group (control); Incidence rate = n/T(per 100); n= number of subjects reporting at least one event in each group and T(years) = sum of follow-up period (censored at the first occurrence of an event) expressed.

Comparison groups	Cervarix Group v Havrix Group

Number of subjects included in analysis	15581
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	1-Rate Ratio
Point estimate	86.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	39.7
upper limit	98.7

Notes:

[3] - Efficacy

Statistical analysis title	Vaccine efficacy against CIN2+ analysis 4

Statistical analysis description:

Vaccine efficacy against CIN2+ for HPV-16 or HPV-18 (by PCR) in HPV DNA negative subjects at baseline, regardless of initial serostatus, using conditional exact method. The VE was defined as follows: VE = 1-Rate Ratio (RR), where RR = incidence rate in HPV Group (vaccine)/ incidence rate in HAV Group (control); Incidence rate = n/T(per 100); n= number of subjects reporting at least one event in each group and T(years) = sum of follow-up period (censored at the first occurrence of an event).

Comparison groups	Havrix Group v Cervarix Group
Number of subjects included in analysis	15581
Analysis specification	Pre-specified
Analysis type	other[4]
Parameter estimate	1-Rate Ratio
Point estimate	90.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	78.1
upper limit	96.9

Notes:

[4] - Efficacy

Statistical analysis title	Vaccine efficacy against CIN2+ analysis 5

Statistical analysis description:

Vaccine efficacy against CIN2+ for HPV-16 (by PCR) in HPV DNA negative subjects at baseline, regardless of initial serostatus, using conditional exact method. The VE was defined as follows: VE = 1-Rate Ratio (RR), where RR = incidence rate in HPV Group (vaccine)/ incidence rate in HAV Group (control); Incidence rate = n/T(per 100); n= number of subjects reporting at least one event in each group and T(years) = sum of follow-up period (censored at the first occurrence of an event).

Comparison groups	Havrix Group v Cervarix Group
Number of subjects included in analysis	15581
Analysis specification	Pre-specified
Analysis type	other[5]
Parameter estimate	1-Rate Ratio
Point estimate	92.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	79.3
upper limit	98.2

Notes:

[5] - Efficacy

Statistical analysis title	Vaccine efficacy against CIN2+ analysis 6

Statistical analysis description:

Vaccine efficacy against CIN2+ for HPV-18 (by PCR) in HPV DNA negative subjects at baseline, regardless of initial serostatus, using conditional exact method. The VE was defined as follows: VE = 1-Rate Ratio (RR), where RR = incidence rate in HPV Group (vaccine)/ incidence rate in HAV Group (control); Incidence rate = n/T(per 100); n= number of subjects reporting at least one event in each group and T(years) = sum of follow-up period (censored at the first occurrence of an event).

Comparison groups	Havrix Group v Cervarix Group
Number of subjects included in analysis	15581
Analysis specification	Pre-specified
Analysis type	other[6]
Parameter estimate	1-Rate Ratio
Point estimate	87.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	44.1
upper limit	98.8

Notes:

[6] - Efficacy

Primary: Number of subjects with histopathologically-confirmed cervical intraepithelial neoplasia (CIN)2+ associated with HPV-16 and/or -18 cervical infection

End point title	Number of subjects with histopathologically-confirmed cervical intraepithelial neoplasia (CIN)2+ associated with HPV-16 and/or -18 cervical infection

End point description:

CIN2+ was defined as CIN grades 2 and 3, endocervical adenocarcinoma in situ (AIS) and invasive cervical cancer. Detection was done in subjects: 1. DNA- and sero-: HPV deoxyribonucleic acid (DNA) negative (DNA-) at Month 0 and Month 6 for the corresponding HPV-type and seronegative (sero-) for HPV-16 and/or HPV-18 by Enzyme-linked Immunosorbent Assay (ELISA) at baseline (Month 0) 2. Overall: subjects HPV DNA- at Month 0 and Month 6 for the corresponding HPV-type and regardless of initial serostatus at baseline.

End point type	Primary

End point timeframe:

at Month 48

End point values	Havrix Group	Cervarix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7767	7806		
Units: Subjects				
HPV-16/18, DNA- & sero- subjects (n= 7305, 7338)	97	5		
HPV-16, DNA- & sero- subjects (n= 6160, 6296)	81	2		
HPV-18, DNA- & sero- subjects (n= 6739, 6789)	23	3		
HPV-16/18, overall (n= 7760, 7806)	108	7		

HPV-16, overall (n= 7267, 7364)	91	4		
HPV-18, overall (n= 7577, 7638)	24	3		

Statistical analyses

Statistical analysis title	Vaccine efficacy against CIN2+ analysis 1

Statistical analysis description:

Vaccine efficacy against CIN2+ associated with HPV-16 or HPV-18 (by PCR) in HPV DNA negative and seronegative subjects at baseline, using conditional exact method. The VE was defined as follows: VE = 1-Rate Ratio (RR), where RR = incidence rate in HPV Group (vaccine)/ incidence rate in HAV Group (control); Incidence rate = n/T(per 100); n= number of subjects reporting at least one event in each group and T(years) = sum of follow-up period (censored at the first occurrence of an event) expressed

Comparison groups	Cervarix Group v Havrix Group
Number of subjects included in analysis	15573
Analysis specification	Pre-specified
Analysis type	other[7]
Parameter estimate	1-Rate Ratio
Point estimate	94.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	87.7
upper limit	98.4

Notes:

[7] - Efficacy

Statistical analysis title	Vaccine efficacy against CIN2+ analysis 2

Statistical analysis description:

Vaccine efficacy against CIN2+ associated with HPV-16 (by PCR) in HPV DNA negative and seronegative subjects at baseline, using conditional exact method. The VE was defined as follows: VE = 1-Rate Ratio (RR), where RR = incidence rate in HPV Group (vaccine)/ incidence rate in HAV Group (control); Incidence rate = n/T(per 100); n= number of subjects reporting at least one event in each group and T(years) = sum of follow-up period (censored at the first occurrence of an event) expressed

Comparison groups	Havrix Group v Cervarix Group
Number of subjects included in analysis	15573
Analysis specification	Pre-specified
Analysis type	other[8]
Parameter estimate	1-Rate Ratio
Point estimate	97.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	91
upper limit	99.7

Notes:

[8] - Efficacy

Statistical analysis title	Vaccine efficacy against CIN2+ analysis 3

Statistical analysis description:

Vaccine efficacy against CIN2+ associated with HPV-16 (by PCR) in HPV DNA negative and seronegative subjects at baseline, using conditional exact method. The VE was defined as follows: VE = 1-Rate Ratio (RR), where RR = incidence rate in HPV Group (vaccine)/ incidence rate in HAV Group (control); Incidence rate = n/T(per 100); n= number of subjects reporting at least one event in each group and T(years) = sum of follow-up period (censored at the first occurrence of an event) expressed

Comparison groups	Havrix Group v Cervarix Group
Number of subjects included in analysis	15573
Analysis specification	Pre-specified
Analysis type	other[9]
Parameter estimate	1-Rate Ratio
Point estimate	87.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	57.2
upper limit	97.5

Notes:

[9] - Efficacy

Statistical analysis title	Vaccine efficacy against CIN2+ analysis 4

Statistical analysis description:

Vaccine efficacy against CIN2+ for HPV-16 or HPV-18 (by PCR) in HPV DNA negative subjects at baseline, regardless of initial serostatus, using conditional exact method. The VE was defined as follows: VE = 1-Rate Ratio (RR), where RR = incidence rate in HPV Group (vaccine)/ incidence rate in HAV Group (control); Incidence rate = n/T(per 100); n= number of subjects reporting at least one event in each group and T(years) = sum of follow-up period (censored at the first occurrence of an event).

Comparison groups	Havrix Group v Cervarix Group
Number of subjects included in analysis	15573
Analysis specification	Pre-specified
Analysis type	other[10]
Parameter estimate	1-Rate Ratio
Point estimate	93.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	86.3
upper limit	97.5

Notes:

[10] - Efficacy

Statistical analysis title	Vaccine efficacy against CIN2+ analysis 5

Statistical analysis description:

Vaccine efficacy against CIN2+ for HPV-16 (by PCR) in HPV DNA negative subjects at baseline, regardless of initial serostatus, using conditional exact method. The VE was defined as follows: VE = 1-Rate Ratio (RR), where RR = incidence rate in HPV Group (vaccine)/ incidence rate in HAV Group (control); Incidence rate = n/T(per 100); n= number of subjects reporting at least one event in each group and T(years) = sum of follow-up period (censored at the first occurrence of an event).

Comparison groups	Cervarix Group v Havrix Group

Number of subjects included in analysis	15573
Analysis specification	Pre-specified
Analysis type	other[11]
Parameter estimate	1-Rate Ratio
Point estimate	95.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	88.5
upper limit	98.9

Notes:

[11] - Efficacy

Statistical analysis title	Vaccine efficacy against CIN2+ analysis 6

Statistical analysis description:

Vaccine efficacy against CIN2+ for HPV-18 (by PCR) in HPV DNA negative subjects at baseline, regardless of initial serostatus, using conditional exact method. The VE was defined as follows: VE = 1-Rate Ratio (RR), where RR = incidence rate in HPV Group (vaccine)/ incidence rate in HAV Group (control); Incidence rate = n/T(per 100); n= number of subjects reporting at least one event in each group and T(years) = sum of follow-up period (censored at the first occurrence of an event).

Comparison groups	Cervarix Group v Havrix Group
Number of subjects included in analysis	15573
Analysis specification	Pre-specified
Analysis type	other[12]
Parameter estimate	1-Rate Ratio
Point estimate	87.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	59.2
upper limit	97.6

Notes:

[12] - Efficacy

Secondary: Number of subjects reporting solicited local and general symptoms

End point title	Number of subjects reporting solicited local and general symptoms

End point description:

Solicited local symptoms assessed include pain, redness and swelling. Solicited general symptoms assessed include arthralgia, fatigue, fever (measured in degree celsius (°C) by axillary route), gastrointestinal symptoms, headache, myalgia, rash and urticaria. Data are presented across the 3 doses.

End point type	Secondary

End point timeframe:

Within 7 days after any vaccination

End point values	Havrix Group	Cervarix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3081	3078		
Units: Subjects				
Pain, total (n= 3080, 3078)	2403	2787		
Pain, sero+ or DNA+ (n= 827, 830)	622	743		
Pain, sero- & DNA- (n=2219,2211)	1758	2013		
Pain, DNA+ (n= 212, 236)	166	219		
Redness, total (n= 3080, 3078)	851	1349		
Redness, sero+ or DNA+ (n= 827, 830)	211	335		
Redness, sero- & DNA- (n=2219,2211)	630	1005		
Redness, DNA+ (n= 212, 236)	56	96		
Swelling, total (n= 3080, 3078)	609	1293		
Swelling, sero+ or DNA+ (n= 827, 830)	145	325		
Swelling, sero- & DNA- (n=2219,2211)	454	959		
Swelling, DNA+ (n= 212, 236)	27	93		
Arthralgia, total (n=3081, 3078)	551	633		
Arthralgia, sero+ or DNA+ (n= 828, 830)	160	149		
Arthralgia, sero- & DNA- (n=2219,2211)	384	480		
Arthralgia, DNA+ (n= 212, 236)	39	58		
Fatigue, total (n=3081, 3078)	1652	1771		
Fatigue, sero+ or DNA+ (n= 828, 830)	415	443		
Fatigue, sero- & DNA- (n=2219,2211)	1215	1311		
Fatigue, DNA+ (n= 212, 236)	116	123		
Fever ≥ 37.5°C, total (n=3081, 3078)	342	385		
Fever ≥ 37.5°C, sero+ or DNA+ (n= 828, 830)	103	126		
Fever ≥ 37.5°C, sero- & DNA- (n=2219,2211)	236	254		
Fever ≥ 37.5°C, DNA+ (n= 212, 236)	23	37		
Gastro-intestinal symptoms, total (n=3081,3078)	847	856		
Gastro-intestinal,sero+ or DNA+ (n= 828, 830)	241	248		
Gastro-intestinal,sero- & DNA- (n=2219,221)	595	601		
Gastro-intestinal symptoms, DNA+ (n= 212, 236)	64	72		
Headache, total (n= 3081, 3078)	1583	1668		
Headache, sero+ or DNA+ (n= 828, 830)	423	425		
Headache, sero- & DNA- (n=2219,2211)	1141	1223		
Headache, DNA+ (n= 212, 236)	112	125		
Myalgia, total (n= 3081, 3078)	1381	1607		
Myalgia, sero+ or DNA+ (n= 828, 830)	347	392		
Myalgia, sero- & DNA- (n=2219, 2211)	1019	1200		
Myalgia, DNA+ (n= 212, 236)	85	119		
Rash, total (n= 3081, 3078)	258	314		
Rash, sero+ or DNA+ (n= 828, 830)	72	91		
Rash, sero- & DNA- (n=2219, 2211)	182	221		
Rash, DNA+ (n= 212, 236)	19	29		
Urticaria, total (n= 3081, 3078)	244	300		

Urticaria, sero+ or DNA+ (n= 828, 830)	73	90		
Urticaria, sero- & DNA- (n=2219, 2211)	169	206		
Urticaria, DNA+ (n= 212, 236)	14	25		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting unsolicited adverse events

End point title	Number of subjects reporting unsolicited adverse events

End point description:

Unsolicited adverse event (AE) covers any AE reported in addition to those solicited during the clinical study and any solicited symptom with onset outside the specified period of follow-up for solicited symptoms.

End point type	Secondary

End point timeframe:

Within 30 days after any vaccination

End point values	Havrix Group	Cervarix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3187	3184		
Units: Subjects				
total (n=3187, 3184)	1466	1448		
sero+ DNA+ (n=858, 854)	400	386		
sero- DNA- (n=2289, 2290)	1048	1049		
DNA+ (n=222, 243)	111	122		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting serious adverse events (SAEs)

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

End point description:

SAEs assessed include medical occurrences that result in death, are life threatening, require hospitalization or prolongation of hospitalization, result in disability/incapacity or are a congenital anomaly/birth defect in the offspring of a study subject.

End point type	Secondary

End point timeframe:

Throughout the entire study period (Month 0 to Month 48)

End point values	Havrix Group	Cervarix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9325	9319		
Units: Subjects				
Total (n=9325, 9319)	829	835		
Sero + and DNA + (n=2419, 2409)	239	251		
Sero- and DNA- (n=6789, 6804)	587	576		
DNA+ (n=649, 690)	69	82		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting new onset of chronic disease (NOCDs)

End point title	Number of subjects reporting new onset of chronic disease (NOCDs)

End point description:

NOCDs include autoimmune disorders, asthma, type I diabetes, allergies.

End point type	Secondary

End point timeframe:

Throughout the entire study (Month 0 to 48)

End point values	Havrix Group	Cervarix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9325	9319		
Units: Subjects				
Total (n= 9325, 9319)	307	285		
sero+ and DNA+ (n= 2419, 2409)	79	79		
sero- and DNA- (n= 6789, 6804)	225	201		
DNA+ (n= 649, 690)	21	24		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting medically significant conditions

End point title	Number of subjects reporting medically significant conditions

End point description:

Medically significant conditions include adverse events (AEs) prompting emergency room or physician visits that are not related to common diseases or routine visits for physical examination or vaccination, or serious adverse events (SAEs) that are not related to common diseases. Common diseases include upper respiratory infections, sinusitis, pharyngitis, gastroenteritis, urinary tract infections, cervico-vaginal yeast infections, menstrual cycle abnormalities and injury.

End point type	Secondary

End point timeframe:

Throughout entire study period (Month 0 to Month 48)

End point values	Havrix Group	Cervarix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9325	9319		
Units: Subjects				
Total (n=9325, 9319)	3378	3298		
sero+ DNA+ (n= 2419, 2409)	957	958		
sero- DNA- (n= 6789, 6804)	2378	2303		
DNA+ (n= 649, 690)	285	296		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with outcome of pregnancies, overall and stratified by initial (Month 0) HPV-16/18 DNA status and according to HPV-16 or -18 serostatus

End point title	Number of subjects with outcome of pregnancies, overall and stratified by initial (Month 0) HPV-16/18 DNA status and according to HPV-16 or -18 serostatus

End point description:

Pregnancy outcomes are normal infant, premature infant, abnormal infant, elective termination, therapeutic abortion, ectopic pregnancy, spontaneous abortion, still birth, lost to follow-up, no pregnancy/molar pregnancy, pregnancy ongoing.

End point type	Secondary

End point timeframe:

Throughout the entire study period (Month 0 to Month 48)

End point values	Havrix Group	Cervarix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2257	2257		
Units: Subjects				
total (n=2257, 2257), normal infant	1671	1642		
total, premature birth	66	77		
total, abnormal infant	22	26		
total, elective termination	228	212		
total, therapeutic abortion	1	2		
total, ectopic pregnancy	9	20		
total, spontaneous abortion	195	205		
total, still birth	11	16		
total, lost to follow-up	42	41		
total, no pregnancy, molar pregnancy	1	4		

total, pregnancy ongoing	11	12		
sero- DNA- (n=1553, 1540), normal infant	1164	1159		
sero- DNA-, premature birth	42	37		
sero- DNA-, abnormal infant	15	18		
sero- DNA-, elective termination	162	138		
sero- DNA-, therapeutic abortion	0	1		
sero- DNA-, ectopic pregnancy	7	13		
sero- DNA-, spontaneous abortion	125	134		
sero- DNA -, still birth	8	10		
sero- DNA-, lost to follow-up	21	21		
sero- DNA-, no pregnancy, molar pregnancy	1	3		
sero- DNA-, pregnancy ongoing	8	6		
sero+ DNA+ (n=676, 685), normal infant	486	464		
sero+ DNA+, premature birth	24	39		
sero+ DNA+, abnormal infant	6	8		
sero+ DNA+, elective termination	62	67		
sero+ DNA+, therapeutic abortion	1	1		
sero+ DNA+, ectopic pregnancy	2	7		
sero+ DNA+, spontaneous abortion	68	67		
sero+ DNA+, still birth	3	6		
sero+ DNA+, lost to follow-up	21	19		
sero+ DNA+, no pregnancy, molar pregnancy	0	1		
sero+ DNA+, pregnancy ongoing	3	6		
DNA+(n=162, 199), normal infant	110	131		
DNA+, premature infant	5	19		
DNA+, abnormal infant	0	0		
DNA+, elective termination	21	18		
DNA+, therapeutic abortion	0	1		
DNA+, ectopic pregnancy	0	2		
DNA+, spontaneous abortion	18	21		
DNA+, still birth	0	1		
DNA+, lost to follow-up	7	5		
DNA+, no pregnancy, molar pregnancy	0	0		
DNA+, pregnancy ongoing	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with persistent infection (6-month definition) with HPV-16 or HPV-18

End point title	Number of subjects with persistent infection (6-month definition) with HPV-16 or HPV-18

End point description:

Persistent cervical HPV infection (6-month definition) was defined as the detection of the same HPV type by polymerase chain reaction (PCR) in cervical samples at 2 consecutive evaluations over approximately a 6-month interval. Detection was done in subjects: 1. DNA- and sero-: subjects HPV DNA- at Month 0 and Month 6 for the corresponding HPV-type and sero- for HPV-16 and/or HPV-18 by Enzyme-linked

Immunosorbent Assay (ELISA) at baseline (Month 0) 2. Overall: subjects HPV DNA- at Month 0 and Month 6 for the corresponding HPV-type and regardless of initial serostatus at baseline

End point type	Secondary

End point timeframe:

Up to the moment when 36 cases of CIN2+ lesions associated with HPV-16 or HPV-18 infection had been detected, including at least 15 cases of CIN2+ associated with HPV-18 infection. Mean follow-up was 34.9 months post dose 3

End point values	Havrix Group	Cervarix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7556	7619		
Units: Subjects				
HPV-16/18, DNA- & sero- (n= 7122, 7177)	488	29		
HPV-16, DNA- & sero- (n= 6018, 6163)	337	22		
HPV-18, DNA- & sero- (n= 6567, 6642)	184	7		
HPV-16/18, overall (n= 7556, 7619)	540	37		
HPV-16, overall (n= 7085, 7196)	380	29		
HPV-18, overall (n= 7377, 7457)	195	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with persistent infection (6-month definition) with HPV-16 or HPV-18

End point title	Number of subjects with persistent infection (6-month definition) with HPV-16 or HPV-18

End point description:

Persistent cervical HPV infection (6-month definition) was defined as the detection of the same HPV type by polymerase chain reaction (PCR) in cervical samples at 2 consecutive evaluations over approximately a 6-month interval. Detection was done in subjects: 1. DNA- and sero-: subjects HPV DNA- at Month 0 and Month 6 for the corresponding HPV-type and sero- for HPV-16 and/or HPV-18 by Enzyme-linked Immunosorbent Assay (ELISA) at baseline (Month 0) 2. Overall: subjects HPV DNA- at Month 0 and Month 6 for the corresponding HPV-type and regardless of initial serostatus at baseline.

End point type	Secondary

End point timeframe:

at Month 48

End point values	Havrix Group	Cervarix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7572	7626		
Units: Subjects				
HPV-16/18, DNA- & sero- (n= 7137, 7182)	588	35		
HPV-16, DNA- & sero- (n= 6029, 6165)	418	24		

HPV-18, DNA- & sero- (n= 6581, 6649)	212	11		
HPV-16/18, overall (n= 7572, 7626)	654	45		
HPV-16, overall (n= 7099, 7202)	437	31		
HPV-18, overall (n= 7394, 7465)	227	14		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with persistent infection (6-month definition) with oncogenic HPV types

End point title	Number of subjects with persistent infection (6-month definition) with oncogenic HPV types

End point description:

Oncogenic types included HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. Detection was done in subjects who were HPV DNA negative at baseline regardless of initial serostatus. HRW-HPV= All high-risk (oncogenic) HPV types excluding HPV-16 and HPV-18 HR-HPV= High-risk (oncogenic) HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68

End point type	Secondary

End point timeframe:

Up to the moment when 36 cases of CIN2+ lesions associated with HPV-16 or HPV-18 infection had been detected, including at least 15 cases of CIN2+ associated with HPV-18 infection. Mean follow-up was 34.9 months post dose 3

End point values	Havrix Group	Cervarix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7553	7587		
Units: Subjects				
HPV-16 (n= 7085, 7196)	380	29		
HPV-18 (n= 7377, 7457)	195	8		
HPV-31 (n= 7398, 7394)	199	45		
HPV-33 (n= 7496, 7527)	100	55		
HPV-35 (n= 7553, 7572)	43	55		
HPV- 39 (n= 7411, 7423)	149	147		
HPV-45 (n= 7540, 7587)	79	19		
HPV-51 (n= 7152, 7188)	354	304		
HPV-52 (n= 7221, 7280)	315	293		
HPV-56 (n= 7435, 7460)	174	182		
HPV-58 (n= 7494, 7512)	101	111		
HPV-59 (n= 7514, 7528)	59	56		
HPV-66 (n= 7358, 7405)	178	168		
HPV-68 (n= 7409, 7441)	134	138		
HRW-HPV (n= 7640, 7665)	1351	1207		
HR-HPV (n= 7640, 7665)	1607	1233		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Persistent Infection (6-month Definition) With Oncogenic HPV Types

End point title	Number of Subjects With Persistent Infection (6-month Definition) With Oncogenic HPV Types

End point description:

Oncogenic types included HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. Detection was done in subjects who were HPV DNA negative at baseline regardless of initial serostatus. HRW-HPV = All high-risk (oncogenic) HPV types excluding HPV-16 and HPV-18 HR-HPV = High-risk (oncogenic) HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68

End point type	Secondary

End point timeframe:

at Month 48

End point values	Havrix Group	Cervarix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7569	7594		
Units: Subjects				
HPV-16 (n= 7099, 7202)	473	31		
HPV-18 (n= 7394, 7465)	227	14		
HPV-31 (n= 7414, 7400)	247	58		
HPV-33 (n= 7513, 7534)	117	65		
HPV-35 (n= 7569, 7579)	56	67		
HPV-39 (n= 7428, 7429)	184	175		
HPV-45 (n= 7556, 7594)	90	24		
HPV-51 (n= 7165, 7190)	416	349		
HPV-52 (n= 7237, 7289)	374	346		
HPV-56 (n= 7451, 7467)	215	226		
HPV-58 (n= 7511, 7518)	122	144		
HPV-59 (n= 7530, 7536)	68	73		
HPV-66 (n= 7375, 7412)	215	211		
HPV-68 (n= 7424, 7450)	169	165		
HRW-HPV (n= 7656, 7672)	1556	1399		
HR-HPV (n= 7656, 7672)	1837	1424		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Histopathologically-confirmed Cervical Intraepithelial Neoplasia (CIN)1+ Associated With HPV-16 or HPV-18 Detected Within the Lesional Component of the Cervical Tissue Specimen

End point title	Number of Subjects With Histopathologically-confirmed Cervical Intraepithelial Neoplasia (CIN)1+ Associated With HPV-16 or HPV-18 Detected Within the Lesional Component of the Cervical Tissue Specimen

End point description:

CIN1+ was defined as histopathologically-confirmed lesions including cervical intraepithelial neoplasia of grade 1 (CIN1), grade 2 (CIN2), grade 3 (CIN3), AIS and invasive cervical cancer. Detection was done in subjects: 1. DNA- and sero-: subjects HPV DNA- at Month 0 and Month 6 for the corresponding HPV-type and sero- for HPV-16 and/or HPV-18 by Enzyme-linked Immunosorbent Assay (ELISA) at baseline (Month 0) 2. Overall: subjects HPV DNA- at Month 0 and Month 6 for the corresponding HPV-type and regardless of initial serostatus at baseline

End point type	Secondary

End point timeframe:

at Month 48

End point values	Havrix Group	Cervarix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7760	7806		
Units: Subjects				
HPV-16/18, DNA- & sero- (n= 7305, 7338)	165	12		
HPV-16, DNA- & sero- (n= 6160, 6296)	124	6		
HPV-18, DNA- & sero- (n= 6739, 6789)	52	6		
HPV-16/18, overall (n= 7760, 7806)	182	16		
HPV-16, overall (n= 7267, 7364)	140	10		
HPV-18, overall (n= 7577, 7638)	53	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with histopathologically-confirmed Cervical Intraepithelial Neoplasia (CIN)1+ associated with HPV-16 or HPV-18 detected within the lesional component of the cervical tissue specimen

End point title	Number of subjects with histopathologically-confirmed Cervical Intraepithelial Neoplasia (CIN)1+ associated with HPV-16 or HPV-18 detected within the lesional component of the cervical tissue specimen

End point description:

CIN1+ was defined as histopathologically-confirmed lesions including cervical intraepithelial neoplasia of grade 1 (CIN1), grade 2 (CIN2), grade 3 (CIN3), AIS and invasive cervical cancer. Detection was done in subjects: 1. DNA- and sero-: subjects HPV DNA- at Month 0 and Month 6 for the corresponding HPV-type and sero- for HPV-16 and/or HPV-18 by Enzyme-linked Immunosorbent Assay (ELISA) at baseline (Month 0) 2. Overall: subjects HPV DNA- at Month 0 and Month 6 for the corresponding HPV-type and regardless of initial serostatus at baseline

End point type	Secondary

End point timeframe:

Up to the moment when 36 cases of CIN2+ lesions associated with HPV-16 or HPV-18 infection had been detected, including at least 15 cases of CIN2+ associated with HPV-18 infection. Mean follow-up was 34.9 months post dose 3

End point values	Havrix Group	Cervarix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7767	7814		
Units: Subjects				
HPV-16/18, DNA- & sero- (n= 7312, 7344)	96	8		
HPV-16, DNA- & sero- (n= 6165, 6303)	70	5		
HPV-18, DNA- & sero- (n= 6746, 6794)	31	3		
HPV-16/18, overall (n= 7767, 7814)	111	12		
HPV-16, overall (n= 7276, 7372)	84	9		
HPV-18, overall (n= 7583, 7645)	32	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects reporting persistent infection (12-month definition) with HPV-16 or HPV-18

End point title	Number of subjects reporting persistent infection (12-month definition) with HPV-16 or HPV-18

End point description:

Persistent cervical HPV infection (12-month definition) was defined as the detection of the same HPV type (by PCR) over a 12-month interval (evaluations were planned at approximately 6-month intervals). Detection was done in subjects: 1. DNA- and sero-: subjects HPV DNA- at Month 0 and Month 6 for the corresponding HPV-type and sero- for HPV-16 and/or HPV-18 by Enzyme-linked Immunosorbent Assay (ELISA) at baseline (Month 0) 2. Overall: subjects HPV DNA- at Month 0 and Month 6 for the corresponding HPV-type and regardless of initial serostatus at baseline

End point type	Secondary

End point timeframe:

Up to the moment when 36 cases of CIN2+ lesions associated with HPV-16 or HPV-18 infection had been detected, including at least 15 cases of CIN2+ associated with HPV-18 infection. Mean follow-up was 34.9 months post dose 3

End point values	Havrix Group	Cervarix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7404	7466		
Units: Subjects				
HPV-16/18, DNA- & sero- (n= 6984, 7035)	227	20		
HPV-16, DNA- & sero- (n= 5903, 6052)	171	17		
HPV-18, DNA- & sero- (n= 6440, 6508)	66	3		
HPV-16/18, overall (n= 7404, 7466)	252	21		
HPV-16, overall (n= 6941, 7057)	192	18		
HPV-18, overall (n= 7231, 7307)	70	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Persistent Infection (12-month Definition) With HPV-16 or HPV-18

End point title	Number of Subjects Reporting Persistent Infection (12-month Definition) With HPV-16 or HPV-18

End point description:

Persistent cervical HPV infection (12-month definition) was defined as the detection of the same HPV type (by PCR) over a 12-month interval (evaluations were planned at approximately 6-month intervals). Detection was done in subjects: 1. DNA- and sero-: subjects HPV DNA- at Month 0 and Month 6 for the corresponding HPV-type and sero- for HPV-16 and/or HPV-18 by Enzyme-linked Immunosorbent Assay (ELISA) at baseline (Month 0) 2. Overall: subjects HPV DNA- at Month 0 and Month 6 for the corresponding HPV-type and regardless of initial serostatus at baseline

End point type	Secondary

End point timeframe:

at Month 48

End point values	Havrix Group	Cervarix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7461	7517		
Units: Subjects				
HPV-16/18, DNA- & sero- (n= 7038, 7082)	354	26		
HPV-16, DNA- & sero- (n= 5949, 6089)	269	19		
HPV-18, DNA- & sero- (n= 6490, 6552)	98	7		
HPV-16/18, overall (n= 7461, 7517)	388	28		
HPV-16, overall (n= 6996, 7103)	300	20		
HPV-18, overall (n= 7288, 7356)	103	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with histopathologically confirmed Cervical Intraepithelial Neoplasia (CIN)1+ associated with oncogenic HPV types detected within the lesional component of the cervical tissue specimen

End point title	Number of subjects with histopathologically confirmed Cervical Intraepithelial Neoplasia (CIN)1+ associated with oncogenic HPV types detected within the lesional component of the cervical tissue specimen

End point description:

Oncogenic HPV types assessed included HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. Detection was done in subjects who were HPV DNA negative at baseline regardless of initial serostatus.

End point type	Secondary

End point timeframe:

Up to the moment when 36 cases of CIN2+ lesions associated with HPV-16 or HPV-18 infection had been detected, including at least 15 cases of CIN2+ associated with HPV-18 infection. Mean follow-up was 34.9 months post dose 3

End point values	Havrix Group	Cervarix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7764	7782		
Units: Subjects				
HPV-16 (n= 7276, 7372)	84	9		
HPV-18 (n= 7583, 7645)	32	3		
HPV-31 (n= 7599, 7583)	49	6		
HPV-33 (n= 7706, 7720)	34	21		
HPV-35 (n= 7764, 7768)	13	4		
HPV-39 (n= 7614, 7609)	29	18		
HPV-45 (n= 7745, 7782)	12	1		
HPV-51 (n= 7352, 7363)	57	42		
HPV-52 (n= 7414, 7461)	44	29		
HPV-56 (n= 7638, 7646)	26	23		
HPV-58 (n= 7702, 7709)	34	11		
HPV-59 (n=7723, 7720)	12	8		
HPV-66 (n= 7564, 7592)	24	15		
HPV-68 (n= 7614, 7633)	22	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Histopathologically Confirmed Cervical Intraepithelial Neoplasia (CIN)1+ Associated With Oncogenic HPV Types Detected Within the Lesional Component of the Cervical Tissue Specimen

End point title	Number of Subjects With Histopathologically Confirmed Cervical Intraepithelial Neoplasia (CIN)1+ Associated With Oncogenic HPV Types Detected Within the Lesional Component of the Cervical Tissue Specimen

End point description:

Oncogenic HPV types assessed included HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. Detection was done in subjects who were HPV DNA negative at baseline regardless of initial serostatus.

End point type	Secondary

End point timeframe:

at Month 48

End point values	Havrix Group	Cervarix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7757	7774		
Units: Subjects				
HPV-16 (n= 7267, 7364)	140	10		
HPV-18 (n= 7577, 7638)	53	6		

HPV-31 (n= 7592, 7575)	79	11		
HPV-33 (n= 7700, 7712)	66	23		
HPV-35 (n= 7757, 7760)	18	7		
HPV-39 (n= 7608, 7602)	48	26		
HPV-45 (n= 7738, 7774)	25	3		
HPV-51 (n= 7341, 7356)	96	61		
HPV-52 (n= 7409, 7455)	81	51		
HPV-56 (n= 7631, 7638)	45	36		
HPV-58 (n= 7696, 7701)	42	25		
HPV-59 (n=7716, 7713)	20	13		
HPV-66 (n= 7559, 7583)	44	30		
HPV-68 (n= 7606, 7626)	43	28		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with histopathologically confirmed Cervical Intraepithelial Neoplasia (CIN)2+ associated with oncogenic HPV types detected within the lesional component of the cervical tissue specimen

End point title	Number of subjects with histopathologically confirmed Cervical Intraepithelial Neoplasia (CIN)2+ associated with oncogenic HPV types detected within the lesional component of the cervical tissue specimen

End point description:

CIN2+ was defined as histopathologically-confirmed lesions including cervical intraepithelial neoplasia of grade 2 (CIN2), grade 3 (CIN3), AIS and invasive cervical cancer. Oncogenic types detected included HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. Detection was done in subjects who were HPV DNA negative at baseline, regardless of initial serostatus.

End point type	Secondary

End point timeframe:

Up to the moment when 36 cases of CIN2+ lesions associated with HPV-16 or HPV-18 infection had been detected, including at least 15 cases of CIN2+ associated with HPV-18 infection. Mean follow-up was 34.9 months post dose 3

End point values	Havrix Group	Cervarix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7764	7782		
Units: Subjects				
HPV-16 (n= 7276, 7372)	54	4		
HPV-18 (n= 7583, 7645)	16	2		
HPV-31 (n= 7599, 7583)	25	2		
HPV-33 (n= 7706, 7720)	25	12		
HPV-35 (n= 7764, 7768)	6	1		
HPV-39 (n= 7614, 7609)	10	3		
HPV-45 (n= 7745, 7782)	4	0		
HPV-51 (n= 7352, 7363)	27	10		
HPV-52 (n= 7414, 7461)	14	12		
HPV-56 (n= 7638, 7646)	10	4		

HPV-58 (n=7702, 7709)	17	6		
HPV-59 (n= 7723, 7720)	4	1		
HPV-66 (n= 7564, 7592)	10	4		
HPV-68 (n= 7614, 7633)	11	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with histopathologically confirmed Cervical Intraepithelial Neoplasia (CIN)2+ associated with oncogenic HPV types detected within the lesional component of the cervical tissue specimen

End point title	Number of subjects with histopathologically confirmed Cervical Intraepithelial Neoplasia (CIN)2+ associated with oncogenic HPV types detected within the lesional component of the cervical tissue specimen

End point description:

CIN2+ was defined as histopathologically-confirmed lesions including cervical intraepithelial neoplasia of grade 2 (CIN2), grade 3 (CIN3), AIS and invasive cervical cancer. Oncogenic types detected included HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. Detection was done in subjects who were HPV DNA negative at baseline, regardless of initial serostatus.

End point type	Secondary

End point timeframe:

at Month 48

End point values	Havrix Group	Cervarix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7757	7774		
Units: Subjects				
HPV-16 (n= 7267, 7364)	91	4		
HPV-18 (n= 7577, 7638)	24	3		
HPV-31 (n= 7592, 7575)	40	5		
HPV-33 (n= 7700, 7712)	41	13		
HPV-35 (n= 7757, 7760)	8	3		
HPV-39 (n= 7608, 7602)	16	4		
HPV-45 (n= 7738, 7774)	11	2		
HPV-51 (n= 7341, 7356)	46	21		
HPV-52 (n= 7409, 7455)	33	24		
HPV-56 (n= 7631, 7638)	13	7		
HPV-58 (n=7696, 7701)	21	15		
HPV-59 (n= 7716, 7713)	5	1		
HPV-66 (n= 7559, 7583)	16	7		
HPV-68 (n= 7606, 7626)	15	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seropositive subjects for anti-HPV-16 and anti-HPV-18 antibody titers by ELISA in the immunogenicity subset, according to initial (Month 0) HPV-16 or HPV-18 serostatus

End point title	Number of seropositive subjects for anti-HPV-16 and anti-HPV-18 antibody titers by ELISA in the immunogenicity subset, according to initial (Month 0) HPV-16 or HPV-18 serostatus

End point description:

Cut-off values assessed for seropositivity include 8 enzyme-linked immunosorbent assay units per milliliter (EL.U/mL) for anti-HPV-16 antibodies and 7 EL.U/mL for anti-HPV-18 antibodies. Results are presented for the total group and stratified according to initial (Month 0) HPV-16 or HPV-18 serostatus by ELISA - seronegative (sero-) or seropositive (sero+)

End point type	Secondary

End point timeframe:

At Months 6, 7, 12, 24, 36 & 48

End point values	Havrix Group	Cervarix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	898	1036		
Units: Subjects				
HPV-16, sero-, pre-vaccination (n= 750, 872)	0	0		
HPV-16, sero-, Month 6 (n= 738, 865)	41	864		
HPV-16, sero-, Month 7 (n= 740, 865)	34	861		
HPV-16, sero-, Month 12 (n= 719, 839)	30	837		
HPV-16, sero-, Month 24 (n= 672, 797)	33	796		
HPV-16, sero-, Month 36 (n= 664, 784)	35	784		
HPV-16, sero-, Month 48 (n= 603, 746)	47	746		
HPV-16, sero+, pre-vaccination (n= 147, 164)	147	164		
HPV-16, sero+, Month 6 (n= 139, 162)	119	161		
HPV-16, sero+, Month 7 (n= 139, 163)	106	162		
HPV-16, sero+, Month 12 (n= 134, 154)	101	154		
HPV-16, sero+, Month 24 (n= 138, 146)	96	146		
HPV-16, sero+, Month 36 (n= 127, 142)	88	142		
HPV-16, sero+, Month 48 (n= 118, 145)	85	145		
HPV-16, total, pre-vaccination (n= 897, 1036)	147	164		
HPV-16, total, Month 6 (n= 877, 1027)	160	1025		
HPV-16, total, Month 7 (n= 879, 1028)	140	1023		
HPV-16, total, Month 12 (n= 853, 993)	131	991		
HPV-16, total, Month 24 (n= 810, 943)	129	942		
HPV-16, total, Month 36 (n= 791, 926)	123	926		
HPV-16, total, Month 48 (n= 721, 891)	132	891		
HPV-18, sero-, pre-vaccination (n= 790,939)	0	0		
HPV-18, sero-, Month 6 (n= 771, 930)	29	927		
HPV-18, sero-, Month 7 (n= 772, 930)	32	925		
HPV-18, sero-, Month 12 (n= 748, 901)	36	901		
HPV-18, sero-, Month 24 (n= 698, 854)	37	853		

HPV-18, sero-, Month 36 (n= 691, 841)	31	841		
HPV-18, sero-, Month 48 (n= 633, 806)	32	804		
HPV-18, sero+, pre-vaccination (n= 108, 97)	108	97		
HPV-18, sero+, Month 6 (n= 105, 97)	90	96		
HPV-18, sero+, Month 7 (n= 105, 97)	90	97		
HPV-18, sero+, Month 12 (n= 106, 92)	89	92		
HPV-18, sero+, Month 24 (n= 102, 89)	84	89		
HPV-18, sero+, Month 36 (n= 98, 86)	73	86		
HPV-18, sero+, Month 48 (n= 91, 86)	70	86		
HPV-18, total, pre-vaccination (n= 898, 1036)	108	97		
HPV-18, total, Month 6 (n= 876, 1027)	119	1023		
HPV-18, total, Month 7 (n= 877, 1027)	122	1022		
HPV-18, total, Month 12 (n= 854, 993)	125	993		
HPV-18, total, Month 24 (n= 800, 943)	121	942		
HPV-18, total, Month 36 (n= 789, 927)	104	927		
HPV-18, total, Month 48 (n= 724, 892)	102	890		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-HPV-16 and anti-HPV-18 ELISA titers in the immunogenicity subset

End point title	Anti-HPV-16 and anti-HPV-18 ELISA titers in the immunogenicity subset

End point description:

Titers are given as Geometric Mean Titers (GMTs) expressed as ELISA Units per milliliter (EL.U/mL). GMTs are presented for the total group and also stratified according to initial (Month 0) HPV-16 or HPV-18 serostatus by ELISA [seronegative (sero-) or seropositive (sero+)].

End point type	Secondary

End point timeframe:

At Months 6, 7, 12, 24, 36 and 48

End point values	Havrix Group	Cervarix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	898	1036		
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Anti-HPV-16, sero-, pre-vaccination (n= 750, 872)	4 (4 to 4)	4 (4 to 4)		
Anti-HPV-16, sero-, Month 6 (n= 738, 865)	4.4 (4.2 to 4.5)	630.7 (591.6 to 672.4)		
Anti-HPV-16, sero-, Month 7 (n= 740, 865)	4.4 (4.2 to 4.6)	9206.5 (8609.4 to 9845.1)		
Anti-HPV-16, sero-, Month 12 (n= 719, 839)	4.3 (4.2 to 4.4)	3281.1 (3064.5 to 3513)		

Anti-HPV-16, sero-, Month 24 (n= 672, 797)	4.4 (4.2 to 4.5)	1592 (1491.6 to 1699.2)		
Anti-HPV-16, sero-, Month 36 (n= 664, 784)	4.4 (4.2 to 4.5)	1265.1 (1184.8 to 1350.8)		
Anti-HPV-16, sero-, Month 48 (n= 603, 746)	4.6 (4.4 to 4.8)	1174.3 (1096.1 to 1258)		
Anti-HPV-16, sero+, pre-vaccination (n= 147, 164)	29.7 (25 to 35.4)	28.9 (24.7 to 33.8)		
Anti-HPV-16, sero+, Month 6 (n= 139, 162)	24.4 (19.9 to 29.8)	1256.9 (1030.1 to 1533.7)		
Anti-HPV-16, sero+, Month 7 (n= 139, 163)	21.7 (17.4 to 27)	6423.1 (5486.3 to 7520)		
Anti-HPV-16, sero+, Month 12 (n= 134, 154)	20.2 (16.3 to 25.1)	2909.6 (2504.3 to 3380.4)		
Anti-HPV-16, sero+, Month 24 (n= 138, 146)	18.7 (15 to 23.2)	1573.2 (1356.7 to 1824.2)		
Anti-HPV-16, sero+, Month 36 (n= 127, 142)	17.7 (14 to 22.2)	1244.3 (1068.9 to 1448.4)		
Anti-HPV-16, sero+, Month 48 (n= 118, 145)	18.3 (14.5 to 23)	1115.9 (959.6 to 1297.7)		
Anti-HPV-16, total, pre-vaccination (n= 897, 1036)	5.6 (5.3 to 5.9)	5.5 (5.2 to 5.8)		
Anti-HPV-16, total, Month 6 (n= 877, 1027)	5.7 (5.4 to 6.1)	703.2 (659.5 to 749.7)		
Anti-HPV-16, total, Month 7 (n= 879, 1028)	5.6 (5.3 to 6)	8695.7 (8171.9 to 9253.1)		
Anti-HPV-16, total, Month 12 (n= 853, 993)	5.5 (5.2 to 5.8)	3220.5 (3026.4 to 3427.1)		
Anti-HPV-16, total, Month 24 (n= 810, 943)	5.6 (5.3 to 5.9)	1589.1 (1497.2 to 1686.6)		
Anti-HPV-16, total, Month 36 (n=791, 926)	5.4 (5.1 to 5.8)	1261.9 (1188.3 to 1340)		
Anti-HPV-16, total, Month 48 (n=721, 891)	5.7 (5.4 to 6.1)	1164.6 (1093.9 to 1239.8)		
Anti-HPV-18, sero-, pre-vaccination (n=790, 939)	3.5 (3.5 to 3.5)	3.5 (3.5 to 3.5)		
Anti-HPV-18, sero-, Month 6 (n=771, 930)	3.7 (3.6 to 3.8)	542.7 (510.2 to 577.2)		
Anti-HPV-18, sero-, Month 7 (n= 772, 930)	3.8 (3.6 to 3.9)	4741.3 (4452.2 to 5049.1)		
Anti-HPV-18, sero-, Month 12 (n= 748, 901)	3.8 (3.7 to 3.9)	1521.7 (1431 to 1618.1)		
Anti-HPV-18, sero-, Month 24 (n= 698, 854)	3.8 (3.7 to 3.9)	704.4 (658.4 to 753.8)		
Anti-HPV-18, sero-, Month 36 (n= 691, 841)	3.7 (3.6 to 3.8)	534.3 (498.9 to 572.1)		
Anti-HPV-18, sero-, Month 48 (n= 633, 806)	3.8 (3.7 to 3.9)	476.2 (443.2 to 511.6)		
Anti-HPV-18, sero+, pre-vaccination (n= 108, 97)	23.4 (18.9 to 29.1)	24.8 (20.1 to 30.6)		

Anti-HPV-18, sero+, Month 6 (n= 105, 97)	19.6 (15.2 to 25.4)	903.8 (714 to 1144.2)		
Anti-HPV-18, sero+, Month 7 (n= 105, 97)	20.8 (16.2 to 26.8)	4135.7 (3548.6 to 4819.9)		
Anti-HPV-18, sero+, Month 12 (n= 106, 92)	19.9 (15.5 to 25.5)	1509.5 (1271.3 to 1792.3)		
Anti-HPV-18, sero+, Month 24 (n= 102, 89)	18.9 (14.6 to 24.4)	745.6 (620.1 to 896.6)		
Anti-HPV-18, sero+, Month 36 (n= 98, 86)	16.8 (12.8 to 22.1)	580.9 (475 to 710.4)		
Anti-HPV-18, sero+, Month 48 (n= 91, 86)	16.5 (12.6 to 21.6)	510.6 (415.7 to 627.2)		
Anti-HPV-18, total, pre-vaccination (n= 898, 1036)	4.4 (4.2 to 4.6)	4.2 (4 to 4.4)		
Anti-HPV-18, total, Month 6 (n= 876, 1027)	4.5 (4.3 to 4.8)	569.5 (536 to 605.1)		
Anti-HPV-18, total, Month 7 (n= 877, 1027)	4.6 (4.4 to 4.9)	4680.5 (4413.4 to 4963.7)		
Anti-HPV-18, total, Month 12 (n= 854, 993)	4.6 (4.4 to 4.9)	1520.5 (1435 to 1611.2)		
Anti-HPV-18, total, Month 24 (n= 800, 943)	4.7 (4.4 to 4.9)	708.2 (664.6 to 754.8)		
Anti-HPV-18, total, Month 36 (n=789, 927)	4.5 (4.3 to 4.8)	538.5 (504.7 to 574.5)		
Anti-HPV-18, total, Month 48 (n=724, 892)	4.6 (4.3 to 4.8)	479.4 (448 to 513)		

Statistical analyses

No statistical analyses for this end point

Secondary: HPV-16 and HPV-18 seroconversion (V5/J4 monoclonal inhibition test)

End point title	HPV-16 and HPV-18 seroconversion (V5/J4 monoclonal inhibition test)

End point description:

HPV-16 V5 cut-off was defined as greater than or equal to 41 ELU/mL. Only seronegative subjects were analysed. Seronegative subjects are subjects who had an antibody titer of less than 41 ELU/mL before vaccination. HPV-18 J4 cut-off was defined as greater than or equal to 110 EL.U/mL. Both seropositive and seronegative subjects were included in the analysis. Seropositive subjects were subjects with an antibody titer of greater than or equal to 110 EL.U/mL. Seronegative subjects were subjects with an antibody titer less than 110 EL.U/mL.

End point type	Secondary

End point timeframe:

Month 0, 7, 12 and 24

End point values	Havrix Group	Cervarix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	17		
Units: Subjects				
pre-vaccination V5 HPV-16 (n= 17,17)	0	0		
Month 7 V5 HPV-16 (n= 17,17)	0	17		
Month 12 V5 HPV-16 (n= 5, 2)	0	2		
Month 24 V5 HPV-16 (n=17, 17)	0	17		
pre-vaccination J4 HPV-18 (n= 17, 17)	0	1		
Month 7 J4 HPV-18 (n= 17,17)	0	17		
Month 12 J4 HPV-18 (n= 5, 2)	1	1		
Month 24 V5 HPV-18 (n=17, 17)	1	11		

Statistical analyses

No statistical analyses for this end point

Secondary: HPV-16 and HPV-18 Geometric Mean Titers (GMT) (V5/J4 monoclonal inhibition test)

End point title	HPV-16 and HPV-18 Geometric Mean Titers (GMT) (V5/J4 monoclonal inhibition test)

End point description:

Titers were expressed as GMTs in ELISA units per milliliter (EL.U/mL).

End point type	Secondary

End point timeframe:

Month 0, 7, 12, 24

End point values	Havrix Group	Cervarix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	17		
Units: U/mL				
geometric mean (confidence interval 95%)				
pre-vaccination V5 HPV-16 (n= 17,17)	20.5 (20.5 to 20.5)	20.5 (20.5 to 20.5)		
Month 7 V5 HPV-16 (n= 17,17)	20.5 (20.5 to 20.5)	816.7 (472.5 to 1411.4)		
Month 12 V5 HPV-16 (n= 5, 2)	20.5 (20.5 to 20.5)	173.5 (25.1 to 1199.3)		
Month 24 V5 HPV-16 (n=17, 17)	20.5 (20.5 to 20.5)	163.3 (104 to 256.6)		
pre-vaccination J4 HPV-18 (n= 17, 17)	55 (55 to 55)	57.7 (52.1 to 63.8)		
Month 7 J4 HPV-18 (n= 17,17)	55 (55 to 55)	679.2 (423.6 to 1088.9)		
Month 12 J4 HPV-18 (n= 5, 2)	71 (35 to 144.2)	83.6 (0.4 to 17024)		
Month 24 V5 HPV-18 (n=17, 17)	58.1 (51.7 to 65.2)	139.5 (90.5 to 215.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects seropositive for anti-HPV-16 and anti-HPV-18 antibodies using pseudovirion based neutralizing assay (PBNA)

End point title	Number of subjects seropositive for anti-HPV-16 and anti-HPV-18 antibodies using pseudovirion based neutralizing assay (PBNA)

End point description:

Seropositivity was defined as subjects with a titer equal to or greater than 40. Subjects with an antibody titer smaller than 40 prior to vaccination were seronegative prior to vaccination and subjects with a titer equal to or greater than 40 were seropositive prior to vaccination.

End point type	Secondary

End point timeframe:

At Month 0, 7, 12, 24, 36 and 48

End point values	Havrix Group	Cervarix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	48		
Units: Subjects				
pre-vaccination HPV-16 (n= 44, 46)	0	0		
Month 7 HPV-16 (n= 44, 46)	0	46		
Month 12 HPV-16 (n= 43, 45)	0	45		
Month 24 HPV-16 (n= 40, 46)	0	46		
Month 36 HPV-16 (n= 33, 41)	0	41		
Month 48 HPV-16 (n= 33, 41)	0	40		
pre-vaccination HPV-18 (n= 47, 48)	0	0		
Month 7 HPV-18 (n= 44, 46)	0	46		
Month 12 HPV-18 (n= 43, 45)	0	44		
Month 24 HPV-18 (n= 40, 46)	0	46		
Month 36 HPV-18 (n= 33, 41)	0	41		
Month 48 HPV-18 (n= 33, 41)	2	39		

Statistical analyses

No statistical analyses for this end point

Secondary: Titers for anti-HPV-16 and anti-HPV-18 antibodies using pseudovirion based neutralizing assay (PBNA)

End point title	Titers for anti-HPV-16 and anti-HPV-18 antibodies using

	pseudovirion based neutralizing assay (PBNA)
End point description: Titers were expressed as GMTs.	
End point type	Secondary
End point timeframe: At month 0, 7, 12, 24, 36 and 48	

End point values	Havrix Group	Cervarix Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	48		
Units: Titer				
geometric mean (confidence interval 95%)				
pre-vaccination HPV-16 (n= 44, 46)	20 (20 to 20)	20 (20 to 20)		
Month 7 HPV-16 (n= 44, 46)	20 (20 to 20)	27364.8 (19780.1 to 37857.9)		
Month 12 HPV-16 (n= 43, 45)	20 (20 to 20)	8385.9 (5857.3 to 12006)		
Month 24 HPV-16 (n= 40, 46)	20 (20 to 20)	3647.4 (2586.5 to 5143.4)		
Month 36 HPV-16 (n= 33, 41)	20 (20 to 20)	2245.1 (1616.6 to 3117.9)		
Month 48 HPV-16 (n= 33, 41)	20 (20 to 20)	1931.1 (1294.4 to 2880.8)		
pre-vaccination HPV-18 (n= 47, 48)	20 (20 to 20)	20 (20 to 20)		
Month 7 HPV-18 (n= 44, 46)	20 (20 to 20)	9052.7 (6851.8 to 11960.5)		
Month 12 HPV-18 (n= 43, 45)	20 (20 to 20)	1889.9 (1316 to 2714.1)		
Month 24 HPV-18 (n= 40, 46)	20 (20 to 20)	1695.6 (1200.7 to 2394.4)		
Month 36 HPV-18 (n= 33, 41)	20 (20 to 20)	1326.9 (948 to 1857.3)		
Month 48 HPV-18 (n= 33, 41)	23.8 (18.6 to 30.4)	1078.1 (714.9 to 1625.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric mean titers of anti-HPV-16 in subjects without and with 6-month persistent infection

End point title	Geometric mean titers of anti-HPV-16 in subjects without and with 6-month persistent infection[13]

End point description:

GMT for anti-HPV-16 antibodies by ELISA in subjects with breakthrough persistent infections 6-month definition, were compared to those in a matched set of subjects without breakthrough persistent infections.

End point type	Secondary

End point timeframe:

At Month 7

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint required results only for the subjects with HPV.

End point values	Cervarix Group			
Subject group type	Reporting group			
Number of subjects analysed	1123			
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Subjects without 6 Month persistent infection	7667.34 (7212.13 to 8151.29)			
Subjects with 6 Month persistent infection	6986.3 (5692.83 to 8573.66)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seroconverted subjects for anti-HPV-16 without and with 6-month persistent infection

End point title	Number of seroconverted subjects for anti-HPV-16 without and with 6-month persistent infection[14]

End point description:

Seroconversion rates for anti-HPV-16 antibodies by ELISA in subjects with breakthrough persistent infections 6-month definition, were compared to those in a matched set of subjects without breakthrough persistent infections.

End point type	Secondary

End point timeframe:

At Month 7

Notes:

[14] - 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 endpoint required results only for the subjects with HPV.

End point values	Cervarix Group			
Subject group type	Reporting group			
Number of subjects analysed	1123			
Units: Subjects				
Subjects without 6 Month persistent infection	1118			

Subjects with 6 Month persistent infection	45			

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric mean titers of anti-HPV-16 in subjects without and with 12-month persistent infection

End point title	Geometric mean titers of anti-HPV-16 in subjects without and with 12-month persistent infection[15]

End point description:

GMTs for anti-HPV-16 antibodies by ELISA in subjects with breakthrough persistent infections 12-month definition, were compared to those in a matched set of subjects without breakthrough persistent infections.

End point type	Secondary

End point timeframe:

At Month 7

Notes:

[15] - 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 endpoint required results only for the subjects with HPV.

End point values	Cervarix Group			
Subject group type	Reporting group			
Number of subjects analysed	1120			
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Subjects without 12 Month persistent infection	7683.56 (7229.22 to 8166.44)			
Subjects with 12 Month persistent infection	6839.71 (5362.44 to 8723.96)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seroconverted subjects for anti-HPV-16 without and with 12-month persistent infection

End point title	Number of seroconverted subjects for anti-HPV-16 without and with 12-month persistent infection[16]

End point description:

Seroconversion rates for anti-HPV-16 antibodies by ELISA in subjects with breakthrough persistent infections 12-month definition, were compared to those in a matched set of subjects without breakthrough persistent infections.

End point type	Secondary

End point timeframe:

At Month 7

Notes:

[16] - 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 endpoint required results only for the subjects with HPV.

End point values	Cervarix Group			
Subject group type	Reporting group			
Number of subjects analysed	1120			
Units: Subjects				
Subjects without 12 Month persistent infection	1115			
Subjects with 12 Month persistent infection	37			

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric mean titers of anti-HPV-18 in subjects without and with 6-month persistent infection

End point title	Geometric mean titers of anti-HPV-18 in subjects without and with 6-month persistent infection[17]

End point description:

GMTs for anti-HPV-18 antibodies by ELISA in subjects with breakthrough persistent infections 6-month definition, were compared to those in a matched set of subjects without breakthrough persistent infections.

End point type	Secondary

End point timeframe:

At Month 7

Notes:

[17] - 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 endpoint required results only for the subjects with HPV.

End point values	Cervarix Group			
Subject group type	Reporting group			
Number of subjects analysed	1248			
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Subjects without 6 Month persistent infection	3963.5 (3750.71 to 4188.37)			
Subjects with 6 Month persistent infection	2945.69 (2271.74 to 3819.58)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seroconverted subjects for anti-HPV-18 without and with 6-month persistent infection

End point title	Number of seroconverted subjects for anti-HPV-18 without and with 6-month persistent infection[18]

End point description:

Seroconversion rates for anti-HPV-18 antibodies by ELISA in subjects with breakthrough persistent infections 6-month definition, were compared to those in a matched set of subjects without breakthrough persistent infections.

End point type	Secondary

End point timeframe:

At Month 7

Notes:

[18] - 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 endpoint required results only for the subjects with HPV.

End point values	Cervarix Group			
Subject group type	Reporting group			
Number of subjects analysed	1248			
Units: Subjects				
Subjects without 6 Month persistent infection	1242			
Subjects with 6 Month persistent infection	28			

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric mean titers of anti-HPV-18 in subjects without and with 12-month persistent infection

End point title	Geometric mean titers of anti-HPV-18 in subjects without and with 12-month persistent infection[19]

End point description:

GMTs for anti-HPV-18 antibodies by ELISA in subjects with breakthrough persistent infections 12-month definition, were compared to those in a matched set of subjects without breakthrough persistent infections.

End point type	Secondary

End point timeframe:

At Month 7

Notes:

[19] - 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 endpoint required results only for the subjects with HPV.

End point values	Cervarix Group			
Subject group type	Reporting group			
Number of subjects analysed	1243			
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Subjects without 12 Month persistent infection	3965.67 (3753.09 to 4190.29)			
Subjects with 12 Month persistent infection	3063.23 (2261.65 to 4148.91)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of seroconverted subjects for anti-HPV-18 without and with 12-month persistent infection

End point title	Number of seroconverted subjects for anti-HPV-18 without and with 12-month persistent infection[20]

End point description:

Seroconversion rates for anti-HPV-18 antibodies by ELISA in subjects with breakthrough persistent infections 12-month definition, were compared to those in a matched set of subjects without breakthrough persistent infections.

End point type	Secondary

End point timeframe:

At Month 7

Notes:

[20] - 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 endpoint required results only for the subjects with HPV.

End point values	Cervarix Group			
Subject group type	Reporting group			
Number of subjects analysed	1243			
Units: Subjects				
Subjects without 12 Month persistent infection	1237			
Subjects with 12 Month persistent infection	21			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited symptoms: Days 0-6 post-vaccination; Unsolicited symptoms: Days 0-29 post-vaccination; Serious Adverse Events: Months 0-48 post-vaccination.

Adverse event reporting additional description:

Results presented per group consist of a summary of the events (SAEs and AEs other than SAEs, respectively) reported, compiling overall number of subjects with events across the different periods of assessment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	Havrix Group

Reporting group description:

Subjects received 3 doses of GSK Biologicals' hepatitis A vaccine [HAV] (Havrix™-based investigational formulation) at Months 0, 1 and 6.

Reporting group title	Cervarix Group

Reporting group description:

Subjects received 3 doses of Cervarix™ (GSK Biologicals' human papillomavirus [HPV] vaccine) at Months 0, 1 and 6.

Serious adverse events	Havrix Group	Cervarix Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	829 / 9325 (8.89%)	835 / 9319 (8.96%)	
number of deaths (all causes)	13	10	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	6 / 9325 (0.06%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian germ cell teratoma benign			
subjects affected / exposed	3 / 9325 (0.03%)	3 / 9319 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Teratoma			

subjects affected / exposed	2 / 9325 (0.02%)	3 / 9319 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign hydatidiform mole			
subjects affected / exposed	1 / 9325 (0.01%)	3 / 9319 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	1 / 9325 (0.01%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian adenoma			
subjects affected / exposed	1 / 9325 (0.01%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibroadenoma of breast			
subjects affected / exposed	2 / 9325 (0.02%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid cancer			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Astrocytoma malignant			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Astrocytoma, low grade			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			

subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone sarcoma			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Carcinoid tumour of the appendix			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gestational trophoblastic tumour			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Leiomyoma			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lung			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neoplasm			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian neoplasm			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid neoplasm			

subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval cancer			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	3 / 9325 (0.03%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Circulatory collapse			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic venous thrombosis			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			

subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose vein			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasculitis			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	3 / 9325 (0.03%)	5 / 9319 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breech extraction			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nail operation			

subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	59 / 9325 (0.63%)	70 / 9319 (0.75%)	
occurrences causally related to treatment / all	1 / 59	2 / 70	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion spontaneous incomplete			
subjects affected / exposed	40 / 9325 (0.43%)	54 / 9319 (0.58%)	
occurrences causally related to treatment / all	0 / 40	0 / 54	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion spontaneous complete			
subjects affected / exposed	46 / 9325 (0.49%)	43 / 9319 (0.46%)	
occurrences causally related to treatment / all	0 / 46	0 / 43	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion missed			
subjects affected / exposed	27 / 9325 (0.29%)	20 / 9319 (0.21%)	
occurrences causally related to treatment / all	1 / 27	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Premature labour			
subjects affected / exposed	12 / 9325 (0.13%)	21 / 9319 (0.23%)	
occurrences causally related to treatment / all	0 / 12	0 / 21	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ectopic pregnancy			
subjects affected / exposed	8 / 9325 (0.09%)	18 / 9319 (0.19%)	
occurrences causally related to treatment / all	0 / 8	0 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pre-eclampsia			
subjects affected / exposed	11 / 9325 (0.12%)	10 / 9319 (0.11%)	
occurrences causally related to treatment / all	0 / 11	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blighted ovum			

subjects affected / exposed	9 / 9325 (0.10%)	10 / 9319 (0.11%)	
occurrences causally related to treatment / all	0 / 9	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-uterine death			
subjects affected / exposed	7 / 9325 (0.08%)	9 / 9319 (0.10%)	
occurrences causally related to treatment / all	0 / 7	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stillbirth			
subjects affected / exposed	7 / 9325 (0.08%)	8 / 9319 (0.09%)	
occurrences causally related to treatment / all	0 / 7	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperemesis gravidarum			
subjects affected / exposed	4 / 9325 (0.04%)	5 / 9319 (0.05%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Premature rupture of membranes			
subjects affected / exposed	3 / 9325 (0.03%)	6 / 9319 (0.06%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy induced hypertension			
subjects affected / exposed	5 / 9325 (0.05%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion threatened			
subjects affected / exposed	2 / 9325 (0.02%)	3 / 9319 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Premature baby			
subjects affected / exposed	2 / 9325 (0.02%)	3 / 9319 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Premature separation of placenta			

subjects affected / exposed	1 / 9325 (0.01%)	4 / 9319 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chorioamnionitis			
subjects affected / exposed	1 / 9325 (0.01%)	3 / 9319 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion incomplete			
subjects affected / exposed	3 / 9325 (0.03%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eclampsia			
subjects affected / exposed	2 / 9325 (0.02%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retained products of conception			
subjects affected / exposed	1 / 9325 (0.01%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ruptured ectopic pregnancy			
subjects affected / exposed	1 / 9325 (0.01%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Threatened labour			
subjects affected / exposed	3 / 9325 (0.03%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breech presentation			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Placenta praevia			

subjects affected / exposed	2 / 9325 (0.02%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retained placenta or membranes			
subjects affected / exposed	0 / 9325 (0.00%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion complete			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Antepartum haemorrhage			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrested labour			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cephalo-pelvic disproportion			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Face presentation			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
False labour			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foetal distress syndrome			

subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foetal growth retardation			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Imminent abortion			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Induced labour			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructed labour			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oligohydramnios			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Placenta accreta			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Placenta praevia haemorrhage			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postpartum uterine subinvolution			

subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prolonged labour			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small for dates baby			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine inversion			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	11 / 9325 (0.12%)	9 / 9319 (0.10%)	
occurrences causally related to treatment / all	0 / 11	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 9325 (0.01%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adverse drug reaction			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyst			

subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drowning			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Fatigue			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (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			
Hypersensitivity			
subjects affected / exposed	5 / 9325 (0.05%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food allergy			
subjects affected / exposed	1 / 9325 (0.01%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic shock			
subjects affected / exposed	0 / 9325 (0.00%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic reaction			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Homicide			
subjects affected / exposed	2 / 9325 (0.02%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Reproductive system and breast			

disorders			
Ovarian cyst			
subjects affected / exposed	10 / 9325 (0.11%)	11 / 9319 (0.12%)	
occurrences causally related to treatment / all	0 / 10	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst ruptured			
subjects affected / exposed	11 / 9325 (0.12%)	4 / 9319 (0.04%)	
occurrences causally related to treatment / all	0 / 11	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometriosis			
subjects affected / exposed	6 / 9325 (0.06%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical dysplasia			
subjects affected / exposed	1 / 9325 (0.01%)	4 / 9319 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bartholinitis			
subjects affected / exposed	2 / 9325 (0.02%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic ovarian cyst			
subjects affected / exposed	1 / 9325 (0.01%)	3 / 9319 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysfunctional uterine bleeding			
subjects affected / exposed	1 / 9325 (0.01%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fallopian tube cyst			
subjects affected / exposed	0 / 9325 (0.00%)	3 / 9319 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst torsion			

subjects affected / exposed	2 / 9325 (0.02%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysmenorrhoea			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parovarian cyst			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			
subjects affected / exposed	2 / 9325 (0.02%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bartholin’s cyst			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspareunia			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian adhesion			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian torsion			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic pain			

subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polycystic ovaries			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine atony			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine malposition			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine polyp			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	8 / 9325 (0.09%)	8 / 9319 (0.09%)	
occurrences causally related to treatment / all	0 / 8	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal septum deviation			
subjects affected / exposed	2 / 9325 (0.02%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 9325 (0.00%)	3 / 9319 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillar hypertrophy			

subjects affected / exposed	2 / 9325 (0.02%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 9325 (0.00%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Apnoeic attack			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperventilation			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal turbinate hypertrophy			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary thrombosis			

subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinitis hypertrophic			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep apnoea syndrome			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status asthmaticus			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	19 / 9325 (0.20%)	25 / 9319 (0.27%)	
occurrences causally related to treatment / all	0 / 19	0 / 25	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	5 / 9325 (0.05%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	3 / 9325 (0.03%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic disorder			
subjects affected / exposed	1 / 9325 (0.01%)	3 / 9319 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorexia nervosa			

subjects affected / exposed	0 / 9325 (0.00%)	3 / 9319 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	3 / 9325 (0.03%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Drug dependence			
subjects affected / exposed	1 / 9325 (0.01%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcoholism			
subjects affected / exposed	0 / 9325 (0.00%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bipolar disorder			
subjects affected / exposed	4 / 9325 (0.04%)	4 / 9319 (0.04%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conversion disorder			
subjects affected / exposed	0 / 9325 (0.00%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eating disorder			
subjects affected / exposed	2 / 9325 (0.02%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abnormal behaviour			

subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol abuse			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bipolar II disorder			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bulimia nervosa			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression suicidal			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dissociative disorder			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug abuse			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysthymic disorder			

subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Emotional distress				
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Generalized anxiety disorder				
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Histrionic personality disorder				
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Intentional self-injury				
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Mania				
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Mental disorder				
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Panic reaction				
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Postpartum depression				

subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizophrenia			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	9 / 9325 (0.10%)	14 / 9319 (0.15%)	
occurrences causally related to treatment / all	0 / 9	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	4 / 9325 (0.04%)	6 / 9319 (0.06%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	4 / 9325 (0.04%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	1 / 9325 (0.01%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	0 / 9325 (0.00%)	3 / 9319 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary colic			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary tract disorder			

subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder disorder			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder pain			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder polyp			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis alcoholic			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis cholestatic			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver disorder			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Weight increased			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Road traffic accident			
subjects affected / exposed	10 / 9325 (0.11%)	9 / 9319 (0.10%)	
occurrences causally related to treatment / all	0 / 10	0 / 9	
deaths causally related to treatment / all	0 / 3	0 / 1	
Concussion			
subjects affected / exposed	6 / 9325 (0.06%)	7 / 9319 (0.08%)	
occurrences causally related to treatment / all	0 / 6	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament rupture			
subjects affected / exposed	10 / 9325 (0.11%)	3 / 9319 (0.03%)	
occurrences causally related to treatment / all	0 / 10	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	7 / 9325 (0.08%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	7 / 9325 (0.08%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	6 / 9325 (0.06%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	4 / 9325 (0.04%)	3 / 9319 (0.03%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	2 / 9325 (0.02%)	4 / 9319 (0.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			

subjects affected / exposed	3 / 9325 (0.03%)	3 / 9319 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	3 / 9325 (0.03%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 9325 (0.01%)	3 / 9319 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	2 / 9325 (0.02%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			
subjects affected / exposed	2 / 9325 (0.02%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	2 / 9325 (0.02%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	2 / 9325 (0.02%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	3 / 9325 (0.03%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus lesion			

subjects affected / exposed	3 / 9325 (0.03%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple injuries			
subjects affected / exposed	0 / 9325 (0.00%)	3 / 9319 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			
subjects affected / exposed	2 / 9325 (0.02%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 9325 (0.01%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion induced incomplete			
subjects affected / exposed	2 / 9325 (0.02%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental needle stick			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental overdose			
subjects affected / exposed	2 / 9325 (0.02%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol poisoning			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain contusion			

subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Excoriation			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	2 / 9325 (0.02%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gun shot wound			
subjects affected / exposed	0 / 9325 (0.00%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injury			
subjects affected / exposed	0 / 9325 (0.00%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaw fracture			
subjects affected / exposed	0 / 9325 (0.00%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle strain			

subjects affected / exposed	0 / 9325 (0.00%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion induced complete complicated			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accident			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Animal bite			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial injury			

subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthropod bite			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone fissure			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Burns second degree			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cartilage injury			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon injury			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diaphragmatic injury			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			

subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ilium fracture			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint sprain			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle injury			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nerve injury			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Poisoning			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post lumbar puncture syndrome			

subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scapula fracture			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skeletal injury			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fracture			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Snake bite			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue injury			

subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic rupture			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon injury			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic liver injury			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulnar nerve injury			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine perforation			

subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine rupture			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Whiplash injury			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Coarctation of the aorta			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermoid cyst			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroglossal cyst			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular septal defect			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	1 / 9325 (0.01%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Supraventricular tachycardia			
subjects affected / exposed	1 / 9325 (0.01%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 9325 (0.00%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	2 / 9325 (0.02%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocarditis			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			

subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wolff-parkinson-white syndrome			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	3 / 9325 (0.03%)	3 / 9319 (0.03%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 9325 (0.01%)	5 / 9319 (0.05%)	
occurrences causally related to treatment / all	1 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	2 / 9325 (0.02%)	4 / 9319 (0.04%)	
occurrences causally related to treatment / all	0 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis			
subjects affected / exposed	1 / 9325 (0.01%)	3 / 9319 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic neuritis			
subjects affected / exposed	1 / 9325 (0.01%)	3 / 9319 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	2 / 9325 (0.02%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	0 / 9325 (0.00%)	3 / 9319 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial palsy			
subjects affected / exposed	1 / 9325 (0.01%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 9325 (0.00%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Grand mal convulsion			
subjects affected / exposed	0 / 9325 (0.00%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Syncope			

subjects affected / exposed	2 / 9325 (0.02%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anoxic encephalopathy			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign intracranial hypertension			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain injury			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cubital tunnel syndrome			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dystonia			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paresis			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			

subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intracranial aneurysm			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial venous sinus thrombosis			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine with aura			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peroneal nerve palsy			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleocytosis			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			

subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tension headache			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 9325 (0.03%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis			
subjects affected / exposed	1 / 9325 (0.01%)	3 / 9319 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperchromic anaemia			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Idiopathic thrombocytopenic purpura			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			

Deafness			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deafness bilateral			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniere's disease			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tympanic membrane perforation			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Blindness unilateral			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conjunctivitis			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dacryostenosis acquired			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			

subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Strabismus			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vision blurred			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	15 / 9325 (0.16%)	16 / 9319 (0.17%)	
occurrences causally related to treatment / all	0 / 15	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	4 / 9325 (0.04%)	9 / 9319 (0.10%)	
occurrences causally related to treatment / all	0 / 4	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	4 / 9325 (0.04%)	4 / 9319 (0.04%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	5 / 9325 (0.05%)	3 / 9319 (0.03%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	3 / 9325 (0.03%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	3 / 9325 (0.03%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 9325 (0.02%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	2 / 9325 (0.02%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 9325 (0.00%)	3 / 9319 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 9325 (0.01%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Irritable bowel syndrome			
subjects affected / exposed	1 / 9325 (0.01%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth impacted			
subjects affected / exposed	1 / 9325 (0.01%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			

subjects affected / exposed	2 / 9325 (0.02%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 9325 (0.00%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 9325 (0.00%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coeliac disease			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyclic vomiting syndrome			

subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faeces hard			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal inflammation			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileitis			

subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammatory bowel disease			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal mass			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal polyp			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malocclusion			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth cyst			

subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal polyp			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reflux gastritis			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reflux oesophagitis			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth malformation			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toothache			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			

subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (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			
Urticaria			
subjects affected / exposed	2 / 9325 (0.02%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Henoch-schonlein purpura			
subjects affected / exposed	0 / 9325 (0.00%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis atopic			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema nodosum			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriasis			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyoderma gangrenosum			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin disorder			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin necrosis			

subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stevens-johnson syndrome			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria chronic			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (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			
Nephrolithiasis			
subjects affected / exposed	1 / 9325 (0.01%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus bladder			
subjects affected / exposed	0 / 9325 (0.00%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus ureteric			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerulonephritis acute			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerulonephritis membranoproliferative			

subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephritis			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			

subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune thyroiditis			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basedow’s disease			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 9325 (0.03%)	6 / 9319 (0.06%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	4 / 9325 (0.04%)	3 / 9319 (0.03%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic lupus erythematosus			
subjects affected / exposed	0 / 9325 (0.00%)	3 / 9319 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bone cyst			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot deformity			
subjects affected / exposed	0 / 9325 (0.00%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			

subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis reactive			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthropathy			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament disorder			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myofascial pain syndrome			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			

subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriatic arthropathy			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovitis			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	59 / 9325 (0.63%)	46 / 9319 (0.49%)	
occurrences causally related to treatment / all	0 / 59	0 / 46	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	13 / 9325 (0.14%)	22 / 9319 (0.24%)	
occurrences causally related to treatment / all	0 / 13	0 / 22	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	10 / 9325 (0.11%)	20 / 9319 (0.21%)	
occurrences causally related to treatment / all	0 / 10	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	12 / 9325 (0.13%)	18 / 9319 (0.19%)	
occurrences causally related to treatment / all	0 / 12	0 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	14 / 9325 (0.15%)	14 / 9319 (0.15%)	
occurrences causally related to treatment / all	0 / 14	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
tonsillitis			

subjects affected / exposed	8 / 9325 (0.09%)	13 / 9319 (0.14%)	
occurrences causally related to treatment / all	0 / 8	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	13 / 9325 (0.14%)	8 / 9319 (0.09%)	
occurrences causally related to treatment / all	0 / 13	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious mononucleosis			
subjects affected / exposed	10 / 9325 (0.11%)	8 / 9319 (0.09%)	
occurrences causally related to treatment / all	0 / 10	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic inflammatory disease			
subjects affected / exposed	5 / 9325 (0.05%)	13 / 9319 (0.14%)	
occurrences causally related to treatment / all	0 / 5	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar abscess			
subjects affected / exposed	8 / 9325 (0.09%)	8 / 9319 (0.09%)	
occurrences causally related to treatment / all	0 / 8	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute tonsillitis			
subjects affected / exposed	7 / 9325 (0.08%)	7 / 9319 (0.08%)	
occurrences causally related to treatment / all	0 / 7	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	7 / 9325 (0.08%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic tonsillitis			
subjects affected / exposed	6 / 9325 (0.06%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			

subjects affected / exposed	3 / 9325 (0.03%)	3 / 9319 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	3 / 9325 (0.03%)	3 / 9319 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	3 / 9325 (0.03%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometritis decidual			
subjects affected / exposed	4 / 9325 (0.04%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 9325 (0.01%)	3 / 9319 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis viral			
subjects affected / exposed	1 / 9325 (0.01%)	3 / 9319 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	2 / 9325 (0.02%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 9325 (0.01%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital herpes			

subjects affected / exposed	1 / 9325 (0.01%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 9325 (0.00%)	3 / 9319 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis tuberculous			
subjects affected / exposed	3 / 9325 (0.03%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peritonsillitis			
subjects affected / exposed	2 / 9325 (0.02%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 9325 (0.01%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pilonidal cyst			
subjects affected / exposed	2 / 9325 (0.02%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post abortion infection			
subjects affected / exposed	2 / 9325 (0.02%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	2 / 9325 (0.02%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			

subjects affected / exposed	2 / 9325 (0.02%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	2 / 9325 (0.02%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion infected			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	2 / 9325 (0.02%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervicitis			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis			
subjects affected / exposed	0 / 9325 (0.00%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear infection			
subjects affected / exposed	2 / 9325 (0.02%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometritis			

subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epidemic nephropathy			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	2 / 9325 (0.02%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gynaecological chlamydia infection			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis a			
subjects affected / exposed	0 / 9325 (0.00%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	0 / 9325 (0.00%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastitis			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	2 / 9325 (0.02%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia mycoplasmal			

subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salpingitis			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salpingo-oophoritis			
subjects affected / exposed	0 / 9325 (0.00%)	2 / 9319 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubo-ovarian abscess			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Typhoid fever			

subjects affected / exposed	0 / 9325 (0.00%)	2 / 9319 (0.02%)		
occurrences causally related to treatment / all	0 / 0	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Varicella				
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Vulvitis				
subjects affected / exposed	2 / 9325 (0.02%)	0 / 9319 (0.00%)		
occurrences causally related to treatment / all	0 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Wound infection				
subjects affected / exposed	0 / 9325 (0.00%)	2 / 9319 (0.02%)		
occurrences causally related to treatment / all	0 / 0	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Abdominal wall abscess				
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Abscess				
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Abscess limb				
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Acquired immunodeficiency syndrome				
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Acute sinusitis				

subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendiceal abscess			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial toxaemia			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bartholin’s abscess			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Beta haemolytic streptococcal infection			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone tuberculosis			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast abscess			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carbuncle			

subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral toxoplasmosis			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis infectious			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiglottitis			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epstein-barr virus infection			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extrapulmonary tuberculosis			

subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye infection toxoplasmal			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis bacterial			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic fever			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis c			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes oesophagitis			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hordeolum			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Induced abortion infection			

subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected bites			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection parasitic			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis bacterial			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis pneumococcal			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroborreliosis			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			

subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media acute			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian abscess			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotid abscess			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal tuberculosis			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal sepsis			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia bacterial			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyoderma			

subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinitis			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (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 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin infection			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal infection			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sweat gland infection			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis streptococcal			

subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trichomoniasis			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval abscess			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	4 / 9325 (0.04%)	5 / 9319 (0.05%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	3 / 9325 (0.03%)	4 / 9319 (0.04%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	4 / 9325 (0.04%)	3 / 9319 (0.03%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	1 / 9325 (0.01%)	4 / 9319 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gestational diabetes			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 9325 (0.01%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 9325 (0.01%)	0 / 9319 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
obesity			
subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			

subjects affected / exposed	0 / 9325 (0.00%)	1 / 9319 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Havrix Group	Cervarix Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2403 / 9325 (25.77%)	2787 / 9319 (29.91%)	
Nervous system disorders			
Headache (unsolicited adverse events AE)			
subjects affected / exposed[1]	250 / 3178 (7.87%)	228 / 3184 (7.16%)	
occurrences (all)	250	228	
General disorders and administration site conditions			
Pain at injection site			
alternative assessment type: Systematic			
subjects affected / exposed[2]	2403 / 3080 (78.02%)	2787 / 3078 (90.55%)	
occurrences (all)	2403	2787	
Redness at injection site			
alternative assessment type: Systematic			
subjects affected / exposed[3]	851 / 3080 (27.63%)	1349 / 3078 (43.83%)	
occurrences (all)	851	1349	
Swelling at injection site			
alternative assessment type: Systematic			
subjects affected / exposed[4]	608 / 3080 (19.74%)	1293 / 3078 (42.01%)	
occurrences (all)	608	1293	
Arthralgia			
alternative assessment type: Systematic			
subjects affected / exposed[5]	551 / 3081 (17.88%)	633 / 3078 (20.57%)	
occurrences (all)	551	633	
Fatigue			
subjects affected / exposed[6]	1652 / 3081 (53.62%)	1771 / 3078 (57.54%)	
occurrences (all)	1652	1771	

Fever ≥ 37.5 degrees Celsius			
alternative assessment type: Systematic			
subjects affected / exposed[7]	342 / 3081 (11.10%)	385 / 3078 (12.51%)	
occurrences (all)	342	385	
Gastro-intestinal symptoms			
alternative assessment type: Systematic			
subjects affected / exposed[8]	847 / 3081 (27.49%)	856 / 3078 (27.81%)	
occurrences (all)	847	856	
Headache (solicited general symptoms AE)			
alternative assessment type: Systematic			
subjects affected / exposed[9]	1583 / 3081 (51.38%)	1668 / 3078 (54.19%)	
occurrences (all)	1583	1668	
Myalgia			
alternative assessment type: Systematic			
subjects affected / exposed[10]	1381 / 3081 (44.82%)	1607 / 3078 (52.21%)	
occurrences (all)	1381	1607	
Rash			
alternative assessment type: Systematic			
subjects affected / exposed[11]	258 / 3081 (8.37%)	314 / 3078 (10.20%)	
occurrences (all)	258	314	
Urticaria			
alternative assessment type: Systematic			
subjects affected / exposed[12]	244 / 3081 (7.92%)	300 / 3078 (9.75%)	
occurrences (all)	244	300	
Infections and infestations			
Influenza			
subjects affected / exposed[13]	176 / 3187 (5.52%)	157 / 3184 (4.93%)	
occurrences (all)	176	157	
Gynaecological Chlamydia infection			
subjects affected / exposed	1085 / 9325 (11.64%)	1035 / 9319 (11.11%)	
occurrences (all)	1085	1035	

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.

[13] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: 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
03 December 2004	In order to improve the robustness of the data on vaccine efficacy in the prevention of CIN2+ lesions, the final analysis will be performed when 36 cases of CIN2+ associated with HPV-16 and/or HPV-18 cervical infection in the ATP cohort are confirmed. This will allow the sponsor to perform the HPV-008 study as a stand alone trial (without the need of pooling with study HPV-009). Therefore, a total of 18,000 subjects will be enrolled (instead of 13,000) and the overall targeted recruitment period will be approximately 15 months. Further timings will be unchanged and there will be no impact on the recruitment strategy for immunogenicity and safety subsets. In order to strengthen the association of histopathologically confirmed CIN2+ with HPV-16 or HPV-18 cervical infection for the primary objective, PCR analysis will be performed on the lesional component of the tissue specimen (not on the preceding cytological specimen). Validation studies of this methodology have been performed. As the specificity of the Amplicor® screening test is not optimal for Neisseria gonorrhea (i.e. false positives since sensitivity of the test is high), a confirmatory test is offered (Aptima Combo 2 assay® by Gen-Probe Inc., San Diego, USA). In addition, this test (Aptima Combo 2 assay®) may be run on samples reported as equivocal or inhibitory for either Neisseria gonorrhea or Chlamydia trachomatis after Amplicor® testing. Data from the HPV-001 pilot efficacy study have been published in The Lancet medical journal. Reference to this publication has been made. A number of logistic procedures have been updated, i.e. contact addresses, the storage temperature of endocervical specimen and the type of endocervical brush to be used. The protocol has been reformatted to meet GSK Biologicals @standard requirements.
17 August 2005	As the total number of study subjects has increased to 18,000 (see amendment 1), CIN2+ efficacy data will be available at the time of the first interim analysis. Therefore, the analysis plan has been simplified: one interim analysis will be performed (to evaluate safety, efficacy and immunogenicity) when at least 23 cases of CIN2+ associated with HPV-16/18 infection have been detected. In addition, pooling with data from study HPV-009 is no longer required to provide a robust estimate of overall vaccine efficacy in the prevention of CIN2+ associated with HPV-16 or HPV-18 infection. Therefore, the protocol has been adapted accordingly. A prospective meta-analysis however may still be considered. The protocol has been updated to indicate that for solicited and unsolicited adverse events school or work absenteeism (as applicable) will be recorded besides occurrence, intensity and relationship to vaccination. In addition, we have clarified the post-vaccination time period for collecting unsolicited AEs which ends 30 days after each dose of study vaccine, meaning days 0-29. The clinical management algorithms have been updated to indicate that women with ASC-US/oncogenic HPV positive results or LSIL may be immediately referred for colposcopic evaluation. The protocol has been updated to take into account that in certain populations with very low prevalence of Neisseria gonorrhea infection, the benefits of screening for Neisseria gonorrhea infection in test subjects may not outweigh the risks and inconveniences associated with the false positive test results that would result from screening a low prevalence population. In such cases, investigators may decide to forgo testing for Neisseria gonorrhea in their study subjects. At Visit 1 (Month 0), concomitant medication/vaccination needs to be recorded.Anti-HPV-16/18 ELISA will be performed in all subjects at Month 0.

27 July 2006	Merck's HPV vaccine, Gardasil®, has been licensed and is now becoming commercially available in an increasing number of countries. Therefore, the study procedures have been revised to include questions at every visit to determine if subjects have received an HPV vaccine outside of the study. Data obtained after a subject has been found to have received an HPV vaccine outside of the study will be confounded, and therefore such subjects will be withdrawn from further participation in the study. Data from subjects who request information about their treatment group assignment (i.e., request unblinding) to determine if they will consider immunization with a licensed HPV vaccine outside of the study will be similarly confounded; therefore such subjects will be withdrawn from further participation in the study after they are unblinded. The analysis plan for vaccine efficacy against persistent infection with oncogenic HPV types has been slightly modified. Because of the limited number of persistent infections (12-month definition) expected at time of the interim analysis, persistent infection (6-month definition) will replace persistent infection (12-month definition) as a secondary endpoint. Consequently, vaccine efficacy against persistent infection (12-month definition) will be evaluated as exploratory endpoint. Additional exploratory objectives have been included as vaccine efficacy will also be evaluated against histopathologically confirmed vulval and vaginal intraepithelial neoplasia (VIN and VAIN). The analysis of safety has been further clarified for pregnancies, new onset chronic diseases and medically significant AEs (as detailed in the RAP). In case an autoimmune disease is diagnosed during the study, autoantibody testing may be performed on baseline sera collected at Month 0 and other sera samples collected during the study if agreed by the subject (see Section 8.1.1). Data from the HPV-007 long-term efficacy study have been published in The Lancet med.
17 March 2008	The aim of the current protocol amendment is to clarify the cross-over immunization procedure for subjects at their last study visit: • It was previously described that all subjects would be offered cross-over immunization after the trial was completed. Following the results of the interim analysis, it was recommended by the IDMC to provide the option of cross-over immunization after the database is frozen for final analysis. • Each subject will be informed of the possibility of requesting unblinding after completion of their end of study activities (Visit 10, Month 48) and of the procedure involved. • Exit colposcopy for women that have normal cytology and are high-risk HPV negative at the end of the study has been removed • For all histopathological outcomes, an exploratory analysis referred to as HPV type assignment algorithm will be assessed. In this analysis, the association with HPV types will be based not only on the detection of HPV DNA in the lesion, but also will consider the presence of HPV types in the two immediately preceding cytology samples in case more than one HPV type was found in the lesion. • The secondary endpoint for immunogenicity regarding vaccine breakthrough cases has been modified to state that inhibition and/or neutralisation assays may be performed in addition to ELISA assays on these samples. • Priority ranking for serology assays has been modified to place neutralization assays above inhibitions assays • Recent references regarding the HPV vaccine and results of the interim analysis of this study are included and the reference to the investigator brochure is updated. • Clarification of suspension of study related pelvic examinations during pregnancy, and guidance for collection of vaginal and vulval samples are added. • Reference to other vaccines containing MPL and licensure of Cervarix in some countries has been added. • Material Safety Data Sheets have been updated

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported