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

Summary

EudraCT number	2007-001731-55
Trial protocol	FI
Global end of trial date	14 December 2015

Results information

Result version number	v2
This version publication date	11 May 2016
First version publication date	22 May 2015
Version creation reason	• New data added to full data set Data for secondary endpoints have been added.

Trial information

Trial identification

Sponsor protocol code	106636

Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 December 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Finland: 34206
Worldwide total number of subjects	34206
EEA total number of subjects	34206

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)	34206
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

At study start, Cervarix™ vaccine was not licensed for use in boys so male subjects receiving the vaccine were considered as part of a Phase III trial. Although 34206 subjects were enrolled, only 32175 subjects were vaccinated and started the study.

Pre-assignment period milestones

Number of subjects started	34206
Number of subjects completed	32175

Pre-assignment subject non-completion reasons

Reason: Number of subjects	No vaccination received: 2031

Period 1

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

Blinding implementation details:

Blinding was as follows:
- Study participants in Arm A communities and female study participants in Arm B communities were blinded to their
treatment allocation (HPV or HBV vaccine).
- Study participants (males and females) in Arm C communities and male study participants in Arm B communities
were aware of their treatment allocation as they all received HBV vaccine.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cervarix pooled Group

Arm description:

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

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

Dosage and administration details:

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

Arm title	Engerix-B pooled Group

Arm description:

Male and female subjects receiving Engerix™-B vaccine. The vaccine was administered intramuscularly

in the deltoid region of the non-dominant arm according to a 0, 1, 6-month schedule.

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

Dosage and administration details:

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

Number of subjects in period 1[1]	Cervarix pooled Group	Engerix-B pooled Group
Started	14837	17338
Completed Month 12	14713	17188
Completed	8346	5547
Not completed	6491	11791
Subject unable to read	-	1
Migrated/Moved from the study area	14	13
Mentally disabled	1	-
Refused participation to study	1665	883
ICF not returned	-	1
Consent withdrawn by subject	4	5
Already received HPV vaccine	-	1
Adverse event, non-fatal	1	-
Death	5	5
Pregnancy	6	4
Lost to follow-up	4793	10875
Blinded treatment broken	2	-
Received without ICF	-	1
Rejected origin of signature	-	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Although 34206 subjects were enrolled, only 32175 subjects were vaccinated and started the study.

Baseline characteristics

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

Reporting group values	Cervarix pooled Group	Engerix-B pooled Group	Total
Number of subjects	14837	17338	32175
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	14.1	14.1	
standard deviation	± 0.8	± 0.8	-
Gender categorical			
Units: Subjects			
Female	12399	8119	20518
Male	2438	9219	11657

End points

End points reporting groups

Reporting group title	Cervarix pooled Group
Reporting group description:	
Male and female subjects receiving Cervarix™ vaccine. The vaccine was administered intramuscularly in the deltoid region of the non-dominant arm according to a 0, 1, 6-month schedule.	
Reporting group title	Engerix-B pooled Group
Reporting group description:	
Male and female subjects receiving Engerix™-B vaccine. The vaccine was administered intramuscularly in the deltoid region of the non-dominant arm according to a 0, 1, 6-month schedule.	
Subject analysis set title	Cervarix/Engerix-B A Group
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
90% of male and female adolescents received Cervarix™ vaccine. Rest of the subjects received Engerix™-B vaccine. Vaccines were administered intramuscularly in the deltoid region of the non-dominant arm according to a 0, 1, 6-month schedule.	
Subject analysis set title	Cervarix/Engerix-B B Group
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
90% of the female adolescents received Cervarix™ vaccine. Male adolescents and rest of the female adolescents received Engerix™-B vaccine. Vaccines were administered intramuscularly in the deltoid region of the non-dominant arm according to a 0, 1, 6-month schedule.	
Subject analysis set title	Engerix-B Group
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All adolescents were vaccinated with Engerix™-B vaccine. The vaccine was administered intramuscularly in the deltoid region of the non-dominant arm according to a 0, 1, 6-month schedule.	
Subject analysis set title	No-vaccine Group
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects who were enrolled but not vaccinated.	
Subject analysis set title	Cervarix/Engerix-B pooled Group
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Male and female subjects receiving Cervarix™/Engerix™-B vaccine. The vaccine was administered intramuscularly in the deltoid region of the non-dominant arm according to a 0, 1, 6-month schedule.	

Primary: Number of female subjects with vaccine overall effectiveness against genital infection with Human Papilloma Virus (HPV) 16/18 serotypes

End point title	Number of female subjects with vaccine overall effectiveness against genital infection with Human Papilloma Virus (HPV) 16/18 serotypes
End point description:	
The analysis of overall effectiveness was based on stratified Mantel-Haenszel adjusted for clustering. The effectiveness was computed as 1- the prevalence odd ratio in all subjects from the investigated group (prevalence rate in all subjects from the investigated arm/prevalence rate in all subjects from Arm C).	
End point type	Primary
End point timeframe:	
At the time of Visit 5 (at 18.5 years of age)	

End point values	Cervarix/Engerix-B A Group	Cervarix/Engerix-B B Group	Engerix-B Group	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3629	4029	3168	
Units: Subjects				
Anti-HPV16/18	139	117	329	

Statistical analyses

Statistical analysis title	Overall efectiveness against HPV-16/18 Arm A vs C

Statistical analysis description:

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

Comparison groups	Cervarix/Engerix-B A Group v Engerix-B Group
Number of subjects included in analysis	6797
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.232
Method	Mantel-Haenszel
Parameter estimate	1-Odds Ratio
Point estimate	23.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19
upper limit	51.1

Notes:

[1] - Efectiveness

Statistical analysis title	Overall efectiveness against HPV-16/18 Arm B vs C

Statistical analysis description:

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

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

Notes:

[2] - Effectiveness

Statistical analysis title	Overall efectiveness against HPV-16/18 Arm A vs B

Statistical analysis description:

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

Comparison groups	Cervarix/Engerix-B B Group v Cervarix/Engerix-B A Group
Number of subjects included in analysis	7658
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.069
Method	Mantel-Haenszel
Parameter estimate	1-Odds Ratio
Point estimate	-52.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-139.4
upper limit	3.3

Notes:

[3] - Effectiveness

Secondary: Number of subjects with solicited local symptoms, in a subset of subjects.

End point title	Number of subjects with solicited local symptoms, in a subset of subjects.

End point description:

End point type	Secondary

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with solicited general symptoms, in a subset of subjects.

End point title	Number of subjects with solicited general symptoms, in a subset of subjects.

End point description:

The analysis was based on the Total vaccinated cohort - the Diary card subset, which included a subset of male adolescents from Cervarix/Engerix-B and Engerix-B groups, who were selected for active assessment of safety using diary cards.

End point type	Secondary

End point timeframe:

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

End point values	Cervarix pooled Group	Engerix-B pooled Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	604	1028		
Units: Subjects				
Arthralgia, Any	107	97		
Arthralgia, Grade 3	1	4		
Arthralgia, Related	87	81		
Fatigue, Any	291	411		
Fatigue, Grade 3	7	21		
Fatigue, Related	233	351		
Fever (axillary), Any	48	85		
Fever (axillary), Grade 3	6	9		
Fever (axillary), Related	28	53		
Gastrointestinal, Any	106	163		
Gastrointestinal, Grade 3	11	13		
Gastrointestinal, Related	70	128		
Headache, Any	261	371		
Headache, Grade 3	15	14		
Headache, Related	176	280		
Myalgia, Any	321	250		
Myalgia, Grade 3	12	3		
Myalgia, Related	291	211		
Rash, Any	29	33		
Rash, Grade 3	0	0		
Rash, Related	14	23		
Urticaria, Any	4	15		
Urticaria, Grade 3	0	0		
Urticaria, Related	3	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with unsolicited adverse events (AEs), in a subset of subjects.

End point title	Number of subjects with unsolicited adverse events (AEs), in a subset of subjects.

End point description:

End point type	Secondary

End point timeframe:

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

End point values	Cervarix pooled Group	Engerix-B pooled Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	643	1047		
Units: Subjects				
Subjects with any AEs	157	202		
Subjects with Grade 3 AEs	31	46		
Subjects with related AEs	12	19		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

End point type	Secondary

End point timeframe:

Within 30 minutes following vaccination

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

From Dose 1 (at Day 0) until Month 12 (phone contact)

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

During the entire study period (from Dose 1-Day 0 to Visit 5-18.5 years of age)

End point values	Cervarix pooled Group	Engerix-B pooled Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14837	17338		
Units: Subjects				
Subjects with SAEs assessed as related to vaccine	25	30		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

End point type	Secondary

End point timeframe:

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

End point values	Cervarix pooled Group	Engerix-B pooled Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14837	17338		
Units: Subjects				
Subjects with any related SAE(s)	22	30		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

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

End point values	Cervarix pooled Group	Engerix-B pooled Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14837	17338		
Units: Subjects				
Subjects with any NOAD(s)	144	176		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

End point type	Secondary

End point timeframe:

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

End point values	Cervarix pooled Group	Engerix-B pooled Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	728	524		
Units: Subjects				
Live infant no apparent anomaly	232	161		
Elective termination no apparent anomaly	431	314		
Spontaneous abortion no apparent anomaly	58	41		
Stillbirth no apparent congenital anomaly	0	1		
Lost to follow up	0	1		
Ectopic pregnancy	5	5		
Molar pregnancy	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of female subjects with vaccine effectiveness against

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

End point description:

The analysis of total effectiveness was based on stratified Mantel-Haenszel adjusted for clustering. The effectiveness was computed as 1- the prevalence odd ratio in HPV vaccinated subjects from the investigated group (prevalence rate in HPV vaccinated subjects from the investigated arm/prevalence rate in all subjects from Arm C).

End point type	Secondary

End point timeframe:

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

End point values	No-vaccine Group	Cervarix/Engerix-B pooled Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3192	233		
Units: Subjects				
Anti-HPV 16/18	9	9		

Statistical analyses

No statistical analyses for this end point

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

End point description:

The antibody concentrations against HPV-16 and HPV-18 were determined by Enzyme-linked immunosorbent assay (ELISA). The cut-off of the assay was 8 ELISA units per millilitre (EL.U/mL) for anti-HPV-16 and 7 EL.U/mL for anti-HPV-18 at Visits 1 and 4 and 19 EL.U/mL for HPV-16 and 18 EL.U/mL for HPV-18 at Visit 5. The Immunogenicity subset comprised the male study participants from the Cervarix/Engerix-B A Group plus female study participants from the same Cervarix/Engerix-B A

End point type	Secondary

End point timeframe:

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

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The results were only assessed in subsets of subjects.

End point values	Cervarix pooled Group			
Subject group type	Reporting group			
Number of subjects analysed	1163			
Units: Subjects				
anti-HPV-16 >=8 EL.U/mL males [Day 0] (N=536)	40			

anti-HPV-16 >=8 EL.U/mL males [Month 7] (N=536)	536			
anti-HPV-16 >=8 EL.U/mL females [Day 0] (N=1163)	86			
anti-HPV-16 >=8 EL.U/mL females [Month 7] (N=1163)	1163			
anti-HPV-18 >=7 EL.U/mL males [Day 0] (N=535)	31			
anti-HPV-18 >=7 EL.U/mL males [Month 7] (N=535)	535			
anti-HPV-18 >=7 EL.U/mL females [Day 0] (N=1160)	84			
anti-HPV-18 >=7 EL.U/mL females [Month 7] (N=1160)	1160			
anti-HPV-16 >=19 EL.U/mL males [18.5Y] (N=217)	217			
anti-HPV-16 >=19 EL.U/mL females [18.5Y] (N=688)	688			
anti-HPV-18 >=18 EL.U/mL males [18.5Y] (N=217)	217			
anti-HPV-18 >=18 EL.U/mL females [18.5Y] (N=686)	685			

Statistical analyses

No statistical analyses for this end point

Secondary: Titres for anti-HPV-16 and anti-HPV-18 antibodies, by gender, in a subset of subjects

End point title	Titres for anti-HPV-16 and anti-HPV-18 antibodies, by gender, in a subset of subjects[5]

End point description:

The antibody concentrations against HPV-16 and HPV-18 were determined by Enzyme-linked immunosorbent assay (ELISA). The cut-off of the assay was 8 ELISA units per millilitre (EL.U/mL) for anti-HPV-16 and 7 EL.U/mL for anti-HPV-18 at Visits 1 and 4 and 19 EL.U/mL for HPV-16 and 18 EL.U/mL for HPV-18 at Visit 5. The Immunogenicity subset comprised the male study participants from the Cervarix/Engerix-B A Group plus female study participants from the same Cervarix/Engerix-B A

End point type	Secondary

End point timeframe:

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

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The results were only assessed in subsets of subjects.

End point values	Cervarix pooled Group			
Subject group type	Reporting group			
Number of subjects analysed	1163			
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
anti-HPV-16 >=8 EL.U/mL males [Day 0] (N=536)	4.5 (4.3 to 4.6)			

anti-HPV-16 >=8 EL.U/mL males [Month 7] (N=536)	23959.1 (22301 to 25740.4)			
anti-HPV-16 >=8 EL.U/mL females [Day 0] (N=1163)	4.5 (4.4 to 4.6)			
anti-HPV-16 >=8 EL.U/mL females [Month 7] (N=1163)	21327.2 (20338.9 to 22363.5)			
anti-HPV-18 >=7 EL.U/mL males [Day 0] (N=535)	3.8 (3.7 to 4)			
anti-HPV-18 >=7 EL.U/mL males [Month 7] (N=535)	8583.9 (7974.7 to 9239.5)			
anti-HPV-18 >=7 EL.U/mL females [Day 0] (N=1160)	3.9 (3.8 to 4)			
anti-HPV-18 >=7 EL.U/mL females [Month 7] (N=1160)	8227.3 (7847.7 to 8625.4)			
anti-HPV-16 >=19 EL.U/mL males [18.5Y] (N=217)	2759.5 (2432.1 to 3130.9)			
anti-HPV-16 >=19 EL.U/mL females [18.5Y] (N=688)	2609.6 (2444.4 to 2785.9)			
anti-HPV-18 >=18 EL.U/mL males [18.5Y] (N=217)	837.7 (727.3 to 964.9)			
anti-HPV-18 >=18 EL.U/mL females [18.5Y] (N=686)	890 (826.2 to 958.7)			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

From Dose 1 (at Day 0) until Month 12

End point values	Cervarix pooled Group	Engerix-B pooled Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2436	1267		
Units: Subjects				
Any SAEs	58	25		
Related SAEs	4	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of female subjects reporting any SAEs that are causally related to vaccination

End point title	Number of female subjects reporting any SAEs that are causally related to vaccination

End point description:

Serious adverse events (SAEs) assessed include medical occurrences that result in death, are life threatening, require hospitalization or prolongation of hospitalization or result in disability/incapacity. The outcome was assessed only in female subjects in the respective groups.

End point type	Secondary

End point timeframe:

During the entire study period (from Dose 1-Day 0 to Visit 5-18.5 years of age)

End point values	Cervarix pooled Group	Engerix-B pooled Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12399	8119		
Units: Subjects				
Related SAEs	20	16		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of male subjects reporting any SAEs that are causally related to vaccination

End point title	Number of male subjects reporting any SAEs that are causally related to vaccination

End point description:

Serious adverse events (SAEs) assessed include medical occurrences that result in death, are life threatening, require hospitalization or prolongation of hospitalization or result in disability/incapacity. The outcome was assessed only in male subjects in the respective groups.

End point type	Secondary

End point timeframe:

During the entire study period (from dose1-Day 0 to Visit 5-18.5 years of age)

End point values	Cervarix pooled Group	Engerix-B pooled Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2438	9219		
Units: Subjects				
Related SAEs	5	14		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited symptoms: up to Day 7 post vaccination. AEs: up to Day 30 post vaccination. SAEs up to Visit 5 at Month 96

Adverse event reporting additional description:

Adverse Events were collected in the Total Vaccinated Cohort Diary Card subset (TVC-DcS = a subset of males from Cervarix/Engerix-B and Engerix-B groups selected for active safety assessment using diary cards). SAEs were collected in the TVC-DcS and remaining Cervarix/Engerix-B Group male subjects. Related SAEs were collected in the TVC.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Engerix-B Pooled Group

Reporting group description:

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

Reporting group title	Cervarix Pooled Group

Reporting group description:

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

Serious adverse events	Engerix-B Pooled Group	Cervarix Pooled Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 1267 (1.97%)	58 / 2436 (2.38%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Astrocytoma, low grade			
subjects affected / exposed	1 / 1267 (0.08%)	0 / 2436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 1267 (0.00%)	1 / 2436 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			

subjects affected / exposed	0 / 1267 (0.00%)	1 / 2436 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Testicular torsion			
subjects affected / exposed	0 / 1267 (0.00%)	1 / 2436 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 1267 (0.08%)	0 / 2436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 1267 (0.00%)	1 / 2436 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 1267 (0.08%)	0 / 2436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disturbance in social behaviour			
subjects affected / exposed	0 / 1267 (0.00%)	1 / 2436 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emotional disorder of childhood			
subjects affected / exposed	0 / 1267 (0.00%)	1 / 2436 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic disorder			
subjects affected / exposed	1 / 1267 (0.08%)	0 / 2436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Psychotic disorder			
subjects affected / exposed	0 / 1267 (0.00%)	1 / 2436 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	1 / 1267 (0.08%)	0 / 2436 (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			
Alcohol poisoning			
subjects affected / exposed	1 / 1267 (0.08%)	3 / 2436 (0.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	0 / 1267 (0.00%)	4 / 2436 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand Fracture			
subjects affected / exposed	1 / 1267 (0.08%)	2 / 2436 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 1267 (0.00%)	2 / 2436 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot Fracture			
subjects affected / exposed	2 / 1267 (0.16%)	0 / 2436 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forearm Fracture			
subjects affected / exposed	1 / 1267 (0.08%)	1 / 2436 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Radius fracture			
subjects affected / exposed	0 / 1267 (0.00%)	2 / 2436 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 1267 (0.00%)	2 / 2436 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			
subjects affected / exposed	0 / 1267 (0.00%)	1 / 2436 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 1267 (0.08%)	0 / 2436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	0 / 1267 (0.00%)	1 / 2436 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 1267 (0.00%)	1 / 2436 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle rupture			
subjects affected / exposed	0 / 1267 (0.00%)	1 / 2436 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck injury			
subjects affected / exposed	0 / 1267 (0.00%)	1 / 2436 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic rupture			

subjects affected / exposed	1 / 1267 (0.08%)	0 / 2436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 1267 (0.08%)	0 / 2436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic renal injury			
subjects affected / exposed	1 / 1267 (0.08%)	0 / 2436 (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			
Vitello-intestinal duct remnant			
subjects affected / exposed	0 / 1267 (0.00%)	1 / 2436 (0.04%)	
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	0 / 1267 (0.00%)	1 / 2436 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 1267 (0.00%)	2 / 2436 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Splenomegaly			
subjects affected / exposed	0 / 1267 (0.00%)	1 / 2436 (0.04%)	
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	0 / 1267 (0.00%)	2 / 2436 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 1267 (0.00%)	1 / 2436 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
subjects affected / exposed	0 / 1267 (0.00%)	1 / 2436 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 1267 (0.00%)	1 / 2436 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 1267 (0.00%)	1 / 2436 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis			
subjects affected / exposed	0 / 1267 (0.00%)	1 / 2436 (0.04%)	
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			
Exostosis			
subjects affected / exposed	0 / 1267 (0.00%)	1 / 2436 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Juvenile arthritis			
subjects affected / exposed	0 / 1267 (0.00%)	1 / 2436 (0.04%)	
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	3 / 1267 (0.24%)	5 / 2436 (0.21%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious mononucleosis			
subjects affected / exposed	1 / 1267 (0.08%)	4 / 2436 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsilitis			
subjects affected / exposed	0 / 1267 (0.00%)	4 / 2436 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	1 / 1267 (0.08%)	1 / 2436 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar abscess			
subjects affected / exposed	1 / 1267 (0.08%)	1 / 2436 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 1267 (0.00%)	2 / 2436 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 1267 (0.08%)	0 / 2436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis bacterial			
subjects affected / exposed	1 / 1267 (0.08%)	0 / 2436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			

subjects affected / exposed	0 / 1267 (0.00%)	1 / 2436 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
subjects affected / exposed	0 / 1267 (0.00%)	1 / 2436 (0.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 1267 (0.08%)	0 / 2436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis bacterial			
subjects affected / exposed	1 / 1267 (0.08%)	0 / 2436 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Type 1 diabetes mellitus			
subjects affected / exposed	1 / 1267 (0.08%)	1 / 2436 (0.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Engerix-B Pooled Group	Cervarix Pooled Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	411 / 1267 (32.44%)	506 / 2436 (20.77%)	
General disorders and administration site conditions			
Pain			
subjects affected / exposed[1]	251 / 1028 (24.42%)	506 / 603 (83.91%)	
occurrences (all)	251	506	
Redness			
subjects affected / exposed[2]	131 / 1028 (12.74%)	169 / 603 (28.03%)	
occurrences (all)	131	169	

Swelling			
subjects affected / exposed[3]	46 / 1028 (4.47%)	131 / 603 (21.72%)	
occurrences (all)	46	131	
Arthralgia			
subjects affected / exposed[4]	97 / 1028 (9.44%)	107 / 604 (17.72%)	
occurrences (all)	97	107	
Fatigue			
subjects affected / exposed[5]	411 / 1028 (39.98%)	291 / 604 (48.18%)	
occurrences (all)	411	291	
Fever (Axilarry)			
subjects affected / exposed[6]	85 / 1028 (8.27%)	48 / 604 (7.95%)	
occurrences (all)	85	48	
Gastrointestinal			
subjects affected / exposed[7]	163 / 1028 (15.86%)	106 / 604 (17.55%)	
occurrences (all)	163	106	
Headache			
subjects affected / exposed[8]	371 / 1028 (36.09%)	261 / 604 (43.21%)	
occurrences (all)	371	261	
Myalgia			
subjects affected / exposed[9]	250 / 1028 (24.32%)	321 / 604 (53.15%)	
occurrences (all)	250	321	
Rash			
subjects affected / exposed[10]	33 / 1028 (3.21%)	29 / 604 (4.80%)	
occurrences (all)	33	29	
Urticaria			
subjects affected / exposed[11]	15 / 1267 (1.18%)	4 / 604 (0.66%)	
occurrences (all)	15	4	
Infections and infestations			
Nasopharyngitis			
alternative assessment type: Non-systematic			
subjects affected / exposed[12]	17 / 1047 (1.62%)	33 / 643 (5.13%)	
occurrences (all)	17	33	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The analysis was performed on the Total vaccinated cohort, only on subjects with their

symptom sheets completed.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed.

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed.

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed.

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed.

[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed.

[8] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed.

[9] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed.

[10] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed.

[11] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed.

[12] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: The analysis was performed on the Total vaccinated cohort, only on subjects with their symptom sheets completed.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported