Clinical trial results:
Multinational study assessing the acceptability and determinants of compliance to HPV vaccination to women in screening ages 25 to 45 years.

Summary

EudraCT number	2014-003177-42
Trial protocol	DK ES BE FI SI NL SE
Global end of trial date	30 April 2019

Results information

Result version number	v1 (current)
This version publication date	01 May 2020
First version publication date	01 May 2020

Trial information

Trial identification

Sponsor protocol code	COHEAHR-WP4

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02837926
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Catalan Institute of Oncology
Sponsor organisation address	Av. Gran Via de l'Hospitalet 199-203, L'Hospitalet de Llobregat, Barcelona, Spain, 08908
Public contact	Laia Bruni, Catalan Institute of Oncology, +34 932607812, coheahr-@wp4iconcologia.net
Scientific contact	Xavier Bosch, Catalan Institute of Oncology, +34 932607812, coheahr-@wp4iconcologia.net

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	01 April 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 October 2018
Global end of trial reached?	Yes
Global end of trial date	30 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1) Assessment of uptake and compliance of HPV vaccination by women aged 25-45 years attending routine cervical cancer screening.
2) Identification of local determinants of HPV vaccine acceptability, and of logistic and programmatic issues associated with HPV vaccination of adult women, such as which information should be provided to women that are offered the vaccine and how should that information be offered.

Protection of trial subjects:

All HPV vaccines administered to study subjects are approved and commercialized treatments. Therefore, measures taken to protect subjects were those of routine medical care.

Background therapy:

There was no other study therapy apart from HPV vaccine administration.

Evidence for comparator:

No comparator to HPV vaccine was used in this study.

Actual start date of recruitment	12 April 2016
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	United Kingdom: 434
Country: Number of subjects enrolled	France: 63
Country: Number of subjects enrolled	Germany: 323
Country: Number of subjects enrolled	Belgium: 308
Country: Number of subjects enrolled	Denmark: 347
Country: Number of subjects enrolled	Finland: 510
Country: Number of subjects enrolled	Slovenia: 610
Country: Number of subjects enrolled	Spain: 693
Country: Number of subjects enrolled	Sweden: 360
Worldwide total number of subjects	3648
EEA total number of subjects	3648

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)	3648
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Enrollment period: April 2016 - May 2018.
Enrollment strategies:
- Population-based (Denmark, Sweden). Women were invited by postal mail through cervical cancer screening registration lists.
- Convenience (all other countries). Women were invited directly in cervical cancer screening clinics or private practices during their screening visit.

Pre-assignment

Screening details:

Eligible subjects were adult women aged 25-45 attending cervical cancer screening, non-HPV-vaccinated.
Eligible subjects for HPV vaccinated were not pregnant or planning to be, with no history of allergy to vaccine components, immune disease or hysterectomy.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Single arm

Arm description:

Study with a single arm in which all participating subjects completed a questionnaire assessing HPV vaccine acceptance. In all countries except the United Kingdom, women accepting HPV vaccine were offered to get it administered for free.

Arm type	Experimental
Investigational medicinal product name	Cervarix (HPV vaccine)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

1.5 millilitres at 0, 1 and 6 months

Investigational medicinal product name	Gardasil (HPV vaccine)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

1.5 millilitres at 0, 2 and 6 months

Investigational medicinal product name	Gardasil 9 (HPV vaccine)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

1.5 millilitres at 0,2 and 6 months

Number of subjects in period 1	Single arm
Started	3648
Completed	3648

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	3648	3648	
Age categorical			
Adult women within the age range of 25-45 attending cervical cancer screening with no previous history of HPV vaccine administration			
Units: Subjects			
Aged <30 yrs	924	924	
Aged 30-34 yrs	916	916	
Aged 35-39 yrs	887	887	
Aged >39 yrs	911	911	
No questionnaire	10	10	
Age continuous			
Units: years			
arithmetic mean	34.3		
standard deviation	± 6.13	-	
Gender categorical			
Units: Subjects			
Female	3648	3648	
Male	0	0	
Countries			
Units: Subjects			
Belgium	308	308	
Denmark	347	347	
Finland	510	510	
France	63	63	
Germany	323	323	
Slovenia	610	610	
Spain	693	693	
Sweden	360	360	
United Kingdom	434	434	

Subject analysis sets

Subject analysis set title	Entire Cohort
Subject analysis set type	Full analysis

Subject analysis set description:

Total number of eligible study subjects that participated in the study by filling the questionnaire or accepting to receive HPV vaccination. All countries

Subject analysis set title	Entire Cohort (Compliance)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Total number of eligible study subjects that participated in the study by filling the questionnaire or accepting to receive HPV vaccinationin countries where HPV vaccine was administered as part of the study. Therefore, it does not include subjects from the United Kingdom.

Subject analysis set title	Safety cohort
Subject analysis set type	Safety analysis

Subject analysis set description:

Total number of subjects that returned the self-reported safety card and/or reported AEs after the 6-month follow-up
period out of those that received at least one dose of HPV vaccine (n=2151)

Reporting group values	Entire Cohort	Entire Cohort (Compliance)	Safety cohort
Number of subjects	3648	3214	1921
Age categorical			
Adult women within the age range of 25-45 attending cervical cancer screening with no previous history of HPV vaccine administration			
Units: Subjects			
Aged <30 yrs	924	924	669
Aged 30-34 yrs	916	776	427
Aged 35-39 yrs	887	752	402
Aged >39 yrs	911	752	418
No questionnaire	10	0	5
Age continuous			
Units: years			
arithmetic mean	34.3	33.9	33.2
standard deviation	± 6.13	± 6.17	± 6.36
Gender categorical			
Units: Subjects			
Female	3648	3214	1921
Male	0	0	0
Countries			
Units: Subjects			
Belgium	308	308	197
Denmark	347	347	144
Finland	510	510	425
France	63	63	22
Germany	323	323	188
Slovenia	610	610	303
Spain	693	693	538
Sweden	360	360	103
United Kingdom	434	0	0

End points

End points reporting groups

Reporting group title	Single arm

Reporting group description:

Study with a single arm in which all participating subjects completed a questionnaire assessing HPV vaccine acceptance. In all countries except the United Kingdom, women accepting HPV vaccine were offered to get it administered for free.

Subject analysis set title	Entire Cohort
Subject analysis set type	Full analysis

Subject analysis set description:

Total number of eligible study subjects that participated in the study by filling the questionnaire or accepting to receive HPV vaccination. All countries

Subject analysis set title	Entire Cohort (Compliance)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Total number of eligible study subjects that participated in the study by filling the questionnaire or accepting to receive HPV vaccinationin countries where HPV vaccine was administered as part of the study. Therefore, it does not include subjects from the United Kingdom.

Subject analysis set title	Safety cohort
Subject analysis set type	Safety analysis

Subject analysis set description:

Total number of subjects that returned the self-reported safety card and/or reported AEs after the 6-month follow-up
period out of those that received at least one dose of HPV vaccine (n=2151)

Primary: HPV Vaccine Uptake

End point title	HPV Vaccine Uptake[1]

End point description:

Number of study subjects in each participating country that received at least the 1st dose of vaccine.

End point type	Primary

End point timeframe:

Baseline

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Not applicable. Only proportions were estimated.

End point values	Single arm	Entire Cohort		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	2567	2567		
Units: Subjects				
Belgium	238	238		
Denmark	145	145		
Finland	443	443		
France	50	50		
Germany	299	299		
Slovenia	303	303		
Spain	564	564		
Sweden	109	109		
United Kingdom	416	416		

Statistical analyses

No statistical analyses for this end point

Primary: HPV Vaccine Compliance

End point title	HPV Vaccine Compliance[2]

End point description:

Number of study subjects in each participating country that received all three doses of vaccine.

End point type	Primary

End point timeframe:

One year for all study participants except for pregnant women who temporarily interrupted the vaccine schedule.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Not applicable. Only proportions were estimated.

End point values	Single arm	Entire Cohort (Compliance)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	1958	1958		
Units: subjects				
Belgium	204	204		
Denmark	141	141		
Finland	421	421		
France	29	29		
Germany	254	254		
Slovenia	290	290		
Spain	513	513		
Sweden	106	106		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 6 months after administration of the third dose of HPV vaccine

Adverse event reporting additional description:

AEs reported by vaccinated subjects that either returned the self-reported safety card and/or provided data on the 6-month follow-up period (Safety dataset)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Cervarix

Reporting group description:

Subjects from Spain, Finland and Belgium that received Cervarix HPV vaccine and subsequently reported data on adverse events.

Reporting group title	Gardasil

Reporting group description:

Subjects from Denmark, France and Germany that received Gardasil HPV vaccine and subsequently reported data on adverse events.

Reporting group title	Gardasil 9

Reporting group description:

Subjects from Spain, Finland, Sweden and Slovenia that received Gardsail 9 HPV vaccine and subsequently reported data on adverse events.

Serious adverse events	Cervarix	Gardasil	Gardasil 9
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 738 (0.27%)	0 / 355 (0.00%)	0 / 828 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Skull fracture	Additional description: Study participant was hospitalised due to a skull fracture caused by a bike accident		
subjects affected / exposed	1 / 738 (0.14%)	0 / 355 (0.00%)	0 / 828 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Intracranial venous sinus thrombosis	Additional description: Study participant hospitalised due to sinus thrombosis related to acute sinusitis, tobacco consumption and birth control pills use.		

subjects affected / exposed	1 / 738 (0.14%)	0 / 355 (0.00%)	0 / 828 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Cervarix	Gardasil	Gardasil 9
Total subjects affected by non-serious adverse events			
subjects affected / exposed	308 / 738 (41.73%)	117 / 355 (32.96%)	244 / 828 (29.47%)
Injury, poisoning and procedural complications			
Injection site induration			
subjects affected / exposed	8 / 738 (1.08%)	0 / 355 (0.00%)	0 / 828 (0.00%)
occurrences (all)	9	0	0
Vaccination site pain			
subjects affected / exposed	170 / 738 (23.04%)	34 / 355 (9.58%)	127 / 828 (15.34%)
occurrences (all)	299	55	232
vaccination site swelling			
subjects affected / exposed	7 / 738 (0.95%)	7 / 355 (1.97%)	22 / 828 (2.66%)
occurrences (all)	8	10	27
Nervous system disorders			
dizziness			
subjects affected / exposed	13 / 738 (1.76%)	10 / 355 (2.82%)	0 / 828 (0.00%)
occurrences (all)	14	14	0
Headache			
subjects affected / exposed	41 / 738 (5.56%)	23 / 355 (6.48%)	27 / 828 (3.26%)
occurrences (all)	49	37	39
Migraine			
subjects affected / exposed	7 / 738 (0.95%)	4 / 355 (1.13%)	0 / 828 (0.00%)
occurrences (all)	8	10	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	18 / 738 (2.44%)	16 / 355 (4.51%)	14 / 828 (1.69%)
occurrences (all)	26	22	14
Pyrexia			

subjects affected / exposed	13 / 738 (1.76%)	9 / 355 (2.54%)	33 / 828 (3.99%)
occurrences (all)	19	11	44
Influenza like illness			
subjects affected / exposed	0 / 738 (0.00%)	9 / 355 (2.54%)	9 / 828 (1.09%)
occurrences (all)	0	11	11
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	7 / 738 (0.95%)	4 / 355 (1.13%)	10 / 828 (1.21%)
occurrences (all)	8	4	12
Nausea			
subjects affected / exposed	0 / 738 (0.00%)	12 / 355 (3.38%)	6 / 828 (0.72%)
occurrences (all)	0	14	9
Vomiting			
subjects affected / exposed	0 / 738 (0.00%)	4 / 355 (1.13%)	0 / 828 (0.00%)
occurrences (all)	0	4	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 738 (1.08%)	0 / 355 (0.00%)	8 / 828 (0.97%)
occurrences (all)	8	0	12
Oropharyngeal pain			
subjects affected / exposed	12 / 738 (1.63%)	4 / 355 (1.13%)	19 / 828 (2.29%)
occurrences (all)	15	5	23
Skin and subcutaneous tissue disorders			
Injection site erythema			
subjects affected / exposed	9 / 738 (1.22%)	0 / 355 (0.00%)	9 / 828 (1.09%)
occurrences (all)	10	0	17
Musculoskeletal and connective tissue disorders			
Musculoskeletal stiffness			
subjects affected / exposed	24 / 738 (3.25%)	0 / 355 (0.00%)	0 / 828 (0.00%)
occurrences (all)	35	0	0
Pain in extremity			
subjects affected / exposed	19 / 738 (2.57%)	14 / 355 (3.94%)	16 / 828 (1.93%)
occurrences (all)	21	20	25
Musculoskeletal pain			
subjects affected / exposed	0 / 738 (0.00%)	1 / 355 (0.28%)	0 / 828 (0.00%)
occurrences (all)	0	5	0

Myalgia subjects affected / exposed occurrences (all)	0 / 738 (0.00%) 0	5 / 355 (1.41%) 6	0 / 828 (0.00%) 0
Infections and infestations Influenza subjects affected / exposed occurrences (all)	52 / 738 (7.05%) 82	0 / 355 (0.00%) 0	49 / 828 (5.92%) 83

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 September 2015	The marketing authorization in Europe of the 9-valent vaccine (Gardasil 9®) by centralised procedure was approved by the European Commission on 10th June 2015. Participating countries originally planned to use Gardasil® (see Table 5, Section C4) were offered the possibility to use Gardasil 9® instead.
13 February 2017	Due to changes in the screening programmes of United Kingdom, Italy and the Netherlands, the participation of these countries in the interventional part of the study was not feasible. Instead, UK conducted an observational study using the baseline questionnaire to assess vaccine acceptance. Moreover, the number of patients to be recruited in Spain was increased, from 300 to 500, in order to maintain the total sample size of the study.
07 April 2017	Cervarix® will be used in Finland for 250 addiitonal women to be enrolled during 2017.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Potential misrepresentation of general population due to low participation rate among women invited by postal mail (Denmark and Sweden) and over-representation of highly health-concerned / seeking free vaccination women invited in health centers

Notes: