14 November 2024
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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Cervarix

human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed)

Procedure no: EMEA/H/C/000721/P46/102

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	16/09/2024	16/09/2024	☐
☐	CHMP Rapporteur Assessment Report	21/10/2024	14/10/2024	☐
☐	CHMP members comments	04/11/2024	04/11/2024	☐
☐	Updated CHMP Rapporteur Assessment Report	07/11/2024	07/11/2024	☐
☒	CHMP adoption of conclusions:	14/11/2024	14/11/2024	☐

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1. Introduction

On 26th August 2024, the MAH submitted a completed paediatric study for Cervarix, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. This procedure concerns the final study report for study EPI-HPV-096 VS CN DB PMS (212380), entitled: "A database study to monitor the safety-related endpoints in female subjects aged between 9 and 45 years in China prior to and following Cervarix launch."

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that 'A database study to monitor the safety-related endpoints in female subjects aged between 9 and 45 years in China prior to and following Cervarix launch' (EPI-HPV-096 VS CN DB PMS; 212380) is a stand alone study.

The MAH stated that study 212380 is not part of any Paediatric Investigation Plan. A full waiver for paediatric studies in EU was obtained from Paediatric Committee (PDCO).

The EPI-HPV-096 VS CN DB PMS study was designed to address National Medical Products Administration (NMPA)'s request to evaluate Cervarix impact in China: "Setup the follow-up register system following vaccination and collect related information on immune-mediated diseases, the effect on pregnancy outcome (including neonates birth defect, etc.) and other serious diseases related to human papillomavirus (HPV) infection, etc.".

To perform such evaluations, the Yinzhou Regional Health Information Platform (YRHIP) database was identified by GSK following literature review, expert opinion, feasibility assessment and consultation meetings with local Center for Disease Control and Prevention (CDC) in 2018 [Welby, 2023]. The same YRHIP database was used to collect related information on immune-mediated diseases, the effect on pregnancy outcome (including neonates' birth defect) and other serious diseases related to HPV infection in study 212381 (EPI-HPV-097 VE CN DB PMS) (EMA/H/C/000721/P46 101).

2.2. Information on the pharmaceutical formulation used in the study

Cervarix is an adjuvanted non-infectious recombinant vaccine developed by GlaxoSmithKline Biologicals SA (GSK). It is approved in the European Union (EU) since 20 September 2007 via the Centralized Procedure. Cervarix is currently approved in the United States, all European Economic Area countries, the United Kingdom, Japan and in 67 other countries.

Cervarix is indicated for use in Europe from the age of 9 years for the prevention of premalignant ano-genital lesions (cervical, vulvar, vaginal and anal) and cervical and anal cancers causally related to certain oncogenic Human Papillomavirus (HPV) types.

Cervarix is a recombinant C-terminally truncated HPV-16 L1 and HPV-18 L1 proteins, assembled into virus-like particles (VLPs) adjuvanted with the GSK proprietary adjuvant AS04. The HPV 16 L1 VLP and HPV 18 L1 VLP proteins constitute the active ingredient of the vaccine and are produced with a recombinant baculovirus expression system. The AS04 adjuvant is composed of an aluminium salt, Al(OH)3 and 3-O-desacyl-4'-monophosphoryl lipid A (MPL).

A two dose (0.5 ml each) immunization schedule is recommended in children 9 to and including 14 years of age (the second dose is given between 5 and 13 months after the first dose) while a three dose (0.5 ml each) regimen is recommended in case of individuals ≥15 years of age given at 0, 1, and 6 months [EMA, 2023].

In China, Cervarix was approved by National Medical Products Administration (NMPA) in July 2016, for use in a 3-dose schedule at 0, 1, 6 months in females between 9 and 25 years of age, for the prevention of cervical cancer, cervical intraepithelial neoplasia grade 1 (CIN1), cervical intraepithelial neoplasia grade 2, grade 3 (CIN 2/3) and adenocarcinoma in situ caused by high risk-human papillomavirus (HR-HPV) types 16 and 18. In May 2018, Cervarix was also approved for use in females up to 45 years of age.

Assessors comments

During the study period, the posology of Cervarix varied between Europe and China.

In Europe, the immunization schedule for children aged 9 to 14 years consisted of 2 doses, with the second dose administered 5 to 13 months after the first. For individuals aged 15 years and older, a 3-dose regimen was recommended, given at 0, 1, and 6 months.

In China, as of July 2016, Cervarix was approved for a 3-dose schedule (0, 1, and 6 months) for females aged 9 to 25 years. By May 2018, this approval extended to females up to 45 years, following the same schedule.

Notably, after the study period, in May 2022, China's National Medical Products Administration (NMPA) approved a 2-dose schedule for females aged 9 to 14 years, which is aligning with the posology in Europe.

Cervarix is not authorized for use in males in China.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for study 212380 (EPI-HPV-096 VS CN DB PMS), entitled: A database study to monitor the safety-related endpoints in female subjects aged between 9 and 45 years in China prior to and following Cervarix launch.

Safety of Cervarix has been well demonstrated in the other parts of the world [Einstein, 2009; Wheeler, 2016]. In China, safety, immunogenicity and efficacy of Cervarix were assessed in 5 clinical trials, involving more than 8000 Chinese females between 9 through 45 years of age [Descamps, 2009; Zhu, 2011; Zhu, 2014a; Zhu, 2014b; Zhu, 2019; Cervarix package insert, 2022]. In addition, safety of Cervarix was assessed in a prospective, multi-center post-marketing surveillance (PMS) cohort study (EPI-HPV-070) in 3000 female Chinese participants aged between 9 and 45 years. The study assessed the occurrence of safety-related endpoints such as medically attended adverse events following immunization (AEFIs), serious AEFIs, potential immunemediated diseases (pIMDs) and pregnancy-related outcomes following vaccination with Cervarix according to the prescribing information (PI) between 31 May 2018 and 03 December 2020 [Wu, 2023b]. Cervarix vaccine has been well-tolerated and no safety issues have been raised in Chinese women when administered

according to the local PI as per routine practice. This study was assessed in procedure EMEA/H/C/000721/P46/098.

The EPI-HPV-096 VS CN DB PMS study was designed to address National Medical Products Administration (NMPA)'s request to evaluate *Cervarix* impact in China: "Setup the follow-up register system following vaccination and collect related information on immune-mediated diseases, the effect on pregnancy outcome (including neonates birth defect, etc.) and other serious diseases related to human papillomavirus (HPV) infection, etc.".

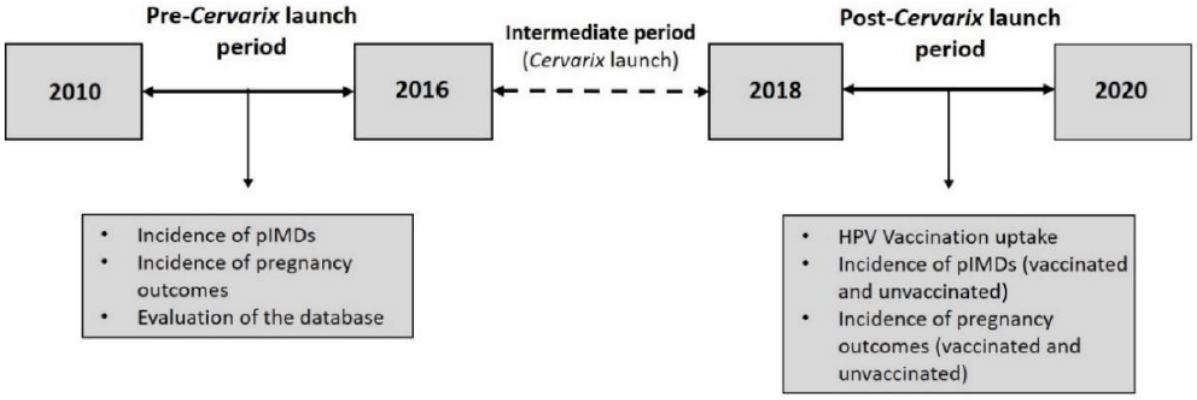
The aim of this study was to assess the safety-related endpoints of *Cervarix* vaccination in accordance with local PI using a sequential approach. In a first step, an assessment of YRHIP database performance for the detection of safety-related endpoints of interest (such as pIMDs, abnormal pregnancy outcomes [including neonatal birth defects etc.] and other rare/serious adverse events) based on pre-launch data was performed. In the second step, baseline incidence rates of safety-related endpoints and vaccination rates was computed. Then, in a third step, the pre- and post-launch rates of the most common identifiable safety-related endpoints and identifiable abnormal pregnancy outcomes were assessed. Finally, as the pre-defined criteria were met, the probability of occurrence of the most common identifiable safety-related endpoints and identifiable pregnancy outcomes among vaccinated and unvaccinated participants during post-launch period were assessed.

A stepwise approach proposed for assessment of safety-related endpoints was used to ensure mitigation of the limitations inherent to real-world evidence study. According to a report in 2021, the HPV vaccine coverage rate in China for adolescents was lower than 3%, and for the whole population was lower than 6% [Yin, 2023]. The estimated low Cervarix uptake constitute limitations in this study. This study aimed to assess those factors and delivering rates of safety-related endpoints in vaccinated and unvaccinated cohorts. The sequential approach developed in this study enabled adaptation of the study design based on the results generated in the initial steps e.g., case identification validation and incidence rates.

2.3.2. Clinical study number 212380

Description

This study was an observational, descriptive, retrospective, database study to monitor the safety-related endpoints prior to and following Cervarix launch, among female participants aged between 9 and 45 years, registered in the YRHIP from 01 January 2010 to 31 December 2020. The overview of the study design is provided in Figure 1.



Pre-*Cervarix* launch period for pIMDs: 01 January 2010 to 31 December 2016.
Pre-*Cervarix* launch period for pregnancy outcomes: 01 January 2012 to 31 December 2016.
Post-*Cervarix* launch period: 01 January 2018 to 31 December 2020.
Note: Data was collected during the intermediate period for continuous monitoring. The number of HPV vaccinated participants in the intermediate period was negligible and it was merged with the pre-launch period.

Figure 1. Study design overview (source: Clinical overview figure 1)

- Type of study and design: Observational database study.
- General study aspects: Participant level data were retrieved from the database.
- Study period:
    - Pre-Cervarix launch period for pIMDs: 01 January 2010 to 31 December 2016.
    - Pre-Cervarix launch period for pregnancy outcomes: 01 January 2012 to 31 December 2016. The database included maternal and child health information relevant for assessment of pregnancy and pregnancy outcomes from 2012 onwards.
    - Post-Cervarix launch period: 01 January 2018 to 31 December 2020.
    - For Cervarix vaccine uptake: from first Cervarix vaccination record to 31 December 2020.
    - Intermediate period: 01 January 2017 to 31 December 2017. This period was to ensure no over or under estimation in pre- and post-launch period due to few vaccinated participants. Cervarix was licensed in China in July 2016 and the first vaccinations with Cervarix took place in 2017. Therefore, the Cervarix vaccination rate in 2017 was expected to be low. As the number of HPV vaccinated participants in the intermediate period was negligible, it was merged with the pre-Cervarix launch period.
- Epoch 001: Retrospective data collection from existing electronic database of medical and health records.
- Primary completion Date: Primary completion date was defined as the date of final extraction of data for all primary outcomes.
- End of Study: End of Study was defined as the date when the last database analyses were completed.

Assessors comments

The study is divided into 3 periods, a pre-Cervarix launch period (01 January 2012 to 31 December 2016), intermediate period and post-Cervarix launch period (01 January 2018 to 31 December 2020). Cervarix was licensed in China in July 2016 and the first subject in China was vaccinated in July 2017. Since the number of HPV-vaccinated participants during the intermediate period was negligible, the MAH merged the data of these subjects with those from the pre-Cervarix launch period. The number of HPV-vaccinated participants in each period is not provided.

No information has been provided regarding the availability and recommendations for the use of other HPV vaccines (i.e. Gardasil and Gardasil 9), during the study period in China.

Methods

Study participants

Inclusion Criteria

All participants satisfied ALL the following criteria at study entry:

- Female and male* permanent residents aged between 9-45 years and registered in the Yinzhou database/YRHIP during the observation period (01 January 2010 through 31 December 2020).
- Participants with at least 12 months (365 days) of continuous registration in YRHIP database over the study period, defined by minimum of 2 or more observations recorded in YRHIP at 12 month or more apart.

*Note: Male participants were included only to account for time-confounding bias.

Exclusion Criteria

None.

Approximately 250 000 female permanent residents aged 9-45 years were estimated to be registered in YRHIP each year.

Data Sources

The YRHIP was identified by GSK following literature review, expert opinion, feasibility assessment and consultation meetings with local CDC in 2018 [Welby, 2023]. YRHIP was identified as the best available data source for post-marketing drug surveillance in 2018. Immunization data are sourced from all vaccination sites in Yinzhou, with all data captured within the Yinzhou CDC Immunization Administration Registry and integrated in the YRHIP [Welby, 2023].

The Yinzhou District CDC has linked different administrative databases of general demographic characteristics, health check information, inpatient and outpatient electronic medical records (EMRs), health insurance database, disease management and death certificates, and others within the health information systems in Yinzhou by a unique and encoded identifier for each individual. This health

information system was continuously updated with important information such as vital status, clinical outcomes, and claims data for all cohort members annually.

The Yinzhou District CDC initiated the set-up of this system in 2005 to facilitate routine primary care services for local general practitioners. It was then gradually integrated with information on public health surveillance, population screening, disease management, health information system in hospitals and other healthcare services. Since its creation, this database platform has been gradually expanding to cover all information sources, from information on public health surveillance, population screening, disease management, EMRs (relevant to assessment of autoimmune diseases from 2009 onwards) and other healthcare services including maternal and child health information (relevant for assessment of pregnancy and pregnancy outcomes from 2012 onwards) and vaccination records for children (from 2005 onwards), for HPV vaccinations (from May 2017 onwards) and for adult vaccinations (from November 2017 onwards).

Objective(s)

Objectives	Endpoints
Step 1: Assessment of database performance on safety-related endpoints (Secondary objective) • To assess the performance of case identification method for the detection of pIMDs of interest* and pregnancy outcomes of interest#.	**Step 1:** • Onset of pIMDs of interest* and pregnancy outcomes of interest# defined by ICD-10 codes, symptoms, diagnostic tests/procedures, prescriptions, and/or case narratives when available among female participants (aged 9-45 years per calendar year).
Step 2: Baseline analysis (Secondary objective) • To assess incidence of pIMDs among female participants aged 9-45 years during pre-*Cervarix* launch period, by age and overall, per calendar year. • To assess incidence of pregnancy outcomes among pregnant female participants aged 9-45 years during pre-*Cervarix* launch period, by age and overall, per calendar year. • To assess *Cervarix* vaccination uptake among female participants aged 9-45 years, by age and overall, per calendar year.	**Step 2-4:** • Onset of new identifiable** most common*** pIMDs among female participants (aged 9-45 years per calendar year). • Occurrence of identifiable** pregnancy outcomes among pregnant female participants (aged 9-45 years per calendar year). • Number of participants with at least one dose of HPV vaccine administered, per type of vaccine and per number of administered doses among female participants (aged 9-45 years per calendar year).
Step 3: Main analysis (Primary objective) • To assess incidence of the identifiable** most common*** pIMDs among female participants aged 9-45 years during pre- and post-launch period, by age and overall, per calendar year. • To assess incidence of the identifiable** pregnancy outcomes among pregnant female participants aged 9-45 years during pre- and post-launch period by age and overall, per calendar year.	
Step 4: Conditional analysis (Secondary objective) • To assess the probability of occurrence of identifiable** most common*** pIMDs within 12 months following *Cervarix* vaccination in vaccinated and unvaccinated participants, during the pre- and post-launch period, conditional on vaccine uptake and observed incidences. • To assess the probability of identifiable** abnormal pregnancy outcomes following *Cervarix* vaccination in vaccinated and unvaccinated pregnant participants, during the pre- and post-launch period, conditional on vaccine uptake and observed incidence.	

pIMDs: potential immune-mediated diseases.
Note: To account for time-confounding bias, incidence of pIMDs in male participants aged 9-45 years during pre- and post-launch period, by age and overall, per calendar year were described.

*pIMD of interest, defined as pIMD for which clear case ascertainment can be performed (based on a combination of International Classification of Diseases-10 [ICD-10] code, diagnostic procedures, prescription, lab results) (For the purpose of this study: autoimmune thyroiditis, type 1 diabetes mellitus, rheumatoid arthritis, inflammatory bowel disease, idiopathic thrombocytopenic purpura).
**"identifiable" endpoints were defined as those with optimal case identification as assessed in step 1.
***"most common" endpoints were defined based on the incidences observed in step 2.
#pregnancy outcomes of interest include spontaneous abortion and live infant congenital anomaly.

Case definition

In this study, for case identification a list of ICD-10 codes was used for the extraction. However, endpoint definitions in an electronic medical health records database could be a challenge. Therefore, case validation was performed for pIMD of interest (for the purpose of this study, these were: autoimmune thyroiditis, type 1 diabetes mellitus, rheumatoid arthritis, inflammatory bowel disease, idiopathic thrombocytopenic purpura) and for pregnancy outcomes of interest (spontaneous abortion and live infant congenital anomaly) based on ICD-10 codes and a combination of disease terms in Chinese, examination, medications and/or procedures, as well as narratives, either alone or in combination. Depending on the complexity of these case definitions, specific case identification methods (i.e., combination of diagnostic codes, medications and/or procedures) were developed.

Challenges in determining the date of the first symptom of an autoimmune disease in YRHIP was a potential limitation, and therefore emphasis were on new onset focusing on the case definition process, and a 12-month period was considered to ensure that only incident cases were measured and not prevalent ones.

Definition of new pIMD

An event was defined as an occurrence of an endpoint in a participant. The event date was the date of diagnosis. Each pIMD was identified by the case identification method detailed in the SAP. The diagnosis was defined by ICD-10 code and/or in combination of other medical terms.

A new episode of specific pIMD during study period was identified with a first confirmed diagnosis date (i.e., earliest of diagnosis dates) occurring at any time between reference date and end of follow-up in a participant with no such event (i.e., specific pIMD) diagnosis within preceding 12 months before reference date. Refer to Table 1 for details on the definition of reference and end-of-follow-up dates.

Sensitivity analysis to measure the impact of using symptom onset date (based on case validation form data) versus diagnosis date was performed.

Table 1. Definition of reference and end-of-follow-up dates (Source: Final Report Table 7.1)

Period	Reference date	End of follow-up date
Pre-*Cervarix* launch period	The latest of the following dates: 12 months after initial registry in the Yinzhou database, or The date of 9th birthday, or 1 Jan 2010.	The earliest of the following dates: 31 Dec 2016, or The date of 46th birthday, or Date of death, or Date of discontinuation from Yinzhou database
Post-*Cervarix* launch period	The latest of the following dates: 12 months after initial registry in the Yinzhou database and The date of 9th birthday, or 1 Jan 2018.	The earliest of the following dates: 31 Dec 2020, or The date of 46th birthday, or Date of deaths, or Date of discontinuation from Yinzhou database
Cervarix vaccinated person	Date of first *Cervarix* dose administration	The earliest of the following dates: 12 months after the Date of first *Cervarix* dose administration, or 31 Dec 2020, or The date of 46th birthday, or Date of death, or Date of discontinuation from Yinzhou database

Note: Reference and end of follow-up dates were also defined for intermediate period.

Definition of pregnancy outcomes

Pregnancy outcome event was identified by case identification method detailed as above using ICD-10 code, between the pregnancy onset, last menstrual period and 6 months after the expected end of pregnancy in pregnant participants.

Assessors comments

The study includes all individuals in the YRHIP database aged between 9-45 yoa during the period from 01 January 2010 through 31 December 2020 who were registered for at least 12 months and had a least 2 or more observations recorded at 12 months or more apart.

The study objectives are defined in 4 steps. The primary objective, step 3, is to assess the incidence of the identifiable most common pIMDs and pregnancy outcomes in females during the pre- and post-Cervarix-launch periods, by age and overall, per calendar year. It would have been relevant to evaluate in addition incidence densities over the entire pre- and post- Cervarix-launch periods, instead of only by calendar year. However, these analyses are not provided. The secondary objectives include the assessment of database performance on safety-related endpoints (Step 1); baseline analysis of Cervarix vaccine uptake and the indicende of pIMDs and pregnancy outcomes (Step 2); and assessment of the probability of occurrence of identifiable most common pIMDs and pregnancy outcomes in the 12 months following Cervarix vaccination, conditional on vaccine uptake and observed incidences (Step 4). There are no exploratory objectives.

To account for time confounding bias, incidence of pIMDs in male subjects aged 9-45 years during pre- and post-launch period, by age and overall, per calendar year are described.

Cases were identified by using a list of ICD-10 codes corresponding to pIMDs and pregnancy outcomes. After this initial case identification, pIMDs of interest and pregnancy outcomes of interest

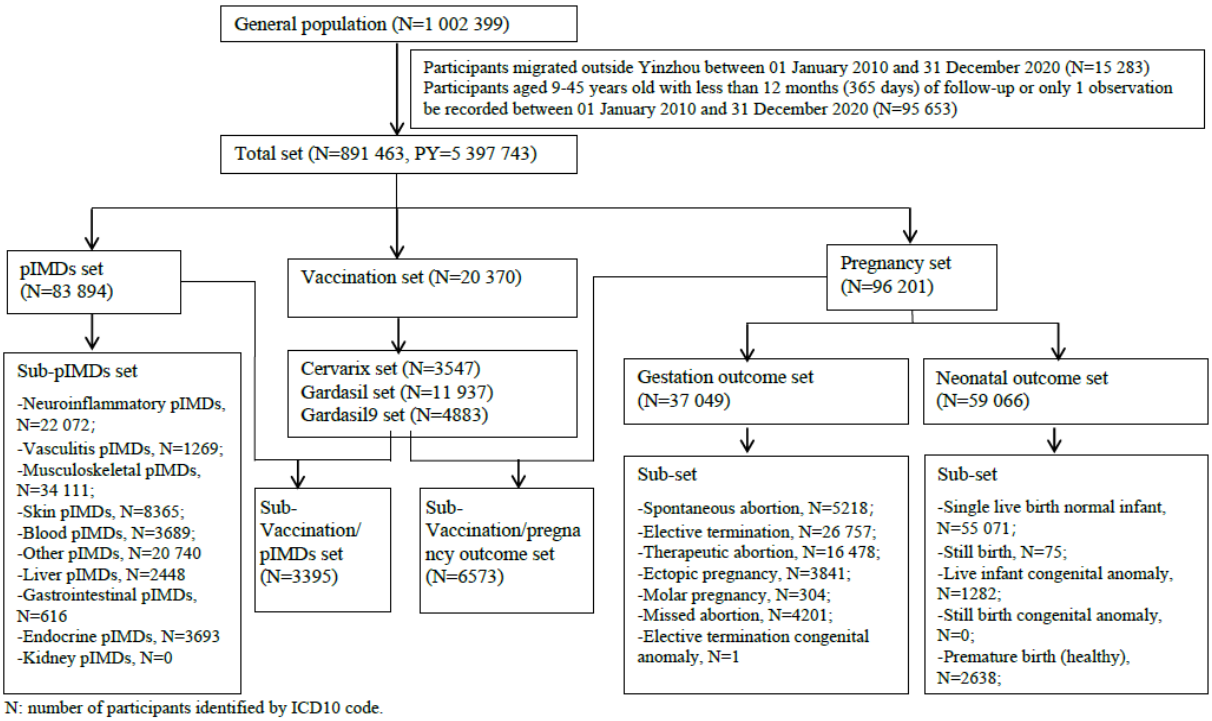
were validated by using in addition to the ICD-10 codes also a combination of disease terms in Chinese, examination, medications, procedures and narratives. The pIMDs of interest are Autoimmune Thyroiditis (AT), Type 1 Diabetes Mellitus (T1DM), Inflammatory Bowel Disease (IBD), Rheumatoid Arthritis (RA) and Idiopathic Thrombocytopenic Purpura (ITP). Pregnancy outcomes of interest are Spontaneous Abortion and Live Infant Congenital Anomaly.

Results

Participant disposition

Data of a total of 1 002 399 participants was extracted from the YRHIP database (2010-2020), out of which 891 463 eligible participants who met the inclusion criteria were included in the Total Set (Figure 2). Within the Total Set, the following subsets were considered:

- The Vaccination Set consisted of 20 370 participants who received at least 1 dose of any HPV vaccine. Of these, 3547 participants received Cervarix, 11 937 participants received Gardasil and 4883 participants received Gardasil 9.
- The pIMD Set consisted of 83 894 participants with diagnosis of pIMDs.
- The Pregnancy Set consisted of 96 201 female pregnant participants. Of these, 37 049 participants were included in the Gestational Outcome Set and 59 066 participants in the Neonatal Outcome Set.



N: number of participants identified by ICD10 code.

PY: person-year, calculated as sum of person-year for all participants in the category.

Total set: eligible participants which met the inclusion criteria (a. female and male aged between 9-45 years; b. participants registered in the YRHIP between 1 January 2010 and 31 December 2020; c. participants with at least 12 months of continuous registration in Yinzhou Regional Health Information Platform (YRHIP) database over the study period, defined by minimum 2 or more observations recorded in YRHIP at 12 month or more apart).

pIMDs set: eligible participants from the total set with potential Immune Mediated Diseases (pIMDs) diagnosed.

Pregnancy set: female pregnant participants from the total set, and repeated pregnancies for one participant were counted separately (A total of 80 049 female participants experienced 96 201 pregnancies).

Vaccination set: female participants from the total set with at least one dose of any human papilloma virus (HPV) vaccine (including *Cervarix*, and other HPV vaccines) administered.

The ICD-10 term has been showed in Statistical Analysis Plan (Appendix 1 and Appendix 2).

Figure 2. Participant disposition (Total Set) (Source: Clinical Overview Figure 2)

Assessors comments

In total data of 1 002 399 participants was extracted from the YRHIP database between 2010 and 2020.

The Total Set, including participants who meet the inclusion criteria, contains 891 463 participants.

The Vaccination set, including participants who received at least one dose of any HPV vaccine, contains 20 370 participants. This indicates a very low degree of vaccination against HPV in China in that period (only 2.3% of the population), which is a limitation of the study. Of this group, only a minority of the participants (n = 3547) received Cervarix, while the others received at least one dose of Gardasil (n = 11 937) or Gardasil 9 (n = 4883). The number of participants that received one, two or 3 doses of these vaccines is discussed in the results of the secondary analysis of HPV and Cervarix vaccination uptake (Step 2).

The pIMD Set, including participants who were diagnosed with at least one pIMD, includes 83 894 participants, of which the majority experienced a musculoskeletal (n = 34 111) or a neuroinflammatory pIMD (n = 22 072).

The Pregnancy Set includes in total 96 201 cases of pregnancy. As repeated pregnancies for one participant were counted separately, the total number of female participants was less (n = 80 049). Of

the Pregnancy Set, 37 049 participants were included in the Gestational Outcome Set and 59 066 participants in the Neonatal Outcome Set.

Two sub-sets are defined for the analysis of pIMDs and pregnancy outcomes in the vaccinated subjects. The Sub-vaccination/pIMDs set includes 3395 participants and the Sub-vaccination/pregnancy outcome set includes 6573 participants. As only a minority of vaccinated individuals received Cervarix, the same is expected for these subsets, however the numbers are not specified.

Baseline data

The demographic and baseline characteristics for participants in various analysis data sets are as follows:

- Among 891 463 participants (pooled age group 9-45 years) in the Total Set, the highest number of participants was in the age group 40-45 years (163 154 participants). The majority of participants were married (608 888 participants) with primary school and junior high school as the maximum educational qualification of most of the participants (418 293 participants). Between 2010-2019, most participants (n = 282 862) were reported in database in the Year 2010. This set consisted of 469 611 females and 421 852 males (Table 2).
- Among 83 894 participants (pooled age group 9-45 years) in the pIMD Set, the highest number of participants was in the age group 35-39 years (21 201 participants). The majority of participants were married (64 890 participants) with primary school and junior high school as the maximum educational qualification of most of the participants (36 578 participants). Between 2010-2019, most participants (n = 39 108) were reported in the database in the Year 2010. This set consisted of 44 505 females and 39 389 males (Table 3).
- Among 20 370 participants (pooled age group 9-45 years) in the Vaccination Set, the highest number of participants was in the age group 25-29 years (4703 participants). The majority of participants were married (12 197 participants) with junior college or above degree as the maximum educational qualification of most of the participants (11 085 participants). Between 2010-2019, most participants (n = 7728) were reported in the database in the Year 2010. This set consisted of 20 337 females and 33 males (Table 4).
- Among 80 049 female participants (pooled age group 9-45 years) in the Pregnancy Set, the highest number of participants was in the age group 25-29 years (31 548 participants). The majority of participants were married (59 371 participants) with junior college or above degree as the maximum educational qualification of most of the participants (33 547 participants). Between 2010-2019, most participants (n = 22 196) were reported in the database in the Year 2010 (Table 5).

Table 2. Demographic characteristics at inclusion (Total Set) (Source: Clinical Overview Table 1)

Variables	Total number	Female	Male	Statistical parameters	P-value
Total number	891463	469611	421852		
Age group at inclusion date				3514.49	<0.001
09-14Y	64005	30557	33448		
15-19Y	68371	34048	34323		
20-24Y	119492	65846	53646		
25-29Y	158203	91602	66601		
30-34Y	159773	85105	74668		
35-39Y	158465	80667	77798		
40-45Y	163154	81786	81368		
Education level				2507.31	<0.001
Illiterate and semi-illiterate	3826	2364	1462		
Primary school and junior high school	418293	222971	195322		
Senior high school/technical school	149418	73188	76230		
Junior college or above degree	193758	108805	84953		
Unknown	126168	62283	63885		
Married status				4726.25	<0.001
Unmarried	183319	83745	99574		
Married	608888	332020	276868		
Divorced/ widowed	5145	3275	1870		
Unknown	94111	50571	43540		
Year of inclusion				2548.57	<0.001
2010	282862	145801	137061		
2011	98929	58382	40547		
2012	200857	103707	97150		
2013	83114	41939	41175		
2014	22420	10894	11526		
2015	14363	6894	7469		
2016	5218	2659	2559		
2017	138507	73857	64650		
2018	15050	8582	6468		
2019	30143	16896	13247		

Note: Statistical tests were conducted comparing female and male using chi-square tests. For example, $p<0.05$ presented at "age group at inclusion date" indicates a significant difference in the overall distribution of age category between female and male.

Y=Years.

Inclusion criteria required at least 12 months of continuous registration in Yinzhou Regional Health Information Platform (YRHIP) database over the study period (01 January 2010 through 31 December 2020), thus the study participants are included only till Year 2019.

Table 3. Demographic characteristics at inclusion (pIMD Set) (Source: Clinical Overview Table 2)

Variables	Total number	Female	Male	Statistical parameters	P-value
Total number	83894	44505	39389		
Age group at inclusion date				113.25	<0.001
09-14Y	3471	1726	1745		
15-19Y	4953	2475	2478		
20-24Y	9700	5052	4648		
25-29Y	15257	8620	6637		
30-34Y	19493	10252	9241		
35-39Y	21201	11182	10019		
40-45Y	9819	5198	4621		
Education level				340.48	<0.001
Illiterate and semi-illiterate	307	197	110		
Primary school and junior high school	36578	19964	16614		
Senior high school/technical school	15769	7400	8369		
Junior college or above degree	23209	12819	10390		
Unknown	8031	4125	3906		
Married status				605.76	<0.001
Unmarried	12503	5382	7121		
Married	64890	35543	29347		
Divorced/ widowed	619	387	232		
Unknown	5882	3193	2689		
Year of inclusion				245.51	<0.001
2010	39108	20506	18602		
2011	11833	6833	5000		
2012	13768	6986	6782		
2013	5096	2552	2544		
2014	1443	691	752		
2015	1265	611	654		
2016	503	275	228		
2017	9618	5262	4356		
2018	714	462	252		
2019	546	327	219		

Note: Statistical tests were conducted comparing female and male using chi-square tests. For example, $p<0.05$ presented at "age group at inclusion date" indicates a significant difference in the overall distribution of age category between female and male.

Y=Years.

Inclusion criteria required at least 12 months of continuous registration in Yinzhou Regional Health Information Platform (YRHIP) database over the study period (01 January 2010 through 31 December 2020), thus the study participants are included only till Year 2019.

Table 4. Demographic characteristics at inclusion (Vaccination Set) (Source: Clinical Overview Table 3)

Variables	Total number	Female	Male	Statistical parameters	P-value
Total number	20370	20337	33		
Age group at inclusion date				1.86	0.932
09-14Y	3462	3458	4		
15-19Y	2885	2879	6		
20-24Y	3362	3356	6		
25-29Y	4703	4694	9		
30-34Y	4059	4054	5		
35-39Y	1523	1521	2		
40-45Y	376	375	1		
Education level				6.49	0.165
Illiterate and semi-illiterate	29	29	0		
Primary school and junior high school	4002	3991	11		
Senior high school/technical school	3447	3443	4		
Junior college or above degree	11085	11072	13		
Unknown	1807	1802	5		
Married status				47.10	<0.001
Unmarried	6939	6932	7		
Married	12197	12182	15		
Divorced/ widowed	72	72	0		
Unknown	1162	1151	11		
Year of inclusion				63.40	<0.001
2010	7728	7715	13		
2011	2913	2911	2		
2012	1360	1358	2		
2013	730	722	8		
2014	319	319	0		
2015	391	391	0		
2016	241	238	3		
2017	5207	5205	5		
2018	574	574	0		
2019	907	907	0		

Note: Statistical tests were conducted comparing female and male using chi-square tests. For example, $p<0.05$ presented at "age group at inclusion date" indicates a significant difference in the overall distribution of age category between female and male.

Y=Years.

Inclusion criteria required at least 12 months of continuous registration in Yinzhou Regional Health Information Platform (YRHIP) database over the study period (01 January 2010 through 31 December 2020), thus the study participants are included only till Year 2019.

Table 5. Demographic characteristics at inclusion (Pregnancy Set) (Source: Clinical Overview Table 4)

Variables	Female
Total number*	80049
Age group at inclusion date	
09-14Y	19
15-19Y	1142
20-24Y	12073
25-29Y	31548
30-34Y	20699
35-39Y	10267
40-45Y	4301
Education level	
Illiterate and semi-illiterate	121
Primary school and junior high school	23810
Senior high school/technical school	14342
Junior college or above degree	33547
Unknown	8229
Married status**	
Unmarried	10626
Married	59371
Divorced/ widowed	317
Unknown	9735
Year of inclusion***	
2010	22196
2011	11627
2012	11825
2013	10004
2014	2592
2015	1699
2016	811
2017	13417
2018	2873
2019	3005

Note: * A total of 80 049 female participants experienced 96 201 pregnancies.

** The married status was investigated as participant registered in the Yinzhou Regional Health Information Platform (YRHIP), not until pregnancy.

*** The participants have been registered in the YRHIP from 01 January 2010 to 31 December 2020, but the observational period for pregnancy outcome was 01 January 2012 through 31 December 2020. Inclusion criteria required at least 12 months of continuous registration in YRHIP database over the study period, thus the study participants are included only till Year 2019.

Y=Years.

Assessors comments

Overall, in the Total Set, a higher number of females than males are included (n = 469 611 vs. 421 852). The highest number of participants were in the highest age group of 40-45 years (n = 163 154), with overall a stronger representation of the higher age categories compared to the lower ones. The mean age was not provided. The majority of participants in the Total set were married and had an education level of primary school and junior high school. Regarding time of reporting in the database between 2010 and 2019, most participants (n = 282 862) were reported in the year 2010. Overall,the number of participants included in the YRHIP database varies significantly across different calendar years in all datasets. Much more participants were included during the pre-Cervarix launch period (2021 – 2016) compared to the post-Cervarix launch period (2018-2020). The reason for this variability is unclear.

Of note, as the inclusion criteria required a least 12 months continuous registration in the YRHIP database over the study period (2010 – 2020), participants are included only until 31 December 2019.

The Vaccination Set includes almost exclusively females (only 33 males) and the majority of participants are below 35 yoa. The educational level is clearly higher compared to the total set, with the majority of participants having a degree of junior college or above (n = 11 085). The majority of participants in the Vaccination set are married (n = 12 197), however, compared to the Total set, the martial status is lower. Similar as in the Total set, the majority of participants were reported in the database in the year 2010 (n = 7728), with the second highest number of participants reported in the year 2017 (n = 5207). To conclude, the vaccinated set seems to be quiet different when compared to the Total set. This implies that data will have to be interpreted with caution. In addition, demographics correspond to the whole vaccinated set, i.e. not restricted to the Cervarix vaccinated set.

The baseline characteristics in the pIMD set are relatively similar to the Total Set in regards to gender, education level, marital status and year of inclusion. Most participants have an age of 35-39 years at time of inclusion (n = 21 201), followed by 30-34 yoa (n = 19 493) and 25-29 yoa (n = 15 257). There are less participants with an age of 40-45 years at inclusion (n = 9819) compared to the Total Set. Overall, mean age was not provided, but seems to be lower compared to the Total Set.

In the Pregnancy set, most women have an age of 25-29 years (n = 31 548) or 30-34 years (n = 20 699). The majority are married (n = 59 371) and the marital status is similar to the Total Set. Most participants obtained a degree of Junior college or above (n = 33 547). It seems that the education level is higher in the Pregnancy set vs. the Total Set, which is unexpected and the reason is unknown. Similar as in the Total set, the majority of participants were reported in the database in the year 2010 (n = 22 196), with the second highest number of participants reported in the year 2017 (n = 13 417).

Safety results

Primary objectives

Incidence of identifiable most common pIMDs during pre-Cervarix and post-Cervarix launch period (Step 3)

The incidence density (per 100 000 person-year [PY]) of identifiable most common pIMDs was assessed during the pre-Cervarix (2010-2017) and post-Cervarix (2018- 2020) launch period. As the number of HPV vaccinated participants in the intermediate period (01 January 2017 to 31 December 2017) was negligible, it was merged with the pre-Cervarix launch period. The highest incidence density of identifiable most common pIMDs was observed as follows:

- Pre-Cervarix launch period (2010-2017)
    - Overall, in females, the highest incidence density (per 100 000 PY) of identifiable most common pIMDs was reported for demyelinating peripheral neuropathies (i.e., neuralgia and neuritis [unspecified], radiculopathy, neuritis, or radiculitis; International Classification of Diseases-10 code [ICD-10 code]: M79.2 vs M54.1) (532.26; 95% confidence interval [CI] = 507.46, 557.96) in 2015 for the pooled age group 9-45 years.
    - Overall, in males, the highest incidence density (per 100 000 PY) of identifiable most common pIMDs was reported for demyelinating peripheral neuropathies (i.e., neuralgia and neuritis [unspecified], radiculopathy, neuritis, or radiculitis; ICD-10 code: M79.2 vs M54.1) (448.88; 95% CI = 424.95, 473.81) in 2015 for the pooled age group 9-45 years.
- Post-Cervarix launch period (2018-2020)
    - Overall, in females, the highest incidence density (per 100 000 PY) of identifiable most common pIMDs was reported for other spondylopathies (ICD- 10 code: M48) (769.12; 95% CI = 736.84, 802.44) in 2019 for the pooled age group 9-45 years.
    - Overall, in males, the highest incidence density (per 100 000 PY) of identifiable most common pIMDs was reported for other spondylopathies (ICD-10 code: M48) (637.15; 95% CI = 605.98, 669.51) in 2019 for the pooled age group 9-45 years.

<u>Incidence of identifiable pregnancy outcomes among pregnant female participants during pre-Cervarix and post-Cervarix launch period (Step 3)</u>

The incidence of identifiable pregnancy outcome was assessed during the pre-Cervarix (2012-2017) and post-Cervarix (2018-2020) launch period and the highest incidence rate of pregnancy outcome was observed as follows:

- Pre-Cervarix launch period (2012-2017)
    - Overall, in pregnant females, the highest incidence rate (per 1000 persons) was reported for single live birth normal infant (ICD-10 code: Z37.0) (783.98; 95% CI = 775.86, 791.94) in 2012 for the pooled age group 9-45 years. Among the various age groups, the incidence rate was highest in the age group 20-24 years (812.20; 95% CI = 797.99, 825.81).
- Post-Cervarix launch period (2018-2020)
    - Overall, in pregnant females, the highest incidence rate (per 1000 persons) was reported for elective termination (ICD-10 code: O04, O05, O06, P96.4) (526.27; 95% CI = 514.85, 537.66) in 2019 for the pooled age group 9-45 years. Among the various age groups, the incidence rate was highest in the age group 35-39 years (721.00; 95% CI = 695.51, 745.47).

Assessors comments

<u>Incidence of identifiable most common pIMDs during pre-Cervarix and post-Cervarix launch period (Step 3)</u>

The first primary objective is to assess the incidence of the most common identifiable pIMDs (based on the incidences observed in the pre-Cervarix launch period as evaluated in Step 2) among female participants aged 9-45 years during pre- and post-launch period.

In the pre-Cervarix launch period (2012-2017), demyelinating peripheral neuropathies (i.e., neuralgia and neuritis [unspecified], radiculopathy, neuritis, or radiculitis; ICD-10 code: M79.2 vs M54.1) was the pIMD with highest incidence, both in females and males, in 2015. A higher incidence density (per 100 000 person years [95% CI]) is observed in females (532.26 [507.46, 557.96]) vs. males (448.88 [424.95, 473.81]). Although this pIMD was not the most frequently observed pIMD in the post-Cervarix launch period, the actual incidence density in females was similar in 2018 (500.05 [474.04; 527.12]) and 2019 (489.77 [464.05; 516.54]) and slightly lower in 2020 (383.69 [360.91; 407.54]). It is observed that in the pre-launch period, in the years 2011, 2012 and 2013, the appearance of this pIMD is significantly lower (ranging between 83.29 and 135.86 per 100 000 person years, in females and males). The reason for this is unclear. Furthermore, in general, there seems to be a higher incidence density of this pIMD with increasing ages, except for the age group from 40-45 yoa where there is some variability.

Of note, in the prospective post marketing surveillance cohort study EPI-HPV-070 in China (evaluated in procedure EMEA/H/C/000721/P46/098), 1 subject out of 3016 reported a pIMD, which was also neuritis. This pIMD was considered by the investigator not to be causally related to the vaccination, and the subject had recovered following treatment.

In the post-Cervarix launch period (2018-2020), other spondylopathies (ICD-10 code: M48) was the pIMD with highest incidence in females and males, in 2019. A higher incidence density (per 100 000 person years [95% CI]) is observed in females (769.12 [736.84, 802.44]) vs. males (637.15 [605.98, 669.51]). The incidence density of this pIMD in the pre-launch period was clearly lower, ranging between 83.70 and 364.32 between the years 2012 and 2016. The reason for this is unclear. In general, there seems to be a higher incidence density of this pIMD with increasing ages.

Incidence of identifiable pregnancy outcomes among pregnant female participants during pre-Cervarix and post-Cervarix launch period (Step 3)

The second primary objective is to assess the incidence of pregnancy outcomes among female participants aged 9-45 years during pre- and post-launch period.

In the pre-Cervarix launch period, single live birth normal infant (ICD-10 code: Z37.0) was the pregnancy outcome with highest incidence rate (per 1000 persons [95% CI]) reported in 2012 (783.98 [775.86; 791.94]). The incidence rate of this outcome reduces over the years, with the lowest incidence rate observed in 2019 (271.93 [261.85; 282.20]). It is observed that the total number of pregnancies is lowest in the years 2019 and 2020.

In the post-Cervarix launch period, the highest incidence rate was reported for elective termination (ICD-10 code: O04, O05, O06, P96.4) outcome in 2019 (526.27 [514.85; 537.66]). There is a clear evolution over the years towards higher incidence rates of elective termination. In particular in the years 2019 and 2020, approximately 50% or more of the pregnancies end in elective termination.

Of note, in the prospective post marketing surveillance cohort study EPI-HPV-070 in China (evaluated in procedure EMEA/H/C/000721/P46/098), 65 subjects out of 3031 subjects reported pregnancies during the entire follow-up period. Of these, 34 subjects (52.3%) had a live infant with no apparent congenital anomaly and 20 subjects (30.8%) had an elective termination with no apparent congenital anomaly. The year when this study was conducted is not specified in the EPAR.

Secondary objectives

Performance of case identification method for the detection of pIMDs of interest and pregnancy outcomes of interest (Step 1)

The algorithm's performance on pIMDs of interest during the pre-Cervarix launch period was determined and the positive predictive value (PPV) was greater than 70% for all algorithms for pIMDs of interest, except algorithm 2 (66.67%) for rheumatoid arthritis.

The algorithm's performance on pregnancy outcomes of interest during the pre-Cervarix launch period was determined and the PPV was greater than 70% for both spontaneous abortion (90.84%) and live infant congenital anomaly (98.31%).

Incidence of pIMDs and pregnancy outcomes during pre-Cervarix launch period (Step 2)

Among all the identifiable pIMDs in the pre-Cervarix launch period, the highest incidence density (per 100 000 PY) was reported for neuralgia and neuritis (unspecified), radiculopathy, neuritis, or radiculitis (ICD-10 code: M79.2 vs M54.1) in males (273.80; 95% CI = 266.27, 281.48) and females (323.48; 95% CI = 315.68, 331.41) for pooled age group 9-45 years.

Among all pregnancy outcomes in the pre-Cervarix launch period, the highest incidence rate (per 1000 persons) was reported for single live birth normal infant (ICD-10 code: Z37.0) (783.98; 95% CI = 775.86, 791.94) in 2012 for the pooled age group 9-45 years.

HPV and Cervarix vaccination uptake (Step 2)

The HPV and Cervarix vaccination uptake were as follows:

- Overall, 20 449* female participants received at least 1 dose of HPV vaccination, among which 3611* participants received Cervarix vaccination in the pooled age group 9-45 years.
- Overall, the HPV vaccination rate was 67.68 per 1000 persons (95% CI = 66.79, 68.58) and the Cervarix vaccination rate was 11.95 per 1000 persons (95% CI = 11.57, 12.35) in the pooled age group 9-45 years. The HPV and Cervarix vaccination uptake rate per 1000 persons were maximal in the age group 20-24 years (159.32; 95% CI = 155.00, 163.71) and 35-39 years (15.59; 95% CI = 14.62, 16.6), and minimal in the age group 9-14 years (9.53; 95% CI = 7.44, 12.03) and 25-29 years (8.73; 95% CI = 8.01, 9.50), respectively.
- Out of all vaccinated participants, most participants received HPV vaccination (10 497 participants) in 2020, including participants who received Cervarix vaccination (1466 participants). The vaccination uptake rate was 34.74 per 1000 persons (95% CI = 34.09, 35.40) for HPV vaccination and 4.85 per 1000 persons (95% CI = 4.61, 5.11) for Cervarix vaccination in 2020.
- Out of all vaccinated participants, most participants received 3 doses of HPV vaccination (9393 participants) and 1 dose of Cervarix vaccination (1335 participants). The vaccination uptake rate for 3 doses of HPV vaccination was 29.34 per 1000 persons (95% CI = 28.76, 29.93) and 1 dose of Cervarix vaccination was 4.17 per 1000 persons (95% CI = 3.95, 4.40), respectively.

*Note: The number of participants with HPV/Cervarix vaccination in the pooled age group 9-45 years was calculated as the sum of number of participants in each age category. As vaccinee might receive separate vaccination dose at different age category, the total number of participants who received HPV

vaccination (20 499 participants) and Cervarix vaccination (3611 participants) was more than the number of participants in the Vaccination Set as mentioned in participants disposition section.

Incidence of identifiable most common pIMDs by vaccination strata (Step 4)

The incidence of identifiable most common pIMDs by the vaccination strata was assessed in females within 12 months after Cervarix vaccination, with more than 12 months following Cervarix vaccination and in females who did not receive any HPV vaccination during the study period (2010-2020).

- In females within 12 months after Cervarix vaccination, other spondylopathies (ICD- 10 code: M48) showed the highest incidence density per 100 000 PY of 1140.52 (95% CI = 795.66, 1582.65) and the highest incidence rate (per 100 000) of 988.42 (95% CI = 689.41, 1372.00).
- In females with more than 12 months period following Cervarix vaccination, other spondylopathies (ICD-10 code: M48) showed the highest incidence density per 100 000 PY of 3042.48 (95% CI = 1748.84, 4893.87) and the highest incidence rate (per 100 000) of 1092.15 (95% CI = 625.51, 1767.54).
- In females who did not receive any HPV vaccination during the study period (2010- 2020), other spondylopathies (ICD-10 code: M48) showed the highest incidence density per 100 000 PY of 393.05 (95% CI = 385.60, 400.61) and the highest incidence rate (per 100 000) of 2347.57 (95% CI = 2303.49, 2392.26).

Incidence rate of identifiable pregnancy outcomes by vaccination strata (Step 4)

The incidence rate of identifiable pregnancy outcome by the vaccination strata was assessed in females who received Cervarix during pregnancy or within 60 days before pregnancy and in females who did not receive Cervarix during pregnancy or within 60 days before pregnancy. The highest incidence rate of identifiable pregnancy outcome was as follows:

- In females who received *Cervarix* during pregnancy or within 60 days before pregnancy, live birth (ICD-10 code: Z37.0) showed the highest incidence rate (per 1000) of 406.32 (95% CI = 361.51, 528.21).
- In females who did not receive *Cervarix* during pregnancy or within 60 days before pregnancy, live birth (ICD-10 code: Z37.0) showed the highest incidence rate (per 1000) of 573.23 (95% CI = 570.09, 584.88).

Probability of occurrence of identifiable most common pIMDs within 12 months following Cervarix vaccination in vaccinated and unvaccinated participants, during the pre- and post-Cervarix launch period (Step 4)

The probability of the identifiable most common pIMDs associated with Cervarix vaccination was assessed using a Poisson regression model. The risk window was defined as 12 months following Cervarix vaccination. Conditional analysis was performed for identifiable pIMDs related to neuroinflammatory disorders, musculoskeletal disorder and other pIMDs category. Due to the low disease incidence, no pIMD related to vasculitis, skin disorders, blood disorders, liver disorders, gastrointestinal disorders, endocrine disorders, and kidney disorders met the prespecified sample size threshold as mentioned in the statistical analysis plan for conditional analysis.

There was no significant difference in the incidence density for neuralgia and neuritis, unspecified (ICD-10 code: M79.2) and other neuroinflammatory disorders (neuralgia and neuritis [unspecified], radiculopathy, neuritis, or radiculitis; [ICD-10 code: M79.2 vs M54.1]) within 12 months risk window in females vaccinated with any dose of *Cervarix* compared to females who were not vaccinated with any HPV vaccine during the study period.

Using multivariable regression model (12 months risk window),

- The incidence density was significantly higher in females vaccinated with any dose of *Cervarix* compared to females who were not vaccinated with any HPV vaccine during the study period for:
    - Other spondylopathies (ICD-10 code: M48; adjusted rate ratio [RR] = 1.92; 95% CI = 1.38, 2.68; p-value <0.01),
    - Sarcoidosis (ICD-10 code: D86; adjusted RR = 2.81; 95% CI = 1.97, 4.01; p-value <0.01), and
    - Sarcoidosis of lung (ICD-10 code: D86.0; adjusted RR = 5.15; 95% CI = 3.94, 6.74; p-value <0.01).
- The incidence density of sarcoidosis and sarcoidosis of lung significantly increased over time in the post-*Cervarix* launch period (2018-2020).
- There was no increase in the risk between other age groups compared to the reference group (40-45 years) for other spondylopathies, sarcoidosis and sarcoidosis of lung.

Probability of identifiable abnormal pregnancy outcomes following Cervarix vaccination in vaccinated and unvaccinated pregnant participants, during the pre- and post-Cervarix launch period (Step 4)

The probability of the identifiable pregnancy outcomes associated with Cervarix vaccination during pregnancy or within 60 days before pregnancy was assessed using a logistic regression model. Using multivariable regression model,

- The incidence rate of live birth (ICD-10 code: Z37.0; adjusted RR: 1.39; 95% CI = 1.13, 1.70; p-value <0.01) was significantly higher in females vaccinated with any dose of *Cervarix* compared to females who were not vaccinated with any HPV vaccine during pregnancy or within 60 days before pregnancy.
- There was no significant increase in incidence rate over time for live birth.
- A significant difference in the incidence rate between various age groups was observed for live birth (p-value <0.01; adjusted RR for age groups: 15-19 years = 7.96 [95% CI = 5.21, 12.16]; 20-24 years = 13.15 [95% CI = 10.77, 16.06]; 25-29 years = 13.95 [95% CI = 11.62, 16.76]; 30-34 years = 9.19 [95% CI = 7.65, 11.04]; 35-39 years: 4.53 [95% CI = 3.74, 5.48]) when compared to the reference age group (40-45 years).
- A significant difference in the incidence rate of therapeutic abortion (ICD-10 code O04; adjusted RR: 0.80; 95% CI = 0.65, 0.98; p-value: 0.031) and elective termination (ICD-10 code: O04, O05, O06, P96.4; adjusted RR: 0.74; 95% CI = 0.60, 0.90; p-value <0.01) was observed in females vaccinated with any dose of *Cervarix* compared to females who were not vaccinated with any HPV vaccine during pregnancy or within 60 days before pregnancy. There was a lower risk of therapeutic abortion (adjusted RR: 0.80) and elective termination (adjusted

RR: 0.74) in females vaccinated with any dose of *Cervarix* compared to females who were not vaccinated with any HPV vaccine during pregnancy or within 60 days before pregnancy.

- There was no significant difference in the incidence rate for other pregnancy outcomes in females vaccinated with any dose of *Cervarix* compared to females who were not vaccinated with any HPV vaccine during pregnancy or within 60 days before pregnancy.

Assessors comments

Performance of case identification method for the detection of pIMDs of interest and pregnancy outcomes of interest (Step 1)

Multiple algorithms were used for case identification of pIMDs and pregnancy outcomes. The algorithm's performance was evaluated in the pre-Cervarix launch period.

The performance of the algorithm was assessed based on evaluating the positive predictive value (PPV). For each endpoint, the PPV was calculated by determining the proportion of confirmed cases, based on medical records (considered the "gold" standard), among those identified as cases by the ICD-10-based algorithm. Only algorithms with a PPV of 70% or higher (indicating they correctly identify true cases at least 70% of the time) were included in further analyses.

The PPV was >70% for all algorithms for pIMDs of interest, except for algorithm 2 for Rheumatoid arthritis (66.67%). This was however based on a very small sample size, where the algorithm detected 3 cases while only 2 cases were confirmed using medical chart review and adjudication.

Both pregnancy outcomes of interest (Spontaneous Abortion and Live Infant Congenital Anomaly) have a PPV >70% for all algorithms.

Incidence of pIMDs and pregnancy outcomes during pre-Cervarix launch period (Step 2)

The incidence of neuroinflammatory disorders, vasculitis, musculoskeletal disorders, skin disorders, blood disorders, other pIMDs, liver disorders, gastrointestinal disorders, endocrine disorders, and kidney disorders during the pre-Cervarix launch period has been evaluated in total and per calendar year, both for females and males (who are included as a control group). In the pre-Cervarix launch period, the overall incidence density (per 100 000 PY) of all identifiable pIMDs was higher in females (2000.91 [95% CI = 1981.62, 2020.34]) than in males (1859.64 [95% CI: 1840.09, 1879.33]) in the pooled age group 9-45 years. Neuralgia and neuritis (unspecified), radiculopathy, neuritis, or radiculitis (ICD-10 code: M79.2 vs M54.1), reported the highest incidence both in females and males, followed by other spondylopathies (ICD-10 code: M48). The maximum number of cases were reported in the years 2015 and 2017, respectively. The maximum number of pIMDs were reported in the age group 35-39 years.

The most frequently reported pregnancy outcome during the pre-Cervarix launch period was single live birth normal infant (ICD-10 code: Z37.0) (783.98 per 1000 persons [95% CI: 775.86, 791.94]).

HPV and Cervarix vaccination uptake (Step 2)

The number of vaccinated participants considered in this analysis is slightly higher than the number of participants in the Vaccination Set as mentioned in the section 'Participants disposition' (20 499 participants vs. 20 370 participants). This is because the age group 9-45 years was calculated as the

sum of the number of participants in each age category separately. As some vaccinees received separate vaccination dose in different age categories, these participants are counted twice in the pooled age group. The difference is however limited and has no impact on data interpretation.

The overall HPV vaccination rate is rather low (67.68 per 1000 persons) and very low for participants vaccinated with Cervarix (11.95 per 1000 persons).

The HPV vaccination uptake rate is highest in the age group of 20-24 yoa (159.32 per 1000 persons). The second highest uptake rate is observed in the age group of 35-39 yoa (15.59 per 1000 persons), which is clearly lower. The lowest uptake rate is observed in the intermediate age group of 25-29 years (8.73 per 1000 persons), which is somewhat unexpected and the reason for this is unclear.

More than half of the HPV and Cervarix doses were administered in 2020. It is possible that a substantial number of participants received the vaccine close to the end of the post-Cervarix launch period. This could imply that some pregnancy outcomes or onset of pIMD possibly occurred after the end of the study. This could potentially result in an underestimation of the occurrence of pIMDs or specific pregnancy outcomes.

A substantial number of participants received an incomplete vaccination schedule with only one or two doses. For HPV vaccination overall, approximately half of the participants received three doses (n = 9393), while 5372 participants received one dose and 5477 participants received two doses. For Cervarix, only approximately 1/3th of the participants received a complete vaccination with 3 doses (n = 1171). The majority received only one dose (n = 1335) and 898 participants received two doses.

Incidence of identifiable most common pIMDs by vaccination strata (Step 4)

The incidence of most common pIMDs in females vaccinated with Cervarix (within 12 months after vaccination or with more than 12 months following vaccination) or in females who did not receive any HPV vaccination was evaluated during the entire study period (2010-2020). However, as it concerns females vaccinated with Cervarix, almost all will be vaccinated in the post-Cervarix launch period. Other spondylopathies (ICD-10 code: M48) was identified as the pIMD with highest incidence density and incidence rate, irrespective of vaccination status.

Other spondylophathies (ICD-10 code: M48) was also identified as the pIMD with highest incidence overall in the post-Cervarix launch period (refer to primary objective analysis).

Incidence rate of identifiable pregnancy outcomes by vaccination strata (Step 4)

The incidence rate of pregnancy outcomes was assessed in females who received Cervarix during or within 60 days before pregnancy, and those who did not. In both groups, live birth (ICD-10 code: Z37.0) showed the highest incidence rate (per 1000 [95% CI]) (406.32 [361.51; 528.21] vs. 573.23 [570.09; 584.88]).

Probability of occurrence of identifiable most common pIMDs within 12 months following Cervarix vaccination in vaccinated and unvaccinated participants, during the pre- and post-Cervarix launch period (Step 4)

The probability of common pIMDs associated with Cervarix vaccination was assessed over a 12-month risk window following vaccination using a multivariable regression model. Conditional analysis was done for identifiable pIMDs related to neuroinflammatory, musculoskeletal, and other pIMDs. Due to

low incidence, pIMDs related to vasculitis, skin, blood, liver, gastrointestinal, endocrine, and kidney disorders did not meet the sample size threshold for analysis.

Neuralgia and neuritis, unspecified (ICD-10 code: M79.2) and other neuroinflammatory disorders (neuralgia and neuritis [unspecified], radiculopathy, neuritis, or radiculitis; [ICD-10 code: M79.2 vs M54.1]), which were the pIMDs with with the highest incidence density in the pre-Cervarix launch period, did not show a difference in incidence density within 12 months following vaccination with Cervarix or not vaccinated with any HPV vaccine.

For several pIMDs, including other spondylopathies (ICD-10 code: M48; adjusted rate ratio [RR] = 1.92; 95% CI = 1.38, 2.68), Sarcoidosis (ICD-10 code: D86; adjusted RR = 2.81; 95% CI = 1.97, 4.01) and Sarcoidosis of lung (ICD-10 code: D86.0; adjusted RR = 5.15; 95% CI = 3.94), the incidence density was significantly higher in females vaccinated with any dose of Cervarix (within 12 months following vaccination) compared to females who were not vaccinated with any HPV vaccine. Of note, the observed higher incidence density for Sarcoidosis is mainly due to an increase in the cases of Sarcoidosis of the lung. It is important to consider that this difference might be related to varying healthcare-seeking behaviors between those who choose to get vaccinated against HPV and those who do not.

The incidence of sarcoidosis and lung sarcoidosis significantly increased from 2018 to 2020, both in females and males.

There was no increased risk over the age groups.

Probability of identifiable abnormal pregnancy outcomes following Cervarix vaccination in vaccinated and unvaccinated pregnant participants, during the pre- and post-Cervarix launch period (Step 4)

The probability of the identifiable pregnancy outcomes associated with Cervarix vaccination during pregnancy or within 60 days before pregnancy was evaluated using a multivariable regression model.

The incidence rate of live birth (ICD-10 code: Z37.0) was significantly higher in females vaccinated with any dose of Cervarix compared to females who were not vaccinated with any HPV vaccine. Highest incidence rates for live birth are observed in the age groups from 20-24 years and 25-29 years.

The risk of therapeutic abortion and elective termination is significantly lower in females who received any dose of Cervarix during or 60 days before pregnancy vs. HPV unvaccinated females (adjusted RR: 0.80 [95% CI = 0.65; 0.98 - p-value: 0.031] and 0.74 [95% CI = 0.60; 0.90 - p-value <0.01]), respectively.

For other pregnancy outcomes, no significant differences were observed.

2.3.3. Discussion on clinical aspects

Cervarix is an adjuvanted non-infectious recombinant vaccine developed by GlaxoSmithKline Biologicals SA (GSK). It is indicated for use in Europe from the age of 9 years for the prevention of premalignant anogenital lesions (cervical, vulvar, vaginal and anal) and cervical and anal cancers causally related to certain oncogenic Human Papillomavirus (HPV) types. It is approved in the European Union (EU) since 20 September 2007.

In China, Cervarix was approved by National Medical Products Administration (NMPA) in July 2016, for use in a 3-dose schedule at 0, 1, 6 months in females between 9 and 25 years of age, for the prevention of cervical cancer, cervical intraepithelial neoplasia grade 1 (CIN1), cervical intraepithelial

neoplasia grade 2, grade 3 (CIN 2/3) and adenocarcinoma in situ caused by high risk-human papillomavirus (HR-HPV) types 16 and 18. In May 2018, Cervarix was also approved for use in females up to 45 years of age.No information has been provided regarding the availability and recommendations for the use of other HPV vaccines (i.e. Gardasil and Gardasil 9), during the study period in China. To date no universal mass vaccination programs exist for HPV vaccination in China.

Study 212380 (EPI-HPV-096 VS CN DB PMS) is an observational, descriptive, retrospective, database study to monitor the safety-related endpoints prior to and following Cervarix launch, among female participants aged between 9 and 45 years, registered in the YRHIP from 01 January 2010 to 31 December 2020. The study was designed to address National Medical Products Administration (NMPA)'s request to evaluate Cervarix impact in China by collecting related information on immune-mediated diseases and pregnancy outcomes. The study is divided into 3 periods, a pre-Cervarix launch period (01 January 2012 to 31 December 2016), intermediate period and post-Cervarix launch period (01 January 2018 to 31 December 2020). As the number of HPV-vaccinated participants during the intermediate period was negligible, the MAH merged the data of these subjects with those from the pre-Cervarix launch period.

The study objectives are defined in 4 steps. The primary objective, step 3, is to assess the incidence of the identifiable most common pIMDs and pregnancy outcomes in females during the pre- and post-Cervarix-launch periods, by age and overall, per calendar year. The secondary objectives include the assessment of database performance on safety-related endpoints (Step 1); baseline analysis of Cervarix vaccine uptake and the indicende of pIMDs and pregnancy outcomes (Step 2); and assessment of the probability of occurrence of identifiable most common pIMDs and pregnancy outcomes in the 12 months following Cervarix vaccination, conditional on vaccine uptake and observed incidences (Step 4). To account for time confounding bias, incidence of pIMDs in male subjects aged 9-45 years during pre- and post-launch period, by age and overall, per calendar year are described.

In total data of 1 002 399 participants was extracted from the YRHIP database between 2010 and 2020. The Total Set, including all individuals aged between 9-45 yoa during the period from 01 January 2010 through 31 December 2020, who were registered for at least 12 months and had a least 2 or more observations recorded at 12 months or more apart, contains 891 463 participants. The Vaccination set, including participants who received at least one dose of any HPV vaccine, contains 20 370 participants, of which only a minority received Cervarix (n = 3547). The pIMD Set, including participants who were diagnosed with at least one pIMD, includes 83 894 participants. The Pregnancy Set includes in total 96 201 cases of pregnancy. The Sub-vaccination/pIMDs set includes 3395 participants and the Sub-vaccination/pregnancy outcome set includes 6573 participants. The number of participants in the Sub-vaccination/pIMDs set and Sub-vaccination/pregnancy outcome set that were vaccinated with Cervarix is not specified, but is expected to be low.

When evaluating the baseline data, the Total Set includes more females than males, with the highest number of participants in the 40-45 age group. Most participants were married and had primary or junior high school education, with the majority of participants reported in 2010. The Vaccination Set includes almost exclusively females below 35 years of age, with a higher-education levels and a lower marital status compared to the Total Set. The pIMD Set characteristics were similar to the Total Set, but with a slightly younger age distribution. The Pregnancy Set had higher education levels and similar marital status to the Total Set, with most participants reported in 2010. It is noted that the number of participants included in the YRHIP database varies significantly across different calendar years in all datasets. The reason for this variability is unclear.

Multiple algorithms were used to identify cases of pIMDs and pregnancy outcomes, with their performance evaluated in the pre-Cervarix launch period. Only algorithms with a Positive Predictive Value of 70% or higher were included in further analyses.

The primary analysis shows that the most common identified pIMD is different in the pre- and post-Cervarix lauch periods (in pre-Cervarix launch period: neuralgia and neuritis [unspecified], radiculopathy, neuritis, or radiculitis; ICD-10 code: M79.2 vs M54.1; in post-Cervarix launch period: other spondylopathies (ICD-10 code: M48)). However, in both periods, the pIMD identified with highest prevalence was the same both in females and males. This suggests that it is unlikely that the use of Cervarix or another HPV vaccine is related to this difference. Furthermore, incidence densities of several pIMDs seem to be very variable in different calendar years, suggesting there must be other factors that may relate to the occurrence of certain pIMDs. In particular for the years 2011, 2012 and 2013, in general low incidences of most pIMDs are observed. Overall, for most pIMDs, a higher incidence has been observed in females, which is not unexpected as immune mediated disorders are overall more prevalent in females.

The primary analysis related to pregnancy outcomes indicates that single live birth normal infant in 2012 was the pregnancy outcome with highest incidence in the pre-Cervarix launch period, while in the post-Cervarix launch period this was elective termination in 2019. It seems there has been an evolution in behaviour in China during the study period from 2012 to 2020 in relation to birth planning, towards very high rates of elective termination (up to approximately 50% and more) by the end of the study period.

As one of the secondary objectives, the probability of common pIMDs associated with Cervarix vaccination over a 12-month period was evaluated. Neuroinflammatory disorders, which were pIMDs with the highest incidence density in the pre-Cervarix launch period, showed no difference in incidence density post-vaccination. However, the incidence density of other spondylopathies and sarcoidosis, particularly lung sarcoidosis, was significantly higher in vaccinated females vs. unvaccinated. Sarcoidisis of the lung has been diagnoses in 55 out of 3076 vaccinated females (1.8%) vs. 2507 out of 765 927 unvaccinated females (0.3%). A significant increase in incidence was noted from 2018 to 2020 (both in females and males), with no increased risk across age groups. The worldwide incidence of sarcoidosis ranges from 1.0 to 35.5 cases in 100 000 per year[1], which is clearly lower than what has been observed in the current study.

The probability of abnormal pregnancy outcomes associated with Cervarix vaccination during pregnancy or within 60 days before pregnancy was evaluated as another secondary objective. The incidence rate of live births was found to be significantly higher in vaccinated females, especially in the 20-24 and 25-29 age groups. The risk of therapeutic abortion and elective termination was significantly lower in vaccinated females compared to unvaccinated ones. No significant differences were observed for other pregnancy outcomes.

However, data of this study must be interpreted very cautiously because there are many limitations.

One of the challenges is the geographic localization and the specific ethnic and racial composition of the Chinese population. These factors can influence the applicability of the study findings, as the safety profile observed in China may not be directly applicable to other regions with different demographic characteristics.

Another critical limitation is the low vaccine coverage. The HPV and Cervarix vaccination rate in China are very low (67.68 per 1000 persons for any HPV vaccine and 11.95 per 1000 persons for Cervarix). Furthermore, the follow-up period after vaccination in the study is short. The post-Cervarix launch period spans from 2018 to 2020, with more than half of the HPV and Cervarix doses only being

[1] Li CW, Tao RJ, Zou DF, et al. Pulmonary sarcoidosis with and without extrapulmonary involvement: a cross-sectional and observational study in China. BMJ open. 2018;8(2):e018865.

administered in 2020. Such a limited sample size hinders the ability to draw robust conclusions about the vaccine's safety.

The retrospective nature of the database study introduces inherent limitations. Retrospective studies rely on pre-existing data, which may not have been collected with the same rigor as prospective studies. This can result in information bias, in the current study particularly because the YRHIP database is new (accessible since 2009) and may not be performing optimally. Misclassification of conditions is a significant concern. This could have been one of the reasons why Sarcoidosis of lung was found to have a significantly higher incidence in HPV vaccinated females and in the later years of the study. Sarcoidosis of lung is diagnosed through exclusion and requires multiple tests to confirm definitively[2]. Therefore, there are doubts that the high number of cases are really confirmed Sarcoidosis of lung. The potential for misclassification can skew the study results and undermine the validity of the findings.

Selection bias is another issue, as the study population may not be representative of the general population. Health-seeking behaviour can vary widely, and individuals who choose to get vaccinated may differ systematically from those who do not. This can introduce bias and affect the observed safety outcomes.

Residual confounding factors are likely to exist but it is not be possible to address them adequately as supplemental appropriate data (such as socioeconomic status, comorbidities, lifestyle, individual susceptibility, environmental factors, etc) were not collected in the study. These unmeasured or unknown confounders can influence the results and lead to incorrect conclusions about the vaccine's safety. Without comprehensive data on all potential confounders, the study findings remain uncertain.

Due to these limitations, the reliability of the data is questionable. Therefore, based on this study, no definitive conclusions can be made regarding the safety aspects of Cervarix.

Because of the many limitations of the study, it is agreed with the MAH that results of study EPI-HPV-096 VS CN DB PMS (212380) do not impact the PI for Cervarix and no update of the SmPC is needed.

3. CHMP overall conclusion and recommendation

Taking into account all limitations, the databased registry results of this study imply caution in the interpretation of the findings and preclude any robust conclusions. No changes to the SmPC for *Cervarix* are considered necessary.

☒ Fulfilled:

No regulatory action required.

[2] Bernardinello, N.; Petrarulo, S.; Balestro, E.; Cocconcelli, E.; Veltkamp, M.; Spagnolo, P. Pulmonary Sarcoidosis: Diagnosis and Differential Diagnosis. Diagnostics 2021, 11, 1558