PASS INFORMATION

Title:	An observational, retrospective database post-authorisation safety study (PASS) to assess trends and changes over time in incidence of anal cancer and feasibility for a case-control study in European countries that introduced *Cervarix* in their National Immunisation Programmes (NIP)
Protocol version identifier:	217743 (EPI-HPV-099 VS EUR DB)
Date of last version of the protocol:	Protocol Amendment 2 Final: 25 May 2022
EU PAS Register No:	To be determined
Active substance:	HPV-16 L1 VLP protein HPV-18 L1 VLP protein
Medicinal product:	Bivalent human papillomavirus (HPV-16/18 L1 VLP AS04) recombinant vaccine
Product reference:	EMEA/H/C/000721
Procedure number:	To be allocated
Marketing Authorisation Holder (MAH):	GlaxoSmithKline Biologicals SA Rue de l'Institut, 89 1330 Rixensart, Belgium
Joint PASS:	No
Research question and objectives: **(Amended 25 May 2022)**	To assess trends and changes over time in incidence of anal cancer using data reported to the national cancer registries in Finland, the Netherlands, England, Denmark, and Norway and to carry out an assessment of feasibility to conduct a case-control study in any of these 5 European countries, aiming to determine the impact and effectiveness of *Cervarix* against anal cancer in females and males
Countries of study:	Finland, the Netherlands, England, Denmark, and Norway
Author:	PPD , Epidemiology Lead, GlaxoSmithKline Biologicals SA

MARKETING AUTHORISATION HOLDER

MAH:	GlaxoSmithKline Biologicals SA Rue de l'Institut, 89 1330 Rixensart, Belgium
MAH contact person: **(Amended 25 May 2022)**	PPD **,** ***MD*** ***Clinical & Epidemiology Project Lead*** ***GlaxoSmithKline Biologicals SA***

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2. LIST OF ABBREVIATIONS

AIN	Anal intraepithelial neoplasia
APC	Annual percentage change
CI	Confidence interval
DNA	Deoxyribonucleic acid
EMA	European Medicines Agency
EU-RMP	European Union Risk Management Plan
GPP	Good Pharmacoepidemiology Practices
GSK	GlaxoSmithKline Biologicals SA
HIV	Human immunodeficiency virus
HPV	Human papilloma virus
IACR	International Association of Cancer Registries
ICD	International Classification of Diseases
MAH	Marketing Authorisation Holder
MPL	3-*O*-desacyl-4'-monophosphoryl lipid A
MSM	Men who have sex with men
NCR	Netherlands Cancer Registry
NCRAS	National Cancer Registration and Analysis Service
NIP	National Immunisation Programme
PASS	Post-authorisation safety study
PHE	Public Health England
SCC	Squamous cell carcinoma
TSS	Targeted safety study
UK	United Kingdom
VE	Vaccine effectiveness
VLP	Virus-like particle
WHO	World Health Organisation

3. RESPONSIBLE PARTIES

(Amended 25 May 2022)

Biologicals SA (GSK) has the overall responsibility for the conduct of the study.

PPD **, *MD, Clinical & Epidemiology Project Lead, GlaxoSmithKline Biologicals SA.***

4. ABSTRACT

Title	An observational, retrospective database post-authorisation safety study (PASS) to assess trends and changes over time in incidence of anal cancer and feasibility for a case-control study in European countries that introduced *Cervarix* in their National Immunisation Programmes (NIP).
Version and date of the protocol	Protocol Amendment 2 Final: 25 May 2022
Main author	PPD, Epidemiology Lead, GlaxoSmithKline Biologicals SA
Rationale and background	Anal cancer is an uncommon type of cancer, representing around 0.3% of all incident cancers diagnosed in 2020 worldwide [Sung, 2021]. Squamous cell carcinoma (SCC) is the most frequent histopathological type of anal cancer [Hoff, 2017]. There is evidence to suggest that human papillomavirus (HPV) infection is associated with anal cancer, particularly with SCC [Hoff, 2017; De Martel, 2020]. Moreover, in a recent worldwide study, HPV deoxyribonucleic acid (DNA) was detected in more than 88% of anal cancers and more than 95% of anal intraepithelial neoplasia (AIN) grades 2/3. The most frequently detected virus type, detected in over 80.7% of invasive anal cancer cases was HPV-16,followed by HPV-18 (3.6% of cases) [Alemany, 2015; Clifford, 2019]. Over the last 4 decades, anal cancer incidence has been gradually increasing and is more common in women than in men, except for certain high-risk groups such as human immunodeficiency virus (HIV)-infected people, and this raise is more relevant in high-income countries [Lum, 2020]. Risk factors for anal cancer are HPV infection, including a former HPV-related malignancy, HIV infection, more than 10 lifetime sexual partners, ano-receptive intercourse, chronic immunosuppression, cigarette smoking, a history of gynaecological or haematologic malignancy, and age. Hence, HIV and immunocompromised patients, and men who have sex with men (MSM) are particularly vulnerable populations [Nelson, 2017; Van der Zee, 2013; Clifford, 2021]. GlaxoSmithKline Biologicals SA (GSK) has developed a prophylactic HPV vaccine, *Cervarix*, based on L1 proteins of HPV-16 and HPV-18 formulated with AS04

(comprising of aluminium hydroxide [Al(OH)3] and 3-O-desacyl-4'-monophosphoryl lipid A [MPL]).

Cervarix is a vaccine for use 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 HPV types.

In the context of the European Union Risk Management Plan (EU-RMP) for *Cervarix*, a safety concern was raised linked to missing information on the impact and effectiveness of the vaccine against anal lesions and cancer, since it was not prospectively evaluated in clinical trials.

This study will assess the data on anal cancer in countries where *Cervarix* vaccination has been introduced in the NIP. Five European countries were initially preselected: Finland, the Netherlands, England, Denmark, and Norway to perform a trend analysis and to assess feasibility for a case-control study.

Research question and objectives

(Amended 25 May 2022)

The aim of this PASS is to assess trends and changes over time in incidence of anal cancer using data reported to the national cancer registries in Finland, the Netherlands, England, Denmark, and Norway and to carry out an assessment of feasibility to conduct a case-control study in any of these 5 European countries, aiming to determine the impact and effectiveness of *Cervarix* against anal cancer in females and males.

Primary Objectives:

- To assess trends and changes over time in the age-standardised incidence of anal cancer by sex, HPV type and histological classification for each country* separately.
- To assess trends and changes over time in the crude incidence of anal cancer by age category, by sex, HPV type and histological classification for each country* separately.

Secondary Objective:

- To conduct a feasibility assessment for a case-control study to determine the effectiveness of *Cervarix* against anal cancer.

**Five European countries are considered for this study, and each country will be selected based on a set of criteria (please refer to Section 9.2 for country eligibility criteria).*

Study design

(Amended 25 May 2022)

- **Type of study and design**: This is a Targeted Safety Study (TSS) and a PASS. The study is designed as an observational, retrospective database study.
- **Study population**: Females and males of all age groups in the 5 selected European countries.

  Please refer to Section 9.2 for country eligibility criteria.
- **Data collection**: Retrospective data collection from national cancer registries.
- **Study period**:
  - Pre-*Cervarix* launch period (i.e., before *Cervarix* introduction in the NIP): The start and end calendar year for each country will be considered based on the data availability in their respective cancer registries.
  - Post-*Cervarix* launch period (i.e., after *Cervarix* introduction in the NIP): The start calendar year for each country will be the date when *Cervarix* was introduced in their NIP. An interim analysis will be performed in 2022. For ***the*** analysis, data up to the most recent and complete available calendar year in each cancer registry will be considered.
- This study will be a trend analysis of incidence of anal cancer in 5 selected European countries.
- The feasibility assessment for a case-control study will be conducted considering the 5 selected European countries that are approached for the trend analysis. The interaction with the national cancer registries will provide insights on the population and setting, the exposure (HPV vaccination), and the outcome (anal cancer). This exercise is intended to facilitate the understanding whether this case-control study to determine *Cervarix* effectiveness against anal cancer can be performed.
- Additionally, as negative control to detect potential bias due to changes in the surveillance and reporting systems, data of small intestine cancer in the same population will be analysed. Small intestine cancer is relatively rare, with an occurrence of similar magnitude to anal cancer.

Small intestine cancer also has a similar mean age of diagnosis as anal cancer, and there is no screening programme for it. It is not associated with HPV infection. This analysis may allow to control for potential changes in cancer surveillance systems and reporting over time.

Population

The study population will include females and males of all age groups in the 5 selected European countries.

Please refer to Section 9.2 for country eligibility criteria.

Variables

(Amended 25 May 2022)

Primary endpoint:

- Occurrence and age-standardised incidence of anal cancer during the period (i.e., pre- and post-*Cervarix* launch period) by sex, HPV type and histological classification for each country* separately.
- Occurrence and crude incidence of anal cancer during the study period (i.e., pre- and post-*Cervarix* launch period) by age category, by sex, HPV type and histological classification for each country* separately.

Note: Additionally, as negative control to detect potential bias due to changes in the surveillance and reporting systems, data of small intestine cancer in the same population will be analysed, by age category and sex for each country* separately.

Please refer to Section 7 for details on choice of control.

Secondary endpoint:

- ***Expected number of anal cancer cases needed to conduct the case-control study based on the vaccine coverage rate and the expected VE and other factors for each country* separately.***

Note: Other feasibility assessment checks with findings for the conduct of a case-control study will be further described in the study report.

**Five European countries are considered for this study and each country will be selected based on a set of criteria (please refer to Section 9.2 for country eligibility criteria).*

Data sources

(Amended 25 May 2022)

- Eurostat will be the source for data on the European Standard Population for age distribution used to estimate the age-standardised incidence rates [Pace, 2013]. It will also be the source for the population data and birth cohort data, except for England, for which the source for population data will be the UK Health Security Agency and for birth cohort data it will be Office for National Statistics.
- Vaccine coverage data will be retrieved from the respective websites of national public health institutes.
- This study will collect anal cancer data from the following national cancer registries:
  - The Finnish Cancer Registry [FCR]
  - The Netherlands Cancer Registry [NCR]
  - National Cancer Registration and Analysis Service [NCRAS] ***(UK)***
  - The Danish Cancer Registry [Danish Cancer Registry]
  - The Cancer Registry of Norway [CRN]
- ***Vaccination registries:***
  - ***Finnish National Vaccination Registry since 2009***
  - ***Dutch vaccination registry (Prœventis) since 2005***
  - ***Immunisations are registered in Child Health Information Systems (school-based vaccinations from school nurses, including HPV, reorganised as of 2002) (UK)***
  - ***Danish vaccination registry since 2009, although compulsory as of 15 November 2015***
  - ***Norwegian vaccination registry since 1995***

Note: More details on vaccine coverage data and data collection are provided in Section 9.4.

Study size **(Amended 25 May 2022)**	Sample size computation ***for the primary objective*** is not applicable, as there is no *a priori* hypothesis to be tested. Only aggregated data reported in the national cancer registries of the 5 selected European countries will be collected within the established timeframe. Please refer to Section 9.3 for details on variables and Section 9.4 for details on data sources. *Note: National cancer registries are nationwide and thus this study is population-based.*
Data analysis	Analysis will be performed using the country-specific data extracted from the national cancer registries as per defined population and timeframe (please refer to Section 9.1.1 for details on study population and study period). *Note: Details on primary analysis and secondary analysis are provided in Section 9.7.*
Milestones	The first round of data collection is planned to start in Quarter 3, 2021 and end in Quarter 4, 2021. The second round of data collection is planned to start in Quarter 3, 2026 and end in Quarter 4, 2026. The interim report is planned for Quarter 1, 2022. The final report of study results is planned for Quarter 1, 2027. *Note*: *The above-mentioned timelines are tentative and are subject to change*.

5. AMENDMENTS AND UPDATES

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
1	31 March 2022	Section 4 Abstract, Section 8 Primary objective and Section 9.3.1.1 Primary endpoint	Primary objective and its corresponding endpoint updated	For clarity: The primary objective and its corresponding endpoint has been split into 2 independent objectives and endpoints, respectively (i.e., for age-standardised incidence and for crude incidence)
		Section 4 Abstract and Section 9.1.1 Discussion of study design	Study population updated	For better interpretation of the study results so it can be comparable with publications across countries and to align with the age definition as per the European standardised population, the entire age group from 0 – 80+ population will be considered instead of the adult population (>18 years of age)
		Section 4 Abstract and Section 9.1.1 Discussion of study design	Study population updated	Study period (i.e., pre- and post-*Cervarix* launch period) will be considered based on the *Cervarix* introduction in the National Immunisation Programme (NIP)
		Section 4 Abstract, Section 7 Rationale and background, Section 8 Research question and objectives, Section 9.4.3 Websites of national public health institutes and Section 9.9 Limitations of the research methods	County specified: Changed from United Kingdom (UK) to England	For the UK, all analyses will be based specifically on data from England, and not data from UK. The National Cancer Registration and Analysis Service (NCRAS) is the cancer registry in England. As the population of England comprises around 84% of the total UK population, the NCRAS is considered to be representative of the population in the UK
		Section 9.7.2.1 Primary analysis	Inclusion of Poisson / Negative binomial regression model for pre- and post-*Cervarix* launch periods	The trend in the incidence of anal cancer and small intestine cancer will be assessed using the Poisson / Negative binomial regression model. The model will include number of anal cancer/small intestine cancer incidences as outcome variable and calendar year as the independent variables. The model will include the population followed up as the offset variable. APC will be

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
				estimated based on the parameter estimates of the regression model. The same model will be generated for the pre- and post-*Cervarix* launch periods separately
		Section 4 Abstract and Section 9.4.3 Eurostat	Data source updated	Eurostat will be the source for population data and birth cohort data, except for England, for which the source for population data will be UK Health Security Agency and for birth cohort data it will be Office for National Statistics
		Section 9.7.2 Statistical analysis	Updated to clarify HPV type and histological classification assessment	A sentence has been added to clarify HPV type and histological classification assessment
		Title page, Section 3 Responsible parties and Section 4 Abstract	Sponsor signatory updated	Change in the study team
2	25 May 2022	Section 4 Abstract, Section 8.2 Secondary objective and Section 9.3.1.2 Secondary endpoint	Secondary objective and its corresponding endpoint updated	• The feasibility assessment for a case-control study to determine the effectiveness of *Cervarix* will be conducted only against anal cancer. The data for anal lesions is not available in the cancer registries • Expected number of anal cancer cases is the endpoint which can be used to estimate the time frame by when the estimated sample size for a case-control study would be reached
		Section 9.1.2 Feasibility assessment	Feasibility assessment updated	Additional information added for clarity
		Section 4 Abstract, Section 9.4 Data sources	Data sources updated	Vaccination registry for each of the 5 selected European countries was added
		Section 9.7.2.2 Secondary analysis	Secondary analysis updated	Additional information added for clarity
		Section 9.9 Strengths and limitations of the research methods	Updated to add the strengths of the study	Additional points on strengths of the study included
		Title page and Section 3 Responsible parties	Marketing Authorisation Holder (MAH) contact person updated	The sponsor signatory should be the MAH contact person

The summary of the amendment is provided in Annex 5.

6. MILESTONES

Note: The timelines mentioned below are tentative and are subject to change.

Milestone	Planned date
Start of first round data collection	Quarter 3, 2021
End of first round data collection	Quarter 4, 2021
Interim report 1	Quarter 1, 2022
Start of second round data collection	Quarter 3, 2026
End of second round data collection	Quarter 4, 2026
Registration in the EU PAS register	To be determined
Final report of study results	Quarter 1, 2027

7. RATIONALE AND BACKGROUND

Cervarix is a prophylactic HPV vaccine developed by GSK. It is based on the L1 proteins of HPV-16 and HPV-18 formulated with AS04 (comprising of aluminium hydroxide [$Al(OH)_3$] and 3-*O*-desacyl-4'-monophosphoryl lipid A), indicated for use 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 HPV types [*Cervarix* Summary of Product Characteristics, 2020].

In the context of the EU-RMP for *Cervarix*, a safety concern was raised linked to missing information on the impact and effectiveness of the vaccine against anal lesions and cancer, since it was not prospectively evaluated in clinical trials.

Anal cancer is an uncommon type of cancer, representing around 0.3% of all incident cancers diagnosed in 2020 worldwide [Sung, 2021]. SCC is the most frequent histopathological type of anal cancer [Hoff, 2017]. There is evidence to suggest that HPV infection is associated with anal cancer, particularly with SCC [Hoff, 2017; De Martel, 2020]. Moreover, in a recent worldwide study, HPV DNA was detected in more than 88% of anal cancers and more than 95% of anal AIN grades 2/3. The most frequently detected virus type, detected in over 80.7% of invasive anal cancer cases was HPV-16, followed by HPV-18 (3.6% of cases) [Alemany, 2015; Clifford, 2019]. Over the last 4 decades, anal cancer incidence has been gradually increasing and is more common in women than in men, except for certain high-risk groups such as HIV-infected people, and this raise is more relevant in high-income countries [Lum, 2020]. Risk factors for anal cancer are HPV infection, including a former HPV-related malignancy, HIV infection, more than 10 lifetime sexual partners, ano-receptive intercourse, chronic immunosuppression, cigarette smoking, a history of gynaecological or haematologic malignancy, and age. Hence, HIV and immunocompromised patients, and MSM are particularly vulnerable populations [Nelson, 2017; Van der Zee, 2013; Clifford, 2021].

An observational study of effectiveness of *Cervarix* against HPV anal positivity in Dutch women showed a pooled vaccine effectiveness of approximately 90% for HPV-16/18 [Woestenberg, 2020], with adjusted VEs of 88.2% (95% confidence interval [CI],

41.3%– 97.6%) against anal HPV-16 and 91.9% (95% CI, 30.5%–99.1%) against anal HPV-18 [Woestenberg, 2020]. The results also demonstrated cross-protection against anal HPV-45 and HPV-31 and a high correlation between anal and cervicovaginal VE. The results support the notion that *Cervarix* may offer protection against HPV-related anal cancer (including cross-protection against HPV-31/33/45) [Clifford, 2019].

Population-based cancer registries are platforms that collect, store, validate and analyse data on incidence and survival of the most relevant types of cancer and are crucial for the planning and evaluation of prevention activities. For instance, the World Health Organisation (WHO) global initiative to eliminate cervical cancer points to sound surveillance and monitoring systems as crucial to monitor the evolution of cervical cancer incidence and the impact of interventions over time [WHO; Piñeros, 2021].

This study will assess the data on anal cancer in countries where *Cervarix* vaccination has been introduced in the NIP. Five European countries were initially preselected: Finland, the Netherlands, England, Denmark, and Norway to perform a trend analysis and to assess feasibility for a case-control study.

Additionally, as negative control to detect potential bias due to changes in the surveillance and reporting systems, data of small intestine cancer in the same population will be analysed. Small intestine cancer is relatively rare, with an occurrence of similar magnitude to anal cancer. Small intestine cancer also has a similar mean age of diagnosis as anal cancer, and there is no screening programme for it. It is not associated with HPV infection. This analysis may allow to control for potential changes in cancer surveillance systems and reporting over time.

8. RESEARCH QUESTION AND OBJECTIVES

(Amended 25 May 2022)

The aim of this PASS is to assess trends and changes over time in incidence of anal cancer using data reported to the national cancer registries in Finland, the Netherlands, England, Denmark, and Norway and to carry out an assessment of feasibility to conduct a case-control study in any of these 5 European countries aiming to determine the impact and effectiveness of *Cervarix* against anal cancer in females and males.

Please refer to Section 6 for details on study milestones.

8.1. Primary objectives

- To assess trends and changes over time in the age-standardised incidence of anal cancer by sex, HPV type and histological classification for each country* separately.
- To assess trends and changes over time in the crude incidence of anal cancer by age category, by sex, HPV type and histological classification for each country* separately.

8.2. Secondary objective

(Amended 25 May 2022)

- To conduct a feasibility assessment for a case-control study to determine the effectiveness of *Cervarix* against anal cancer.

**Five European countries are considered for this study and each country will be selected based on a set of criteria (please refer to Section 9.2 for country eligibility criteria).*

9. RESEARCH METHODS

9.1. Study design

9.1.1. Discussion of study design

- Type of study and design: This is a TSS and a PASS. The study is designed as an observational, retrospective database study.
- Study population: Females and males of all age groups in the 5 selected European countries.

Please refer to Section 9.2 for country eligibility criteria.

- Data collection: Retrospective data collection from national cancer registries ***and national vaccination registries***.
- Study period:
  - Pre-*Cervarix* launch period (i.e., before *Cervarix* introduction in the NIP): The start and end calendar year for each country will be considered based on the data availability in their respective cancer registries.
  - Post-*Cervarix* launch period (i.e., after *Cervarix* introduction in the NIP): The start calendar year for each country will be the date when *Cervarix* was introduced in their NIP. An interim analysis will be performed in 2022. For ***the*** analysis, data up to the most recent and complete available calendar year in each cancer registry will be considered.
- This study will be a trend analysis of incidence of anal cancer in 5 selected European countries.
- Additionally, as negative control to detect potential bias due to changes in the surveillance and reporting systems, data of small intestine cancer in the same population will be analysed. Small intestine cancer is relatively rare, with an occurrence of similar magnitude to anal cancer. Small intestine cancer also has a similar mean age of diagnosis as anal cancer, and there is no screening programme for it. It is not associated with HPV infection. This analysis may allow to control for potential changes in cancer surveillance systems and reporting over time.

9.1.2. Feasibility assessment

(Amended 25 May 2022)

As mentioned above , the objectives of the feasibility assessment are:

- ***To describe the main requirements for the conduct of an additional study assessing the effectiveness of Cervarix in the prevention of anal cancer***
- ***To assess a case-control study design and the data sources that would meet those requirements.***

The feasibility assessment for a case-control study will be conducted considering the 5 selected European countries that are approached for the trend analysis. The interaction with the national cancer registries ***and national vaccination registries*** will provide insights on the population and setting, the exposure (HPV vaccination), and the outcome (anal cancer). This exercise is intended to facilitate the understanding whether this case-control study to determine ***Cervarix*** effectiveness against anal cancer can be performed.

9.1.3. Case definition

In this study, for case identification of anal cancer and small intestine cancer, [International Classification of Diseases (ICD)-10] codes will be used.

For histological classification of anal cancer, the WHO ICD-O-2 (or) 3 will be used based on the coding version of the cancer registries in the selected countries.

9.2. Setting

The following country eligibility criteria should be checked in order to perform analysis:

- Should have a stable, consolidated and validated cancer registry.
- The cancer registry should preferably be population-based and nationwide.
- Administration of *Cervarix* for at least 5 birth cohorts (either routine or catch-up campaign cohorts) within the NIP.

9.3. Variables

(Amended 25 May 2022)

The following variables will be assessed for each country separately:

- Incidence of anal cancer by age category, by sex, by HPV type (if available), by histological classification (if available) and by calendar year.
- Number of anal cancer cases by age category, by sex, by HPV type (if available), by histological classification (if available) and by calendar year.
- Incidence of small intestine cancer by age category, by sex and by calendar year.
- Number of small intestine cancer cases by age category, by sex and by calendar year.

- Population data by age category, by sex and by calendar year.
- Birth cohort data, by sex and by calendar year.
- HPV vaccine coverage of the eligible birth cohorts by calendar year and by age category and by sex if possible.

9.3.1. Endpoints

9.3.1.1. Primary endpoints

(Amended 25 May 2022)

- Occurrence and age-standardised incidence of anal cancer during the study period (i.e., pre- and post- *Cervarix* launch period) by sex, HPV type and histological classification for each country* separately.
- Occurrence and crude incidence of anal cancer during the study period (i.e., pre- and post-*Cervarix* launch period) by age category, by sex, HPV type and histological classification for each country* separately.

Note: Additionally, as negative control to detect potential bias due to changes in the surveillance and reporting systems, data of small intestine cancer in the same population will be analysed by age category and sex for each country* separately.

Please refer to Section 7 for details on choice of control.

9.3.1.2. Secondary endpoint

(Amended 25 May 2022)

- ***Expected number of anal cancer cases needed to conduct the case-control study based on the vaccine coverage rate and the expected VE and other factors for each country* separately.***

Note: Other feasibility assessment checks with findings for the conduct of a case-control study will be further described in the study report.

**Five European countries are considered for this study and each country will be selected based on a set of criteria (please refer to Section 9.2 or country eligibility criteria).*

9.4. Data sources

(Amended 25 May 2022)

9.4.1. National cancer registries

This study will collect anal cancer data from the following national cancer registries:

- The Finnish Cancer Registry [FCR]:

The Cancer Registry of the National Institute for Health and Welfare maintained by the Finnish Cancer Society, contains data on all cancer cases and suspected cancer cases detected in Finland. The health care organisations in Finland are obliged to report this information. The registry holds data on anal cancer cases reported from 1953 to 2019. The reporting of cancer cases has been mandatory since 1961 [International Association of Cancer Registries (IACR)].

Information on cancer cases (from hospitals, physicians, pathology laboratories, and death certificates) are available from Statistics Finland. In order to ensure correctness of data, the notifiers are requested to check accuracy of information about primary site, patient identity, and date of diagnosis. A physician oversees or performs coding. Since 1967, Finland is using personal identification numbers for identification of cases. This allows for accurate follow-up of patients (including death) through official sources. Formal evaluations are also conducted in addition to the continuous quality control procedures [IACR].

FCR data is subjected to computerised checks for validity and internal consistency. Comparability of data is ensured by following the ICD-O-3 introduced in 2007, and earlier codes were converted to ICD-O-3. The completeness of the FCR for all sites was estimated at 95% (96% for solid tumours and 86% for non-solid tumours). The FCR publishes annual statistics with a delay of approximately 2 years. This is due to a latency of one full calendar year for submitting cancer data for registration and having access to data on causes of death [Leinonen, 2017].

- The Netherlands Cancer Registry [NCR]:

NCR is a population-based cancer registry with nationwide coverage since 1989. Cancer diagnoses are notified by the nationwide network and registry of histology and cytopathology (PALGA) and in addition through linkage with the Landelijke Medische Registratie hosted by Dutch Hospital Data. Each cancer case is coded by trained registration clerks (internal education of 1 year) according to ICD-O-3 based on information gathered from medical files at the hospital. Date of diagnosis is coded according to international coding rules and mostly based on the date of first pathological confirmation, or if unavailable, date of first hospital admission [Van der Willik, 2020].

The database is managed by the Netherlands Comprehensive Cancer Organisation (IKNL). NCR is the only oncological hospital registry in the Netherlands with data on all cancer patients. Data on incidence, prevalence, survival, mortality and risk are included in the website and are available at a national level from 1989 to 2020. However, data available for 2019 and 2020 are provisional.

- National Cancer Registration and Analysis Service ***(UK)*** [NCRAS]:

NCRAS is managed by Public Health England (PHE) and captures a wide range of data sources, including data such as: histopathology and haematology services, medical records, radiotherapy departments, hospices, independent hospitals, screening services, death certificates, general practitioners, other UK cancer registries. The registry holds data on anal cancer from 1993 to ***2018***. The final registrations are released approximately 1 year following the end of a diagnosis year, but it can take up to 5 years to achieve 100% completeness [Henson, 2020].

Each year, NCRAS collects data on over 300 000 cases of cancer, which includes patient details (i.e., their name, age, address sex, and date of birth etc), and also data about the type of cancer, how advanced it is and the treatment the patient receives.

In order to allow contemporaneous, comprehensive and cost-effective data collection and to ensure quality assurance, the registry obtains data from across the National Health Service. The data quality in term of validity, completeness, timeliness etc. is assessed. Quality checks are performed both at the level of individual records as well as at the level of the registry. In addition, records are validated against other records and against expected values [Henson, 2020].

- The Danish Cancer Registry [Danish Cancer Registry]:

The Danish Cancer Registry was founded in 1942 and contains data of the incidence of cancer among the Danish population from 1943 to 2019. The purpose of the cancer registry is to collect and process data on new cases of cancer, in order to produce statistics on the incidence and prevalence of cancer in Denmark, to provide information for the planning of the Danish health services, and to provide a basis for research into the causes of cancer and the course of cancer diseases. Reporting to the cancer registry has been mandatory since 1987. From 2004 to 2008 it underwent a process of modernisation. As a result, the reporting became electronic through integration of patient administrative systems and the manual coding was partly replaced by an automatic coding logic.

The Danish cancer registry has been repeatedly validated for data quality (validity and completeness). Internal validation for lung and breast cancer detected low proportions of errors or missing reports. Moreover, the automated registration ensures high quality and data completeness. Continued improvements following validation studies are implemented [Validation of The Danish Cancer Registry and selected Clinical Cancer Databases; Lund, 2013].

- The Cancer Registry of Norway [CRN]:

The Cancer Registry of Norway was established in 1951 and includes data on anal cancer from 1953 to 2019. It is organised as an independent institution under the Oslo University Hospital Trust. Annual data on cancer are published in the *Cancer in Norway* report. Cancer statistics of Norway from 2019 were published in October 2020 [Cancer in Norway, 2019]. Suspected cancer cases (without a verified cancer diagnosis), and cancer first diagnosed by autopsy, need to be mandatorily notified. The cancer registry is in charge for the national screening programmes: Breast Cancer Screening Programme and Cervical Cancer Screening Programme. The cancer registry regulations demands the

following 3 main objectives for the cancer registry: registration, research and information.

In Norway, population-based data with high-quality cancer incidence are favourable. Such data requires mandatory reporting, unique personal identification numbers and more than 50 years of experience in cancer registration [Larsen, 2009].

A study of the data quality at the Cancer Registry of Norway showed that data from the registry are reasonably accurate, and that completeness (close-to-completeness) and timely reporting is among the best in Europe [Larsen, 2009].

9.4.2. Vaccination registries

Country	*Vaccination registry*
Finland	*Finnish National Vaccination Registry since 2009*
The Netherlands	*Dutch vaccination registry (Præventis) since 2005*
England	*Immunisations are registered in the Child Health Information Systems (school-based vaccinations from school nurses, including HPV, reorganised as of 2002)*
Denmark	*Danish vaccination registry since 2009, although compulsory as of 15 November 2015 (UK)*
Norway	*Norwegian vaccination registry since 1995*

9.4.3. Eurostat

Eurostat will be the source for data on the European Standard Population for age distribution used to estimate the age-standardised incidence rates [Pace, 2013]. It will also be the source for population data and birth cohort data**,** except for England, for which the source for population data will be UK Health Security Agency and for birth cohort data it will be Office for National Statistics.

9.4.4. Websites of national public health institutes

- Vaccine coverage data will be retrieved from the respective websites of national public health institutes:
  - Finland
  - The Netherlands
  - England
  - Denmark
  - Norway

Please refer to Annex 4 for details on vaccination schedules and vaccine coverage in the selected 5 European countries.

9.5. Study size

(Amended 25 May 2022)

Sample size computation ***for the primary objective*** is not applicable, as there is no *a priori* hypothesis to be tested. Only aggregated data reported in the national cancer registries of the 5 selected European countries will be collected within the established timeframe.

Please refer to Section 9.3 for details on variables and Section 9.4 for details on data sources.

Note: National cancer registries are nationwide and thus this study is population-based.

9.6. Data management

9.6.1. Data collection

Please refer to Section 9.3 for details on study variables and Section 9.4 for details on study data sources.

9.7. Data analysis

9.7.1. Analysis set

The country-specific data extracted from the national cancer registries as per defined population and timeframe.

Please refer to Section 9.1.1 for details on study population and study period.

9.7.2. Statistical Analysis

All analyses will be performed for each country separately. The analysis planned by HPV type and histological classification will be performed based on the data availability during the time of the analysis.

9.7.2.1. Primary analysis

(Amended 25 May 2022)

To assess trends and changes over time in incidence of anal cancer by age category and by sex.

- Age-standardised incidence with 95% CI during the period from 1992 until the most recent and complete available calendar year in the cancer registries (i.e., during pre- and post- *Cervarix* launch period) will be presented by sex.

Note: Age-standardised incidence rates of anal cancer will be calculated by calendar year and sex using the European Standard Population (age distribution).

Additionally,

- Crude incidence with 95% CI during the period from 1992 until the most recent and complete available calendar year in the cancer registries (i.e., during pre- and post-*Cervarix* launch period) will be presented by age category, sex, HPV type and histological classification.
- The trend in the incidence of anal cancer will be assessed using the Poisson / Negative binomial regression model. The model will include number of anal cancer incidences as outcome variable and calendar year as the independent variables. The model will include the population followed up as the offset variable. Annual Percentage Change (APC) will be estimated based on the parameter estimates of the regression model.
  The same model will be generated for the pre- and post-*Cervarix* launch periods separately.
- The trend in the incidence of anal cancer will be assessed using the Poisson / Negative binomial regression model. The model will include number of anal cancer incidences as outcome variable; calendar year, age category, study period (pre-launch = 0 and post-launch = 1), HPV type and sex as the independent variables (risk factors). The model will include the population followed up as the offset variable. Similar analysis will be performed by subcategories – age category, sex, HPV type and histological classification.
- Observed and predicted counts of the anal cancer cases will be presented by calendar year. Predicted counts of the anal cancer cases will be estimated using the Poisson / Negative binomial regression univariate model with number of anal cancer cases as the outcome variable and year as the independent variable on the pre-vaccination data.
  Percentage reduction of the anal cancer cases in the observed counts compared to the predicted will be presented with its Wald's 95% CI.
  Similar analysis will be performed by subcategories – age category, sex, HPV type and histological classification.

Analysis for negative control:

- Age-standardised incidence with 95% CI of small intestine cancer during the period from 1992 until the most recent and complete available calendar year in the cancer registries (i.e., during pre- and post- *Cervarix* launch period) will be presented by age category and sex.

Note: Age-standardised incidence rates of small intestine cancer will be calculated by calendar year and sex using the European Standard Population (age distribution).

- Crude incidence with 95% CI of small intestine cancer during the period from 1992 until the most recent and complete available calendar year in the cancer registries (i.e., during pre- and post- *Cervarix* launch period) will be presented by age category, sex.

- The trend in the incidence of small intestine cancer will be assessed using the Poisson / Negative binomial regression model. The model will include number of small intestine cancer incidences as outcome variable and calendar year as the independent variables. The model will include the population followed up as the offset variable. APC will be estimated based on the parameter estimates of the regression model.
  The same model will be generated for the pre- and post-*Cervarix* launch periods separately.

9.7.2.2. Secondary analysis

(Amended 25 May 2022)

To assess ***the*** feasibility for ***the conduct of*** a case-control study to determine the effectiveness of *Cervarix* against anal cancer in each country.

The number of expected anal cancer cases (estimated sample size) required to demonstrate the expected vaccine effectiveness will be determined. ***Also the timeframe for generating meaningful VE estimates will be assessed for each country of interest.***

The cases would be those in the cancer registry with HPV-related anal cancer, whereas controls would be subjects with a non-HPV related cancer. Controls would be sex- and age-matched, retrieved from the same cancer registry to ensure that the comparison group is representative of the source population as that of the cases. ***Investigations will need to be done to understand if brand-specific HPV (Cervarix) vaccination status of the cases and controls could be retrieved from national vaccine registries effectively linked to national cancer registries by country of interest.***

9.8. Quality control

To ensure compliance with Good Pharmaco-epidemiology Practices (GPP) or other applicable guidelines and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study.

9.9. *Strengths and* limitations of the research methods

(Amended 25 May 2022)

The study has the following ***strengths and*** limitations:

<u>Strengths</u>

- ***Use of nationwide longitudinal data from national cancer registries using the same case definition (aligned with ICD-10 codes).***
- ***A harmonised and coordinated approach in the analysis allowing comparisons across countries and with external similar studies.***

- ***Use of an HPV negative control (i.e., small intestine cancer) would permit to assess for potential bias owed to changes in the surveillance and reporting system of anal cancer over time.***

<u>Limitations</u>

- ***The cancer registry of Finland does not provide the number of cancer cases when less than 5 cases are reported in a given year, by sex and age category, due to potential risk of patient identification. Therefore, in those instances, the number of cancer cases will be back-computed using the provided crude incidence and population data. This may introduce some bias by round-offs and back-calculation.***
- Limitations in the cancer registry data such as accuracy in the cancer diagnosis methods, case ascertainment, misclassification of primary location (i.e., misclassification as rectal cancer).
- Lack of/limited information on the existence of targeted anal cancer screening programmes (i.e., directed towards at-risk groups such as MSM, HIV-positive patients, or subjects previously diagnosed of an HPV-related cancer), that may lead to overdiagnosis and may also have an impact on temporal incidence trends.
- Lack of information of the aetiology of the anal cancer cases (i.e., whether HPV-related) may introduce some bias and limit the interpretation. Additionally, if no causative HPV type could be provided, further sub-analysis of the incidence by HPV type will be limited by this constraint.
- Percentage of anal cancers with unspecified histology (unspecified carcinomas or unspecified morphology).
- Variations in registry practices in diagnosis and information collection may introduce some bias in international comparisons (i.e., consistency of histological classifications).
- Changes in trends may occur over time for reasons other than HPV vaccination (i.e., changes in the surveillance and reporting system, increment of anal cancer diagnosis due to increased awareness among physicians, implementation of an anal cancer screening programme).

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

GSK will not have access to individual data (i.e., only aggregated data by age group will be provided). No protected personal data will be transferred to GSK.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Not applicable since this study is an observational, retrospective PASS, based on data extracted from the national cancer registry databases.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1. Posting of information on publicly available registers and publication policy

Studies that do not evaluate vaccines are progressed for publication in the scientific literature when the results provide important scientific or medical knowledge or are relevant for patient care, and will be considered for disclosure on the GSK website and in publicly accessible regulatory registry(ies) such as EU PAS register as applicable.

12.2. Provision of study results to investigators/database owners

Where required by applicable regulatory requirements, an investigator/database owner signatory will be identified for the potential review of the results and approval of the study report.

13. REFERENCES

(Amended 25 May 2022)

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Annex 1 List of stand-alone documents

No.	Document Reference No	Date	Title
1	217743	25 May 2022	List of stand-alone documents
2	217743	25 May 2022	Glossary of terms
3	217743	25 May 2022	Sponsor information
4	217743	25 May 2022	Additional information
5	217743	25 May 2022	ENCePP checklist for study protocols

Annex 2 Glossary of terms

Case-control study:	A form of epidemiological study where the study population is selected based on whether the participants do (cases) or do not (controls) have the particular outcome (disease) under study. The groups are then compared with respect to exposure/characteristic of interest.
Commitment:	Agreement made with Regulatory Authorities as specific condition of regulatory approval and authorisation, either made at the time of product approval or during the lifecycle of the approved product.
Database:	A database is a set of pre-existing tables and views containing data. The term "pre-existing" implies that the analysis will be done on retrospective data and the term "views" implies that the data can be made readily available in an electronic format through a straightforward extract, without re-encoding and manual manipulation (like a transpose, a translation, split of a field into several fields, etc).
Database study:	A study involving the use of pre-existing data maintained in an electronic format; this will not include collection of new data that requires (re-) encoding via CRF/eCRF and retesting of human biological samples.
Epidemiological study:	An observational or interventional study without administration of medicinal product(s) as described in a research protocol.
eTrack:	GSK's tracking tool for clinical/epidemiological studies.
Participant:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the epidemiological study or a person about whom some medical information has been recorded in a database. Synonym: subject
Protocol amendment:	The International Council on Harmonisation (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK further details this to include a change to an approved protocol that affects the safety of participants,

	scope of the investigation, study design, or scientific integrity of the study.
Post-Authorisation Safety Study:	A pharmaco-epidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorisation, conducted with the aim of identifying or quantifying a safety hazard relating to an authorised medicinal product. This includes all GSK sponsored non-interventional studies and clinical trials conducted anywhere in the world that are in accordance with the terms of the European marketing authorisation and where the investigation of safety is the specific stated objective. Note: The phrase 'In accordance with the terms of the European marketing authorisation' means that the product is used according to the European label (e.g. within the recommended dose range, the approved formulation, indication, etc.).
Retrospective study:	A study that looks backward in time (e.g. at events that occurred in the past; outcomes and exposure can no longer be influenced), usually using medical records, databases or interviews in order to address one or more study objectives.
Study population:	Sample of population of interest.
Surveillance:	The ongoing systematic collection, collation, analysis, and interpretation of descriptive epidemiological health data on a specific disease. Surveillance can monitor incidence and/or prevalence, and/or inform about when and where health problems are occurring and who is affected.
Targeted Safety Study:	Studies specifically planned or conducted to examine an actual or hypothetical safety concern in a product marketed anywhere in the world. This includes any GSK sponsored pharmaco-epidemiological study or clinical trial conducted anywhere in the world with the aim of identifying or quantifying a safety hazard. Although all clinical trials collect safety information as a matter of routine, only those initiated to examine a specific safety concern are considered a targeted safety study.

Annex 3 Sponsor Information

(Amended 25 May 2022)

1. Sponsor:

GlaxoSmithKline Biologicals (GSK)
Rue de l'Institut, 89, B-1330 Rixensart
Belgium

2. Sponsor medical expert for the study:

Nadia Meyer, MD, Clinical & Epidemiology Project Lead, GlaxoSmithKline Biologicals SA.

Refer to the local study contact information document.

Annex 4 Additional information

(Amended 25 May 2022)

The table below presents details on vaccination schedules and vaccine coverage in the 5 selected European countries.

Country	Date HPV vaccine first introduced	Vaccine given	Immunisation schedule	Age cohort	Catch-up campaigns	Vaccine coverage	Date modification immunisation schedule	Modification immunisation schedule
Denmark	January 2009	Quadrivalent HPV (*Gardasil*)	0m, 2m, 6m	12 yo girls (born 1996) (GP-based)	13-15 yo girls Women born 1985-1992 (August 2012 to December 2013)	79% 3-dose	August 2014 February 2016 November 2017 July 2019	*Gardasil* (0m, 6m) *Cervarix* (0m, 6m) *Gardasil 9* (0m, 6m) for girls *Gardasil 9* (0m, 6m) for boys 12 yo on 1 July 2019 or later
Finland	November 2013	Bivalent HPV (*Cervarix*)	0m, 1m, 6m	11-12 yo (born 2005) (school-based)	13-15 yo girls (November 2013)	68% 3-dose in 2015 72% 3-dose in 2016	Autumn 2020	*Cervarix* (0m, 6m) girls and boys 12 yo + Catch-up for boys in grades 7-9 (2020-21 and 2021-22)
Netherlands	September 2009	Bivalent HPV (*Cervarix*)	0m, 1m, 6m	12 yo girls 10 yo girls/boys	13-16 yo girls (2009/2010) ***12-18 yo girls/boys (2022/2023)***	58% 3-dose (cohort 1998)	January 2014 ***January 2022***	*Cervarix* (0m, 6m) *Cervarix* (0m, 6m) girls and boys
Norway	August 2009	Quadrivalent HPV (*Gardasil*)	0m, 2m, 6m	12 yo (born 1997) (school-based)	Girls born in 1991 or later (2016-2018)	1997 cohort-65% 3-dose in 2011 2004 cohort- 83% 3-dose in 2016/2017 school year	September 2017 September 2018	*Cervarix* (0m, 6m) girls *Cervarix* (0m, 6m) girls and boys 12 yo

Country	Date HPV vaccine first introduced	Vaccine given	Immunisation schedule	Age cohort	Catch-up campaigns	Vaccine coverage	Date modification immunisation schedule	Modification immunisation schedule
England	September 2008	Bivalent HPV (*Cervarix*)	0m, 1m, 6m	12-13 yo girls (school-based)	14 to < 18 yo	86.7% 3-dose in 2013/2014 83.9% 2-dose in 2018/2019 64.7% 2-dose in 2019/2020	September 2012 September 2014 April 2018 September 2019	*Gardasil* (0m, 2m, 6m) for girls *Gardasil* (0m, 6m or 12m) for girls *Gardasil* (0m, 6m) for MSM ≤ 45 yo *Gardasil 9* (0m, 6m or 12m) for boys 12-13 yo + Catch-up girls and boys up to 25th birthday

HPV: human papillomavirus; m: month; ***MSM: Men who have sex with men;*** yo: years old.

Annex 5 Amendments and administrative changes to the protocol

GlaxoSmithKline Biologicals SA

Vaccines R & D
Protocol Amendment 1

eTrack study number and Abbreviated Title:	217743 (EPI-HPV-099 VS EUR DB)
Amendment number:	Amendment 1 Final
Amendment date:	Final: 31 March 2022

Rationale/background for changes:

The protocol amendment 1 was developed to account for the following changes:

1. For clarity, the primary objective and its corresponding endpoint has been split into 2 independent objectives and endpoints, respectively (i.e., for age-standardised incidence and for crude incidence).
2. For better interpretation of the study results so it can be comparable with publications across countries and to align with the age definition as per the European standardised population, the entire age group from 0 – 80+ population will be considered instead of the adult population (>18 years of age).
3. Study period (i.e., pre- and post-*Cervarix* launch period) will be considered based on the *Cervarix* introduction in the National Immunisation Programme (NIP).
4. For the UK, all analyses will be based specifically on data from England, and not data from UK. The National Cancer Registration and Analysis Service (NCRAS) is the cancer registry in England. As the population of England comprises around 84% of the total UK population, the NCRAS is considered to be representative of the population in the UK.
5. Inclusion of Poisson / Negative binomial regression model for pre- and post-*Cervarix* launch periods: The trend in the incidence of anal cancer and small intestine cancer will be assessed using the Poisson / Negative binomial regression model. The model will include number of anal cancer/small intestine cancer incidences as outcome variable and calendar year as the independent variables. The model will include the population followed up as the offset variable. APC will be estimated based on the parameter estimates of the regression model.
   The same model will be generated for the pre- and post-*Cervarix* launch periods separately.
6. Eurostat will be the source for population data and birth cohort data, except for England, for which the source for population data will be UK Health Security Agency and for birth cohort data it will be Office for National Statistics.
7. The analysis planned by HPV type and histological classification will be performed based on the data availability during the time of the analysis.

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

In the PASS information page:

Research question and objectives: To assess trends and changes over time in incidence of anal cancer using data reported to the national cancer registries in Finland, the Netherlands, ~~the United Kingdom (UK)~~***England***, Denmark and Norway and to carry out an assessment of feasibility to conduct a case-control study in any of these 5 European countries, aiming to determine the impact and~~/or~~ effectiveness of *Cervarix* against anal lesions and cancer in females and males

Countries of study: Finland, the Netherlands, ~~the UK~~***England***, Denmark and Norway

Author: PPD ~~, MD, Clinical and Epidemiology R&D Project Lead, HPV, Hepatitis and Pneumococcal vaccines, GlaxoSmithKline Biologicals SA~~ PPD **, *Epidemiology Lead, GlaxoSmithKline Biologicals SA***

MAH contact person: PPD ~~, MD, Clinical and Epidemiology R&D Project Lead, HPV, Hepatitis and Pneumococcal vaccines, GlaxoSmithKline Biologicals SA~~ PPD **, *Epidemiology Lead, GlaxoSmithKline Biologicals SA***

In Section 3 Responsible parties:

PPD ~~(Clinical and Epidemiology R&D Project Lead) is GSK's designated contact person for this study~~PPD ***Epidemiology Lead, GlaxoSmithKline Biologicals SA***.

In Section 4 Abstract:

Main author: PPD ~~, MD, Clinical and Epidemiology R&D Project Lead, HPV, Hepatitis and Pneumococcal vaccines, GlaxoSmithKline Biologicals SA~~ PPD ***Epidemiology Lead, GlaxoSmithKline Biologicals SA***

Rationale and background: In the context of the European Union Risk Management Plan (EU-RMP) for *Cervarix*, a safety concern was raised linked to missing information on the impact and~~/or~~ effectiveness of the vaccine against anal lesions and cancer, since it was not prospectively evaluated in clinical trials.

This study will assess the data on anal cancer in countries where *Cervarix* vaccination has been introduced in the NIP. Five European countries were initially preselected: Finland, the Netherlands, ~~the United Kingdom (UK)~~***England***, Denmark and Norway to perform a trend analysis and to assess feasibility for a case-control study.

Research question and objectives: The aim of this PASS is to assess trends and changes over time in incidence of anal cancer using data reported to the national cancer registries in Finland, the Netherlands, ~~the UK~~ ***England***, Denmark and Norway and to carry out an assessment of feasibility to conduct a case-control study in any of these 5 European countries, aiming to determine the impact and~~/or~~ effectiveness of *Cervarix* against anal lesions and cancer in females and males.

Primary Objective:

- To assess trends and changes over time in ***the age-standardised*** incidence of anal cancer by ~~age,~~ sex, HPV type and histological classification for each country* separately.
- ***To assess trends and changes over time in the crude incidence of anal cancer by age category, by sex, HPV type and histological classification for each country* separately.***

Secondary Objective:

- To conduct a feasibility assessment for a case-control study to determine the impact and~~/or~~ effectiveness of *Cervarix* against anal lesions and cancer.

Study design:

Study population: Females and males ~~aged 18 years** and above~~***of all age groups*** in the 5 selected European countries.

Study period:

- Pre-*Cervarix* launch period (i.e., before *Cervarix* ~~commercialisation~~***introduction in the NIP***): ~~From 1992 to 2006 inclusive~~***The start and end calendar year for each country will be considered based on the data availability in their respective cancer registries***.
- Post-*Cervarix* launch period ***(i.e., after Cervarix introduction in the NIP)***: ~~From 2007 to 2026 (i.e., final analysis)~~***The start calendar year for each country will be the date when Cervarix was introduced in their NIP***. An interim analysis will be performed in 202***2***~~1~~. For each analysis, data up to the most recent and complete available calendar year in each cancer registry will be considered.

The feasibility assessment for a case-control study will be conducted considering the 5 selected European countries that are approached for the trend analysis. The interaction with the national cancer registries will provide insights on the population and setting, the exposure (HPV vaccination), and the outcome (anal cancer). This exercise is intended to facilitate the understanding whether this case-control study to determine vaccine impact and~~/or~~ effectiveness against anal lesions and cancer can be performed.

Population:

The study population will include females and males ~~aged 18** years and above~~***of all age groups*** in the 5 selected European countries.

~~***The exact lower limit of age will depend on each cancer registry.***~~

Variables:

Primary endpoint:

- Occurrence and ***the age-standardised*** incidence of anal cancer during the period ~~from 1992 until the most recent and complete available calendar year in the cancer registries~~ (i.e., ~~during~~ pre- and post- *Cervarix* launch period) by ~~age,~~ sex, HPV type and histological classification for each country* separately.
- ***Occurrence and the crude incidence of anal cancer during the study period (i.e., pre- and post-Cervarix launch period) by age category, by sex, HPV type and histological classification for each country* separately.***

Note: Additionally, as negative control to detect potential bias due to changes in the surveillance and reporting systems, data of small intestine cancer in the same population will be analysed, by age ***category*** and sex for each country* separately.

Data sources: Eurostat will be the source for data on the European Standard Population for age distribution used to estimate the age-standardised incidence rates for the 5 selected European countries [Pace, 2013]. It will also be the source for the population data and birth cohort data, ***except for England, for which the source for population data will be the UK Health Security Agency and for birth cohort data it will be Office for National Statistics.***

This study will collect anal cancer data from the following national cancer registries:

- National Cancer Registration and Analysis Service [NCRAS] ~~in the UK~~

In Section 7 Rationale and background: In the context of the EU-RMP for *Cervarix*, a safety concern was raised linked to missing information on the impact and~~/or~~ effectiveness of the vaccine against anal lesions and cancer, since it was not prospectively evaluated in clinical trials.

This study will assess the data on anal cancer in countries where *Cervarix* vaccination has been introduced in the NIP. Five European countries were initially preselected: Finland, the Netherlands, ~~the UK~~***England***, Denmark and Norway to perform a trend analysis and to assess feasibility for a case-control study.

In Section 8 Research question and objectives: The aim of this PASS is to assess trends and changes over time in incidence of anal cancer using data reported to the national cancer registries in Finland, the Netherlands, ~~the UK~~ ***England***, Denmark and Norway and to carry out an assessment of feasibility to conduct a case-control study in any of these 5 European countries, aiming to determine the impact and~~/or~~ effectiveness of *Cervarix* against anal lesions and cancer in females and males.

Primary Objective:

- To assess trends and changes over time in ***the age-standardised*** incidence of anal cancer by ~~age,~~ sex, HPV type and histological classification for each country* separately.

- ***To assess trends and changes over time in the crude incidence of anal cancer by age category, by sex, HPV type and histological classification for each country* separately.***

Secondary Objective:

- To conduct a feasibility assessment for a case-control study to determine the impact and~~/or~~ effectiveness of *Cervarix* against anal lesions and cancer.

In Section 9.1.1 Discussion of study design:

- Study population: Females and males ~~aged 18** years and above~~***of all age groups*** in the 5 selected European countries.

~~***The exact lower limit of age will depend on each cancer registry.***~~

- Study period:
  - Pre-*Cervarix* launch period (i.e., before *Cervarix* ~~commercialisation~~***introduction in the NIP***): ~~From 1992 to 2006 inclusive~~***The start and end calendar year for each country will be considered based on the data availability in their respective cancer registries***.
  - Post-*Cervarix* launch period ***(i.e., after Cervarix introduction in the NIP)***: ~~From 2007 to 2026 (i.e., final analysis)~~***The start calendar year for each country will be the date when Cervarix was introduced in their NIP***. An interim analysis will be performed in 202***2***~~1~~. For each analysis, data up to the most recent and complete available calendar year in each cancer registry will be considered.

In Section 9.1.2. Feasibility assessment: The feasibility assessment for a case-control study will be conducted considering the 5 selected European countries that are approached for the trend analysis. The interaction with the national cancer registries will provide insights on the population and setting, the exposure (HPV vaccination), and the outcome (anal cancer). This exercise is intended to facilitate the understanding whether this case-control study to determine vaccine impact and~~/or~~ effectiveness against anal lesions and cancer can be performed.

In Section 9.1.3 Case definition

In this study, for case identification ***of anal cancer and small intestine cancer,*** [International Classification of Diseases (ICD)-10~~]/ International Classification of Diseases for Oncology, third Edition (ICD-O-3)~~ codes will be used~~ (i.e., C21 for anal cancer and C17 for small intestine cancer)~~.

For histological classification of anal cancer, the WHO ICD-O-2 (or) 3 will be used based on the coding version of the cancer registries in the selected countries.~~Cancer registries in the selected countries use the WHO ICD-O-3 for classification and coding of neoplasms.~~

In Section 9.3 Variables: The following variables will be assessed for each country separately:

- Incidence of anal cancer by age ***category***, by sex, by HPV type ***(if available)***, by histological classification ***(if available)*** and by calendar year.
- Number of anal cancer cases by age ***category***, by sex, by HPV type ***(if available)***, by histological classification ***(if available)*** and by calendar year.
- Incidence of small intestine cancer by age ***category***, by sex and by calendar year.
- Number of small intestine cancer cases by age ***category***, by sex and by calendar year.
- Age distribution data as per European Standard Population ***and UK Health Security agency (for England)***.
- Population data by age ***category***, by sex and by calendar year.
- Birth cohort data by age ***category***, by sex and by calendar year.
- HPV vaccine coverage of the eligible birth cohorts by calendar year and by age ***category*** and by sex if possible.

In Section 9.3.1.1 Primary endpoint:

- Occurrence and ***the age-standardised*** incidence of anal cancer during the period ~~from 1992 until the most recent and complete available calendar year in the cancer registries~~ (i.e., ~~during~~ pre- and post- *Cervarix* launch period) by ~~age,~~ sex, HPV type and histological classification for each country* separately.

- ***Occurrence and the crude incidence of anal cancer during the study period (i.e., pre- and post-Cervarix launch period) by age category, by sex, HPV type and histological classification for each country* separately.***

Note: Additionally, as negative control to detect potential bias due to changes in the surveillance and reporting systems, data of small intestine cancer in the same population will be analysed, by age ***category*** and sex for each country* separately.

In Section 9.4.2 Eurostat: Eurostat will be the source for data on the European Standard Population for age distribution used to estimate the age-standardised incidence rates [Pace, 2013]. It will also be the source for population data and birth cohort data***, except for England, for which the source for population data will be UK Health Security Agency and for birth cohort data it will be Office for National Statistics.***

In Section 9.4.3 Websites of national public health institutes:

- Vaccine coverage data will be retrieved from the respective websites of national public health institutes:
  - ~~**The UK**~~ ***England***

In Section 9.7.2. Statistical Analysis: All analyses will be performed for each country separately. ***The analysis planned by HPV type and histological classification will be performed based on the data availability during the time of the analysis.***

In Section 9.7.2.1. Primary analysis: To assess trends and changes over time in incidence of anal cancer by age ***category*** and by sex. ~~Additionally, based on availability of data, the same will be assessed also by HPV type and by histological classification.~~

- Age-standardised incidence ***with 95% CI*** during the period from 1992 until the most recent and complete available calendar year in the cancer registries (i.e., during pre- and post- *Cervarix* launch period) will be presented by ~~age category and~~sex. ~~Additionally, based on availability of data, the same will be assessed also by HPV type and by histological classification.~~

Note: Age-standardised incidence rates of anal cancer will be calculated by calendar year and sex using the European Standard Population (age distribution)***, except for England, for which the source for population data will be UK Health Security Agency.***

Additionally,

- ***Crude i***ncidence ***with 95% CI*** ~~rates~~ during the period from 1992 until the most recent and complete available calendar year in the cancer registries (i.e., during pre- and post- *Cervarix* launch period) will be presented by age category, sex, HPV type and histological classification.
- The trend in the incidence of anal cancer will be assessed using the Poisson / Negative binomial regression model. The model will include number of anal cancer incidences as outcome variable and calendar year as the independent variables. The model will include the population followed up as the offset variable. Annual Percentage Change (APC) will be estimated based on the parameter estimates of the regression model.
  The same model will be generated for the pre- and post-Cervarix launch periods separately.
- The trend in the incidence of anal cancer will be assessed using the Poisson / Negative binomial regression model. The model will include number of anal cancer incidences as outcome variable; ***calendar year,*** age category, study period (pre-launch = 0 and post-launch = 1), ***HPV type and*** sex and histological classification as the independent variables ***(risk factors)***. The model will include the population followed up as the offset variable.
  Similar analysis will be performed by subcategories – age category, sex, HPV type and histological classification.

Analysis for negative control:

- Age-standardised incidence ***with 95% CI*** of small intestine cancer during the period from 1992 until the most recent and complete available calendar year in the cancer registries (i.e., during pre- and post- *Cervarix* launch period) will be presented by age category and sex.

Note: Age-standardised incidence rates of small intestine cancer will be calculated by calendar year and sex using the European Standard Population (age distribution)***, except for England, for which the source for population data will be UK Health Security Agency.***

- ***Crude*** incidence ***with 95% CI*** of small intestine cancer during the period from 1992 until the most recent and complete available calendar year in the cancer registries (i.e., during pre- and post- *Cervarix* launch period) will be presented by age category, sex.
- The trend in the incidence of small intestine cancer will be assessed using the Poisson / Negative binomial regression model. The model will include number of small intestine cancer incidences as outcome variable and calendar year as the independent variables. The model will include the population followed up as the offset variable. APC will be estimated based on the parameter estimates of the regression model.
  The same model will be generated for the pre- and post-Cervarix launch periods separately.

In Section 9.7.2.2 Secondary analysis: To assess feasibility for a case-control study to determine the impact and~~/or~~ effectiveness of *Cervarix* against anal lesions and cancer in each country.

In Section 9.9 Limitations of the research methods:

- The cancer registr***y***~~ies~~ of Finland~~, the Netherlands and the UK~~ cannot provide year of ~~birth~~***cancer*** data for calendar years with less than 5 cases due to potential risk for patient identification. Therefore, ***in those instances, the number of cases will be back-computed using the provided crude incidence and population data***~~the sub-group incidence analysis by age will be limited by this constraint~~.
- ~~For the UK, incidence data may derive from regional registries and data might not be representative of the entire country since reports to this cancer registry only cover England.~~

In Section 13 References:

Office for National Statistics: Home - Office for National Statistics (ons.gov.uk). Accessed: 31 March 2022.

The UK Health Security Agency (UKHSA): https://www.gov.uk/government/organisations/uk-health-security-agency. Accessed: 31 March 2022.

GlaxoSmithKline Biologicals SA

Vaccines R & D
Protocol Amendment 2

eTrack study number and Abbreviated Title:	217743 (EPI-HPV-099 VS EUR DB)
Amendment number:	Amendment 2 Final
Amendment date:	Final: 25 March 2022

Rationale/background for changes:

The protocol amendment 2 was developed to account for the following changes:

1. Secondary objective and its corresponding endpoint was updated:
   - The feasibility assessment for a case-control study to determine the effectiveness of *Cervarix* will be conducted only against anal cancer. The data for anal lesions is not available in the cancer registries
   - Expected number of anal cancer cases is the endpoint which can be used to estimate the time frame by when the estimated sample size for a case-control study would be reached.
2. Feasibility assessment was updated to add additional information for clarity.
3. Vaccination registry for each of the 5 selected European countries was added.
4. Secondary analysis was updated to add additional information for clarity.
5. Additional points on strengths of the study were included.

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

In the PASS information page:

Research question and objectives: To assess trends and changes over time in incidence of anal cancer using data reported to the national cancer registries in Finland, the Netherlands, England, Denmark, and Norway and to carry out an assessment of feasibility to conduct a case-control study in any of these 5 European countries, aiming to determine the impact and effectiveness of *Cervarix* against anal ~~lesions and~~ cancer in females and males

In the Marketing authorisation holder page:

MAH contact person: PPD ~~, Epidemiology Lead, GlaxoSmithKline Biologicals SA~~PPD ***MD, Clinical & Epidemiology Project Lead, GlaxoSmithKline Biologicals SA***

In Section 3 Responsible parties: PPD ~~, Epidemiology Lead, GlaxoSmithKline Biologicals SA~~PPD ***MD, Clinical & Epidemiology Project Lead, GlaxoSmithKline Biologicals SA***

In Section 4 Abstract:

Research question and objectives: To assess trends and changes over time in incidence of anal cancer using data reported to the national cancer registries in Finland, the Netherlands, England, Denmark, and Norway and to carry out an assessment of feasibility to conduct a case-control study in any of these 5 European countries, aiming to determine the impact and effectiveness of *Cervarix* against anal ~~lesions and~~ cancer in females and males

Secondary objective:

- To conduct a feasibility assessment for a case-control study to determine the ~~impact and~~ effectiveness of *Cervarix* against anal cancer.

Study design:

Data collection: Retrospective data collection from national cancer registries ***and national vaccination registries***.

Study period:

- Post-*Cervarix* launch period (i.e., after *Cervarix* introduction in the NIP): The start calendar year for each country will be the date when *Cervarix* was introduced in their NIP. An interim analysis will be performed in 2022. For ***the***~~each~~ analysis, data up to the most recent and complete available calendar year in each cancer registry will be considered.

- The feasibility assessment for a case-control study will be conducted considering the 5 selected European countries that are approached for the trend analysis. The interaction with the national cancer registries will provide insights on the population and setting, the exposure (HPV vaccination), and the outcome (anal cancer). This exercise is intended to facilitate the understanding whether this case-control study to determine ***Cervarix***~~vaccine~~ impact and effectiveness against anal ~~lesions and~~ cancer can be performed.

Variables:

Primary endpoint:

- Occurrence and ~~the~~ age-standardised incidence of anal cancer during the period (i.e., pre- and post- *Cervarix* launch period) by sex, HPV type and histological classification for each country* separately.
- Occurrence and ~~the~~ crude incidence of anal cancer during the study period (i.e., pre- and post-*Cervarix* launch period) by age category, by sex, HPV type and histological classification for each country* separately.

Secondary endpoint:

- ~~Incidence of anal cancer during the pre-~~*Cervarix* ~~launch period for each country* separately.~~ ***Expected number of anal cancer cases needed to conduct the case-control study based on the vaccine coverage rate and the expected VE and other factors for each country* separately.***

Note: Other feasibility assessment checks with findings for the conduct of a case-control study will be further described in the study report.

Data sources:

  - National Cancer Registration and Analysis Service [NCRAS] ***(UK)***
- ***Vaccination registries:***
  - ***Finnish National Vaccination Registry since 2009***
  - ***Dutch vaccination registry (Præventis) since 2005***
  - ***Immunisations are registered in Child Health Information Systems (school-based vaccinations from school nurses, including HPV, reorganised as of 2002) (UK)***
  - ***Danish vaccination registry since 2009, although compulsory as of 15 November 2015***
  - ***Norwegian vaccination registry since 1995***

Study size:

Sample size computation ***for the primary objective*** is not applicable, as there is no *a priori* hypothesis to be tested. Only aggregated data reported in the national cancer registries of the 5 selected European countries will be collected within the established timeframe.

In Section 8 Research question and objectives:

The aim of this PASS is to assess trends and changes over time in incidence of anal cancer using data reported to the national cancer registries in Finland, the Netherlands, England, Denmark and Norway and to carry out an assessment of feasibility to conduct a case-control study in any of these 5 European countries aiming to determine the impact and effectiveness of *Cervarix* against anal ~~lesions and~~ cancer in females and males.

In Section 8.2 Secondary objective:

- To conduct a feasibility assessment for a case-control study to determine the impact and effectiveness of *Cervarix* against anal ~~lesions and~~ cancer.

In Section 9.1.1 Discussion of study design:

Data collection: Retrospective data collection from national cancer registries ***and national vaccination registries***.

Study period:

- Post-*Cervarix* launch period (i.e., after *Cervarix* introduction in the NIP): The start calendar year for each country will be the date when *Cervarix* was introduced in their NIP. An interim analysis will be performed in 2022. For ***the***~~each~~ analysis, data up to the most recent and complete available calendar year in each cancer registry will be considered.

In Section 9.1.2 Feasibility assessment

As mentioned above , the objectives of the feasibility assessment are:

- ***To describe the main requirements for the conduct of an additional study assessing the effectiveness of Cervarix in the prevention of anal cancer***
- ***To assess a case-control study design and the data sources that would meet those requirements.***

The feasibility assessment for a case-control study will be conducted considering the 5 selected European countries that are approached for the trend analysis. The interaction with the national cancer registries ***and national vaccination registries*** will provide insights on the population and setting, the exposure (HPV vaccination), and the outcome (anal cancer). This exercise is intended to facilitate the understanding whether this case-control study to determine ***Cervarix*** effectiveness against anal cancer can be performed.

In Section 9.3 Variables:

- ~~Age distribution data as per European Standard Population and UK Health Security agency (for England).~~

In Section 9.3.1.1 Primary endpoints:

- Occurrence and ~~the~~ age-standardised incidence of anal cancer during the study period (i.e., pre- and post- *Cervarix* launch period) by sex, HPV type and histological classification for each country* separately.
- Occurrence and ~~the~~ crude incidence of anal cancer during the study period (i.e., pre- and post-*Cervarix* launch period) by age category, by sex, HPV type and histological classification for each country* separately.

In Section 9.3.1.2 Secondary endpoint:

- ~~Incidence of anal cancer during the pre-*Cervarix* launch period for each country* separately.~~ ***Expected number of anal cancer cases needed to conduct the case-control study based on the vaccine coverage rate and the expected VE and other factors for each country* separately.***

Note: Other feasibility assessment checks with findings for the conduct of a case-control study will be further described in the study report.

In Section 9.4 Data sources:

- National Cancer Registration and Analysis Service ***(UK)*** [NCRAS]:

NCRAS is managed by Public Health England (PHE) and captures a wide range of data sources, including data such as: histopathology and haematology services, medical records, radiotherapy departments, hospices, independent hospitals, screening services, death certificates, general practitioners, other UK cancer registries. The registry holds data on anal cancer from 1993 to ***2018***. The final registrations are released approximately 1 year following the end of a diagnosis year, but it can take up to 5 years to achieve 100% completeness [Henson, 2020].

Added Section 9.4.2 Vaccination registries:

Country	***Vaccination registry***
Finland	***Finnish National Vaccination Registry since 2009***
The Netherlands	***Dutch vaccination registry (Præventis) since 2005***
England	***Immunisations are registered in the Child Health Information Systems (school-based vaccinations from school nurses, including HPV, reorganised as of 2002)***
Denmark	***Danish vaccination registry since 2009, although compulsory as of 15 November 2015 (UK)***
Norway	***Norwegian vaccination registry since 1995***

In Section 9.5 Study size:

Sample size computation ***for the primary objective*** is not applicable, as there is no *a priori* hypothesis to be tested. Only aggregated data reported in the national cancer registries of the 5 selected European countries will be collected within the established timeframe.

In Section 9.7.2.2 Secondary analysis:

To assess ***the*** feasibility for ***the conduct of*** a case-control study to determine the impact and effectiveness of *Cervarix* against anal ~~lesions and~~ cancer in each country.

~~***Step1:***~~ **The** ~~N~~number of expected anal cancer cases (estimated sample size) required to demonstrate the expected vaccine effectiveness based on the vaccine coverage data will be determined. ***Also the timeframe for generating meaningful VE estimates will be assessed for each country of interest.***

~~***Step2:*** Assuming that the number of anal cancer cases will increase over time, based on the incidence data of anal cancer cases, birth cohort, vaccine effectiveness and HPV vaccination coverage, assessment of the time frame for conducting the matched case-control study will be done.~~
The cases would be those in the cancer registry with HPV-related anal cancer, whereas controls would be subjects with a non-HPV related cancer. Controls would be sex- and age- matched, retrieved from the same cancer registry to ensure that the comparison group is representative of the source population as that of the cases. ***Investigations will need to be done to understand if brand-specific HPV (Cervarix) vaccination status of***

the cases and controls could be retrieved from national vaccine registries effectively linked to national cancer registries by country of interest.

In Section 9.9 *Strengths and* limitations of the study:

The study has the following ***strengths and*** limitations:

Strengths

- ***Use of nationwide longitudinal data from national cancer registries using the same case definition (aligned with ICD-10 codes).***
- ***A harmonised and coordinated approach in the analysis allowing comparisons across countries and with external similar studies.***
- ***Use of an HPV negative control (i.e., small intestine cancer) would permit to assess for potential bias owed to changes in the surveillance and reporting system of anal cancer over time.***

Limitations

- ~~The cancer registry of Finland cannot provide year of cancer data for calendar years with less than 5 cases due to potential risk for patient identification. Therefore, in those instances, the number of cases will be back-computed using the provided crude incidence and population data~~***The cancer registry of Finland does not provide the number of cancer cases when less than 5 cases are reported in a given year, by sex and age category, due to potential risk of patient identification. Therefore, in those instances, the number of cancer cases will be back-computed using the provided crude incidence and population data. This may introduce some bias by round-offs and back-calculation.***

In Section 13 References:

~~World Health Organization (WHO). Draft Global Strategy towards eliminating cervical cancer as a public health problem 2020. Available from: https://www.who.int/publications/m/item/draft-global-strategy-towards-eliminating-cervical-cancer-as-a-public-health-problem. Accessed: 31 March 2022.~~

WHO International Classification of Diseases for Oncology, 2nd and 3rd Edition (ICD-O-2 and ICD-O-3). Available from: https://apps.who.int/iris/handle/10665/39441 (ICD-O-2); https://www.who.int/standards/classifications/other-classifications/international-classification-of-diseases-for-oncology (ICD-O-3). Accessed: 25 May 2022.

Annex 6 Protocol Amendment 2 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	217743 (EPI-HPV-099 VS EUR DB)
Date of protocol amendment	Amendment 2 Final: 25 May 2022
Title	An observational, retrospective database post-authorisation safety study (PASS) to assess trends and changes over time in incidence of anal cancer and feasibility for a case-control study in European countries that introduced *Cervarix* in their National Immunisation Programmes (NIP)
Sponsor signatory	Nadia Meyer, MD Clinical & Epidemiology Project Lead GlaxoSmithKline Biologicals SA
Signature	_____
Date	_____

Note: Not applicable if an alternative signature process (e.g. electronic signature or email approval) is used to get the sponsor approval.

Annex 7 ENCePP Checklist for study protocols

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	4, 6
1.1.2 End of data collection[2]	☒	☐	☐	4, 6
1.1.3 Progress report(s)	☐	☐	☒	-
1.1.4 Interim report(s)	☒	☐	☐	4, 6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	4, 6

Comments:

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	4, 7
2.1.2 The objective(s) of the study?	☒	☐	☐	4, 8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	4, 9.1.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	-
2.1.5 If applicable, that there is no a priori hypothesis?	☒	☐	☐	4, 9.5

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	4, 9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	4, 7
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☒	☐	-
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	-

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	4, 9.1.1
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	4, 9.1.1
4.2.2 Age and sex	☒	☐	☐	4, 9.1.1
4.2.3 Country of origin	☒	☐	☐	4, 9.1.1
4.2.4 Disease/indication	☒	☐	☐	4, 7
4.2.5 Duration of follow-up	☐	☐	☒	-
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☐	☐	☒	-

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	-
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	-
5.3 Is exposure categorised according to time windows?	☐	☐	☒	-
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	-
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	-
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	-

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3, 9.7
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	-
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	-

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	-
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	-
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☐	☒	-

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	-

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	4, 9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	4, 9.4
9.1.3 Covariates and other characteristics?	☐	☐	☒	-
9.2 Does the protocol describe the information available from the data source(s) on:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	4, 9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	4, 9.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	4, 9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	-
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.1.3
9.3.3 Covariates and other characteristics?	☐	☐	☒	-
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	-

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	4, 9.7.2
10.2 Is study size and/or statistical precision estimated?	☐	☐	☒	-
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.2
10.4 Are stratified analyses included?	☒	☐	☐	9.7.2
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	-
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	-
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	-
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	-

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	4, 9.4
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	-

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☒	-
12.1.2 Information bias?	☐	☐	☒	-
12.1.3 Residual/unmeasured confounding?	☐	☐	☒	-
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).				
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	4, 9.1.2

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☐	☒	☐	-
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	-
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12.1, 12.2
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12.1

Comments:

***Note*: The Sponsor confirms his/her agreement with the completed ENCePP checklist by signing the Protocol Sponsor Signatory Approval page.**