EMA/612496/2021
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Procedure No. EMEA/H/C/000721/II/0110

Invented name: Cervarix

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

Note

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

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	20 Jun 2020	20 Jun 2020	☐
☐	CHMP Rapporteur Assessment Report	14 Aug 2020	18 Aug 2020	☐
☐	CHMP Co-Rapporteur Assessment Report	14 Aug 2020	24 Aug 2020	☐
☐	PRAC Rapporteur Assessment Report	21 Aug 2020	21 Aug 2020	☐
☐	PRAC members comments	26 Aug 2020	n/a	☐
☐	Updated PRAC Rapporteur Assessment Report	27 Aug 2020	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	04 Sep 2020	04 Sep 2020	☐
☐	CHMP members comments	07 Sep 2020	07 Sep 2020	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	10 Sep 2020	10 Sep 2020	☐
☐	Request for supplementary information	17 Sep 2020	17 Sep 2020	☐
	Submission of responses	19 Mar 2021	19 Mar 2021	
☐	Start of procedure	22 Mar 2021	22 Mar 2021	☐
☐	Joint CHMP Rapporteur Assessment Report	28 Apr 2021	28 Apr 2021	☐
☐	PRAC Rapporteur Assessment Report	28 Apr 2021	28 Apr 2021	☐
☐	PRAC members comments	30 Apr 2021	n/a	☐
☐	Updated PRAC Rapporteur Assessment Report	03 May 2021	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	06 May 2021	06 May 2021	☐
☐	CHMP members comments	10 May 2021	10 May 2021	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	12 May 2021	12 May 2021	☐
☒	Request for supplementary information	20 May 2021	20 May 2021	☐

Procedure resources	
CHMP Rapporteur: CHMP Co-rapporteur:	Christophe Focke Jan Mueller-Berghaus

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List of abbreviations

ATP	According-to-protocol
CI	Confidence Interval
CSR	Clinical study report
DEIA	DNA-based enzyme immunoassay
ELISA	Enzyme-linked immunosorbent assay
EI.U/mL	ELISA units per milliliter
EU	European Union
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GSK	GlaxoSmithKline Biologicals SA
HAV	Inactivated hepatitis A vaccine
HBV	Hepatitis B virus
HNC	Head and neck cancer
HNSCC	HNC squamous cell carcinoma
HPV	Human papillomavirus
IARC	International Agency for Research on Cancer
IgG	Immunoglobulin G
LL	Lower limit
MPTS	Multiplex type-specific
NCI	US National Cancer Institute
OPC	Oropharyngeal carcinoma
PI	Product Information
SCC	Squamous cell carcinoma
TVC	Total vaccinated cohort
UL	Upper limit
US	United States
VE	Vaccine effectiveness
VLP	Virus-like particle

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, GlaxoSmithKline Biologicals SA submitted to the European Medicines Agency on 29 May 2020 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the prevention of head and neck cancers causally related to certain oncogenic human papillomavirus types for Cervarix; as a consequence, sections 4.1 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 24.0 of the RMP has also been submitted to mainly reflect the updated indication.

In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version 10.1.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/11/2009 and on the granting of a (product-specific) waiver P/0008/2015.

This application relates to a new indication for an authorised medicinal product, which is protected by a supplementary protection certificate under Regulation (EC) No 469/2009.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific advice at the CHMP.

2. Scientific discussion

2.1. Introduction

In the EU, Cervarix is indicated 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. The applicant proposes to extend Cervarix' indication with protection against HPV-related head and neck cancers in males and females from 9 years of age.

The applicant intents to base the indication extension on Study HPV-040. This trial was initially conducted to evaluate different vaccine strategies with respect to effectiveness of vaccination with Cervarix against prevalent genital HPV infection in healthy female study subjects 12 – 15 years of Age. Evaluation of effectiveness against oropharyngeal infection was added as a secondary endpoint when the trial was already ongoing. Study HPV-040 was a phase III/IV study, partially-blind, controlled, community randomized multi-centre study in Finland. Study HPV-040 also provides supportive data on the immune response in males and females (12-15 years of age) following Cervarix vaccination.

The applicant further submitted study HPV-011 as supportive study for an immune-bridging approach, since effectiveness against HNC was only evaluated in female participants in study HPV-040. Study HPV-011 documents the immune response following administration of Cervarix in males. The study demonstrates that the immune response elicited by Cervarix in males (10-18 years of age) is non-inferior with respect to seroconversion rates and antibody geometric mean concentrations (GMCs) to the immune response elicited by Cervarix in females 15-25 years of age (the population in which clinical vaccine efficacy against cervical lesions was demonstrated).

In addition to the pivotal effectiveness data from study HPV-040, efficacy data from randomized, controlled study HPV-009 (the Costa Rica Vaccine Trial) are considered also supportive by the applicant for approval of the indication extension.

Data from studies HP-040 and HPV-011 were previously submitted to EMA and have been evaluated within procedures EMEA/H/C/721/II/0081 (HPV-040) and procedure EMEA/H/C/721/II/067 (HPV-011). Study HPV-011 was conducted by the NCI in collaboration with GSK. An overview of the study design was submitted and efficacy data against oral HPV infection were presented and discussed in the submitted dossier.

Finally, the applicant performed a systematic literature review with the existing data on efficacy and effectiveness of HPV vaccination using Cervarix and/or Gardasil to conclude on enough evidence of positive impact from HPV vaccination on oropharyngeal infections with HPV-16. Final data lock point for the review was 26 March 2020.

2.1.1. Problem statement

Disease or condition

Head and neck cancer (HNC) comprise a diverse group of tumours, with an incidence of over 500,000 cases annually worldwide (Spence, 2016). In 2018, 92,887 new cases of oropharynx cancers were diagnosed and 51,005 deaths for oropharyngeal cancer were reported worldwide (Bray, 2018). According to 2015 estimates for the US, HNC constitutes 3% of all malignancies, and there are approximately 60,000 new cases each year, with approximately 12,000 resulting deaths (Siegel, 2015). In 2016, in the United States, 45,543 new cases of oral cavity and pharynx cancer were

reported, and 10,170 people died of oral cavity and pharynx cancer. For every 100,000 people, 12 new oral cavity and pharynx cancer cases were reported and 3 died of cancer (US Cancer Statistics Working Group, 2019). While younger people can develop the disease, most people are older than 50 years when they are diagnosed (American Cancer Society and National Cancer Institute, 2019).

In Europe, 121,300 new lip, oral cavity and pharynx cancer cases were diagnosed and 53,200 resulted in deaths in 2018 (Ferlay, 2018).

In the US, an increase in HPV-related HNC is observed over the 2 last decades and this trend is more obvious in the male population (Chaturvedi, 2018a; Siegel, 2015). Similar trends are observed in Europe (Näsman, 2015; Carlander, 2017; Haeggblom, 2019). Emergence of novel diagnostic techniques also contributed to this increasing trend (Araldi, 2018).

State the claimed therapeutic indication

The MAH seeks CHMP's concurrence with their proposed strategy to seek extensions of the approved indications to add prevention of head and neck cancers:

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 and head and neck cancers causally related to certain oncogenic Human Papillomavirus (HPV) types.

The application is supported by study HPV-040, which documents the effectiveness of vaccination with Cervarix against prevalent oropharyngeal HPV infection in healthy female subjects 12-15 years old.

Epidemiology and risk factors

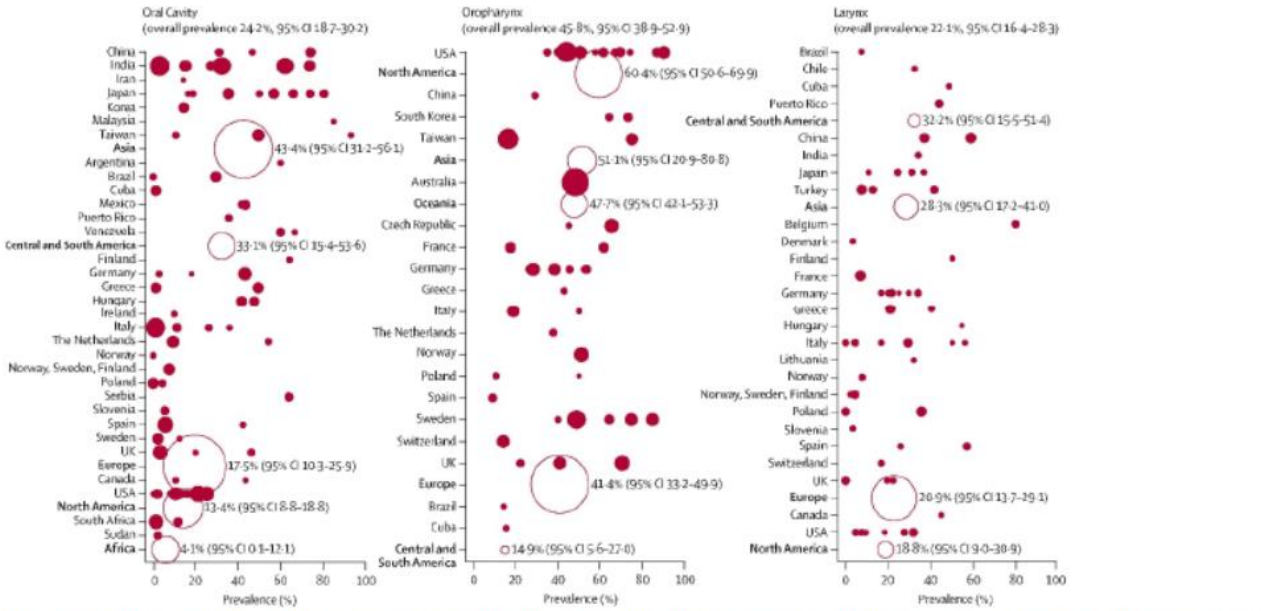
Head and neck squamous cell carcinoma pathogenesis has historically been considered associated with tobacco and alcohol use, but over the past 20 years, extensive evidence has cumulated to support causal role of HPV in a sizeable fraction of these cancers. It is today well established that HPV is associated with head and neck cancers, in particular with oropharyngeal cancer. Current evidence suggests that HPV-16 being the most frequent type that is associated with tonsil cancer (including Waldeyer ring cancer), base of tongue cancer and other oropharyngeal cancer sites.

Associations of HPV with non-oropharyngeal HNC sites are less consistent when compared to molecular-epidemiological data on HPV and oropharyngeal cancer see also **Figure 1**. Due to variant factors such as insufficient description and fractionation of anatomical localizations, different risk factors, and non-uniform detection methods, the way in which prevalence rates of HPV-associated head and neck squamous cell carcinoma (HNSCC) are described in the literature varies greatly. About 20–30% of sinonasal squamous cell carcinomas (SCC) harbour high-risk HPV, but pathologic features and clinical behaviour of HPV-related carcinomas at the sinonasal tract remain unclear (Bishop, 2017; Bishop, 2018). Three meta-analyses on larynx cancer cases reported an overall HPV-positivity around 20% (range 15-58%), with HPV-16 accounting for 13.4- 16.6% of laryngeal tumours (Kreimer, 2005; Ndiaye, 2014, Götz, 2019). It should be noted that the detection methods and study cohorts may provide bias on HPV infection in non-oropharyngeal HNSCC, but growing evidence suggests HPV involvement in different anatomical HNC sites.

In recent decades, there has been a significant increase in the incidence of HPV-positive HNC, particularly in oropharyngeal tumours (i.e., OPC). A recent meta-analysis of 139 studies estimates that the HPV prevalence among HNSCC cases is 42.6% (95% CI: 39, 46). Although both men and women can suffer from HNC, it seems that up to 75% of the HNC burden occurs in men. The oropharynx and tonsils are the sub-sites with strongest associations with HPV, with some variation across anatomical

sites and geographical regions. For details on HPV prevalence by HNC anatomical site, country, and geographical region, refer to **Figure 1**. In some regions of the world such as the US or Northern Europe, more than 70% of oropharyngeal cancer cases are estimated to be HPV-related, as compared with only 17% in Southern Europe. In Sweden, the proportion of oropharyngeal cancers that are HPV positive has steadily increased, from 23% in the 1970s to 57% in the 1990s, and as high as 93% in 2007.

Current evidence shows that HPV-16 and HPV-18 are the most commonly detected HPV-types in HNSCC. In the recent meta-analysis by Götz et al 2019, the prevalence among HPV-associated HNSCC cases was 87.32% for HPV-16 and 11.65% for HPV-18.



HPV=human papillomavirus. Larynx includes hypopharynx cases. Filled circles correspond to study-specific prevalence. Unfilled circles correspond to pooled estimated prevalence for corresponding region. Sizes of filled circles and unfilled circles are proportional to the number of cases. Two studies presented the information aggregated for Norway, Sweden, and Finland. One study with 507 cases was excluded for the regional analysis because data were presented aggregated for Central Europe and Central and South America.

Figure 1: HPV DNA prevalence in head and neck squamous cell carcinoma by anatomical site, study, country, and geographical region (Ndiaye, 2014, Figure 2)

Evidence strongly suggests that oropharyngeal HPV is predominantly transmitted by sexual contact. An increase in oral sex is suspected as the cause of the increase in the prevalence of oropharyngeal HPV infection, although several sexual behaviours seem to be related to HPV prevalence.

The risk of infection increases with an increasing number of lifetime or recent sexual partners for any type of sexual behaviour (vaginal sex, oral sex). With 20 or more lifetime sexual partners, the prevalence of oropharyngeal HPV infection reaches 20 percent. Smokers are also at greater risk than non-smokers, with current heavy smokers at particularly high risk.

Natural History: The natural history is similar in all HPV-related cancers. HPV is epitheliotropic and infects keratinized and non-keratinized epithelium at various anatomic sites. HPV predominantly infects squamous epithelial cells at all sites, such as tonsil, base of tongue, anus, and cervix, see **Figure 2**. In the cervix and the anal canal, experts have concluded that productive infections originate from the basal cells of the stratified squamous epithelium. The epithelial cells at the squamo-columnar junction are highly susceptible for transforming infections (characterized by an aborted viral life cycle and a deregulated E6 and E7 oncoprotein expression), which generate most HPV-related cervical and anal carcinomas. Similarly, productive HPV infections in the head and neck area generally originate from the squamous epithelium. In both HPV-related cervical and head and neck cancers, infection is a

necessary, but not necessarily sufficient, precursor to subsequent disease, and it may take more than 10 years from a transforming infection to development of cancer.

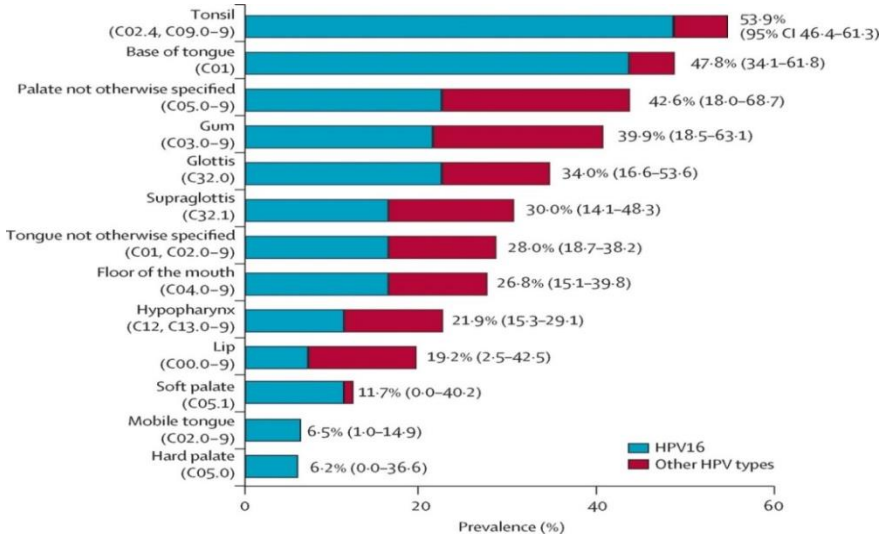


Figure 2: HPV Prevalence in Head and Neck Cancers by Anatomical site (as measured by polymerase chain reaction (PCR)

Epidemiology: The epidemiology of HPV-related cancers is similar among all anatomic sites. While HPV is considered the necessary cause of cervical cancer, a subset of non-cervical cancers are also attributable to HPV, including oropharyngeal cancer which is the best studied head and neck cancer with respect to the involvement of HPV, as well as other head and neck cancers. HPV-positive cancers represent a distinct entity in the subsets of non-cervical HPV-associated sites that have etiologic heterogeneity. HPV-positive cancers are generally characterized by a younger age at onset and an increased risk in populations with a prior HPV-related cancer and are associated with sexual behaviour when compared with their HPV-negative counterparts. The main identified risk factors are the same for all HPV-related cancers including cancers of the oropharynx. These risk factors predominantly include HPV infection and sexual behaviours (e.g., increased lifetime number of sex/oral sex partners), which results in virus transmission and subsequent infection. In addition, the temporality of the association, with HPV infection preceding development of cancer by several years, has been identified for HPV-related cancers including oropharyngeal cancer. Another important common feature of HPV-related cancers is that HPV16 is the predominant HPV type identified regardless of anatomic site, including the oropharynx where >90% of HPV-positive OPCs are attributed to HPV16.

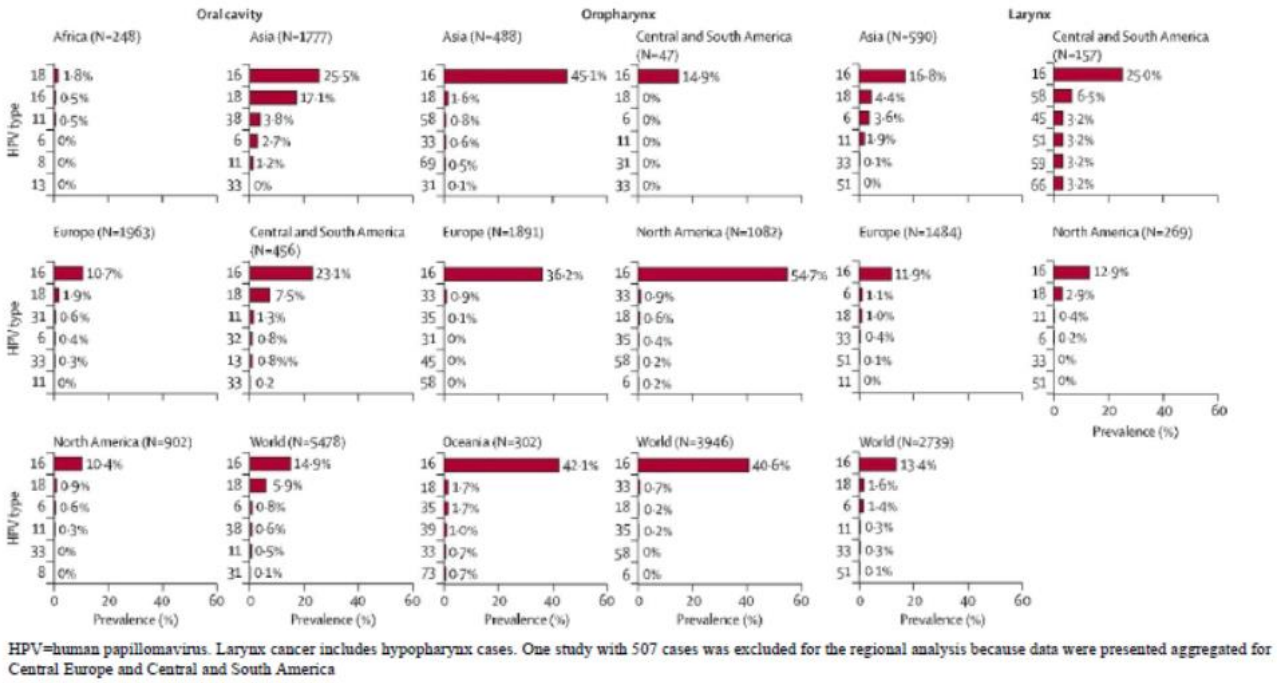
Aetiology and pathogenesis

All HPV-related cancers have a similar pathogenesis. HPV-transformed cells critically depend on the continuous expression of HPV oncogenes E6 and E7. Accepted diagnosis criteria for both HPV-related anogenital cancers and HPV-related head and neck cancers include the presence of HPV DNA and the overexpression of p16INK4a (a surrogate parameter for E7 oncoprotein activity). These diagnosis criteria are clinically relevant since HPV-related anogenital and head and neck cancers have different prognosis and response to therapy compared with HPV-unrelated cancers at the same anatomic locations.

Biologic features

About 19 high-risk HPV types (16, 18, 26, 31, 33, 35, 39, 45, 51–53, 56, 58, 59, 66, 68, 70, 73, and 82) have been detected in the head and neck regions; they have been detected in oral washes, tonsillar and oropharyngeal wall-swabs, and in laryngeal tissue specimens. Although all high-risk HPV types have been detected in the head and neck regions, most head and neck HPV infections (as high as 80%) are cleared, in normal healthy individuals, within 6–20 months of infection; HPV16 has the lowest clearance rate with infection persisting for up to 20 months. Thus, only a percentage of HPV infections, transmitted orally, become persistent infections that would ultimately cause HNC. HPV16 and HPV18 contribute to the majority (~85%) of HPV + HNC cases worldwide while the remaining ~15% of HPV + HNC are caused by HPV33, HPV35, HPV52, HPV45, HPV39, HPV58.

Current evidence shows that HPV-16 and HPV-18 are the most commonly detected HPV-types in HNSCC (Dayyani et al., 2010; Götz et al., 2019; Kreimer et al., 2005; Näsman et al., 2020). In the recent meta-analysis by Götz et al 2019, the prevalence among HPV-associated HNSCC cases was 87.32% for HPV-16 and 11.65% for HPV-18. Proportion of HPV types in HNC per anatomical site may vary, for example, HPV-16 was more common in oropharyngeal SCC (OPSCC) than in oral SCC (OSCC) (90.6 vs. 69.7%), and HPV-18 was more often detected in oral SCC than in oropharyngeal SCC (26.0 vs. 8.1%) (Götz et al., 2019; Kreimer et al., 2005). For details on HPV type distribution by anatomical site and geographical region, refer to **Figure 3**.



HPV=human papillomavirus. Larynx cancer includes hypopharynx cases. One study with 507 cases was excluded for the regional analysis because data were presented aggregated for Central Europe and Central and South America

Figure 3: Prevalence of the six most common HPV types in head and neck squamous cell carcinoma by anatomical site and geographical region (Ndiaye, 2014, Figure 3)

First direct evidence that oral infection with HPV-16 is associated with increased oropharyngeal carcinoma (OPC) risk was provided by a study among initially cancer free male and females that prospectively examined the temporal association between oral HPV infection and incident head and neck carcinoma (cancers of the oropharynx, oral cavity, and larynx). This study showed that HPV-16 detection precedes the incidence of OPC and thereby provides an important piece of evidence for risk association of prevalent oral HPV-16 infections and subsequent cancer development (Agalliu et al., 2016).

Two molecularly and epidemiologically distinct types of OPSCC exist as classified according to HPV status. HPV-negative oropharyngeal SCC is epidemiologically similar to the traditional type of SCC of the upper aero-digestive tract, in which long-term exposure to tobacco and alcohol products leads to development of malignancy. HPV-positive oropharyngeal SCC starts with exposure to high-risk HPV, most often HPV-16, and can develop independently of tobacco or alcohol exposure (Gillisonet al., 2000; Mork et al., 2001). A meta-analysis including 3946 oropharyngeal SCC cases, estimated that the HPV-attributable proportion of oropharyngeal SCC was 45.8% (95% CI: 38.9 - 52.9) (see **Figure 1**).

HPV role in cancer biology has been well described (Gillison et al., 2012; Kreimer et al., 2005; Näsman et al., 2020; Haeggblom et al., 2017). The histopathological progression of oral cavity squamous cell carcinomas is analogous to that of cervical cancer (IARC Working Group 2014). HPV has specific propensity for the squamous cell epithelium, taking advantage of microlesions in the surface to access the basal cell layer. Tonsil SCC and base of tongue SCC arise from two subsites that share a distinct histological appearance with a reticulated epithelium that invaginates into lymphatic tissue forming crypts (Näsman et al., 2020). Once basal keratinocytes are reached, the L1 protein binds to heparin sulfate proteoglycans, triggering a conformational change in the viral capsid. The virus is internalized and through lysosome binding, there is a reduction in pH leading to viral capsid disassembling and the viral genome is released (Araldi et al., 2018). Once infection is initiated, HPV may lead to epigenetic alterations, downregulation of microRNA expression and genomic instability which can induce the emergence of HNSCC.

Unlike for anal and cervical cancer, no clear precursor lesion has been identified for oropharyngeal cancer, i.e. no intermediate lesions between HPV infection and cancer. There are currently no reliable biomarkers that can be used for tumor screening or to evaluate for cancer recurrence for head and neck cancer.

Out of the malignant neoplasms of the head and neck, approximately 90% are SCCs, while around 5% are adenocarcinomas (Kaatsch et al., 2015). Probably due to the low incidence of adenocarcinomas, the relationship with HPV has not been well studied, but HPV was identified in limited number of adenosquamous carcinoma tumours. Adenosquamous carcinoma is a rare variant of SCC, characterized by mixed differentiation, with both SCC and adenocarcinoma. HPV has also shown to be involved in glandular tumours (i.e. salivary glands) of the sinonasal tract. With this evidence, HPV role in adenocarcinoma cannot be excluded.

Diagnosis and Management

There's no routine screening test or plan for oral cavity and oropharyngeal cancers. Still, some pre-cancers lesions and cancers in these areas can be found early during routine screening exams by a dentist, doctor, dental hygienist, or by self-exam. Most of these cancers don't cause symptoms until they’ve spread to other tissues.

After a thorough history has been taken and a physical examination has been performed, radiologic imaging ideally should be performed before large biopsy specimens are obtained, to avoid possible biopsy-induced anatomical distortion or biopsy-induced false positive results on positronemission tomography. Fine-needle aspiration biopsy is highly sensitive, specific, and accurate for the initial histologic diagnosis. If cervicalnode biopsy is needed, complete nodal resection is preferable to prevent extracapsular metastatic spread and tumour spillage, which would require more radical treatment.

In 2017, the American Joint Cancer Committee recognized the prognostic power of newly validated pathologic features of some primary tumours and of cervical lymph node metastases and differentiating high-risk human papilloma virus (HR-HPV)-associated OPSCC from OPSCC with other causes. Immunohistochemistry for overexpression of the tumour suppressor protein p16 (cyclin-

dependent kinase 2A) is a surrogate biomarker for HPV-mediated carcinogenesis; it is also an independent positive prognosticator in the context of OPSCC. Hence, OPSCCs are now staged according to 2 distinct systems, depending on whether or not they overexpress p16 (Amin et al., 2017). For HNC, biopsy samples are tested to see if HPV infection is present. This is a key part of staging (finding out the extent of the cancer) and is considered when making treatment decisions.

Staging is needed to determine therapy for head and neck squamous-cell cancer. Staging differs at each anatomical site. Generally, early stages (I and II) involve smaller tumours without prominent lymphnode involvement. Later stages (III and IV) are characterized by locally advanced disease and invasion of surrounding structures or an increased number of involved lymph nodes, with distant metastatic spread also defining stage IV. Oropharyngeal cancer staging requires an assessment of HPV status, which involves in situ hybridization or polymerase-chain-reaction techniques for determining HPV DNA or the viral load, or immunohistochemical testing to detect p16 expression (surrogate marker for HPV positivity).

HNC is an important consumer of health care resources (Van Agthoven et al., 2001; Wissinger et al., 2014; Polesel et al., 2019). Although therapeutic strategies are effective for the treatment of HPV-associated oropharyngeal cancer, they may also generate a long-term negative effect on the quality of life of a patient (Accetta et al., 2010; Chung et al., 2020; Yin et al., 2020). However due to the absence of screening and no obvious precancerous lesions in most HNC, these cancers are often diagnosed at a later stage.

Evaluation by a multispecialty team is very important in the choice of treatment for head and neck squamous-cell carcinoma, since treatment differs according to the stage of disease, anatomical site, and surgical accessibility. Centres with expertise in specialized multidisciplinary treatment of patients with head and neck cancers are associated with better outcomes and increased survival.

HPV-related cancers generally receive the same treatment as patients with tumours at the same site that are not related to HPV infection, i.e. surgery, radiation, chemotherapy, targeted therapy and immunotherapy with significant treatment-associated side effects (HPV Information Centre)[1].

Structural and functional preservation, amelioration of morbidity when feasible, and long-term maintenance of quality of life require multidisciplinary care encompassing surgery, radiotherapy, and medical oncology, with support from dental, nutritional, and speech and language services, as well as audiometry, occupational and physical therapy, and psychosocial services. Because of the essential role of the oropharynx in swallowing, speech and protecting the airway, treatments often result in side effects resolving after treatment, or remaining as a long-term negative sequela of HNC treatment (Howard et al., 2016; Perry et al., 2016). Finally, the overall survival rate for oral squamous cell carcinoma (OSCC) (~50%) has remained unchanged for decades.

Secondary prevention and early detection through screening is not currently feasible due to lack of an identifiable HPV induced precancerous lesion, screening modalities, and risk-mitigation strategies. In view of the considerable disease burden and treatment implications of HNC, prophylaxis including vaccination against HPV could be considered as valuable tool for HNC prevention.

The following new indication has been recently accepted in the US by FDA for the vaccine Gardasil 9: prevention of oropharyngeal and other head and neck cancers caused by Human Papillomavirus (HPV) types targeted. However, it is an accelerated approval under the condition of running an adequate and well-controlled clinical trial must been conducted to verify and describe the clinical benefit attributable to this product (such as prevention of oral persistent infection with HPV Types 16, 18, 31, 33, 45, 52 or 58).

[1] HPV Information Centre. Accessed on 03 March 2020: https://www.hpvcentre.net.

2.1.2. About the product

GlaxoSmithKline Biologicals SA (GSK) has developed the prophylactic human papillomavirus (HPV) vaccine, Cervarix.

One dose (0.5 mL) contains 20 µg of both HPV-16 L1 and HPV-18 L1 proteins assembled as virus-like particles (VLPs) as active ingredients. The L1 proteins are formulated with the AS04 Adjuvant System, which is composed of 50 µg of 3-O-desacyl-4'-monophosphoryl-lipid A (MPL) and aluminium hydroxide [Al(OH)3] (0.5 mg Al3+).

Cervarix was first approved in May 2007 in Australia and then in the European Union (EU) in September 2007. The vaccine is currently licensed for use in more than 120 countries worldwide. In the EU, Cervarix is indicated 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 is administered according to age, as a 2- or 3-dose schedule. When immunisation occurs in subjects aged 9 to 14 years, the vaccine can be administered according to the 2-dose schedule (the second dose being administered between 5 and 13 months after the first dose), whereas the 3-dose schedule is recommended in subjects 15 years of age and above (administered at 0, 1, 6 months). If flexibility in the vaccination schedule is necessary, the second dose can be administered between 1 month and 2.5 months after the first dose and the third dose between 5 and 12 months after the first dose.

HPV prophylactic vaccines have been successful at preventing healthy patients from acquiring HPV infections as well as previously infected patients from being re-infected. However, they are not able to treat or clear established HPV infections and HPV-associated lesions.

This application intends to include the prevention of head and neck cancers causally related to certain oncogenic human papillomavirus types for Cervarix.

Of note, the MAH does not include in its proposed indication the prevention of premalignant oral lesions which are currently not well established.

2.1.3. General comments on compliance with GCP

All clinical studies were approved by Ethics Committees, followed the International Conference on Harmonisation (ICH)-Good Clinical Practice (GCP) guidelines, conformed to the Declaration of Helsinki and informed, written consent was obtained from all subjects or legal guardians as per GCP requirements.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

2.3. Clinical aspects

2.3.1. Introduction

Data on effectiveness against prevalent oropharyngeal infection were generated as part of study **HPV-040** in healthy females 12-15 years of age (main pivotal clinical study).

Supportive vaccine efficacy against oral prevalent infection HPV-16/18 in women 18–25 yoa were generated from study **HPV-009 (the Costa Rica Vaccine Trial).**

Supportive HPV oropharyngeal prevalence data collected in women 12-24 years of age undergoing tonsillectomy were generated in an **Effectiveness cross-sectional study in UK.**

Supportive immunogenicity data following vaccination with Cervarix were obtained from study **HPV-011** in males 10-18 years of age (including non-inferiority to the immune response in females 15-25 years of age in study HPV-012) and from study **HPV-040** in males and females 12-15 years of age.

The existing data on efficacy and effectiveness of HPV vaccination using Cervarix and/or Gardasil were assessed by GSK using a methodology of systematic literature review with final data lock point of **26 March 2020.**

Assessor's comment

Main efficacy data (HPV-040 clinical study) are only available for females 12-15 years of age at the time of vaccination.

The results of the final analyses of efficacy and immunogenicity of study HPV-040 as well as the immunogenicity results of study HPV-011 have previously been submitted in procedures EMEA/H/C/000721/II/0081 (PAM: final effectiveness results of clinical study HPV-040) and EMEA/H/C/000721/II/067 (extension of the therapeutic indication of Cervarix to include prevention against premalignant anal lesions and anal cancer in males and females aged 9 years and older). Please refer to these procedures for more details. Only data relevant to the new applied indication (HNC) will be discussed here.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH in the clinical overview.

- Tabular overview of clinical studies

Table 1: *Overview of GSK-sponsored clinical studies supporting the submission*

Study ID	Study country	Study Design Objectives	Population (age) Schedule of vaccination	Study groups	Number of subjects		References
					ATP cohort immuno*	TVC	
Pivotal study							
HPV-040 (106636)	Finland	Phase III/IV, partially-blinded for subjects but open for Investigators, community-randomised, controlled Secondary objectives: • To evaluate the total effectiveness of *Cervarix* in reducing the prevalence of HPV-16/18 oropharyngeal infection in females following community-based HPV vaccination of 12-15 year old females or females and males • To evaluate the total effectiveness of *Cervarix* in reducing the prevalence of HPV oropharyngeal infection with oncogenic HPV types (overall and individually, including but not necessarily limited to HPV-16, -18, -31, -33, -35, -45, -52 and -58) in females following community-based HPV vaccination of 12-15 year old females or females and males • To assess the immunogenicity of *Cervarix* in a subset of males and females (Arm A immunogenicity subset) Tertiary objectives: • To evaluate the overall (total and indirect) effectiveness of *Cervarix* in reducing the prevalence of HPV-16/18 oropharyngeal infection in females approximately 18.5 years of age, following community-based HPV vaccination of 12-15 year old females or females and males versus control (pooled Arms A and B versus Arm C) • To evaluate the overall (total and indirect) effectiveness of *Cervarix* in reducing the prevalence of HPV oropharyngeal infection with oncogenic HPV types (overall and individually, including but not necessarily limited to HPV-16, -18, -31, -33, -35, -45, -52 and -58) in females approximately 18.5 years of age, following community-based HPV vaccination of 12-15 year old females or females and males versus control (pooled Arms A and B versus Arm C)	Females and males (12-15 years of age) *Cervarix* or *Engerix-B* vaccination in 3-dose schedule (0, 1, 6 months)	**Arm A** (90% of male and female subjects vaccinated with *Cervarix* and 10% with *Engerix-B*) **Arm B** (90% of female subjects vaccinated with *Cervarix* and 10% with *Engerix-B*; all male subjects vaccinated with *Engerix-B*) **Arm C** (All male and female subjects vaccinated with *Engerix-B*; no *Cervarix* administered)	HPV: 989 (764F;225M) HepB: 114 (94F;20M)	HPV: 8234 (5798 F;2436 M) HepB: 968 (669F;299 M) HPV: 6603 (6601 F;2 M) HepB: 5646 (766F;4880M) HPV: 0 HepB: 10724 (6684F;4040M)	Lehtinen, 2016; Lehtinen, 2018a; Lehtinen, 2018b Lehtinen, 2019 Gray, 2018 Bi, 2019
Supportive study							
HPV-011	Finland	Phase I/II, observer-blind, randomized, controlled Primary Objective: To evaluate 1 month after the third dose (i.e. at Month 7), the immune responses to *Cervarix* (as determined by anti-HPV-16/18 ELISA) in healthy male subjects 10-18 years of age. Secondary objectives: • To evaluate 1 month after the second dose (i.e., at Month 2) the immune responses to *Cervarix* (as determined by anti-HPV-16/18 ELISA) in healthy male subjects 10-18 years of age. • To demonstrate the non-inferiority of the immune responses to *Cervarix* (as determined by anti-HPV-16/18 ELISA) in healthy male subjects 10–18 years of age in this study, compared to the responses measured in sera from a subset of 15-25 year old females from the HPV-012 study, one month after administration of the third vaccine dose (i.e. at Month 7). *Criteria for non-inferiority: (1) one month after the third dose, the upper limits of the 95% Confidence Interval (CI) on the difference of seroconversion rates for HPV-16 and HPV-18 between the 15-25 year old female Cervarix recipients in study HPV-012 and the 10-18 year old males in the Cervarix group of this study were below 10%, (2) one month after the third dose, the upper limits of the 95% CI on the GMC ratios for HPV-16 and HPV-18 between the 15-25 year old females group of study HPV-012 and the 10-18 year old males in the Cervarix vaccine group of this study were below 2.*	Males (10-18 years of age) *Cervarix* or *Engerix-B* vaccination in 3-dose schedule (0, 1, 6-month)	HPV *Cervarix* HepB *Engerix-B*	173 86	181 89	Petäjä, 2009

ATP: According-to-protocol; ELISA: Enzyme-Linked Immunosorbent Assay; F: female; M: male; TVC: Total vaccinated cohort.
* ATP cohort for immunogenicity at 18.5 year of age (Visit 5) for study HPV-040 (immunogenicity subset in Arm A). Baseline HPV serostatus in the TVC for immunogenicity subset is available for 1887 subjects (1285 females; 602 males) for anti-HPV-16, and for 1882 subjects (1281 females; 601 males) for anti-HPV-18.
Please note that this table presents only study objectives relevant for the current submission.
Data source: HPV-040 PRI (106636) Report (13-Apr-2016); HPV-011 (580299/011) Report Amendment 1 (05-Dec-2013)

Table 2: *Overview of clinical study HPV-009 (conducted by NCI in collaboration with GSK) supporting the submission*

580299 (HPV-009)	Costa Rica	Phase III, double-blind, randomized, controlled, single-center (with 7 satellite sites) Tertiary objective: Evaluation of vaccine efficacy of *Cervarix* against HPV infections that occur at extra-cervical sites	Females (18-25 years of age) *Cervarix* or HepA control vaccination in 3-dose schedule (0, 1, 6 months)	HPV *Cervarix* HepA *Havrix*-based investigational formulation	2910 2924	3727 3739

Please note that this table presents only study objectives relevant for the current submission.
HepA: hepatitis A; TVC: Total vaccinated cohort.
*Full analytical cohort for efficacy: including all vaccinated females with oral and cervical samples and HPV results available.
Data source: Herrero, 2013

2.3.2. Pharmacokinetics

In line with the Guideline on Clinical Evaluation of New Vaccines (EMEA/CHMP/VWP/164653/2005), the Company did not conduct pharmacokinetic studies with the product as they are of the opinion that traditional pharmacokinetic studies would not be informative to support the assessment of the efficacy or safety of Cervarix. The immune response of Cervarix in the target population is described and discussed in the Immunogenicity section.

2.3.3. Immunogenicity analysis

This section presents immunogenicity data obtained with Cervarix in study HPV-011 in males (as compared to females in study HPV-012) and in males and females in study HPV-040.

Immunization with HPV VLP L1-based vaccines provides antibody-mediated immunity and protection against cervical and anal cancers [2]. Although no serological correlate of protection between immunogenicity and efficacy has been established for HPV vaccines, it is generally accepted that high anti-HPV antibody levels are indicative for protection against HPV infection (Castellsagué et al., 2014; Romanowski et al., 2009; Safaeian et al., 2010; Stanley et al., 2012).

2.3.3.1. Methodology for Immunogenicity Assessment (serological assay)

The antibody determinations in studies HPV-011 and HPV-040 were performed using Enzyme-Linked Immunosorbent Assay (ELISA). The results of the ELISA assay are expressed in ELISA units per millilitre (El.U/mL). The cut-off for seropositivity for the method is 8 El.U/mL and 7 El.U/mL for HPV-16 and HPV-18, respectively, in study HPV-011. The assay used to measure anti-HPV-16/-18 antibody concentrations at the designated laboratory was improved to increase the assay precision and the assay cut-off value changed from 8 EL.U/mL to 19 EL.U/mL for HPV-16 and from 7 EL.U/mL to 18 EL.U/mL for HPV-18. These new cut-off values have been applied in study HPV-040 for the testing of samples from Visit 5 (at 18.5 year of age) onwards. As a result, the cut-off considered for calculation of seropositivity rates in study HPV-040 for samples at Day 0 and Month 7 was different from the cut-off used for samples taken at Visit 5. A summarized description of the method is provided in the CSRs. The description and validation of the improved assays was previously submitted and evaluated in the context of variation procedure EMEA/H/C/721/II/067.

2.3.3.2. Study HPV-011

Study Background

Study HPV-011 was a phase I/II, observer-blind, randomised, controlled study to assess the immunogenicity and safety of Cervarix administered intramuscularly according to a 0, 1, 6 month schedule in healthy male subjects 10-18 years of age. The study was conducted in multiple centres in Finland. A total of 270 subjects were enrolled. Subjects were randomly allocated (2:1) to receive either Cervarix or GSK's Hepatitis B vaccine, Engerix B as control. Randomisation was age-stratified (10-12 years, 13-15 years and 16-18 years).

The study objectives discussed in this variation are non-inferiority assessments of the immune responses to Cervarix in terms of seroconversion rates and antibody GMCs for HPV-16 and HPV-18 in healthy male subjects 10–18 years of age in study HPV-011, compared to the responses measured in

[2] World Health Organization (WHO). The immunological basis for immunization series. Module 19: human papillomavirus infection. 2011. Accessed on 19 March 2020: https://apps.who.int/iris/handle/10665/44604.

sera from a subset of females 15-25 years of age from the HPV-012 study one month after administration of the third vaccine dose (i.e. at Month 7). The primary analysis of the immunogenicity and the non-inferiority evaluation was performed in the ATP cohort for immunogenicity. The following criteria for non-inferiority were applied:

- Seroconversion: the upper limits of the 95% CI on the difference of seroconversion rates for HPV-16 and HPV-18 one month after the third dose between the female subjects 15-25 years of age of the Cervarix group in study HPV-012 and the males 10-18 years of age in the Cervarix group of study HPV-011 should be below 10%.
- Antibody GMC ratios: the upper limit of the 95% CI on the antibody GMC ratios for HPV-16 and HPV-18 one month after the third dose, between the females 15-25 years of age of study HPV-012 and the males 10-18 years of age in the Cervarix group of study HPV-011 should be below 2.

Other immunogenicity objectives and detailed outcomes of study HPV-011 have previously been submitted and approved (EMEA procedure EMEA/H/C/721/II/067).

Immunogenicity Results

The immunogenicity results in the males 10 to 18 years of age in study HPV-011 were compared to the results in females 15 to 25 years of age from study HPV-012. The mean age in the Cervarix group of study HPV-011 (ATP cohort for immunogenicity) was 14.5 ± 2.13 years and in the comparative HPV-012 female population (Cervarix group pooled lots, ATP cohort immunogenicity) the mean age was 20.1 ± 3.0 years. In both studies the population was predominantly of white Caucasian/European heritage (at least 97%).

The Month 7 results of study HPV-011 and the HPV-012 study results have been published (Petäjä et al., 2009; Pedersen et al., 2007; Petäjä et al., 2011).

After vaccination, all subjects in the Cervarix group of study HPV-011 were seropositive for both HPV-16 and HPV-18. High antibody GMCs were observed in the Cervarix group at Month 2 for HPV-16 and HPV-18, respectively, with approximately a four-fold increase for HPV-16 and a two-fold increase for HPV-18 between Month 2 and Month 7 (22564.8 EL.U/mL (95% CI: 19800.3; 25715.4) and 8460.3 EL.U/mL (95% CI: 7306.1; 9796.8) for HPV-16 and HPV-18 respectively at Month 7).

The non-inferiority assessment showed that the upper limits of the 95% CI around the difference in seroconversion rates were 2.30% and 2.50% for HPV-16 and HPV-18, respectively (**Table 3**). For the antibody GMCs, the upper limits of the 95% CI around the GMC ratios were 0.38 and 0.47 for HPV-16 and HPV-18, respectively (**Table 4**).

Table 3: *Non-inferiority assessment in terms of seroconversion rates between males (10-18 years of age) in study HPV-011 and females (15-25 years of age) in study HPV-012, Post-Dose 3, Month 7 (ATP cohort for immunogenicity)*

Antibody	Females (HPV-012)		Males (study HPV-011)		Difference in seroconversion rates (females minus males)			
					Difference	%	95 % CI	
	N	%	N	%			LL	UL
HPV-16	359	100	163	100	Females - Males	0	-1.06	2.30
HPV-18	364	100	150	100	Females - Males	0	-1.04	2.50

N = number of subjects with available results
% = percentage of subjects with HPV-16 VLP IgG concentration ≥ 8 EL.U/ml or HPV-18 VLP IgG concentration ≥ 7 EL.U/ml
95% CI = 95% Standardised asymptotic confidence interval; LL = lower limit, UL = upper limit
Calculation performed on subjects seronegative prior to dose 1
Non-inferiority criterion: upper limit of the 95% CI around the difference in seroconversion rates below 10%
Data source: HPV-011 (580299/011) Report Amendment 1 (05-Dec-2013), adapted from Table 26

Table 4: *Non-inferiority assessment in terms of GMC ratios between males (10-18 years of age) in study HPV-011 and females (15-25 years of age) in study HPV-012, Post-Dose 3, Month 7 (ATP cohort for immunogenicity)*

Antibody	Females		Males		GMC ratio (Females / Males)		
					Value	95% CI	
	N	GMC	N	GMC		LL	UL
HPV-16	359	7292.9	163	22639.7	0.32	0.27	0.38
HPV-18	364	3318.8	150	8416.1	0.39	0.33	0.47

GMC = geometric mean antibody concentrations (EL.U/mL)
N = Number of subjects with pre-vaccination results available
95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance);
LL = lower limit, UL = upper limit
Calculation performed on subjects seronegative prior to dose 1
Non-inferiority criterion: upper limit of the 95% CI around the GMC ratio below 2
Data source: HPV-011 (580299/011) Report Amendment 1 (05-Dec-2013), adapted from Table 27

Assessor's comment

Results of study HPV-011 were compared with results obtained in study HPV-012, both in term of seroconversion rate and GMC. Same definition of seroconversion rate was used in both studies, i.e. percentages of subjects with HPV-16 VLP IgG concentration ≥8 EL.U/ml or HPV-18 VLP IgG concentration ≥ 7 EL.U/ml. Assay to measure the specific IgG was validated. It is therefore considered that results comparison is reliable.

Both criteria for non-inferiority were already used for bridging the efficacy of Cervarix from young adult women to other population (such as adolescent).

Both objectives of non-inferiority of the immune response of 3 doses of Cervarix in males 10-18 years of age, as compared to 3 doses of Cervarix in females 15-25 years of age were met. The 15-25 yoa females are the population in which efficacy against cervical lesions and cancer was demonstrated.

It is evident that the GMCs determined for female and male subjects in studies HPV-011 and HPV-012, respectively, are very different (i. e. much higher in males). Is there any explanation for this observation or are these differences due to different methodologies? In case of the latter, the GMC ratio analysis as conducted in table 7 of the "clinical overview addendum" is considered inappropriate. The applicant has clarified that the same ELISA methodology (with only minor adjustments) has been used for immunogenicity assessment of serum samples from clinical trials. This suggests that the

differences in titers observed are not due to different assay procedures.

Further, the applicant has elaborated on existing knowledge as regards the established age- and gender-specific differences in immunogenicity of the HPV vaccine. Considering this information the observed GMC differences between males and females can be adequately explained. **Issue resolved.**

These immunogenicity results are considered as supportive.

2.3.3.3. Study HPV-040

Study Background

An overview of the study design of study HPV-040 is presented in Section 2.4.1. Anti-HPV-16/18 antibody levels were assessed in study HPV-040 as a secondary endpoint in study participants included in the immunogenicity subset from pre-selected communities in Arm A (male and female adolescents vaccinated with Cervarix), at Month 0 and Month 7 (i.e., one month after completion of the 3-dose vaccination course) and at 18.5 years of age (i.e., approximately 3.5 to 6.5 years after the first dose). Detailed immunogenicity outcomes of study HPV-040 have previously been submitted and approved (procedure EMEA EMEA/H/C/721/II/0081). The analysis of immunogenicity (seropositivity rates and antibody GMCs for HPV-16 and HPV-18) was descriptive and primary analysis was based on the ATP cohort for immunogenicity.

Immunogenicity Results

One month after completion of the 3-dose vaccination course (at Month 7), all initially seronegative male and female study participants in the Cervarix group had seroconverted for anti-HPV-16 and anti-HPV-18 antibodies.

Antibody GMCs at Month 7 in initially seronegative female subjects from the Cervarix group were 21246.5 (95% CI: 20227.5, 22316.8) and 8150.1 (95% CI: 7758.6, 8561.4) EL.U/mL for anti-HPV-16 and anti-HPV-18 antibodies, respectively. GMCs at Month 7 in initially seronegative male subjects from the HPV group were 23813.2 (95% CI: 22110.0, 25647.5) and 8483.9 EL.U/mL (95% CI: 7878.8, 9135.6) for anti-HPV-16 and anti-HPV-18 antibodies, respectively.

Antibody GMCs at 18.5 years of age in initially seronegative female subjects from the Cervarix group were 2642.8 (95% CI: 2469.4, 2828.3) and 884.6 (95% CI: 818.4, 956.3) EL.U/mL for anti-HPV-16 and anti-HPV-18 antibodies, respectively. GMCs at 18.5 years of age in initially seronegative male subjects from the HPV group were 2807.4 (95% CI: 2462.4, 3200.7) and 817.5 (95% CI: 707.2, 944.9) EL.U/mL for anti-HPV-16 and anti-HPV-18 antibodies, respectively.

The following tables depict seropositivity rates and GMCs at months 7 and at 18.5 yoa for anti-HPV-16 (**Table 5**) and anti-HPV-18 antibodies (**Table 6**).

Table 5: *Seropositivity rates and GMCs for anti-HPV-16 antibodies, by gender and pre-vaccination status (ATP cohort for immunogenicity - adapted for each timepoint) - Study HPV-040*

						Seropositivity rates				GMC		
								95% CI			95% CI	
Antibody	Group	Sub-group	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL
anti-HPV-16	HPV	Female	S-	PRE	1111	0	0.0	0.0	0.3	4.0	4.0	4.0
				PIII (M7)	1077	1077	100	99.7	100	21246.5	20227.5	22316.8
				PIII (18.5Y)	640	640	100	99.4	100	2642.8	2469.4	2828.3
			S+	PRE	88	88	100	95.9	100	18.6	15.2	22.8
				PIII (M7)	86	86	100	95.8	100	22363.8	18591.0	26902.3
				PIII (18.5Y)	48	48	100	92.6	100	2204.5	1717.0	2830.4
			Total	PRE	1199	88	7.3	5.9	9.0	4.5	4.4	4.6
				PIII (M7)	1163	1163	100	99.7	100	21327.2	20338.9	22363.5
				PIII (18.5Y)	688	688	100	99.5	100	2609.6	2444.4	2785.9
		Male	S-	PRE	505	0	0.0	0.0	0.7	4.0	4.0	4.0
				PIII (M7)	496	496	100	99.3	100	23813.2	22110.0	25647.5
				PIII (18.5Y)	205	205	100	98.2	100	2807.4	2462.4	3200.7
			S+	PRE	40	40	100	91.2	100	17.2	13.8	21.3
				PIII (M7)	40	40	100	91.2	100	25844.1	19370.5	34481.2
				PIII (18.5Y)	12	12	100	73.5	100	2056.6	1267.4	3337.3
			Total	PRE	545	40	7.3	5.3	9.9	4.5	4.3	4.6
				PIII (M7)	536	536	100	99.3	100	23959.1	22301.0	25740.4
				PIII (18.5Y)	217	217	100	98.3	100	2759.5	2432.1	3130.9

HPV = *Cervarix*
Seropositivity: concentration ≥ 8 EL.U/mL at PRE and PIII (M7), concentration ≥ 19 EL.U/mL at PIII (18.5Y)
S- = seronegative subjects prior to vaccination
S+ = seropositive subjects prior to vaccination
GMC = geometric mean concentration calculated on all subjects
N = number of subjects with pre-vaccination results available
n/% = number/percentage of subjects with concentration ≥ 8 EL.U/mL at PRE and PIII (M7), concentration ≥ 19 EL.U/mL at PIII (18.5Y)
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = Pre-vaccination
PIII (M7) = Post-Dose 3, Month 7
PIII (18.5Y) = Post-Dose 3, 18.5 years of age
Data source: HPV-040 PRI (106636) Report (13-Apr-2016), adapted from Table 37

Table 6: *Seropositivity rates and GMCs for anti-HPV-18 antibodies, by gender and pre-vaccination status (ATP cohort for immunogenicity - adapted for each timepoint) - Study HPV-040*

						Seropositivity rates				GMC		
								95% CI			95% CI	
Antibody	Group	Sub-group	Pre-vacc status	Timing	N	n	%	LL	UL	value	LL	UL
anti-HPV-18	HPV	Female	S-	PRE	1110	0	0.0	0.0	0.3	3.5	3.5	3.5
				PIII (M7)	1076	1076	100	99.7	100	8150.1	7758.6	8561.4
				PIII (18.5Y)	628	627	99.8	99.1	100	884.6	818.4	956.3
			S+	PRE	86	86	100	95.8	100	14.2	12.2	16.5
				PIII (M7)	84	84	100	95.7	100	9283.5	7843.5	10987.9
				PIII (18.5Y)	58	58	100	93.8	100	950.1	735.1	1228.0
			Total	PRE	1196	86	7.2	5.8	8.8	3.9	3.8	4.0
				PIII (M7)	1160	1160	100	99.7	100	8227.3	7847.7	8625.4
				PIII (18.5Y)	686	685	99.9	99.2	100	890.0	826.2	958.7
		Male	S-	PRE	511	0	0.0	0.0	0.7	3.5	3.5	3.5
				PIII (M7)	504	504	100	99.3	100	8483.9	7878.8	9135.6
				PIII (18.5Y)	202	202	100	98.2	100	817.5	707.2	944.9
			S+	PRE	33	33	100	89.4	100	16.8	12.8	22.0
				PIII (M7)	31	31	100	88.8	100	10383.6	6790.8	15877.2
				PIII (18.5Y)	15	15	100	78.2	100	1164.7	600.5	2259.2
			Total	PRE	544	33	6.1	4.2	8.4	3.8	3.7	4.0
				PIII (M7)	535	535	100	99.3	100	8583.9	7974.7	9239.5
				PIII (18.5Y)	217	217	100	98.3	100	837.7	727.3	964.9

HPV = *Cervarix*
Seropositivity: concentration ≥ 7 EL.U/mL at PRE and PIII (M7), concentration ≥ 18 EL.U/mL at PIII (18.5Y)
S- = seronegative subjects prior to vaccination
S+ = seropositive subjects prior to vaccination
GMC = geometric mean concentration calculated on all subjects
N = number of subjects with pre-vaccination results available
n/% = number/percentage of subjects with concentration ≥ 7 EL.U/mL at PRE and PIII (M7), concentration ≥ 18 EL.U/mL at PIII (18.5Y)
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = Pre-vaccination
PIII (M7) = Post-Dose 3, Month 7
PIII (18.5Y) = Post-Dose 3, 18.5 years of age
Data source: HPV-040 PRI (106636) Report (13-Apr-2016), adapted from Table 38

Assessor's comment

In HVP-40, although the cut-offs used to define a seroconversion were higher than those previously used for both HPV-16 and HPV-18, 100% of the seronegative participants had seroconverted 1 month post-dose 3.

Anti-HPV-16 and anti-HPV-18 antibody GMC observed in initially seronegative female and male subjects were comparable between gender, both at 1 month following vaccination and at 18.5 years of age.

Effectiveness was demonstrated in this population.

As for the immunogenicity results of study HPV-011, these results are considered as supportive.

Overall, the immunogenicity data generated and provided are considered appropriate to demonstrate and compare the vaccine-induced immune response in females and males. It is noted that these immunogenicity data have been evaluated already before for variation procedures EMEA/H/C/721/II/067 and EMEA/H/C/721/II/0081.

The applicant shall justify why no neutralising antibody comparison has been performed in support of the claim of the current variation procedure. Neutralising titers are considered the more relevant parameter in terms of prevention of an HPV infection. In its response the applicant refers to published data, WHO guidance docs and the initial licensing procedure to justify its approach for applying an ELISA-based test for the characterization of the serological immune response elicited by Cervarix. Although not all the mentioned details of this justification are supported the overall rationale of the

applicant´s response is deemed appropriate and acceptable. **Issue resolved.**

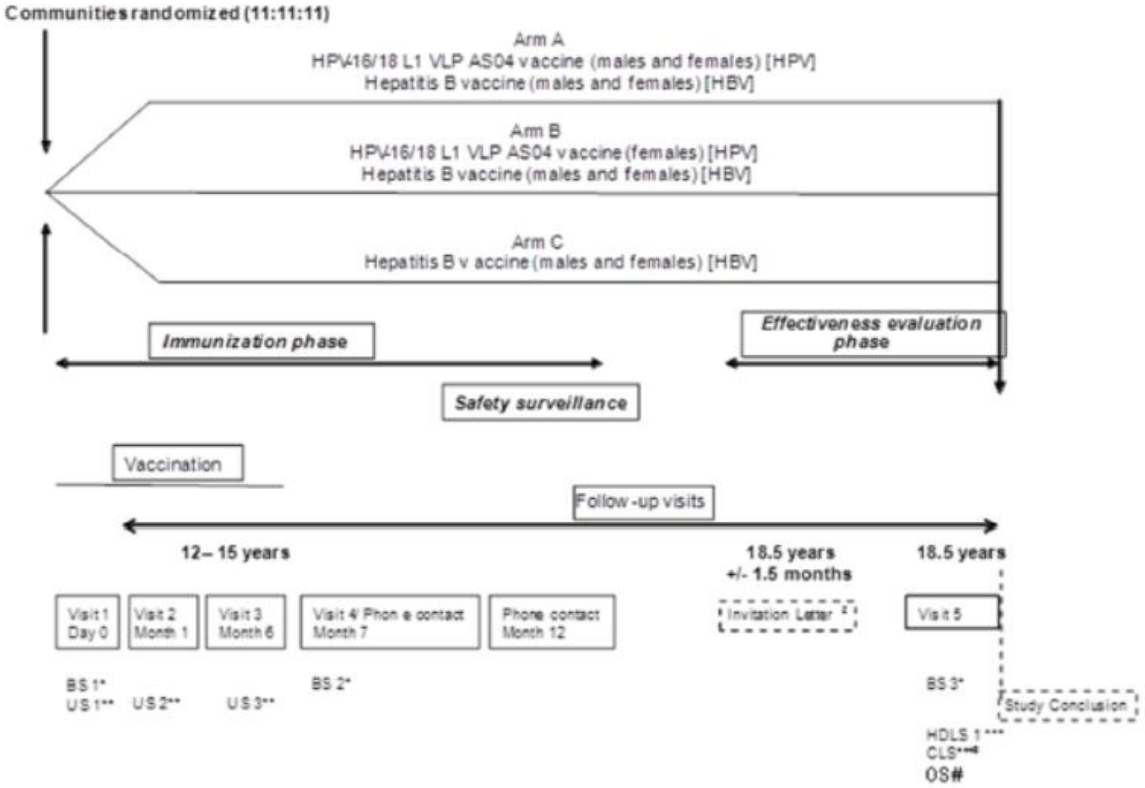
2.3.4. Pharmacodynamics

In line with the Guideline on Clinical Evaluation of New Vaccines (EMEA/CHMP/VWP/164653/2005), the Company performed pharmacodynamic evaluations in clinical studies. Section 2.4. below presents an overview of these data.

2.4. Clinical efficacy

2.4.1. Main pivotal efficacy study: HPV-40

Study HPV-040 was a phase III/IV study, partially-blind, controlled, community randomized multi-centre study in Finland and enabled evaluation of the overall impact (direct and indirect effectiveness) of HPV immunization in a community setting when early adolescents 12 - 15 years of age are targeted for vaccination (when administered intramuscularly according to a 0, 1, 6-month schedule). The study included three treatment arms encompassing communities in which various proportion of study participants received either Cervarix or GSK's hepatitis B (HepB) vaccine Engerix B, depending on gender and treatment allocation.



BS: Blood Sample; US: Urine Sample; HDLS: HPV DNA LBC Sample; CLS: Cytology LBC Sample; OS: Oropharyngeal Sample

* Only a subset of selected study participants had blood drawn at these time points (study participants in the immunogenicity subset)

** Urine sample for pregnancy test collected in female study participants for pregnancy testing if deemed appropriate according to the investigator's clinical judgement

*** Study procedure only applicable to female study participants

£ All community residents born between 1992 and 1995 received an invitation letter, an informed consent form and a behavioural questionnaire. All female community adolescents born in 1992, 1993, 1994, and 1995 were invited to attend Visit 5 including female community adolescents not enrolled in the immunization phase. Male study participants included in the immunogenicity subset were also invited to attend Visit 5, for collection of a blood sample for Hepatitis B or HPV antibody testing. All study participants who participated in the effectiveness evaluation phase joined after informed consent had been obtained.

Oropharyngeal samples for HPV DNA testing were to be collected at Visit 5 from female subjects born in 1993, 1994 and 1995, who joined the effectiveness evaluation phase of the study.

Figure 4: Study design overview (immunization phase and effectiveness evaluation phase)

The trial was conducted in Finland October 2007 till December 2014, where a total of 33 geographically distinct communities were stratified by HPV-16 seroprevalence into three strata, and equally randomized (1:1:1) to the three intervention arms. All communities were generally at a minimum distance of 50 kilometres from each other (25 kilometres in southern Finland) to minimise inter-community transmission of HPV.

The main objective of the study was to evaluate the effectiveness of vaccination with Cervarix in reducing the prevalence of HPV-16/18 genital infection in females. Evaluation of effectiveness against oropharyngeal infection was added as a confirmatory objective when the study was ongoing.

The trial was divided in two phases: the immunization phase (Day 0 to Month 12) and the effectiveness evaluation phase (from the age of 18.5 years, i.e. Visit 5, onwards), during which the impact of the vaccine intervention was assessed in all female community residents born 1992-1995

(duration of follow-up approximately 3.5 to 6.5 years, which was the time needed to reach approximately 18.5 years of age).

For investigators, the study was open. For study participants, the study was partially blinded: all study participants knew in which intervention arm their community had been assigned (Arm A, B or C), but participants in arm A and B did not know the treatment individually received.

2.4.1.1. Methods

This study was a phase III/IV community-randomized, controlled trial with three arms and two phases.

• Study arms:

– Arm A included communities (N = 11) where 70% of male and female adolescents (birth cohorts 1992 - 1995) were to be vaccinated with the HPV-16/18 L1 VLP AS04 vaccine (vaccination strategy #1).

– Arm B included communities (N = 11) where 70% of the female adolescents (birth cohorts 1992 - 1995) were to be vaccinated with the HPV-16/18 L1 VLP AS04 vaccine (vaccination strategy #2).

– Arm C included communities (N = 11) where the adolescents (birth cohorts 1992 - 1995) were not vaccinated against HPV-16/18 (negative control). These male and female adolescents were to receive a Hepatitis B vaccine (HBV vaccine, Engerix-B) as negative control.

• Phases:

– The immunization phase (Visit 1 to Month 12), during which community adolescents born in 1992, 1993, 1994 and 1995 and who met admission criteria were vaccinated with either HPV-16/18 or HBV vaccine.

– The effectiveness evaluation phase (Visit 5), during which the impact of the vaccine intervention was assessed. This assessment was made in female community residents born in 1992, 1993, 1994 and 1995, when they reached approximately 18.5 years of age. Informed consent was to be obtained from all community residents who agreed to participate in the effectiveness evaluation phase (i.e. study participants previously enrolled in the immunization phase, and those who joined the trial at Visit 5).

Treatment

Dosage and administration of study vaccines

The candidate HPV vaccine and the HBV vaccine (Engerix-B) were administered intramuscularly into the deltoid of the non-dominant arm according to a 0, 1, 6-month schedule.

A description of the characteristics of the vaccines used in study HPV-040 is provided in **Table 7**.

Table 7: *Composition of the vaccines used in study HPV-040*

Vaccine	Formulation	Presentation	Volume	Lot numbers
HPV-16/18 L1 VLP AS04 (*Cervarix*)	20 μg HPV-16 L1 protein 20 μg HPV-18 L1 protein 50 μg MPL 500 μg $Al(OH)_3$	Monodose vial	0.5 mL	AHPVA005B AHPVA006A AHPVA013A AHPVA034B
Hep B vaccine (control) (*Engerix-B*)	10 μg HBs antigen 250 μg $Al(OH)_3$ < 0.5 μg Thiomersal	Monodose vial	0.5/1.0 mL	AHBVB307A AHBVB463A AHBVB687A AHBVB787A

Objectives

The effectiveness objectives used in this variation are listed below.

Secondary objectives:

• To evaluate the total effectiveness of Cervarix in reducing the prevalence of HPV- 16/18 oropharyngeal infection in females following community-based HPV vaccination of 12 - 15 year old females or females and males.

• To evaluate the total effectiveness of Cervarix in reducing the prevalence of HPV oropharyngeal infection with oncogenic HPV types (overall and individually, including but not necessarily limited to HPV-16, -18, -31, -33, -35, -45, -52 and -58) in females following community-based HPV vaccination of 12 - 15 year old females or females and males.

Tertiary objectives:

• To evaluate the overall (total and indirect) effectiveness of Cervarix in reducing the prevalence of HPV-16/18 oropharyngeal infection in females approximately 18.5 years of age, following community-based HPV vaccination of 12-15 year old females or females and males versus control (pooled Arms A and B versus Arm C).

• To evaluate the overall (total and indirect) effectiveness of Cervarix in reducing the prevalence of HPV oropharyngeal infection with oncogenic HPV types (overall and individually, including but not necessarily limited to HPV-16, -18, -31, -33, -35, -45, -52 and -58) in females approximately 18.5 years of age, following community-based HPV vaccination of 12-15 year old females or females and males versus control (pooled Arms A and B versus Arm C).

Efficacy Endpoints: PCR testing on oropharyngeal samples

Secondary endpoints:

- Oropharyngeal HPV-16 and/or HPV-18 DNA positivity (by PCR) in female subjects in Arms A, B and C (HPV-vaccinated female subjects from Arm A and Arm B versus all invited females in Arm C)
- Oropharyngeal oncogenic HPV DNA positivity (by PCR) in female subjects in Arms A, B, and C (HPV-vaccinated female subjects from Arm A and Arm B versus all invited females in Arm C)

Tertiary endpoints:

- Oropharyngeal HPV-16 and/or HPV-18 DNA positivity (by PCR) in female subjects approximately 18.5 years of age in Arms A, B and C (all invited female subjects from Arm A and B versus Arm C)

- Oropharyngeal oncogenic HPV DNA positivity (by PCR) in female subjects approximately 18.5 years of age in Arms A, B, and C (all invited female subjects from Arm A and B versus Arm C).

To assess the efficacy endpoints in study HPV-040, HPV DNA polymerase chain reaction (PCR) testing on oropharyngeal samples were the main laboratory assays used (for details on the assays, refer to previously submitted Module 2.7.3, Section 1.6.1).

Evaluation of effectiveness against oropharyngeal infection was added as a confirmatory objective when the study was ongoing. Oropharyngeal samples for HPV DNA testing by PCR were collected at the age of 18.5 years from female subjects born in 1994 and 1995, who joined the effectiveness evaluation phase of the study. Oropharyngeal samples were not collected from female subjects born in 1993 except for one subject. Because the oropharyngeal samples from the 1992 birth cohort were taken after completion of Visit 5 (at the age of approximately 21-22 years), the data for this birth cohort were not pooled with the 1994 and 1995 birth cohorts (1992 birth cohort prevalence rates of oropharyngeal infection are available in Table 103 in the CSR dated 13-Apr-2016).

Oropharyngeal samples were collected in study HPV-040 by means of a 30-second oral rinse and gargle with 5 ml of saline solution. The method of oral rinse and gargle sampling was chosen based on previous reports that a single mouthwash sample provides substantially larger amounts and higher molecular weight DNA than other methods of oral specimen collection (Garcia-Closas, 2001).

Typing of HPV DNA from oropharyngeal samples was done by PCR using short PCR fragment (SPF-10) primers; amplification products were detected by DNA-based enzyme immunoassay (DEIA). HPV-positive specimens were typed by reverse hybridization line probe assay (LiPA) enabling detection of 14 oncogenic HPV types and 11 non-oncogenic HPV types (Kleter, 1999). To ensure maximum sensitivity in the detection of HPV-types, samples initially considered SPF-10/DEIA positive for HPV were to be re-evaluated by a second multiplex type-specific (MPTS) HPV PCR. If either the LiPA or the MPTS assay was positive for a specific HPV type, the sample was considered to be positive for the HPV type (van Alewijk, 2013).

Assessor's comment

Objectives

The first confirmatory objective of the study HPV-40 to demonstrate the overall (total and indirect) effectiveness of Cervarix in reducing the prevalence of HPV-16/18 genital infection in female subjects was not met (Arm A versus Arm C). As a hierarchical procedure was applied to assess the confirmatory objectives and as the first confirmatory objective was not met, it was concluded that none of the confirmatory objectives were met and only exploratory interpretation could be done from the analysis of other confirmatory objectives. (part of **MO**)

Relevance of the endpoint

While there is a common agreement on the surrogate endpoint to be used in clinical trials and for licensure of HPV vaccines for cervical and anal cancers which is prevention of 6 months HPV specific persistent infections, there has been no well-established endpoint for HNC indication.

Since no clear intraepithelial precursor lesion has been identified for oropharyngeal cancer (OPC) (i.e., no surrogate endpoint to establish VE against OPC is available), using persistent HPV infection (≥6 months) as clinical endpoint is the most feasible approach. Although it is the most feasible approach, it is not so closely linked to precancerous lesions as is persistent infection at other sites. Furthermore, while 6 months and 12 months persistent positivity for the same HPV type has been used to define persistent cervical or other anogenital infections, very little is known about the duration of

oropharyngeal infections. HPV persistent infection is not the only sine qua non condition for HNC development. The rates of incidence and persistence, and the predictors of HPV oral infection remain poorly characterized, mainly due to a paucity of studies of the natural history of oral HPV infection.

Only the prevalence at the age of 18.5 years, and not the persistence of the infection, was analysed in this study since the oropharyngeal baseline HPV infection status in the study participants prior to vaccination was unknown. In addition, there was a long lag of 4–6 years in the collection of oral gargle samples post-vaccination.

This is considered insufficient since it has been established that only the prevention of a persistent HPV infection for at least 6 months can be considered a valid and meaningful surrogate endpoint for the prevention of HPV related cancers (such as cervical and ano-genital). (part of **MO**)

PCR testing on oropharyngeal samples

The new testing algorithm was used, according to which if either the LiPA or the MPTS assay was positive for a specific HPV type, the sample was considered to be positive for the HPV type. The testing algorithm, which combines a broad-spectrum PCR assay and a range of type-specific PCR assays offers a highly accurate method for the analysis of HPV infections and diminishes the rate of false-negative results. These new levels of precision and reliability of the testing algorithm may allow for infection endpoints to be used as primary endpoints in clinical studies of prophylactic HPV vaccines for HPV-associated cancers for which no other reliable surrogates exist, e.g., head and neck cancers. Meanwhile, the sensitivity and specificity values of both tests needed to be documented. The Applicant further summarized the outcomes of the validation and discussed the reliability of the results as requested. The rationale for selecting the DNA extraction method for oral rinse samples was summarized. The methods used to detect HPV DNA from oral rinse samples were deemed to be fit for purpose. ***Issue resolved.***

Sample size

Sample size calculations were made for the two primary endpoints based on assumed vaccination rates of 70% in the respective target populations in Arms A and B, a power of 90% in the final analysis, a type 1 error of 5%, a vaccine efficacy against HPV-16/18 incident infection of 70% and further assumptions as outlined in the protocol.

A model was fit to seroprevalence data for 24 communities across Finland in 1983-1997, and PCR data from HPV-008 (see Figure 4). The estimates of HPV prevalence in Arms A and B assume a potential 25% increase in sexual activity resulting in an increase in HPV prevalence in arms A and B after the start of the trial, due to the open label nature of the trial with respect to intervention arms. Community seroprevalence data was used to calculate coefficients of variation for the randomized communities of 0.13 and thus a coefficient of variation of 0.15 was assumed for the power calculations. It is expected that the mean number of enrolled study participants per community will be approximately 650 per year. The Hayes and Bennett equation for cluster RCT was applied [Hayes, 1999]. Approximately 11 communities are required in arms A, B and C to allow statistically powered evaluation of the two primary endpoints (nominal power of 90% for each comparison) and the first secondary endpoint (at least 80%) under the following assumption (two sided alpha of 0.05, a vaccine efficacy of 70% and a cluster coefficient of variation of 0.15).

Assessor's comment

No sample size calculations for VE against oropharyngeal infections were presented. Assumptions especially regarding the vaccination rates in the enrolled age cohorts were obviously too optimistic.

Randomisation

Community randomization
Communities have been stratified by seroprevalence into 3 strata (seroprevalence under 20.5%, between 20.5-23% and over 24%). Within each seroprevalence stratum, communities were randomly assigned in equal numbers to the three intervention arms using a random number generator. Recent seroprevalence data obtained in women younger than 23 years was used.

It was expected that 85% to 90% of study participants would meet admission criteria, and that approximately 90% of them would agree to participate in the immunization phase. To achieve an HPV vaccination coverage of 70% within adolescent residents from Arms A (males and females) and B communities (females only), a 9:1 ratio was planned to be used to allocate study participants to receive HPV and HBV vaccines, respectively.

Randomization of supplies
A randomization list was to be generated by the Sponsor and was to be used to number the vaccines. A randomization blocking scheme (9:1 ratio) was to be used to ensure that balance between treatments is maintained: a treatment number was to identify uniquely the vaccine doses to be administered to the same study participant. The vaccine doses were to be distributed to each study centre, respecting the randomization block size.

Randomization of study participants
The treatment allocation at the investigator site was to be performed using a central randomization system on Internet (SBIR). The randomization algorithm was to use a minimization procedure. Upon providing a study participant number, and identifying the gender and the age of the study participant, the randomization system was to use a minimization algorithm to determine the treatment number to be used for the study participant.

The actual treatment number used for first vaccination of the study participant must be recorded by the investigator or delegate in the CRF (Randomization/Treatment Allocation Section).

Assessor's comment

The study was primarily **randomized on the community level**. However, randomization procedures for supplies and participants exist as well.

The Applicant clarified the randomization approach used in the study. There are two levels of randomization: 1) communities were randomized to intervention schemes (A, B and C) and 2) HPV-vaccination eligible participants (m + f in Arm A, f in Arm B and nobody in arm C) within these communities were randomized in a 9:1 ratio to either HPV or HBV vaccination. Randomization of supplies is only used to label supplies. This is now understood and considered acceptable.

The patient level randomization was achieved using a minimization algorithm (as described in Pocock S, Simon R. Sequential Treatment Assignment with Balancing for Prognostic Factors in the Controlled Clinical Trial. Biometrics 1975; Vol. 31, No. 1.) stratified for community with only 10% randomness. Minimization accounted for age and (in Arm A also gender). This has some consequences: 1) It shows that the trial was primarily planned to compare communities rather than individuals. 2) Statistical theory for hypothesis tests might not hold. Permutation tests might be more reliable here. 3) Minimization factors age (and gender) were not used in the primary analysis model, while it is expected to be the case.

The Applicant is requested to provide adequate analyses for both primary endpoints and the key secondary endpoint adjusting for the minimization factors age and gender and to use

permutation tests for the key secondary endpoint. (OC)

The issue is partially solved. Relevant steps of the randomization procedure have been clarified but gave rise to new questions.

Blinding (masking)

For investigators, the study was open. For study participants, the study was to be partially blinded. All study participants knew in which intervention arm their community had been assigned (Arm A, B or C). Although study participants knew the vaccination strategy used in their community, the study was partially blinded:

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

Assessor's comment

Given the original purpose of the study, which was to evaluate different vaccination strategies, a community randomized trial with partial blinding of participants is considered acceptable, though not optimal as supplies were blinded and it would have been possible to further blind the study. However, given that an extensive interim CSR (dated 25.10.2012 and interim CSR amendment dated 08.10.2013) was developed and submitted to the authorities, maintenance of blinding for the Sponsor does not seem credible. Vaccination rates and further information might have become available and might have influenced further protocol amendments and the development of the SAP.

Statistical method

Analysis populations

According to the protocol, the relevant populations for efficacy analyses was the Total Cohort defined (including all females and males born in 1992, 1993, 1994, and 1995 in the 33 communities and invited to participate in the trial). The Total Cohort was to include all study participants from all communities for whom HPV DNA PCR data was collected at time of effectiveness evaluation phase. The total study cohort for analysis of effectiveness was to include all communities participating in the trial for which data concerning the prevalence of HPV was available, and the unit of analysis was to be the community.

The CSR clarified that the analysis of effectiveness was to be done for female study participants only: analysis of oropharyngeal samples included only females who had oropharyngeal HPV DNA results by PCR.

The primary analysis of effectiveness was an intention-to-treat analysis and was based on the Total enrolled cohort aiming to infer on the effectiveness associated to the Total invited cohort.

Derived and transformed data for analysis of effectiveness

- Prevalence in a community is calculated as the number of PCR positive study participants divided by the total number of female individuals in the birth cohort with Visit 5 HPV DNA data available in the community.

- Prevalence in the control vaccinated population is calculated as the number of PCR positive control vaccinated study participants divided by the total number of control vaccinated participants in the community.
- Vaccine effectiveness at the community level is the difference in the prevalence between the HPV vaccinated communities and the control communities divided by the prevalence in the control communities.
- Indirect effectiveness at the community level is the difference in the prevalence between the control vaccinated study participants in the HPV vaccinated communities and the control communities divided by the prevalence in the control communities.

Primary analyses

Effectiveness was computed as 1 minus the odds ratio of prevalence rates between the investigated arm and the control arm, with the prevalence defined as shown in Table below, depending on the type of effectiveness.

Table 8: *True prevalence rate in the investigated arm and the control arm used for defining overall effectiveness, indirect effectiveness and total effectiveness*

Type of Effectiveness	Prevalence rate in the investigated arm	Prevalence rate in the control arm C
Overall	prevalence rate in all invited subjects from the investigated arm*	prevalence rate in all subjects from arm C*
Indirect	prevalence rate in all subjects not HPV vaccinated from the investigated arm	prevalence rate in all subjects from arm C
Total	prevalence rate in HPV-vaccinated subjects from the investigated arm	prevalence rate in all subjects from arm C

Source: Study HPV-040 PRI (106636) Report (13-Apr-2016), Table 20.
*Note that this rate can also be expressed as (coverage * the prevalence rate in vaccinated subjects) + (1-coverage)* the prevalence rate in unvaccinated subjects

Since HPV seroprevalence status was measured in a subset and not in all invited subjects, this had to be inferred from the prevalence observed among the subset of subjects with measurable prevalence.

When the subset of subjects with measurable HPV seroprevalence was representative from the invited subjects, the prevalence rate observed in subjects with measurable prevalence was used to estimate the true prevalence rate. This assumption was reasonable and was used for estimating the prevalence rates for indirect effectiveness and total effectiveness. However, since in the investigated arm the proportion of HPV vaccinated subjects among evaluable subjects was larger than the proportion of HPV vaccinated subjects among invited subjects, an estimate of prevalence using weighted observation from unvaccinated subjects was used for estimating the overall effectiveness. The weight was the ratio between the rate of evaluable subjects in vaccinated subjects over the rate of evaluable subjects in non-vaccinated subjects, from pooled Arms A, B and C. Using this weight allowed restoring the proportion of non-vaccinated subjects among evaluable subjects.

The estimate of overall and total effectiveness was to be done primarily using the Mantel Haenszel **adjusted** for clustering [Donner, 2000] and **stratified** by the historical seroprevalence used in the randomization (historical seroprevalence under 20.5%, between 20.5-24% and over 24%) (as detailed in the Statistical Analysis Plan). The 95% confidence interval (CI) on effectiveness and 2-sided p-value

for the null hypothesis of no effectiveness were to be computed using the general inverse variance approach.

Hierarchical testing approach (as defined in the CSR)

All analyses were descriptive/exploratory, except the primary analyse described below. A hierarchical procedure was to be used to control the risk of erroneously concluding that effectiveness exceeds 0% based on the following ranking:

1. To demonstrate the overall (total and indirect) effectiveness of Cervarix in reducing the prevalence of HPV-16/18 genital infection in females approximately 18.5 years of age following community-based vaccination of 12-15 year old females and males (Arm A versus Arm C)

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

3. To demonstrate the total effectiveness of Cervarix in reducing the prevalence of HPV-16/18 oropharyngeal infection in females approximately 18.5 years of age, following community-based HPV vaccination of 12-15 year old females or females and males versus control (pooled Arms A and B versus Arm C, birth cohort 1994 & 1995)

4. To demonstrate the indirect effectiveness of Cervarix in reducing the prevalence of HPV-16/18 genital infection in females approximately 18.5 years of age receiving control vaccine, following community-based vaccination of 12-15 year old females and males (Arm A versus Arm C)

To control the 2-sided type I error below 5%, a hierarchical procedure, according to the order of the objectives shown above, was used for the multiple confirmatory objectives. An objective was reached if all previous objectives in the ranking were reached and the 2-sided p-value associated to the objective was below 5%.

Interim Analyses

One interim analysis for safety and immunogenicity and one final analysis was to be performed. No stopping rules were associated with the interim analysis. The interim analysis was to be carried out by an external statistician and dissemination of the results was to be limited. Blinding was to be maintained for the remaining study participants to the end of the study.

Assessor's comment

Statistical methods were only specified in the protocol. An SAP was not provided but reference to the CSR was made. However, the description of statistical methods in the CSR was not detailed enough to allow understanding of all details.

No multiplicity control over primary and key secondary endpoints was defined in the protocol. An hierarchical approach was only defined in the SAP (which was finalized very late and was furthermore not provided). As discussed in the assessment for Conduct of Study this could be considered as a post hoc choice and is hence not endorsed (part of **MO**). Likewise, pooling of Arms A and B for VE against oropharyngeal infection was not defined in the protocol. In the protocol it was stated that "the statistical analysis of the second and third secondary endpoints will be done by evaluating the difference in HPV-16/18 and other oncogenic HPV types PCR prevalence rates in communities in different intervention *arms A vs. C and B vs. C.*" (part of **MO**). Upon request the Applicant provided the SAP for the final analysis, which indeed defined the hierarchy and pooling of groups as stated in the CSR. This provides some reassurance. However, overall, the issue on data-driven choices cannot be fully ruled out, as summary level information was assumingly available at the time of finalization of the

SAP.

VE was to be computed as 1 – the prevalence odds ratio, which is understood as an odds ratio based on prevalence data (i.e. infected) rather than incidence data (i.e. newly infected) as it would usually be the case for VE.

As displayed above, the relevant endpoint for this Type II variation was total effectiveness against oropharyngeal infection in female participants. This raises the question why vaccinated male participants from Arm A were not included in the evaluation. Furthermore, as the primary endpoint (overall effectiveness against HPV-16/18 genital infection in Arm A vs C) was negative, confirmatory testing of subsequent endpoints (including total effectiveness against oropharyngeal infections) is no longer possible. Hence, the type 1 error of the study is no longer controlled.

Given the only partially blinded nature of the study and an interim analysis for safety and immunogenicity possible information leakage cannot be fully excluded. This makes the very late changes, especially relevant for oropharyngeal infection in females which was only added with the final protocol amendment (see conduct of study) at least potentially problematic.

In the protocol it was stated that the primary analysis cohort was the Total Cohort, which was to include all study participants from all communities for whom HPV DNA PCR data was collected. ***As can be seen from Table 3 in response to Q7 only around 50% of vaccinated and 10% of unvaccinated subjects provided oropharyngeal samples and hence contributed to the analysis of VE against oropharyngeal infections. This very high amount of missing data and differential pattern of missingness between study arms makes the derived VE against oropharyngeal infections highly questionable. The Applicant is requested to discuss this issue. Furthermore, an analysis of VE in the total invited cohort with sensible imputation methods for missing oropharyngeal samples (with sound justification) should be conducted to further supplement the primary estimate; a tipping point analysis is requested. (OC)***

Overall, the Applicant explained the weighting approach and showed that it only affected the co-primary analyses in a conservative manner (a significant result in the unadjusted analysis was no longer significant) and did not affect the estimated total effectiveness against oropharyngeal infections.

2.4.1.2. Results

Study participants

Subjects included in study HPV-040 were healthy male or female adolescents between, and including, 12 and 15 years of age at the time of the first vaccination, without previous vaccination with HPV or HBV. All study participants entering the effectiveness evaluation phase (including those enrolled in the immunization phase and those not enrolled in the immunization phase) were to be born between 1992 and 1995 with an age of approximately 18.5 years at the time of Visit 5, and had to live in one of the 33 communities included in the immunization phase of the study.

Details on the inclusion and exclusion criteria are available in the previously submitted Module 2.7.3, Section 3.1.1.

It was expected that 85% to 90% of study participants would meet admission criteria, and that approximately 90% of them would agree to participate in the immunization phase. To achieve an HPV vaccination coverage of 70% within adolescent residents from Arms A (males and females) and B

communities (females only), a 9:1 ratio was used to allocate study participants to receive HPV and HBV vaccines, respectively.

Table 9: *Immunization of study participants within communities*

Arm	Allocation of study participants to receive HPV and HBV vaccines by intervention Arm				Estimated rate of HPV immunization within the communities (%)
	Males (%)		Females (%)		
A (M+F HPV vaccination)	HPV	90	HPV	90	70
	HBV	10	HBV	10	
B* (F HPV vaccination)	HPV	0	HPV	90	70*
	HBV	100	HBV	10	
C (HBV Control)	HPV	0	HPV	0	NA
	HBV	100	HBV	100	

A total of 34412 subjects were enrolled in study HPV-040, and formed the Total enrolled cohort (i.e., all subjects from all communities, including subjects who only completed the behavioural questionnaire at 18.5 years of age), of whom 32175 subjects were vaccinated (14837 subjects received Cervarix and 17338 subjects received Engerix-B).

The demographic profile of subjects enrolled in the study was comparable with respect to mean age and racial distribution across groups. In the Total enrolled cohort, the mean age of the female and male participants was 14.1 years at the time of first vaccination and at Visit 5 the mean age for female and male participants was 18.0 years. The population was predominantly of white Caucasian/European heritage (98.5% in females and 99.2% in males).

The number of female subjects in birth cohorts 1994-1995, with oropharyngeal sample results available at 18.5 year of age (i.e. Visit 5) was 4871, including 3192 HPV vaccinated, 1446 HepB-vaccinated and 233 not vaccinated (**Table 10**).

Table 10: *Total effectiveness of GSK Biological's HPV-16/18 vaccine against HPV-16/18 oropharyngeal infection in pooled Arms A and B versus Arm C, for birth cohorts 1994-1995, using stratified Mantel-Haenszel adjusted for clustering (Female subjects, Total enrolled cohort)*

						VE			
							95%CI		
HPV Type	Arm	Group	N	n	%	%	LL	UL	P-value
HPV-16/18	Pooled A and B	HPV	3192	9	0.3	82.4	47.3	94.1	0.002
	C	HepB	1446	18	1.2	-	-	-	
		Not vaccinated	233	9	3.9				
		Total	1679	27	1.6				

HPV = *Cervarix*; HepB = *Engerix-B*; Not vaccinated = enrolled control without vaccination
Arm A = 90% of vaccinated males and females were randomized to HPV; Arm B = 90% of vaccinated females were randomized to HPV; Arm C = 0% of vaccinated subjects were randomized to HPV
N = number of subjects with available results; n = number of subjects reporting an event
% = n/N; VE (%) = vaccine effectiveness (1-OR); OR = odd ratio
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
P-value = two-sided p-value for H0: pooled Arms A and B is equal to Arm C, based on Mantel-Haenszel adjusted for clustering and stratified by the historical HPV-16/18 seroprevalence used in the randomization
Data source: HPV-040 PRI (106636) Report (13-Apr-2016), adapted from Table 30 and Table 110.

Tabulated data on demographics characteristics are presented in the previously submitted Module 2.7.3, Section 3.1.2 and in Table below.

Table 11: *Summary of demographic characteristics by Arm and Vaccine group, at subject level (All female subjects, Total enrolled cohort) - Study HPV-040*

		Arm A								Arm B								Arm C					
		HPV N = 5799		HepB N = 669		Not vaccinated N = 596		Total N = 7064		HPV N = 6601		HepB N = 766		Not vaccinated N = 732		Total N = 8099		HepB N = 6684		Not vaccinated N = 597		Total N = 7281	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Birth cohort	1992	1382	23.8	163	24.4	141	23.7	1686	23.9	1738	26.3	204	26.6	171	23.4	2113	26.1	1754	26.2	153	25.6	1907	26.2
	1993	1453	25.1	168	25.1	132	22.1	1753	24.8	1656	25.1	192	25.1	166	22.7	2014	24.9	1552	23.2	143	24.0	1695	23.3
	1994	1591	27.4	182	27.2	191	32.0	1964	27.8	1660	25.1	191	24.9	208	28.4	2059	25.4	1732	25.9	158	26.5	1890	26.0
	1995	1373	23.7	156	23.3	131	22.0	1660	23.5	1547	23.4	179	23.4	187	25.5	1913	23.6	1646	24.6	143	24.0	1789	24.6
	Missing or NA	0	0.0	0	0.0	1	0.2	1	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Quarter of birth	Q1-Q2	2986	51.5	353	52.8	298	50.0	3637	51.5	3427	51.9	382	49.9	382	52.2	4191	51.7	3381	50.6	330	55.3	3711	51.0
	Q3-Q4	2813	48.5	316	47.2	297	49.8	3426	48.5	3174	48.1	384	50.1	350	47.8	3908	48.3	3303	49.4	267	44.7	3570	49.0
	Missing or NA	0	0.0	0	0.0	1	0.2	1	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Area type	Urban	5360	92.4	617	92.2	578	97.0	6555	92.8	5304	80.4	611	79.8	598	81.7	6513	80.4	5915	88.5	544	91.1	6459	88.7
	Semi-urban	439	7.6	52	7.8	18	3.0	509	7.2	1297	19.6	155	20.2	134	18.3	1586	19.6	769	11.5	53	8.9	822	11.3
HPV-16/18 seroprevalence strata	<20.5%	1739	30.0	202	30.2	235	39.4	2176	30.8	1850	28.0	218	28.5	242	33.1	2310	28.5	2832	42.4	237	39.7	3069	42.2
	20.5-24%	1418	24.5	162	24.2	153	25.7	1733	24.5	1344	20.4	159	20.8	139	19.0	1642	20.3	1358	20.3	106	17.8	1464	20.1
	>24%	2642	45.6	305	45.6	208	34.9	3155	44.7	3407	51.6	389	50.8	351	48.0	4147	51.2	2494	37.3	254	42.5	2748	37.7
Age [years] at vaccination Dose 1	Mean	14.1	-	14.1	-	-	-	14.1	-	14.1	-	14.1	-	-	-	14.1	-	14.1	-	-	-	14.1	-
	SD	0.75	-	0.76	-	-	-	0.75	-	0.75	-	0.76	-	-	-	0.75	-	0.75	-	-	-	0.75	-
	Median	14.0	-	14.0	-	-	-	14.0	-	14.0	-	14.0	-	-	-	14.0	-	14.0	-	-	-	14.0	-
	Minimum	12	-	12	-	-	-	12	-	12	-	12	-	-	-	12	-	12	-	-	-	12	-
	Maximum	16	-	15	-	-	-	16	-	16	-	16	-	-	-	16	-	16	-	-	-	16	-
	Missing or NA	0	-	0	-	596	-	596	-	0	-	0	-	732	-	732	-	0	-	597	-	597	-
Age [years] at Visit 5	Mean	18.0	-	18.0	-	18.0	-	18.0	-	18.0	-	18.0	-	18.0	-	18.0	-	18.0	-	18.0	-	18.0	-
	SD	0.05	-	0.08	-	0.06	-	0.06	-	0.02	-	0.00	-	0.06	-	0.03	-	0.02	-	0.00	-	0.02	-
	Median	18.0	-	18.0	-	18.0	-	18.0	-	18.0	-	18.0	-	18.0	-	18.0	-	18.0	-	18.0	-	18.0	-
	Minimum	18	-	18	-	18	-	18	-	18	-	18	-	18	-	18	-	18	-	18	-	18	-
	Maximum	19	-	19	-	19	-	19	-	19	-	18	-	19	-	19	-	19	-	18	-	19	-
	Missing or NA	2193	-	236	-	46	-	2475	-	2954	-	320	-	89	-	3363	-	3432	-	108	-	3540	-
Ethnicity	American hispanic or latino	8	0.1	2	0.3	0	0.0	10	0.1	12	0.2	1	0.1	3	0.4	16	0.2	6	0.1	1	0.2	7	0.1
	Not american hispanic or latino	5791	99.9	667	99.7	572	96.0	7030	99.5	6589	99.8	765	99.9	690	94.3	8044	99.3	6678	99.9	532	89.1	7210	99.0
	Missing or NA	0	0.0	0	0.0	24	4.0	24	0.3	0	0.0	0	0.0	39	5.3	39	0.5	0	0.0	64	10.7	64	0.9
Geographic Ancestry	African Heritage / African American	2	0.0	1	0.1	1	0.2	4	0.1	7	0.1	1	0.1	1	0.1	9	0.1	2	0.0	0	0.0	2	0.0
	Asian - Central/South Asian Heritage	1	0.0	0	0.0	1	0.2	2	0.0	1	0.0	0	0.0	0	0.0	1	0.0	1	0.0	0	0.0	1	0.0
	Asian - East Asian Heritage	3	0.1	0	0.0	0	0.0	3	0.0	5	0.1	0	0.0	0	0.0	5	0.1	0	0.0	0	0.0	0	0.0
	Asian - Japanese Heritage	0	0.0	0	0.0	0	0.0	0	0.0	1	0.0	0	0.0	0	0.0	1	0.0	1	0.0	1	0.2	2	0.0
	Asian - South East Asian Heritage	9	0.2	0	0.0	1	0.2	10	0.1	3	0.0	1	0.1	0	0.0	4	0.0	1	0.0	0	0.0	1	0.0
	White - Arabic / North African Heritage	8	0.1	1	0.1	5	0.8	14	0.2	17	0.3	1	0.1	3	0.4	21	0.3	20	0.3	2	0.3	22	0.3
	White - Caucasian / European Heritage	5722	98.7	660	98.7	559	93.8	6941	98.3	6537	99.0	757	98.8	690	94.3	7984	98.6	6631	99.2	527	88.3	7158	98.3
	Other	54	0.9	7	1.0	4	0.7	65	0.9	30	0.5	6	0.8	1	0.1	37	0.5	28	0.4	3	0.5	31	0.4
	Missing or NA	0	0.0	0	0.0	25	4.2	25	0.4	0	0.0	0	0.0	37	5.1	37	0.5	0	0.0	64	10.7	64	0.9

Arm A = 90% of vaccinated female and male subjects were randomised to HPV
Arm B = 90% of vaccinated female subjects were randomised to HPV
Arm C = 0% of vaccinated subjects were randomised to HPV
HPV = *Cervarix*
HepB = *Engerix-B*
Not vaccinated = enrolled control without vaccination
N = number of subjects; n/% = number/percentage of subjects in a given category; Value = value of the considered parameter; SD = standard deviation; NA = not applicable
Data source HPV-040 PRI (106636) Report (13-Apr-2016), Table 25

Assessor's comment

Please refer to the EMA procedure EMA/CHMP/459022/2016 for the assessment on the study participants in general.

A major limitation of this pivotal study is that only oral specimen samples of female subjects were collected and investigated, although the prevalence of HPV-oral infections is more common in men and would be claimed for both gender within this extension of indication. (**MO**)

The applicant is requested to explain the efficacy effect of Hepatitis B vaccination compared to non-vaccinated subjects to prevent prevalent infections demonstrated in **Table 10** (table 4 of the submitted overview)

The data provided by the applicant in Table 1 and 2 are accurate for the studies. Therefore, the efficacy effect of Hepatitis B vaccination is questioned and just by mischance in the groups to understand. ***Issue is solved.***

Participant flow

The number of subjects enrolled into the study, by arm group, gender and vaccine group, at subject level is presented in **Table 12**. The number of subjects vaccinated, completed and withdrawn with reason for withdrawal, by gender and vaccine group, at subject level in the TVC is presented in **Table 13**.

A total of 32,175 subjects were vaccinated in the study, of whom 14,837 subjects received the HPV vaccine (referred to as the 'HPV group') and 17,338 subjects received the HBV vaccine (referred to as the 'HepB group') (please refer to **Table 13**).

A total of 2,236 subjects were enrolled but not vaccinated: 596 female and 73 male subjects in Arm A, 732 female and 129 male subjects in Arm B, and 597 female and 109 male subjects in Arm C (please refer to **Table 12**).

Table 12: *Number of subjects enrolled into the study, by Arm group, gender and Vaccine group, at subject level (Total enrolled cohort)*

	Female						Male					
	Arm A N = 7064		Arm B N = 8099		Arm C N = 7281		Arm A N = 2808		Arm B N = 5011		Arm C N = 4149	
Vaccine group	n	%	N	%	n	%	n	%	N	%	n	%
HPV	5799	82.1	6601	81.5	0	0.0	2436	86.8	2	0.0	0	0.0
HepB	669	9.5	766	9.5	6684	91.8	299	10.6	4880	97.4	4040	97.4
Not vaccinated	596	8.4	732	9.0	597	8.2	73	2.6	129	2.6	109	2.6

Assessor's comment
The applicant should address, why so many subjects were not vaccinated.

The survey conducted in Finland on acceptance of HPV vaccination by adolescents and their parents during the years preceding the study start showed an acceptance rate of 83% and 86%, respectively explains the low enrolment rate. ***Issue solved.***

The HPV group consisted of 5,799 female and 2,436 male subjects in Arm A, 6,601 female and two male subjects in Arm B, and no female or male subjects in Arm C. The HepB group consisted of 669 female and 299 male subjects in Arm A, 766 female and 4,880 male subjects in Arm B, and 6,684 female and 4,040 male subjects in Arm C (please refer to **Table 12**).

Of the 32,175 subjects who were vaccinated, 13,893 subjects completed the study (please refer to **Table 13**).

Table 13: *Number of subjects vaccinated, completed and withdrawn with reason for withdrawal, by gender and Vaccine group, at subject level (Total vaccinated cohort)*

	Female			Male			Total		
	HPV	HepB	Total	HPV	HepB	Total	HPV	HepB	Total
Number of subjects vaccinated	12399	8119	20518	2438	9219	11657	14837	17338	32175
Number of subjects completed	7655	4612	12267	691	935	1626	8346	5547	13893

	Female			Male			Total		
	HPV	HepB	Total	HPV	HepB	Total	HPV	HepB	Total
Number of subjects withdrawn	4744	3507	8251	1747	8284	10031	6491	11791	18282
Reasons for withdrawal :									
Serious Adverse Event	0	0	0	0	0	0	0	0	0
New Onset of Autoimmune Disorder	0	0	0	0	0	0	0	0	0
Protocol violation	0	0	0	0	0	0	0	0	0
Consent withdrawal (not due to an adverse event) or no consent	2	2	4	1	2	3	3	4	7
Migrated/moved from study area	11	10	21	2	1	3	13	11	24
Lost to follow-up (subjects with incomplete vaccination course)	63	40	103	20	77	97	83	117	200
Lost to follow-up (subjects with complete vaccination course)	3358	2618	5976	1349	8139	9488	4707	10757	15464
Others	1310	837	2147	375	65	440	1685	902	2587

A total of 18,282 subjects withdrew from the study for the following reasons: withdrawal or absence of consent (seven subjects), migration from the study area (24 subjects), lost to follow-up (200 subjects who did not complete the vaccination course and 15,464 subjects who completed the vaccination course), and other reasons (2,587 subjects) (please refer to **Table 13**). The 18,275 subjects who were regarded as withdrawals or lost to follow-up but who did not withdraw their consent were followed up for pregnancies and pIMDs by registry search up to the day before the subject reached 19 years of age.

Assessor's comment
The drop-out rate was very high in this study.

Recruitment

Effectiveness of Cervarix against oropharyngeal infection was assessed as subsequent confirmatory (secondary) objective of the study (total effectiveness against HPV-16/18), and as descriptive secondary (total effectiveness against oncogenic HPV types) and descriptive tertiary objectives (overall effectiveness against HPV-16/18 and oncogenic HPV types).

The number of female subjects in birth cohorts 1994-1995, with oropharyngeal sample results available at 18.5 year of age (i.e. Visit 5) was 4.871, including 3.192 HPV-vaccinated, 1.446 HepB-vaccinated and 233 not vaccinated (**Table 10**).

The demographic profile of subjects enrolled in the study was comparable with respect to mean age and racial distribution across groups. In the Total enrolled cohort, the mean age of the female and male participants was 14.1 years at the time of first vaccination and at Visit 5 the mean age for female and male participants was 18.0 years. The population was predominantly of white Caucasian/European heritage (98.5% in females and 99.2% in males).

Conduct of the study

Assessor's comment

The confirmatory analysis for oropharyngeal infection was introduced as secondary endpoint with Protocol Amendment 9 (dated 24 March 2014). Protocol amendments were supplied in Appendix H of the Study Protocol as a list of changes with overall justification for each amendment. No distinct study protocols were provided other than the final Protocol Amendment 9. Study completion date (i.e., last

study visit) was 17 December 2014. Given the study duration of 7 years the final and crucial protocol amendment was very late in the study.

The data base lock was 05 November 2015, which is almost one year after the study completion date. This is not comprehensible.

The SAP (which was not provided, see OC related to statistical methods) was said to be finalized on 09 September 2015, i.e. after study completion and shortly bevor DB-lock. Only within this SAP key secondary endpoints were specified and a hierarchy of statistical tests was fixed. Given other changes such as the "*post-hoc* analysis (…) using urban/semi-urban as stratification factor" (CSR HPV-040 PRI, page 136) which seem to be based on the knowledge of at least some data, these crucial definitions on key secondary endpoint and multiplicity might have been made in the light of the accrued data as well. Hence these changes should be considered *post-hoc*. No confirmatory hypothesis for oropharyngeal infections was defined in the protocol.

Baseline data

No baseline data were elaborated regarding efficacy.

Outcomes and estimation

In study HPV-040 a hierarchical procedure was applied to assess confirmatory objectives. Effectiveness of Cervarix against oropharyngeal infection was assessed as subsequent confirmatory (secondary) objective of the study (total effectiveness against HPV-16/18), and as descriptive secondary (total effectiveness against oncogenic HPV types) and descriptive tertiary objectives (overall effectiveness against HPV-16/18 and oncogenic HPV types). The data have been published[3].

Co-primary Confirmatory Objectives: Effectiveness against Genital HPV-16/18 Infection

The HPV-040 study design included hierarchical statistical assessment of confirmatory objectives. Since one of the confirmatory objectives, preceding the confirmatory objective on effectiveness against oropharyngeal infection, was not met, it is important to present and discuss these results first.

The first confirmatory objective in the hierarchy was not met: the observed overall (total and indirect) effectiveness in Arm A against HPV-16/18 genital infection was 23.8% (95% CI: -19.0, 51.1); p-value = 0.232. The observed overall (total and indirect) effectiveness in Arm B against HPV-16/18 genital infection (second objective in the hierarchy) was 49.6% (95% CI: 20.1, 68.2), p-value= 0.004.

The overall effectiveness was expected to be higher for Arm A (female/male vaccination) as compared to Arm B (female vaccination) with efficient randomization at baseline, similar HPV vaccination coverage in females, and balanced behavioural characteristics during the follow-up years[4]. However, the data suggest that arm A seemed to have a higher transmission of HPV infection than the other two arms, indicating that the original randomization of the study communities using historical seroprevalence stratum may have failed to allocate comparable communities to each Arm. Therefore, a randomization bias may have been detrimental to comparisons between Arm A and Arm C leading to failure of the first objective in the hierarchy.

[3] Lehtinen M, Apter D, Eriksson T, Harjula K, Hokkanen M, Lehtinen T, Natunen K, Damaso S, Soila M, Bi D, Struyf F. Effectiveness of the AS04-adjuvanted HPV-16/18 vaccine in reducing oropharyngeal HPV infections in young females - results from a community-randomized trial. Int J Cancer. 2019. doi: 10.1002/ijc.32791.
[4] Lehtinen M, French KM, Dillner J, Paavonen J, Garnett G. Sound implementation of human papillomavirus vaccination as a community-randomized trial. Therapy 2008; 5(3): 289–294.

It was noted that the area type (urban versus semi-urban) may have been a better prognostic variable for the HPV-16/18 infection rates. Therefore, a post-hoc analysis estimating the overall effectiveness stratified by the area type (urban, semi-urban) was performed.

- Arm A versus Arm C (Control): VE = 29.7% (95% CI: 0.0, 50.6), two-sided p-value = 0.05
- Arm B versus Arm C (Control): VE = 45.4% (95% CI: 11.8, 66.2), two-sided pvalue <0.05

The post-hoc analysis shows improvement in the overall (total and indirect) effectiveness in Arm A against HPV-16/18 genital infection (first objective in the hierarchy). The results from primary and the post-hoc analysis estimating the overall (total and indirect) effectiveness in Arm B against HPV-16/18 genital infection (second objective in the hierarchy) were consistent. The results from the primary and post-hoc analysis showed no statistical evidence of difference in overall effectiveness between gender-neutral (arm A) and females-only (arm B) vaccination strategies.

In addition, a high total effectiveness against genital HPV-16/18 infection in Arm A versus Arm C, Arm B versus Arm C and pooled Arms A and B versus Arm C was observed (VE = 93.8% [95% CI: 84.1, 97.6]; 92.1% [95% CI: 80.0, 96.9]; 93.3% [95% CI: 87.7, 96.4], respectively), consistent with findings in global efficacy studies.

The primary analysis for the overall (total and indirect) effectiveness in Arm A against HPV-16/18 genital infection (first objective in the hierarchy) was not met due to the limitations described above. As the first confirmatory objective was not met and a hierarchical procedure was the subsequent confirmatory objectives of the study could not be considered conclusive.

Tabulated data are presented in the previously submitted Module 2.7.3, Section 3.2.1. (predefined analysis confirmatory objectives) and Section 3.2.2 (exploratory analysis total effectiveness) (see also Annex Table 2 to Annex Table 4 of the submitted Clinical Overview addendum) and in Table 125 in the CSR dated 13-Apr-2016 (post-hoc analysis) (see Annex Table 5 of the submitted Clinical Overview addendum).

Assessor's comment

The strategy of the Applicant to value the findings related to OPC is acknowledged. The interest of the OPC findings was acknowledged in the assessment of the procedure EMEA/H/C/721/II/0081 (see also below, subheading *Confirmatory objective on total effectiveness against oropharyngeal HPV-16/18 infection*).

The results of the final analyses of efficacy of study HPV-040 have previously been assessed in procedure EMEA/H/C/721/II**/0081** on 23 March 2017 (PAM: final effectiveness results of clinical study HPV-040). The conclusion was that study HPV-040 could not identify the best HPV vaccination strategy (gender-neutral versus girls only) in adolescents between the age of 12-15 years in Finland to protect against genital HPV-16/18 incident infections after 3.5 to 6.5 years post-dose 1. The herd effect proved to be not statistically significant in the gender-neutral HPV immunization scenario.

During this procedure, it was also concluded that:

"The Study HPV-040 aimed at comparing the effectiveness of HPV vaccination when vaccinating females and males adolescents versus vaccinating females only. The results of Study HPV-040 are important as the study investigated the direct and indirect effects of both vaccination strategies.

Results are disappointing as no statistical overall and indirect HPV-16/18 effectiveness was observed. The MAH identified potential issues related to the study design and/or the study setting which could potentially explain those findings.

The assessor agrees that the vaccine coverage reached in the Arm A and Arm B communities are

insufficient for the purpose of the study. The HPV vaccination coverage was similar in females of Arm A (47.5%) and Arm B (45.5%), and was 19.8% among Arm A male participants. This was much lower than the expected vaccine coverage of 70% for both genders. A lower proportion of male responded positively to the invitation to participate in the study which probably explains that only 30% for males were vaccinated with HPV-16/18 in Arm A.

Similarly, the MAH's discussion on stratification criteria indicates that the factors of risk for HPV infection were probably not equally distributed among study arms. However, based on the behavioural questionnaire, adjustment could have been made at the time of the analysis. The MAH is requested to present and discuss this adjustment.

Although the hypothesis that the inter-community mobility was limited in adolescents aged 12-15, a higher mobility may be expected in adolescents aged between 16 and 18.5 years old.

In conclusion, Study HPV-040 could not identify the best HPV vaccination strategy (gender-neutral versus girls only) in adolescents between the age of 12-15 years in Finland to protect against genital HPV-16/18 incident infections after 3.5 to 6.5 years post-dose 1. The herd effect proved to be not statistically significant in the gender-neutral HPV immunization scenario."

Stratification based on true baseline HPV status for study subjects probably would have provided a more uniform background exposure than when relying on historical seroprevalence.

The post-hoc results suggest that the difference in vaccine effectiveness between Arm A and Arm B in the primary analysis may have been caused by randomization that failed to prevent allocation bias due to the small number of communities.

Secondary Objectives: Effectiveness against oropharyngeal HPV-16/18 infection

Confirmatory objective on total effectiveness against oropharyngeal HPV-16/18 infection

A subsequent confirmatory objective in the hierarchy was to assess the total effectiveness of Cervarix in reducing the prevalence of HPV-16/18 oropharyngeal infection in females following community-based HPV vaccination of 12 - 15 year old females or females and males. To this end, the prevalence rate in HPV-vaccinated subjects pooled from Arm A and Arm B was considered versus the prevalence rate in all subjects from Arm C. VE was calculated for the 1994 and 1995 birth cohorts only.

Evidence of high total effectiveness of Cervarix against HPV-16/18 oropharyngeal prevalent infection in pooled Arms A and B versus Arm C was observed (VE = 82.4% [95% CI: 47.3, 94.1]). The prevalence of HPV-16/18 oropharyngeal infection to calculate the total effectiveness (birth cohorts 1994-1995) was 0.3% for the HPV group in pooled Arms A and B (male and female or females only vaccinated) and 1.6% in Arm C (**Table 14**).

For HPV-16, effectiveness against oropharyngeal prevalent infection was 81.3% (95% CI: 25.8, 95.3) and for HPV-18 it was 78.9% (95% CI: 32.3, 93.4) (**Table 14**).

Table 14: *Total effectiveness against HPV-16/18 and HPV-16 oropharyngeal infection in pooled Arms A and B for birth cohorts 1994-1995 (Female study participants, Total enrolled cohort)*

						VE			
							95%CI		
HPV Type	Arm	Group	N	n	%	%	LL	UL	P-value
HPV-16/18	Pooled A and B	HPV	3192	9	0.3	82.4	47.3	94.1	0.002
	C	HepB	1446	18	1.2	-	-	-	
		Not vaccinated	233	9	3.9				
		Total	1679	27	1.6				
HPV-16	Pooled A and B	HPV	3192	6	0.2	81.3	25.8	95.3	0.017
	C	HepB	1446	13	0.9	-	-	-	
		Not vaccinated	233	6	2.6				
		Total	1679	19	1.1				
HPV-18	Pooled A and B	HPV	3192	4	0.1	78.9	32.3	93.4	0.009
	C	HepB	1446	7	0.5	-	-	-	
		Not vaccinated	233	3	1.3				
		Total	1679	10	0.6				

HPV = *Cervarix*; HepB = *Engerix-B*; Not vaccinated = enrolled control without vaccination
Arm A = 90% of vaccinated males and females were randomized to HPV; Arm B = 90% of vaccinated females were randomized to HPV; Arm C = 0% of vaccinated subjects were randomized to HPV
N = number of subjects with available results; n = number of subjects reporting an event
% = n/N; VE (%) = vaccine effectiveness (1-OR); OR = odd ratio
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
P-value = two-sided p-value for H0: pooled Arms A and B is equal to Arm C, based on Mantel-Haenszel adjusted for clustering and stratified by the historical HPV-16/18 seroprevalence used in the randomization
Data source: HPV-040 PRI (106636) Report (13-Apr-2016), adapted from Table 30 and Table 110.

Assessor's comment

High effectiveness of Cervarix against prevalent HPV-16/18 oropharyngeal infection (based on assessment at a single timepoint) in young adult females up to 6 years after vaccination was observed (VE = 82.4% [95% CI: 47.3, 94.1]), as well as for HPV-16 only and HPV18 only (**Table 14**), but the statistical test for VE against oropharyngeal infections is not considered to be statistically significant. Please refer to the analysis of the statisticians. (part of **MO**)

As with all cross-sectional studies, data from the HPV-040 cannot be used to establish a causal relationship between variables. Furthermore, due to a low prevalence of oral HPV infection, sub-group analyses assessing the impact of number of vaccine doses, age at vaccination and time since vaccination could not be conducted. Thus limitations of this study are various, including no baseline serology, limited inclusion of males. (part of **MO**)

According to the immunogenicity subset of the study HPV-040 around 87 % of subjects were seronegative for both anti-HPV-16 and anti-HPV-18 at baseline and therefore the detected oropharyngeal HPV infections in both vaccination groups could be considered as incident infections. Nevertheless, persistent instead of prevalent infection should be demonstrated as endpoint for comparison in HPV-vaccinated versus HepB-vaccinated subjects, which is not possible with only one sample per subject of oral specimen. (part of **MO**)

The results of the final analyses of efficacy of study HPV-040 have previously been assessed in procedure EMEA/H/C/721/II/0081 on 23 March 2017 (PAM: final effectiveness results of clinical study HPV-040):

"The secondary objectives concerning the demonstration of overall and total effectiveness against HPV-16/18 oropharyngeal incident prevalent infection were met (pooled Arms A & B versus Arm C). Those findings suggest indirect evidence for oropharyngeal cancer protection (OPC). Considering the lack of data regarding this clinical outcome, those findings are important. However, there is no surrogate

endpoint to establish VE against OPC currently agreed upon and further studies need to be done with the best possible clinical endpoint."

As already discussed in procedure EMEA/H/C/000721/II/0081 in 2017, the Applicant should clarify if an adequately powered clinical study has been initiated with the relevant primary endpoint (prevention of a persistent HPV infection for at least 6 months) for the protection against HNC with adequate serial oral sampling. The Applicant has further clarified that no study has been initiated and that he does no intend to conduct clinical trial. Only post-marketing observational studies are planned. This is not endorsed. It is considered that a RCT must be conducted. (part of the **MO**)

Total effectiveness against oropharyngeal infection with oncogenic HPV types

Exploratory analysis of total effectiveness of Cervarix against oropharyngeal prevalent infection with all oncogenic HPV types combined (HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68) following vaccination of female adolescents or females and male adolescents (pooled Arms A and B versus Arm C) led to a VE of 27.2% (95% CI: -2.2, 48.1).

Tabulated data which were provided in Table 110 in the CSR dated 13-Apr-2016 are shown in the table below.

Table 15: *Exploratory objectives - total effectiveness of GSK Biologicals' HPV-16/18 vaccine against oropharyngeal infection with specific HPV types in pooled Arms A and B versus Arm C, for birth cohorts 1994-1995, using stratified Mantel-Haenszel adjusted for clustering (Female study participants, Total enrolled cohort) - Study HPV-040*

									VE			
										95%CI		
HPV Type	Birth cohort	Arm	N invited	Group	N	n+	n	%	%	LL	UL	P-value
16	1994-1995	Pooled A and B	12889	HPV	3192	5	6	0.2	81.3	25.8	95.3	0.017
		C	6067	HepB	1446	8	13	0.9	-	-	-	-
				Not vaccinated	233	3	6	2.6				
				Total	1679	8	19	1.1				
18	1994-1995	Pooled A and B	12889	HPV	3192	3	4	0.1	78.9	32.3	93.4	0.009
		C	6067	HepB	1446	4	7	0.5	-	-	-	-
				Not vaccinated	233	3	3	1.3				
				Total	1679	6	10	0.6				
31/45	1994-1995	Pooled A and B	12889	HPV	3192	3	3	0.1	75.3	12.7	93.0	0.030
		C	6067	HepB	1446	5	7	0.5	-	-	-	-
				Not vaccinated	233	2	2	0.9				
				Total	1679	7	9	0.5				
31/33/45	1994-1995	Pooled A and B	12889	HPV	3192	7	9	0.3	69.9	29.6	87.1	0.006
		C	6067	HepB	1446	7	14	1.0	-	-	-	-
				Not vaccinated	233	2	2	0.9				
				Total	1679	9	16	1.0				
31/33/45/51	1994-1995	Pooled A and B	12889	HPV	3192	17	53	1.7	33.6	-4.3	57.7	0.075
		C	6067	HepB	1446	10	37	2.6	-	-	-	-
				Not vaccinated	233	4	5	2.1				
				Total	1679	11	42	2.5				
31/33/45/51/52	1994-1995	Pooled A and B	12889	HPV	3192	18	63	2.0	33.6	-6.7	58.7	0.091
		C	6067	HepB	1446	10	43	3.0	-	-	-	-
				Not vaccinated	233	5	6	2.6				
				Total	1679	11	49	2.9				

31/33/35/39/45/51/52/56/58/59/66/68	1994-1995	Pooled A and B	12889	HPV	3192	21	129	4.0	16.0	-19.5	41.0	0.332
		C	6067	HepB	1446	11	67	4.6	-	-	-	-
				Not vaccinated	233	9	12	5.2				
				Total	1679	11	79	4.7				
16/18/31/33/35/39/45/51/52/56/58/59/66/68	1994-1995	Pooled A and B	12889	HPV	3192	21	136	4.3	27.2	-2.2	48.1	0.066
		C	6067	HepB	1446	11	76	5.3	-	-	-	-
				Not vaccinated	233	9	19	8.2				
				Total	1679	11	95	5.7				
6	1994-1995	Pooled A and B	12889	HPV	3192	19	36	1.1	30.0	-19.8	59.1	0.194
		C	6067	HepB	1446	10	19	1.3	-	-	-	-
				Not vaccinated	233	6	8	3.4				
				Total	1679	10	27	1.6				
11	1994-1995	Pooled A and B	12889	HPV	3192	5	5	0.2	47.6	-81.3	84.9	0.307
		C	6067	HepB	1446	3	3	0.2	-	-	-	-
				Not vaccinated	233	2	2	0.9				
				Total	1679	4	5	0.3				
6/11	1994-1995	Pooled A and B	12889	HPV	3192	19	41	1.3	25.8	-21.7	54.8	0.237
		C	6067	HepB	1446	10	21	1.5	-	-	-	-
				Not vaccinated	233	6	8	3.4				
				Total	1679	10	29	1.7				
6/11/53/74	1994-1995	Pooled A and B	12889	HPV	3192	21	72	2.3	16.1	-30.7	46.2	0.437
		C	6067	HepB	1446	10	34	2.4	-	-	-	-
				Not vaccinated	233	6	11	4.7				
				Total	1679	10	45	2.7				

HPV = *Cervarix*; HepB = *Engerix-B*
Not vaccinated = enrolled control without vaccination
Arm A = 90% of vaccinated males and females were randomized to HPV; Arm B = 90% of vaccinated females were randomized to HPV; Arm C = 0% of vaccinated subjects were randomized to HPV
N invited = number of subjects invited to participate in the study; N = number of subjects with available results; n+ = number of communities with at least one event; n = number of subjects reporting an event
% = n/N; VE (%) = vaccine effectiveness (1-OR); OR = odd ratio
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
P-value = exploratory two-sided p-value not adjusted for the number of endpoints, for H0: pooled Arms A and B is equal to Arm C, based on Mantel-Haenszel adjusted for clustering and stratified by the historical HPV-16/18 seroprevalence used in the randomization

Total effectiveness against oropharyngeal infection with non-vaccine HPV oncogenic types 31/33/45

Analysis of total effectiveness of Cervarix in cross protection against oropharyngeal prevalent infection with non-vaccine oncogenic HPV types 31/33/45 combined following vaccination of female adolescents or females and male adolescents (pooled Arms A and B versus Arm C) led to an observed 69.9% VE (95% CI: 29.6, 87.1) (**Table 16**).

The type-specific prevalence rates for oropharyngeal infection with HPV types 31, 33, 45 combined, used to calculate the total effectiveness (birth cohorts 1994-1995) were 0.3% for the HPV group in pooled Arms A and B and 1.0% in Arm C (HBV vaccinated and non-vaccinated).

Table 16: *Total effectiveness against oropharyngeal infection with non-vaccine HPV types 31/33/45 in pooled Arms A and B for birth cohorts 1994-1995 (Female study participants, Total enrolled cohort)*

						VE			
							95%CI		
Arm	N invited	Group	N	n	%	%	LL	UL	P-value
Pooled A and B	12889	HPV	3192	9	0.3	69.9	29.6	87.1	0.006
C	6067	HepB	1446	14	1.0	-	-	-	
		Not vaccinated	233	2	0.9				
		Total	1679	16	1.0				

HPV = *Cervarix*; HepB = *Engerix-B*; Not vaccinated = enrolled control without vaccination
Arm A = 90% of vaccinated males and females were randomized to HPV; Arm B = 90% of vaccinated females were randomized to HPV; Arm C = 0% of vaccinated subjects were randomized to HPV
N = number of subjects with available results; n = number of subjects reporting an event
% = n/N; VE (%) = vaccine effectiveness (1-OR); OR = odd ratio
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
P-value = exploratory two-sided p-value not adjusted for the number of endpoints, for H0: pooled Arms A and B is equal to Arm C, based on Mantel-Haenszel adjusted for clustering and stratified by the historical HPV-16/18 seroprevalence used in the randomization
Data source: HPV-040 PRI (106636) Report (13-Apr-2016), adapted from Table 110.

Assessor's comment

Analysis of total effectiveness in cross-protection against oropharyngeal prevalent infection with non-vaccine oncogenic HPV types (HPV-31/33/45) led to an observed VE of 69.9% (95% CI: 29.6, 87.1) and for all oncogenic HPV types combined the observed VE was 27.2% (95% CI: -2.2, 48.1).

The cross-protective efficacy of Cervarix against cervical histopathological and virological endpoints (persistent infection) has been evaluated in study HPV-008 for 12 non-vaccine oncogenic HPV types. The study was not powered to assess efficacy against disease caused by individual HPV types. The analysis against the primary endpoint was confounded by multiple co-infections in the CIN2+ lesions. Unlike histopathological endpoints, virological endpoints are less confounded by multiple infections. HPV-31, 33 and 45 showed consistent cross-protection for 6-month persistent infection and CIN2+ endpoints in all study cohorts.

Overall effectiveness against oropharyngeal HPV-16/18 infection

Exploratory analysis of overall (total + indirect) effectiveness of Cervarix in reducing the prevalence of HPV-16/18 oropharyngeal infection following vaccination of female adolescents or females and male adolescents (pooled Arms A and B versus Arm C) led to an observed 66.8% VE (95% CI: 19.8, 86.3).

The (weighted) HPV-16/18 oropharyngeal infection prevalence to calculate the overall effectiveness against HPV-16/18 oropharyngeal infection was 0.8% in pooled Arms A and B, and 2.4% in Arm C (HBV vaccinated and non-vaccinated).

Tabulated data which were provided in Table 113 in the CSR dated 13-Apr-2016 are shown in the table below.

Table 17: *Exploratory objectives - overall effectiveness of GSK Biologicals' HPV-16/18 vaccine against HPV-16/18 oropharyngeal infection in pooled Arms A and B versus Arm C, for birth cohorts 1994-1995, using stratified Mantel-Haenszel adjusted for clustering (Female study participants, Total enrolled cohort)*

									VE			
										95%CI		
HPV Type	Birth cohort	Arm	N invited	Group	N	n+	n	%	%	LL	UL	P-value
16/18	1994-1995	Pooled A and B	12889	HPV	3192	5	9	0.3	66.8	19.8	86.3	0.014
				HepB	394	3	4	1.0				
				Not vaccinated	634	7	8	1.3				
				Total	4220	10	21	0.8				
		C	6067	HepB	1446	9	18	1.2	-	-	-	-
				Not vaccinated	233	5	9	3.9				
				Total	1679	10	27	2.4				

HPV = HPV-16/18 L1 VLP AS04 vaccine
HepB = Hepatitis B vaccine
Not vaccinated = enrolled control without vaccination
Arm A = 90% of vaccinated males and females were randomized to HPV
Arm B = 90% of vaccinated females were randomized to HPV
Arm C = 0% of vaccinated subjects were randomized to HPV
N invited = number of subjects invited to participate in the study
N = number of subjects with available results
n+ = number of communities with at least one event
n = number of subjects reporting an event
% = n/N except for the Total where %=(n(HPV)+n(HepB)+w*n(Not vaccinated))/(N(HPV)+N(HepB)+w*N(Not vaccinated))
w = 4.9 (% of evaluable subjects among vaccinated subjects (HPV and HepB)/% of evaluable subjects among subjects invited to participate in the trial and not vaccinated, from pooled Arms A, B and C)
VE (%) = vaccine effectiveness (1-OR)
OR = odd ratio
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
P-value = exploratory two-sided p-value not adjusted for the number of endpoints, for H0: pooled Arms A and B is equal to Arm C, based on Mantel-Haenszel adjusted for clustering and stratified by the historical HPV-16/18 seroprevalence used in the randomization

Overall effectiveness against oropharyngeal infection with oncogenic HPV types

Exploratory analysis of overall (total + indirect) effectiveness of Cervarix in reducing the prevalence of oropharyngeal infection with all oncogenic HPV types combined (HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68) following vaccination of female adolescents or females and male adolescents (pooled Arms A and B versus Arm C) led to a VE of 24.8% (95% CI: -8.1, 47.7).

Tabulated data which were provided in Table 114 in the CSR dated 13-Apr-2016 are shown in the table below.

Table 18: *Exploratory objectives - overall effectiveness of GSK Biologicals' HPV-16/18 vaccine against oropharyngeal infection with specific HPV types in pooled Arms A and B versus Arm C, for birth cohorts 1994-1995, using stratified Mantel-Haenszel adjusted for clustering (Female study participants, Total enrolled cohort)*

									VE			
										95%CI		
HPV Type	Birth cohort	Arm	N invited	Group	N	n+	n	%	%	LL	UL	P-value
16	1994-1995	Pooled A and B	12889	HPV	3192	5	6	0.2	69.7	3.1	90.5	0.044
				HepB	394	2	2	0.5				
				Not vaccinated	634	5	5	0.8				
				Total	4220	8	13	0.5				
		C	6067	HepB	1446	8	13	0.9	-	-	-	-
				Not vaccinated	233	3	6	2.6				
				Total	1679	8	19	1.6				
18	1994-1995	Pooled A and B	12889	HPV	3192	3	4	0.1	46.6	-71.5	83.4	0.292
				HepB	394	3	3	0.8				
				Not vaccinated	634	4	4	0.6				
				Total	4220	6	11	0.4				
		C	6067	HepB	1446	4	7	0.5	-	-	-	-
				Not vaccinated	233	3	3	1.3				
				Total	1679	6	10	0.8				
31/45	1994-1995	Pooled A and B	12889	HPV	3192	3	3	0.1	38.2	-175.8	86.1	0.529
				HepB	394	0	0	0.0				
				Not vaccinated	634	3	3	0.5				
				Total	4220	6	6	0.3				
		C	6067	HepB	1446	5	7	0.5	-	-	-	-
				Not vaccinated	233	2	2	0.9				
				Total	1679	7	9	0.6				
31/33/45	1994-1995	Pooled A and B	12889	HPV	3192	7	9	0.3	13.0	-125.6	66.4	0.775
				HepB	394	1	1	0.3				
				Not vaccinated	634	6	9	1.4				
				Total	4220	9	19	0.8				
		C	6067	HepB	1446	7	14	1.0	-	-	-	-
				Not vaccinated	233	2	2	0.9				
				Total	1679	9	16	0.9				

31/33/45/51	1994-1995	Pooled A and B	12889	HPV	3192	17	53	1.7	8.1	-56.9	46.2	0.756
				HepB	394	4	6	1.5				
				Not vaccinated	634	10	18	2.8				
				Total	4220	18	77	2.2				
		C	6067	HepB	1446	10	37	2.6	-	-	-	-
				Not vaccinated	233	4	5	2.1				
				Total	1679	11	42	2.4				
31/33/45/51/52	1994-1995	Pooled A and B	12889	HPV	3192	18	63	2.0	3.8	-62.9	43.2	0.885
				HepB	394	6	9	2.3				
				Not vaccinated	634	10	22	3.5				
				Total	4220	19	94	2.7				
		C	6067	HepB	1446	10	43	3.0	-	-	-	-
				Not vaccinated	233	5	6	2.6				
				Total	1679	11	49	2.8				
31/33/35/39/45/51/52/56/58/59/66/68	1994-1995	Pooled A and B	12889	HPV	3192	21	129	4.0	9.3	-27.3	35.4	0.573
				HepB	394	12	17	4.3				
				Not vaccinated	634	14	31	4.9				
				Total	4220	22	177	4.5				
		C	6067	HepB	1446	11	67	4.6	-	-	-	-
				Not vaccinated	233	9	12	5.2				
				Total	1679	11	79	4.9				
16/18/31/33/35/39/45/51/52/56/58/59/66/68	1994-1995	Pooled A and B	12889	HPV	3192	21	136	4.3	24.8	-8.1	47.7	0.124
				HepB	394	13	20	5.1				
				Not vaccinated	634	15	36	5.7				
				Total	4220	22	192	5.0				
		C	6067	HepB	1446	11	76	5.3	-	-	-	-
				Not vaccinated	233	9	19	8.2				
				Total	1679	11	95	6.5				
6	1994-1995	Pooled A and B	12889	HPV	3192	19	36	1.1	55.5	17.9	75.9	0.010
				HepB	394	1	2	0.5				
				Not vaccinated	634	4	6	0.9				
				Total	4220	19	44	1.0				
		C	6067	HepB	1446	10	19	1.3	-	-	-	-
				Not vaccinated	233	6	8	3.4				
				Total	1679	10	27	2.3				
11	1994-1995	Pooled A and B	12889	HPV	3192	5	5	0.2	64.6	-122.6	94.4	0.268
				HepB	394	2	2	0.5				
				Not vaccinated	634	1	1	0.2				
				Total	4220	7	8	0.2				
		C	6067	HepB	1446	3	3	0.2	-	-	-	-
				Not vaccinated	233	2	2	0.9				
				Total	1679	4	5	0.5				
6/11	1994-1995	Pooled A and B	12889	HPV	3192	19	41	1.3	50.4	8.4	73.1	0.025
				HepB	394	3	4	1.0				
				Not vaccinated	634	5	7	1.1				
				Total	4220	19	52	1.2				
		C	6067	HepB	1446	10	21	1.5	-	-	-	-
				Not vaccinated	233	6	8	3.4				
				Total	1679	10	29	2.3				
6/11/53/74	1994-1995	Pooled A and B	12889	HPV	3192	21	72	2.3	35.3	0.7	57.9	0.046
				HepB	394	6	9	2.3				
				Not vaccinated	634	10	13	2.1				
				Total	4220	22	94	2.2				
		C	6067	HepB	1446	10	34	2.4	-	-	-	-
				Not vaccinated	233	6	11	4.7				
				Total	1679	10	45	3.4				

HPV = HPV-16/18 L1 VLP AS04 vaccine
HepB = Hepatitis B vaccine
Not vaccinated = enrolled control without vaccination
Arm A = 90% of vaccinated males and females were randomized to HPV
Arm B = 90% of vaccinated females were randomized to HPV
Arm C = 0% of vaccinated subjects were randomized to HPV
N invited = number of subjects invited to participate in the study
N = number of subjects with available results
n+ = number of communities with at least one event

n = number of subjects reporting an event
% = n/N except for the Total where %=(n(HPV)+n(HepB)+w*n(Not vaccinated))/(N(HPV)+N(HepB)+w*N(Not vaccinated))
w = 4.9 (% of evaluable subjects among vaccinated subjects (HPV and HepB)/% of evaluable subjects among subjects invited to participate in the trial and not vaccinated, from pooled Arms A, B and C)
VE (%) = vaccine effectiveness (1-OR)
OR = odd ratio
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
P-value = exploratory two-sided p-value not adjusted for the number of endpoints for H0: pooled Arms A and B is equal to Arm C, based on Mantel-Haenszel adjusted for clustering and stratified by the historical HPV-16/18 seroprevalence used in the randomization

Assessor's comment

Overall (total + indirect) effectiveness against oropharyngeal prevalent infection with HPV-16/18 was 66.8% (95% CI: 19.8, 86.3) and corroborates the results for direct effectiveness against HPV-16/18. This was also true for the regarding the overall (total + indirect) effectiveness of Cervarix in reducing the prevalence of oropharyngeal infection with all oncogenic HPV types combined, i.e. VE of 24.8% (95% CI: -8.1, 47.7).

Overall Rapporteurs comments on efficacy data (please refer to the MO):

The submitted data do not support any reliable conclusion on the efficacy of Cervarix in the prevention of head and neck cancers:

a) The pivotal study endpoint of prevention against HPV infection is a surrogate endpoint for the protection against head and neck cancers. To this end, HPV infection of study subjects has been monitored at one single time point at the age of 18.5 years. This is considered insufficient since it has been established that only the **prevention of a persistent HPV infection for at least 6 months** can be considered a valid and meaningful surrogate endpoint for the prevention of HPV related cancers (such as cervical and ano-genital).

The Applicant refers to the report of the IARC working group mentioning that the best surrogate endpoint for risk of HPV-positive oropharyngeal cancer in a clinical trial would be prevention of incident and persistent oral HPV-16 infection (IARC Working Group, 2014). This was however not completely followed as only the incidence but not the persistence of HPV infection was assessed in study HPV-040 (and study HPV-009). For study HPV-040 (and study HPV-009), the oropharyngeal HPV infection status in study participants prior to vaccination was unknown. Detection of HPV-types in the samples collected 3.5 to 6.5 years later cannot be considered as representative for persistent infection.

In the absence of identifiable precancerous histological and clinical lesions suitable as clinical trial endpoint, experts of IARC and the United States National Cancer Institute have agreed that HPV oral persistent infection could be considered the best appropriate endpoint as a surrogate for HPV-related head and neck cancer (Lowy 2015). Even if prevention of incident infections implies reduction of persistent infections (as incident infection is a precursor of persistent infection), it is recognized that persistence is required for progression to HPV pre-cancer and cancer (Gillison 2012). In addition, measuring incidental infections only is of limited value since most infections regress spontaneously. Of note, VE for the different anogenital indications of HPV vaccines were not approved on the basis of incident infection endpoints.

FDA agreed on oral HPV persistent infection as the primary endpoint in order to demonstrate vaccine efficacy against HPV related oropharyngeal cancer. This issue was further pursued in connection with question 1e of the Major Objection, discussing the options for conducting RCT to support the extension of indication. ***Remaining issue.***

b) The statistical test for VE against oropharyngeal infections **is not considered to be statistically significant**. This endpoint was a key secondary endpoint which was part of a hierarchical approach to control for multiplicity. In this hierarchy, the first endpoint failed to show a statistically significant effect. Hence, all other endpoints are considered descriptive only. Hence, the study is considered to

have failed and no further indication can be derived.

The Applicant was asked to discuss this negative study result in the light of the requested indication and Sec. 6.2 of the Draft Guideline on multiplicity issues in clinical trials (EMA/CHMP/44762/2017).

The issue around the lack of significance for the relevant endpoint is <u>not considered solved</u>. Additionally, an OC was raised on the suitability of the presented analyses. The Applicant is asked to adequately adjust the analysis of VE against oropharyngeal infections for community type. (OC)

c) The negative study result is further to be considered in the light of a **single pivotal trial** (please Cf. points to consider on Application with 1. Meta-Analyses; 2. One pivotal trial; CPMP/EWP/2330/99). These PtC further request specifically compelling results.

The Applicant was asked to further discuss the formally negative study and the results in the light of these requirements.

No discussion of pre-requisites for applications with a single pivotal trial were provided. Literature data and further supportive data do not cover up for replication in a pivotal trial but are always expected. No arguments to resolve the issues with a single pivotal trial were provided. The provided literature could be considered an informal / anecdotal literature based meta-analysis (mainly based on different vaccines) were further requirements would apply. ***Overall, the issue is <u>not considered solved</u>.***

d) Finally, as discussed in the assessment on "Statistical methods" and the "Conduct of the study", it seems that **only within the SAP** a hierarchy of primary and key secondary analyses was defined, which included confirmatory testing for oropharyngeal infections. No multiplicity control over primary and key secondary endpoints was defined within the protocol. Given the very late change after study completion and after extensive interim analyses for immunogenicity and safety this should be considered as a post hoc choice and is hence not endorsed. Likewise, pooling of Arms A and B for the computation of VE against oropharyngeal infection was not defined in the protocol. Whether it was defined within the SAP or only in the CSR currently cannot be assessed due to the lack of the SAP. In contrary, in the protocol it was stated that "the statistical analysis of the second and third secondary endpoints will be done by evaluating the difference in HPV-16/18 and other oncogenic HPV types PCR prevalence rates in communities in different intervention arms A vs. C and B vs. C."

The Applicant was asked to discuss the history of changes in the light of the accruing data and available information to rule out any perceived or real possibilities of data driven analyses.

The Applicant provided the SAP for the final analysis, which indeed defined the hierarchy and pooling of groups as stated in the CSR. This provides some reassurance. However, overall, the issue on data-driven choices cannot be fully ruled out, as summary level information was assumingly available at the time of finalization of the SAP. ***The issue remains as uncertainty but is <u>not further pursued</u>.***

2.4.2. Supportive data

2.4.2.1. Costa Rica Vaccine Trial HPV-009

This study, also referred to as study HPV-009, was a large clinical study conducted by the NCI in collaboration with GSK. In this community-based randomized study, efficacy for the prevention of oral HPV infection was observed in young females 4 years after Cervarix vaccination (Herrero et al., 2013). The study was primarily designed to evaluate efficacy against persistent cervical HPV-16/18 infection and precancerous lesions in young adult women 18 to 25 years of age (Hildesheim et al., 2014) and also evaluated efficacy against anal infection (Kreimer et al., 2011). As part of this study, the efficacy of Cervarix against prevalent oral HPV-16/18 infection has been assessed as a pre-specified tertiary objective. The 7.466 enrolled women were randomised (1:1) to receive either Cervarix or a control vaccine (an investigational formulation of Havrix, GSK's Hepatitis A vaccine).

At the final blinded four-year study visit, after a new informed consent, a questionnaire was administered including oral and anal sexual behaviours and an oral specimen was collected. Oral HPV infection was assessed in oral samples, collected through a collection method similar to the one used in study HPV-040 (rinse and gargle), and using high-sensitive HPV DNA detection methodology (broad-spectrum HPV DNA PCR with LiPA, followed by HPV type-specific PCR).

Efficacy results against oral and cervical infection with HPV-16/18 based on analysis of the full cohort (all women vaccinated regardless of baseline cervical HPV DNA or serology results, treatment for cervical precancer or number of vaccine doses) are presented in **Table 19**.

Table 19: *Efficacy against oral and cervical infection associated with HPV- 16/18 in study HPV-009 (from Herrero, 2013)*

	Number of women*	Number of HPV-16/18 infections	HPV 16/18 vaccine efficacy (95% CI)
Oral			
HPV group	2910	1	93.3% (62.5, 99.7)
Control group	2924	15	
Cervical			
HPV group	2910	61	72.0% (63.0, 79.1)
Control group	2924	219	

HPV group: treatment group vaccinated with *Cervarix* vaccine
Control group: treatment group vaccinated with an investigational formulation of *Havrix* vaccine (Hepatitis A vaccine)
*Including women with oral and cervical specimens available

Vaccine efficacy against oral infection with HPV-16/18 in women 18–25 years of age was 93.3% (95% CI: 62.5, 99.7) in this trial. This exploratory analysis showed that oral HPV-16/18 prevalence at 4 years after Cervarix vaccination was much lower compared to those who received hepatitis A control vaccine. Type-specific vaccine efficacy was 91.6% (95% CI: 51.7, 99.6) against HPV-16 and 100% (95% CI: -12.0, 100.0) against HPV-18. The data suggest Cervarix protects against oral HPV-16/18 infection and thus will afford protection against the development of HPV-positive oropharyngeal cancer, in particular HPV-16, the type most commonly associated with this cancer. Consistent with the high efficacy estimates for HPV-16/18, the efficacy against all oncogenic HPV types combined was 45.7% (95% CI: 6.9%, 69.0%).

These HPV-009 study results are in line with the HPV-040 study results, where an estimated effectiveness of 82.4% (95% CI: 47.3, 94.1) was reported against oropharyngeal HPV-16/18 infection.

As the study was not primarily designed to evaluate efficacy against oral HPV infections, the power for this exploratory analysis was limited and no baseline information on oral HPV was collected from the subjects. Therefore, to calculate oral vaccine efficacy, the study used HPV prevalence at one timepoint,

i.e., 4 years after vaccination, rather than incidence of new infections. Efficacy against oral HPV-16/18 infections was computed using this data set (excluding those who were virgin at the Year 4 visit), stratified by serological baseline status, and the results for the initially seronegative naïve cohort (100.0% [95% CI: -9.1, 100.0]; zero vs 4 cases) corroborated the results for the full cohort (100.0% [95% CI: 60.5, 100.0]; zero vs 9 cases), although the CI was wide due to the low number of cases (Beachler et al., 2016).

Assessor's comment

Costa-Rica trial results are consistent with the results of the main study HPV-040. More prevalent HPV-infections, which was the endpoint, were detected in the control group compared to the HPV-vaccinated women.

However, as for study HPV-040, this study was not primarily designed to evaluate efficacy against oral HPV infections. After an amendment of the study protocol oral specimens were collected and therefore no base-line data were available. Limitations of the study are therefore various, including one cross-sectional sample, no baseline serology, limited analysis power.

Results of this HPV-009 study are considered as supportive.

2.4.2.2. HPV Vaccine Effectiveness in Reducing Oropharyngeal HPV-16 Prevalence in a Cross-sectional Study in the UK

Consistent with the results of studies HPV-040 and HPV-009, the effectiveness cross-sectional study performed in the United Kingdom by Mehanna et al. (Mehanna, 2019) showed that oropharyngeal HPV-16 prevalence in tonsils was significantly lower in vaccinated versus unvaccinated females. The data were collected as part of a study in subjects undergoing tonsillectomy for non-malignant indications (study EPI-HPV-035, a GSK-supported collaborative study), recruited in 6 hospitals from 2013 to 2015. To assess vaccine effectiveness, the analysis concentrated on female subjects 12–24 years of age who could have been vaccinated under the national UK HPV vaccination program, and on contemporaneous males of the same age. HPV vaccination was introduced in the UK in September 2008, with Cervarix offered to all girls 12–13 years of age as well as all girls 14–17 years of age as part of a time-limited catch-up program, with a switch to Gardasil in September 2012. Vaccination data were obtained from regional health authorities. The study assessed the effect of HPV vaccination on HPV oropharyngeal prevalence by means of HPV detection (DNA PCR) in different types of oral samples (oral rinse and gargle, oropharyngeal brushings and tonsillar tissue) collected in women 12-24 years of age undergoing tonsillectomy.

The results showed that oropharyngeal HPV-16 prevalence was significantly lower in vaccinated versus unvaccinated females 12–24 years years of age (in tonsils 0.5% vs 5.6%, p=0.04). These findings indicate that routine vaccination against HPV is associated with significant reductions in tonsillar HPV-16 infections in vaccinated females. The prevalence of oropharyngeal infection with HPV-16/18 types was 1.1% versus 5.6% in vaccinated females and unvaccinated females, respectively (p-value = 0.07). With respect to oropharyngeal infection with any HPV type, there was no statistically significant difference in prevalence between vaccinated and unvaccinated females (19% versus 20%, p-value = 0.76). In unvaccinated males 12–24 years of age, prevalence of oropharyngeal HPV-16 was similar to vaccinated females of the same ages (0 vs 0.5%, p-value >0.99) and lower than unvaccinated females (0% vs 5.6%, p-value =0.8). Results of these comparisons should be interpreted with caution considering that there was no adjustment for multiplicity. The small number of cases, especially with non–HPV-16 oncogenic types, limited the analyses and adjustments that could be undertaken, and no reliable conclusions for non–HPV-16 oncogenic infections could be performed.

Assessor's comment

HPV oropharyngeal prevalence data (via HPV detection [DNA PCR] in different types of oral samples) collected in women 12-24 years of age undergoing tonsillectomy were generated in a cross-sectional effectiveness study in UK with VE estimates of

- HPV-16 in tonsils: 0.5% vs 5.6%, (p=0.04)

- HPV-16/18 types: 1.1% versus 5.6% (p=0.07)

- Any HPV type: 19% versus 20% (p=0.76)

Main limitations are lack of data for males, HPV detection performed in different types of oral samples and design of effectiveness cross-sectional study which cannot be used to establish a causal relationship between variables. Furthermore, due to a low prevalence of oral HPV infection, sub-group analyses assessing the impact of number of vaccine doses, age at vaccination and time since vaccination could not be conducted.

Nevertheless, the effectiveness results of this study are considered supportive to the extension of indication.

2.4.2.3. Data on Protection Against Oropharyngeal HPV Infection using Gardasil

Merck's quadrivalent HPV-6/11/16/18 vaccine Gardasil is indicated in the EU for use from the age of 9 years for the prevention of premalignant genital lesions (cervical, vulvar and vaginal), premalignant anal lesions, cervical cancers and anal cancers causally related to certain oncogenic HPV types and for the prevention of genital warts (condyloma acuminata) causally related to specific HPV types.

Vaccine Efficacy against persistent oral HPV infection 3 Years after vaccination with Gardasil in HIV-infected adults: randomized controlled study in the US and Brazil

This randomized, double-blinded, placebo-controlled, phase 3 clinical trial conducted at 24 sites in the United States and Brazil. The protocol was designed to enrol 464 HIV-infected MSM (men who have sex with men), and a protocol modification added 100 HIV-infected women (both population with high levels of prevalent and prior HPV infections).

A total of 575 HIV-infected adults ≥27 years of age were randomized (1:1) to receive Gardasil or placebo (Wilkin, 2018). The study assessed efficacy of Gardasil in preventing anal (primary outcome) and oral (secondary outcome) HPV infections. Follow-up was planned for 3 years after the last participant was enrolled to a maximum of 4 years participation for an individual participant. Participants underwent 2 pre-vaccination samplings with anal swabs, as well as oral mouthwash rinse for HPV DNA typing, anal swab for cytology, HRA with directed anal biopsies, and blood draw for CD4+ T-cell count, HIV-1 viral load, and HPV antibodies.

The study was prematurely terminated by the Data and Safety Monitoring Board (DSMB) per protocol-defined futility rules (i.e. because the pre-set futility rules were met for time to persistent anal HPV infection and anal high-grade squamous intraepithelial lesions on biopsy). This limited the precision of the point estimate and prevented the observation of outcomes after 3 years.

Wilkin et al specify that vaccine efficacy was 22% (95.1% confidence interval [CI], −31%, 53%) for prevention of persistent anal infection or single detection at the final visit, 0% (95% CI −44%, 31%) for improving bHSIL outcomes and 88% (95.1% CI 2%, 98%) for preventing persistent oral HPV

infection, but was 32% (95.1% CI −80%, 74%) for 6-month persistent oral HPV infection or single detection at the final visit[5] (Wilkin, 2018).

Despite these limitations, the results are consistent with the lower prevalence of oral HPV-16/18 infection in Cervarix-vaccinated women in study HPV-040 (Lehtinen, 2019) and in the Costa-Rica study HPV-009 (Herrero, 2013).

Systematic Literature Review on the Efficacy and Effectiveness of HPV vaccination in Males

A systematic literature review of available evidence on the efficacy (incident and persistent HPV infections), effectiveness and safety of HPV vaccination in males of any age was performed by Harder et al. (Harder, 2018). The authors cited 2 studies evaluating oral HPV infections using oral rinse samples: one randomized, controlled study with Gardasil reporting a vaccine efficacy against persistent oral infections of 88% (95% CI: 2, 98) in HIV-positive adults (study NCT01461096, later published by Wilkin et al. in 2018 and discussed in Section 4.4.2.1) and one small non-randomized cross-sectional study in the US (Kahn, 2015) that assessed the prevalence and correlates of oral HPV infection in 272 HIV-infected male and female youth 12 to 24 years of age. Using the prevalence data (measured at one point in time) from the latter study, Harder et al. calculated a vaccine efficacy against oral HPV-16/18 infection of 91% (95% CI: −59, 99.5). However, the 95% CI was very wide, and no confounder-adjusted estimate was reported (Harder, 2018).

Population-level Effect of HPV Vaccination on Oral HPV Infections Among Young Adults in the United States

Additional supportive evidence for this variation is provided by a report on the population level effect of prophylactic HPV vaccination on the burden of oral HPV infections in US young adults 18 to 33 years of age, within the National Health and Nutrition Examination Survey (NHANES) from 2011 to 2014 (Chaturvedi, 2018b). This cross-sectional study compared oral HPV prevalence (detected in oral rinse and gargle samples) in vaccinated versus unvaccinated male and female subjects (N = 2627). The HPV vaccine predominantly used through 2014 for this study was Gardasil.

The prevalence of vaccine-type oral HPV infections (HPV-16/18/6/11) was significantly reduced in vaccinated versus unvaccinated participants (0.11% vs 1.61%, p-value =0.008), which corresponded to an estimated 88.2 % (95% CI: 5.7, 98.5) reduction in vaccine-type infections, after model adjustment to account for the imbalance in confounders (such as age, sex, and race) between vaccinated and unvaccinated individuals. Notably in male participants, the prevalence of vaccine-type oral HPV infections was significantly reduced: 0.0% in vaccinated versus 2.13% in unvaccinated (p-value =0.007). The oral HPV prevalences observed in this study were low; the limited number of cases (especially in HPV-vaccinated participants) precluded the possibility to calculate adjusted estimates and population-level effects. Also, the analyses were performed on the basis of self-reported vaccination status, which may have resulted in misclassification. While acknowledging these limitations, the authors concluded that their findings have a public health significance given the recent increases in the incidence of oropharynx cancers.

Assessor's comment

Data on the effect of vaccination with Gardasil on oropharyngeal HPV infection have been described in the literature. These include one randomized, controlled clinical study in HIV-infected individuals (Wilkin, 2018); a systematic literature review on the efficacy/effectiveness of HPV vaccination in males (Harder, 2018); and a report on the population level effect of prophylactic HPV vaccination on the burden of oral HPV infections in US young adults (Chaturvedi, 2018b).

[5] Wilkin et al. A Randomized, Placebo-Controlled Trial of the Quadrivalent Human Papillomavirus Vaccine in Human Immunodeficiency Virus-Infected Adults Aged 27 Years or Older: AIDS Clinical Trials Group Protocol A5298. CID 2018:67

In the Gardasil study in HIV-infected adults, which did not show efficacy against persistent anal infection due to the 4 vaccine types, oral persistent infection occurred in 1 vaccinated vs. 8 placebo-group mITT patients, suggesting a role of Gardasil for prevention of oral HPV infections. Nevertheless, these results regarding oral persistent infection should be interpreted with caution due to the wide CI. Also, the author (Wilkin, 2018) concluded the study regarding the role for prevention of oral HPV infections should be investigated in future studies.

Gardasil results could be relevant since all L1 VLP-based HPV vaccines provide protection through the same mechanism (induction of type-specific HPV antibodies). This study is considered as supportive.

2.4.3. Discussion on clinical efficacy

The present application intends to extend the indication of the use of Cervarix for the prevention in males and females against head and neck cancers causally related to certain Human Papillomavirus (HPV) types (from the age of 9 years).

The main study supporting this indication, the study HPV-040, documents the effectiveness of vaccination with Cervarix against prevalent oropharyngeal HPV infection in healthy female subjects 12-15 years old. Supportive immunogenicity and effectiveness data were also submitted.

Overall, data presented in this application suggest the possible benefit of Cervarix vaccination in preventing the oropharyngeal HPV-16/18 infections. VE remains to be proved.

Description of the Main study

The pivotal (HPV-040) is a phase III/IV, partially-blind, community-randomized, controlled study to evaluate the effectiveness of two vaccination strategies using GlaxoSmithKline Biologicals' HPV-16/18 L1 VLP AS04 vaccine in reducing the prevalence of HPV-16/18 infection when administered intramuscularly according to a 0, 1, 6-month schedule in healthy female and male study participants aged 12 - 15 years. The study included three treatment arms and subjects were randomized to receive either Cervarix or Engerix B. The study started 2007 in Finland.

The main objective of the study was to demonstrate the superiority to vaccinate both genders compared to only females in the prevention of reducing the prevalence of HPV-16/18 genital infection in females.

The trial duration was 7 years and within the last year the amendment was introduced to demonstrate efficacy to prevent prevalent HPV 16/18 oropharyngeal infections in females (24 March 2014). Study completion date (i.e., last study visit) was 17 December 2014. No baseline data are available (part of **MO**).

The study was not originally planned for the evaluation of Cervarix against head and neck cancers. Prevention of infection of HPV 16/18 oropharyngeal infections was added rather late as a secondary endpoint and raised to a key secondary endpoint only within the SAP. Details on the final analysis for this endpoint were also not pre-specified in the protocol but only very late in the SAP. The issue of data-driven choices cannot be fully ruled out, as summary level information was assumingly available at the time of finalization of the SAP. Hence, it is questionable to what extend the analysis of oropharyngeal infections can be considered pre-specified.

Only one oral specimen was collected and investigated at the final visit from female subjects only, although the prevalence of HPV-oral infections is more common in men and would be claimed for both gender within this extension of indication.

The number of female subjects in birth cohorts 1994-1995, with oropharyngeal sample results available at 18.5 year of age was 4871, including 3192 HPV vaccinated, 1446 HepB-vaccinated and 233 not vaccinated. VE was calculated for the 1994 and 1995 birth cohorts only. Because the samples from the 1992 birth cohort were taken at the age of approximately 21-22 years, the data for this birth cohort were not pooled with the 1994 and 1995 birth cohorts.

Both vaccinated and non-vaccinated females from the study site communities were invited to attend follow-up visit at the age of 18.5 years during 2012–2014. Cervical and oropharyngeal samples for HPV DNA testing were obtained on each visit. Setting the age for attending the follow-up visit at 18.5 years was per protocol to allow a minimum of 3 years between vaccination and cervical sampling. Study results were submitted in 2016.

HPV infection was analysed on oral samples by using high-sensitive HPV DNA detection methodology (broad-spectrum HPV DNA PCR with LiPA, followed by HPV type-specific PCR). Based on the data presented, it is considered that the methods used to detect HPV DNA from oral rinse samples should be fit for purpose.

The strategy of the Applicant to value the findings related to OPC is acknowledged. The interest of the OPC findings was discussed in the assessment of the procedure EMEA/H/C/721/II/0081 but advice to conduct a study with the best possible efficacy surrogate endpoint was apparently not followed.

Efficacy endpoint

While there is a common agreement on the surrogate endpoint to be used in clinical trials and for licensure of HPV vaccines for cervical and anal cancers, there has been no well-established endpoint for HNC indication. Unlike cervical cancer, it is very challenging to identify precursor lesions of head and neck cancer and tumours may take over decades to develop. According to the IARC working group report from 2014, the best efficacy surrogate endpoint for risk of HPV-positive oropharyngeal cancer in a clinical trial would be prevention of incident and persistent for 6 months or longer with type specific HPV in the oral cavity (IARC Working Group, 2014). It is accepted that it is not possible for an individual to develop HPV positive oropharyngeal cancer in the absence of a preceding oral HPV-16 infection (IARC Working Group, 2014).

To that end, clinical trials evaluating the vaccine efficacy on OPSCC should assess HPV persistent infection by using HPV DNA detection at 2 or more consecutive study visit as a surrogate for HPV-OPC. In other HPV vaccine efficacy studies, the specimens were generally collected every 6 months during the follow-up period. Six months represent adequate length in the clinical practice to monitor a participant situation change. The definition of persistent infection was made based on how many sequential visits are consistently positive for the same HPV type.

In study HPV-040 and in supportive studies for Cervarix, only the prevalence, and not the persistence of the infection, was analysed since the oropharyngeal baseline HPV infection status in the study participants prior to vaccination was unknown. In addition, there was a long lag of 4–6 years in the collection of oral gargle samples post-vaccination. The identification of hrHPV type(s) in these cross-sectional samples taken at the age of 18.5 years is considered insufficient to support the efficacy of Cervarix in the prevention of HPV 16/18 oropharyngeal infections and for an extension of indication for prevention of head and neck cancer. (part of **MO**)

For note, the MAH has previously stated in the EMA procedure EMEA/H/C/000721/II/0081:

"It is generally assumed that HPV-mediated carcinogenesis in cervical and oropharyngeal mucosa is comparable. Whereas it is clear that vaccination will prevent anal and cervical cancer, it remains however to be proven whether such a vaccination program will prevent other malignancies such as OPC. Since no clear intraepithelial precursor lesion has been identified for OPC (i.e., no surrogate

endpoint to establish VE against OPC is available), using persistent HPV infection (≥ 6 months) as clinical endpoint is the most feasible approach. Although it is acknowledged that the data available so far do not constitute direct evidence that HPV vaccines prevent OPC and value of HPV vaccination as a prophylactic measure for OPC is still unproven, the high effectiveness against OP HPV16/18 infection supports the possibility that vaccination may reduce risk of HPV-positive OPC, in particular HPV-16, the type most commonly associated with this cancer."

Although recommended in procedure EMEA/H/C/000721/II/0081 in 2017, the Applicant has not initiated a clinical trial with the relevant primary endpoint (prevention of a persistent HPV infection for at least 6 months) for the protection against HNC with adequate serial oral sampling. (part of **MO**)

It is considered that a trial sized with a case-driven approach and conducted in regions and/or populations expected to have high infection rates should be possible to accrue sufficient cases of persistent oropharyngeal infection in a reasonable timeframe.

The Rapporteurs consider possible to conduct such a study, which could potentially support an indication for prevention of pre-malignant lesions in the oropharynx provided that the SmPC explains that the primary endpoint was persistent infection. Depending on the actual data generated, consideration would have to be given to whether the indication could refer to HPV vaccine types or would need to be qualified by HPV type in accordance with the evidence.

Of note, the following new indication has been accepted by FDA in June 2020 for the vaccine Gardasil 9: prevention of oropharyngeal and other head and neck cancers caused by Human Papillomavirus (HPV) types targeted (without any dedicated trial for this indication). However, adequate and well-controlled clinical trial must be conducted to verify and describe the clinical benefit attributable to this product (such as prevention of oral persistent infection with HPV Types 16, 18, 31, 33, 45, 52 or 58).

The following clinical trial is ongoing since February 2020 and should be completed in 2024 (V503-049 - NCT04199689): 'Efficacy Against Oral Persistent Infection, Immunogenicity and Safety of the 9-valent Human Papillomavirus Vaccine (9vHPV) in Men Aged 20-45 Years (V503-049)'. Primary endpoint: incidence of Human Papillomavirus (HPV)16/18/31/33/45/52/58-related 6-month Persistent Oral Infection. A 6-month persistent infection is defined to have occurred if a participant, after completion of the Month 7 visit, is positive for the same HPV type by the HPV PCR assay to at least 1 common gene in Oral Rinse and Gargle (ORG) samples obtained at 2 or more consecutive visits at 6 months (+/-1 month visit window) apart. The primary hypothesis tested in this study is that administration of a 3-dose regimen of 9vHPV vaccine will reduce the incidence of HPV 16/18/31/33/45/52/58-related oral persistent infection (6 months or longer) compared with placebo.

Protection against Oropharyngeal Infection

Regarding the prevention of prevalent oropharyngeal HPV infection by Cervarix in females, pivotal data are provided by study HPV-040, and are supported by the efficacy data from study HPV-009.

In both randomized, controlled studies HPV-040 and HPV-009, consistently high point estimates of effectiveness/efficacy against prevalent oropharyngeal infection with HPV-16/18 were observed in females: at least 80% with 95% CI lower limit of at least 40%.
In other studies with Cervarix or Gardasil reported in the literature, consistent estimates of efficacy/effectiveness in prevention of oral, oropharyngeal or tonsillar HPV infection were observed in females and males, despite heterogeneity between studies (i.e. in study designs, geographic location, outcome measure, study population size).

However, the study HPV-040 failed its primary objective to demonstrate the overall (total and indirect) effectiveness of Cervarix in reducing the prevalence of HPB-16/18 genital infection in female subject (p=0.232).

Results on the total effectiveness against HPV-16/18 oropharyngeal infection in pooled Arms A and B versus Arm C for the 1994 & 1995 birth cohorts seem numerically promising, but are not statistically significant in the hierarchical test sequence.

Protection against Oropharyngeal Infection in Males

Regarding the prevention of oropharyngeal infection in males, immunogenicity data are provided by study HPV-011, which demonstrated non-inferiority of the immune responses to 3 doses of Cervarix in male subjects 10–18 years of age in this study, compared to the responses measured in females 15-25 years of age from the HPV-012 study. However, no correlate of protection between immunogenicity and efficacy has been established for HPV vaccines.

As for the immunogenicity results of study HPV-011, the immunogenicity results of HPV-040 are considered as supportive. GMT levels were high.

Currently, no correlate of protection are validated for ano-genital and oral HPV-related cancers. However, the use of immunogenicity data in support of extrapolation of data on protective efficacy to other populations is in line with the EMA guideline on the clinical evaluation of new vaccines (EMA, 2006), that also provides guidance for further development of licensed vaccines. Although the approach of immuno-bridging from females to males was previously accepted by EMA for the male cancer indication extension of Cervarix (procedure EMEA/H/C/721/II/067), no vaccine efficacy against oropharyngeal HPV-specific persistent infections have been demonstrated at this point in time.

Limitations of generated data

The limitations of the main pivotal study and of supportive studies are various including no baseline serology, HPV oropharyngeal detection at one point in time (no adequate serial oral sampling), limited inclusion of males. (part of **MO**)

2.4.4. Conclusions on the clinical efficacy

The clinical efficacy based on prevention of prevalent oral infections of HPV-16 and 18 suggests that prevention of persistent infections could be possible but is not yet demonstrated.

In line with previous recommendation (EMA/CHMP/459022/2016), it is considered that the clinically relevant endpoint should at the least be the prevention of >6 month persistent HPV infection.

To confirm the potential benefit of Cervarix vaccination against oropharyngeal persistent HPV infection, the Rapporteurs consider that data of a randomized controlled trial are needed to conclude on the B/R for the new indication, with oral persistent infection as surrogate endpoint for HPV-related HNC. In this submission, the Rapporteurs consider that there is not enough evidence of positive impact from HPV vaccination on oropharyngeal infections with HPV-16/18 which could lead to HNC. **(MO)**

2.5. Clinical safety

This application relates to the introduction of efficacy and immunogenicity data with Cervarix obtained from previously submitted clinical study HPV-040 and other supporting studies (HPV-11, HPV-009). None of these changes relates to the safety of the product.

Data from studies HPV-040 and HPV-011 were previously submitted to EMA and have been evaluated within procedures EMEA/H/C/721/II/0081 (HPV-040) and procedure EMEA/H/C/721/II/067 (HPV-011). The safety profile of Cervarix in both males and females as collected from active reporting and health

registry surveillance was considered acceptable in study HPV-040. In study HPV-011 it was concluded, that Cervarix was well tolerated in 10-18 year old males.

Post marketing experience

Cervarix was first approved on 26 June 2006 in the United Arabic Emirates (UAE). Cervarix is currently approved in the United States (US), all European Economic Area (EEA) countries and Japan, as well as over 90 countries. It is estimated that 88,488,895 doses have been distributed since registration (data lock point 17 November 2019). As vaccination with Cervarix could vary between one and three doses per subject in accordance with local recommendations and compliance with the vaccination schedule, post-marketing exposure to Cervarix since launch until 17 November 2019 is estimated as being between 29,496,298 and 88,488,895 subjects.

Safety information received since licensure has been regularly reviewed by the Vaccines Clinical Safety and Pharmacovigilance (VCSP) of GSK. As concluded in the PRAC assessment report of the PSUR for Cervarix covering the reporting period from 18 November 2018 to 17 November 2019 (EMEA/H/C/PSUSA/00009175/201911), the benefit/risk profile of Cervarix continues to be favourable.

2.5.1. Discussion and conclusion on clinical safety

No new safety data have been submitted. The positive B/R profile remains therefore unchanged.

2.5.2. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

3. Risk management plan

The MAH submitted an updated RMP version with this application. The (main) proposed RMP changes were the following:

- The proposed indication including protection against HPV-related head and neck cancer has been included in the RMP. The proposed indication is:

  "*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, anal and head and neck cancers causally related to certain oncogenic Human Papillomavirus (HPV) types*"

- Final results of supported study EPI-HPV-048 have been updated

3.1. Part II: Safety Specification

3.1.1. Epidemiology of the indications and target population

PRAC Rapporteur's assessment comment: Module SI – Epidemiology of the indication(s) and Target Population(s) has been completely revised and updated. This updated revision is clearer and better presented. Epidemiological data have been accurately updated, based on scientific references.

The chapter on 'screening and treatment options' was also revised and is approvable.

As a minor remark, the MAH was requested to provide figures on the proportion of head and neck cancers (HNCs) which are HPV-related.

The MAH has included an estimation of the proportion of HNCs which are HPV-related, and global estimates for incidence rates of HNCs attributable to HPV in section SI.1 of the RMP. Issue resolved.

3.1.2. Clinical trial exposure

PRAC Rapporteur's assessment comment: The cumulative number of subjects enrolled in the completed and on-going clinical remains unchanged. Editorial revisions are approved.

3.1.3. Post-authorisation experience

PRAC Rapporteur's assessment comment: Data on the number of doses distributed per country were updated. Changes are approved

3.1.4. Identified and potential risks

No new safety concerns have been identified, nor have any existing safety concerns been reclassified since the last RMP update.

3.1.5. Summary of the safety concerns

Table SVIII.1: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	HPV type replacement Impact and effectiveness against anal lesions and cancer

Considering the data in the safety specification, the following issues should be addressed:

- 'Impact and effectiveness against anal lesions and cancer' was maintained among safety concerns at the time of the last revision of the RMP because on-going pharmacovigilance activities are addressing this concern. Trends analysis of anal cancer and other HPV-related cancers will be conducted every 5 years. The first analysis will be submitted in 2021. However, it is recognised that this concern is related to efficacy rather than safety.
- In its assessment, CHMP questions the validity of the clinical endpoints to measure the benefit of Cervarix for the prevention of head & neck cancers. This is the object of a major objection to the extension of the indication to HNC. According to the results of the discussion with CHMP, the inclusion of 'Impact and effectiveness against oropharyngeal cancer' should be considered. However, it is recognised that this concern is related to efficacy rather than safety.

PRAC Rapporteur's assessment comment:

The concerns 'Impact and effectiveness against anal lesions and cancer' and 'Impact and effectiveness against oropharyngeal cancers' should be similarly treated in the RMP.

- The MAH was asked to clarify whether oropharyngeal cancers will be included in the trends analysis to be conducted every 5 years from consulting 5 cancer registries. Similarly, the MAH was asked to clarify whether head & neck cancers are considered for the feasibility of case-control studies. This should be reflected in the RMP, tables 7 and 8.

  The MAH proposed to conduct similar post-marketing surveillance activities for head and neck cancer as those that are conducted to address the impact and effectiveness against anal lesions and cancer, namely a trend analysis every 5 years and a feasibility assessment for a case-control study every 5 years. These pharmacovigilance activities have been added in tables 7 and 8 of the RMP. Issue resolved.

- The PRAC Rapporteur is of opinion that 'Impact and effectiveness against anal lesions and cancer' should be removed from the table of safety concern. However, the category 3 studies addressing this concern should be maintained in the pharmacovigilance plan, tables 7 and 8. The MAH was invited to comment on this proposition. In case of disagreement, the MAH was asked to discuss whether 'Impact and effectiveness against oropharyngeal cancers' should also be included as missing information in the table of safety concern and to adapt the pharmacovigilance plan accordingly.

  The MAH prefers to keep 'Impact and effectiveness against anal lesions and cancer' as missing information in the table of safety concerns and also added 'Impact and effectiveness against head and neck cancers' as missing information. This is acceptable. Issue resolved.

3.2. Part III: Pharmacovigilance plan

Table Part III.3.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3: Required additional pharmacovigilance activities				
EPI-HPV-048 Ongoing	HPV infection type-specific surveillance among sexually active females who have been offered HPV vaccination.	HPV Type replacement	Interim report	Submitted on 18 May 2018
			Final report	~~Q3~~ Q4 ~~2020~~2021
Post-Marketing Surveillance Activity Ongoing	Monitoring of annual reporting of anal cancer by consulting 5 national cancer registries (Finland, The Netherlands, UK, Norway and Denmark) To collect data for the quinquennial trend analysis of the occurrence of anal cancer and other HPV-related cancers	Impact and effectiveness against anal lesions and cancer	N/A	Data collection through consultation of the registries will start in 2016 and will be conducted yearly to prepare the quinquennial trend analysis described below.
Post-Marketing Surveillance Activity Planned	Trend analysis of HPV-related cancer every 5 years To describe the potential changes over time in the occurrence of anal cancer in countries where Cervarix is used.	Impact and effectiveness against anal lesions and cancer	Quinquennial report	The first analysis will be performed in 2021 (submitted with next cyclical PBRER).

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3: Required additional pharmacovigilance activities				
Post-Marketing Surveillance Activity Planned	Feasibility assessment to perform a case-control study to assess the effectiveness and /or impact of HPV vaccination programmes using Cervarix. This feasibility assessment will be performed every 5 years	Impact and effectiveness against anal lesions and cancer	Quinquennial report	The first analysis will be performed in 2021 (submitted with next cyclical PBRER).

PRAC Rapporteur's assessment comment:

The change in the expected data of submission of study EPI-HPV-048 is noted and accepted.

The PRAC Rapporteur disagreed that the results of the studies addressing 'Impact and effectiveness against anal lesions and cancer' would be submitted through PBRER. This was already commented in the last PBRER report. First, it is preferable that study results are submitted through separate procedure. Second, in the last PBRER assessment, the PBRER frequency was changed from one year to three years, which will not be appropriate for the submission of quinquennial reports. The MAH was asked to correct the pharmacovigilance plan, tables 7 and 8, accordingly.

The MAH confirmed that the results of the studies addressing 'Impact and effectiveness against anal lesions and cancer' will be submitted according to the applicable procedures for submission of category 3 study results. The submission procedure for the results of these studies ("submitted with the next cyclical PBRER") has been removed in the pharmacovigilance plan (tables 7 and 8). Issue resolved.

3.2.1. Overall conclusions on the PhV Plan

In case the indication of the vaccine is extended to the prevention of head and neck cancers, the proposed post-authorisation PhV development plan may be sufficient to identify and characterise the risks of the product provided that:

- the pharmacovigilance plan category 3 studies to investigate the impact and effectiveness of the vaccine against oropharyngeal cancers. Those studies could be nested in studies already planned for other HPV-related cancer (i.e. trend analysis and feasibility of case-control studies) but this should be clearly expressed by the pharmacovigilance plan.

3.3. Risk minimisation measures

3.3.1. Routine risk minimisation measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	**Routine risk minimisation activities**
HPV type replacement	None
Impact and effectiveness against anal lesions and cancer	None

3.3.2. Overall conclusions on risk minimisation measures

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

3.4. Elements for a public summary of the RMP

The elements for a public summary of the RMP do not require revision following the conclusion of the procedure.

PRAC Rapporteur's assessment comment: The public summary of the RMP remains unchanged except for the proposed indication.

3.5. Annexes

The annexes have been updated appropriately.

4. Changes to the Product Information

As a result of this variation, modifications to sections 4.1 and 5.1 of the SmPC have been submitted by the MAH. The Package Leaflet (PL) was updated accordingly.

"4.1 Therapeutic indications

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 and head and neck cancers causally

related to certain oncogenic Human Papillomavirus (HPV) types. See sections 4.4 and 5.1 for important information on the data that support this indication.

5.1 Pharmacodynamic properties

Approximately 90% of malignant neoplasms of the head and neck (HN) are squamous cell carcinomas (SCCs), while around 5% are adenocarcinomas. HPV prevalence among HNSCCs cases is approximately 43%. The most prevalent types, among HNSCCs associated with HPV, are HPV-16 (approximately 87%) and HPV-18 (approximately 12%).

Effectiveness against oropharyngeal infection
In study HPV-040, conducted in Finland in 32,175 male and female subjects aged 12-15 years (14,837 received Cervarix), irrespective of initial serostatus, vaccine effectiveness against oropharyngeal prevalent infection was evaluated as a secondary endpoint in 4,871 females (3,192 received Cervarix) up to 6.5 years following community-based HPV vaccination. The vaccine effectiveness against oropharyngeal prevalent infection was 82.4% (95% CI: 47.3, 94.1) for HPV-16/18 and 69.9% (95% CI: 29.6, 87.1) for non-vaccine types HPV-31/33/45. For HPV-16, effectiveness against oropharyngeal prevalent infection was 81.3% (95% CI: 25.8, 95.3).”

However, this variation is currently not approvable (**MO**). Please refer to Attachment 1 which includes all non-agreed changes to the Product Information.

4.1.1. User consultation

The Package Leaflet of Cervarix suspension for injection was subject to user testing at the time of the Marketing authorisation Application (MAA), consistent with the obligations under Articles 59(3) and 61(1) of Directive 2001/83/EC (as amended by Directive 2004/27/EC). The Package Leaflet was tested on clear comprehensibility (content) and clear legibility (format: font size, layout). The results of the user testing were submitted to the EMA during the review process of the MAA. The conclusion of the report after the two rounds of testing was that the Package Leaflet was clear and legible.

According to Article 61(3) of Directive 2001/83/EC for changes to existing marketing authorisations, a justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: this variation does not contain major editorial changes to the package leaflet, and therefore it is agreed with the MAH that the package leaflet is still legible, clear and easy to use. The CHMP agreed that no new user testing should be provided.

5. Benefit-Risk Balance

5.1. Therapeutic Context

5.1.1. Disease or condition

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 Human Papillomavirus (HPV) types. The new proposed indication is the use of Cervarix from

the age of 9 years for the prevention of head and neck cancers causally related to certain oncogenic Human Papillomavirus (HPV) types.

Head and neck cancers are progressive, life-threatening diseases, often diagnosed after spread beyond primary tumour site due to difficulty with early detection. HNC comprises a diverse group of tumours, with an incidence of over 500,000 cases annually worldwide. Although both men and women can suffer from HNC, it seems that up to 75% of the HNC burden occurs in men. Out of the malignant neoplasms of the head and neck, approximately 90% are SCC, while around 5% are adenocarcinomas. A large proportion of HNC cases are associated with HPV, predominantly types HPV-16 and HPV-18. In recent decades, there has been a significant increase in the incidence of HPV-positive HNC, particularly in oropharyngeal tumours, pointing to a growing medical need. White, male, non-smokers are disproportionately impacted by HPV-related head and neck cancers.

Oral HPV is primarily transmitted through oral sex with an infected partner; consequently, infection prevalence is strongly associated with the number of lifetime as well as recent oral sexual partners. Oral HPV prevalence displays a bi-modal age-pattern, with an initial peak at ages 25–30 years and a second peak at ages 55–60 years. It is unknown if this second peak reflects recent acquisition, reactivation of latent (immune controlled) infections due to age-related immune-senescence, or birth-cohort effects. Both oral HPV prevalence and HPV positive oropharyngeal cancer are more common in men. The reasons for the male predominance is unknown. Current hypotheses include a heightened immune-susceptibility in males, e.g. because of less frequent seroconversion after genital infection, as well as greater transmission of HPV through the performance of oral sex on females.

Persistence of infection at mucosal sites, including cervix, vagina, vulva and anus can lead to dysplasia, and eventually to cancer. Persistent oral infection with HPV is associated with cancer development in oropharyngeal, laryngeal and oral cavity cancers. Meanwhile, no pre-cancerous markers or effective screening methods for head and neck cancer are validated (El-Bayoumy et al., 2020; Gillison et al., 2019; Timbang et al., 2019; Kreimer et al., 2020; Schlecht et al., 2019; Rettig et al., 2015; Colevas et al., 2018; Kreimer et al., 2013). Of note, HPV persistent infection is not the only sine qua non condition for HNC development. The rates of incidence and persistence, and the predictors of HPV oral infection remain poorly characterized, mainly due to a paucity of studies of the natural history of oral HPV infection.

5.1.2. Available therapies and unmet medical need

Staging is needed to determine therapy for head and neck squamous-cell cancer. Staging differs at each anatomical site. Generally, early stages (I and II) involve smaller tumours without prominent lymphnode involvement. Later stages (III and IV) are characterized by locally advanced disease and invasion of surrounding structures or an increased number of involved lymph nodes, with distant metastatic spread also defining stage IV. Oropharyngeal cancer staging requires an assessment of HPV status, which involves in situ hybridization or polymerase-chain-reaction techniques for determining HPV DNA or the viral load, or immunohistochemical testing to detect p16 expression, which is a surrogate marker for HPV positivity.

Evaluation by a multispecialty team is very important in the choice of treatment for head and neck squamous-cell carcinoma, since treatment differs according to the stage of disease, anatomical site, and surgical accessibility. Centres with expertise in specialized multidisciplinary treatment of patients with head and neck cancers are associated with better outcomes and increased survival.

Current treatment regimens for HNC such as surgery, radiation, chemotherapy, targeted therapy and immunotherapy are aggressive and have significant treatment-associated side effects (Fakhry et al., 2018; Lewis et al., 2018; Amin et al., 2017). Although these therapeutic strategies are effective for the

treatment of HPV-associated oropharyngeal cancer, they may generate a long-term negative effect on the quality of life of a patient. Further, tumour HPV status is now included in the 8th edition of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) staging manual Amin et al., 2017).

Prevention is otherwise limited to use of condoms and other barrier methods (dental dams, which are minimally effective due to infrequent use in oral sex).

Gardasil, Gardasil 9 and Cervarix are currently licensed HPV vaccine in EU. They have all the indications of use for prevention from the age of 9 years for the prevention of premalignant genital lesions (cervical, vulvar and vaginal), premalignant anal lesions, cervical cancers and anal cancers causally related to certain oncogenic Human Papillomavirus types. Currently, vaccine uptake is especially low in boys and men and there is no licensed vaccine in EU for the prevention of HNC.

In June 2020, the following new indication has been accepted by FDA for the vaccine Gardasil 9 under an Accelerated Approval procedure: prevention of oropharyngeal and other head and neck cancers caused by Human Papillomavirus (HPV) types targeted (without any dedicated trial for this indication). However, adequate and well-controlled clinical trials must be conducted to verify and describe the clinical benefit attributable to this product. The accepted surrogate endpoint was prevention of oral persistent infection with HPV Types 16, 18, 31, 33, 45, 52 or 58[6].

Aside from the HPV vaccines, no other drug or biologic is approved for prevention of HPV infection.

In view of the considerable disease burden particularly in the populations with multiple sex partners and treatment implications of HNC, prophylaxis including vaccination against HPV could be considered as valuable tool for HNC prevention before entering sexual life.

5.1.3. Main clinical studies

The main study HPV-040 was a phase III/IV, community-randomized, controlled study in Finland to evaluate the effectiveness of two vaccination strategies using GlaxoSmithKline Biologicals' HPV-16/18 L1 VLP AS04 vaccine in reducing the prevalence of HPV-16/18 infection when administered intramuscularly according to a 0, 1, 6-month schedule in healthy female and male study participants aged 12 - 15 years. The study included three treatment arms and subjects were randomized to receive either Cervarix or Engerix B.

Oropharyngeal samples were analysed from 4,871 18.5-year-old females who attended follow-up visit 3–6 years postvaccination. In total, 3192 participants were vaccinated with Cervarix, 1446 were vaccinated with Engerix and 233 were unvaccinated. No males were part of this study for effectiveness estimates.

The main objective of the study was to evaluate the effectiveness of vaccination with Cervarix in reducing the prevalence of HPV-16/18 genital infection in females. Evaluation of effectiveness against oropharyngeal infection was added as a confirmatory objective when the study was ongoing.

Additional effectiveness and immunogenicity studies were submitted as supportive studies.

[6] FDA SUPPLEMENT ACCELERATED APPROVAL 12th June 2020. STN Number 125508/868.

5.2. Favourable effects

Pivotal study:

High effectiveness of Cervarix against prevalent HPV-16/18 oropharyngeal infection (based on assessment at a single timepoint at the mean age of 18.5y) in young adult females up to 6 years after vaccination was observed (VE = 82.4% [95% CI: 47.3, 94.1]). These results were corroborated by the overall (total + indirect) effectiveness against oropharyngeal prevalent infection with HPV-16/18 at one-time point (oropharyngeal HPV detection of 66.8% (95% CI: 19.8, 86.3) after 3.5 to 6.5 years post-dose 3 in girls 12-15 yoa at the time of vaccination).

The type-specific vaccine effectiveness were 81.3% (95% CI: 25.8, 95.3), 78.9% (95% CI: 32.3, 93.4), and 69.9% (95% CI: 29.6, 87.1) for respectively HPV-16, HPV-18, and HPV-31/33/45.

Supportive studies:

In an effectiveness study conducted in **Costa-Rica** (HPV-009) on 3192 vaccinated subjects, vaccine efficacy against oral prevalent infection HPV-16/18 in women 18–25 yoa was 93.3% (95% CI: 62.5, 99.7) at 4 years after post-dose 3.

In an effectiveness cross-sectional study conducted in **UK** on subjects, prevalence rate for oral prevalent infection HPV-16/18 (via HPV detection in different types of oral samples) collected in women 12-24 years of age undergoing tonsillectomy was 1.1% versus 5.6% (p=0.07) for vaccinated versus controls respectively.

Immunogenicity in males 10 to 18 yoa was assessed in 2 clinical trials HPV-011 (N=173) and HPV-040 (N=556). The data showed comparable immunogenicity in males and females. In study HPV-011, all subjects seroconverted to both HPV-16 and 18 and GMT levels were non inferior to those observed in females aged 15 to 25 years in study HPV-012. Immuno-bridging studies support the effectiveness of Cervarix in men 10 through 18 years of age.

Supportive study from **Gardasil**:

Randomized, placebo-controlled study in US and Brazil included 575 HIV-infected adults ≥27 years of age who were randomized (1:1) to receive Gardasil or placebo ; VE against persistent oral HPV infections in HIV-infected males and female (at 2 consecutive 6-month assessments) was 88% (95.1% CI: 2, 98, p=0.02). In a cross-sectional study that compared oral HPV prevalence in Gardasil versus unvaccinated male and female subjects (N = 2627) with results of 0.11% vs 1.61%, (p=0.008).

5.3. Uncertainties and limitations about favourable effects

Main Pivotal study HPV-040

- The surrogate endpoint is considered inappropriate and not clinically relevant.

No clear precursor lesion has been identified for HNC oropharyngeal HPV-related cancer. Although using prevalent HPV infection as a clinical endpoint was the most feasible approach at the time of the pivotal study HPV-040, it is not so closely linked to precancerous lesions as is persistent infection at other sites.

Valid endpoints for studies of non-cervical infection or disease are still under discussion (Kreimer et al, 2020; Rodríguez et al., 2010; Gillison et al., 2008; Palefsky et al., 2009; Cornall et al., 2013; Gillison et al., 2012). Unlike cervical cancer, it is very challenging to identify precursor lesions of head and neck cancer, and tumours may take over decades to develop. Therefore, the recognised endpoint is protection against persistent infection for 6 months or longer with type specific HPV in the oral cavity,

as recommended by the IARC/NCI workshop (2014) on primary endpoints for prophylactic HPV vaccine trials.

In HPV-040, efficacy to prevent persistent HPV 16/18 oropharyngeal infections was not demonstrated. The oropharyngeal HPV infection status in study participants prior to vaccination was unknown. Detection of HPV-types in the samples collected at the age of 18.5 years at one time point (3.5 to 6.5 years post-vaccination) cannot be considered as representative for persistent infection. The trial duration was 7 years and within the last year the amendment was introduced to demonstrate efficacy to prevent prevalent HPV 16/18 oropharyngeal infections. Persistent instead of incident infection should be demonstrated as endpoint for comparison in HPV-vaccinated versus HepB-vaccinated subjects, which is not possible with only one sample per subject of oral specimen at the final visit. The study findings do not support the claim for an extension of indication for prevention of head and neck cancer.

The Rapporteurs consider that data of a RCT is needed to conclude on the B/R for the new indication with oral persistent infection as surrogate endpoint for HPV-related HNC. It is considered feasible and ethical to conduct a RCT.

- Efficacy was not tested in men although the majority of HPV-associated head and neck cancers occurs in men.

Only female subjects were included in the pivotal trial to demonstrate the prevalent oropharyngeal infection, although the disease burden is much higher in males compared to females. Additionally, the applicant claimed for both genders the extension of indication.

- The statistical test for VE against oropharyngeal infections is not considered to be statistically significant.

The study was not originally planned for the evaluation of Cervarix against head and neck cancers. Prevention of infection of HPV 16/18 oropharyngeal infections was added rather late as a secondary endpoint and raised to a key secondary endpoint only within the SAP. Details on the final analysis for this endpoint were also not pre-specified in the protocol but only very late in the SAP. The issue of data-driven choices cannot be fully ruled out, as summary level information was assumingly available at the time of finalization of the SAP. Hence, it is questionable to what extend the analysis of oropharyngeal infections can be considered pre-specified. Further, as the primary endpoint was not significant, the key secondary endpoint (which was part of a hierarchical approach to control for multiplicity) could not be statistically confirmed. The level (predominantly communities) and type (minimization algorithm for subject level randomization with a 1:9 randomisation ratio) of randomization further shows that the trial was not intended for derivation of subject level data and to support an extension of indication for the prevention of HNC. The very high (and differential) amount of missing data on oropharyngeal HPV infections further makes interpretation of the VE estimate difficult.

Cervarix protects against prevalent infections that are caused by HPV types 16 and 18 and to some extent against diseases caused by certain other oncogenic related HPV types (31/33/45) but not against any types (27.2% (95% CI: -2.2, 48.1)). Therefore, appropriate precautions against sexually transmitted diseases should continue to be used.

Finally, HPV type replacement is a missing information in the RMP.

Supportive effectiveness studies

HPV-009 Costa-Rica Trial VE against oral prevalent infection HPV-16/18 in women 18–25 yoa was a post-hoc analysis based on exploratory endpoints.

Epidata from the Effectiveness cross-sectional study in UK cannot be used to establish a causal relationship between variables. Furthermore, due to a low prevalence of oral HPV infection, sub-group analyses assessing the impact of number of vaccine doses, age at vaccination and time since vaccination could not be conducted.

Supportive immunogenicity studies

Currently, no immunological correlate of protection are validated for ano-genital and oral HPV-related cancers. Nevertheless, the approach of immuno-bridging from females to males was previously accepted by EMA for the anal cancer indication extension of Cervarix (procedure EMEA/H/C/721/II/067).

No Immunobridging studies support the effectiveness of Cervarix in men 19 through 45 years of age.

5.4. Unfavourable effects

In clinical studies that enrolled girls and women aged from 10 up to 72 years (of which 79.2% were aged 10-25 years at the time of enrolment), Cervarix was administered to 16,142 females whilst 13,811 females received control. These subjects were followed for serious adverse events over the entire study period. In a pre-defined subset of subjects (Cervarix = 8,130 versus control = 5,786), adverse events were followed for 30 days after each injection. In two clinical studies that enrolled males aged 10 to 18 years, 2,617 males received Cervarix and were followed-up with active safety surveillance.

Since launch until 17 November 2019, over 88 million doses of Cervarix have been distributed worldwide.

As demonstrated in previous safety studies of Cervarix, the most substantial risks of vaccination with Cervarix are associated with the inflammation produced at the injection site. Erythema, swelling, and pain are very common. However, the most injection site reactions are mild in severity, and they resolve relatively quickly and without sequelae. Syncope, allergic reactions and headache are the other most commonly reported adverse events.

Spontaneous abortion was detected at a higher rate in women who were exposed to Cervarix within 30 days of conception compared to those who were exposed to Gardasil. Evaluation of risk of spontaneous abortion is ongoing through a pregnancy registry.

No other new safety signals have been detected since licensure through post-marketing studies or safety surveillance.

5.5. Uncertainties and limitations about unfavourable effects

The exposure of Cervarix in males is limited at present.

5.6. Effects Table

Table 20: *Effects Table for Cervarix against HPV 16/18 related HNC (data cut-off: March 2020)*

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Main pivotal study						
Total Vaccine effectiveness Against prevalent HPV 16/18 infections	**Total effectiveness against HPV-16/18 and HPV-16 oropharyngeal infection in pooled Arms A and B for birth cohorts 1994-1995 (Female study participants – 12 to 15 yoa, Total enrolled cohort at the median age of 18,5 yoa**	**% (95% CI) over a median FU of 3–6 years**	**82.4% (95% CI: 47.3–94.1) N=3192 Cases : 9**	**HepB : N=1446 Cases : 18 NotVac: N=233 Cases : 9**	**Explo endpoint ; Cross-sectional samples ; No male data**	**HPV-040 Lehtinen et al. Int. J. Cancer: 147, 170–174**
Total Vaccine effectiveness Against prevalent HPV 31/33/45 infections	Total effectiveness against HPV-31/33/45 oropharyngeal infection in pooled Arms A and B for birth cohorts 1994-1995 (Female study participants– 12 to 15 yoa,, Total enrolled cohort	% (95% CI) over a median FU of 3–6 years	69.9% (95% CI: 29.6–87.1) N=3192 Cases : 9	HepB : N=1446 Cases : 14 NotVac: N=233 Cases : 2	Explo endpoint	HPV-040
Overall (total + indirect) effectiveness of Cervarix in reducing the prevalence for HPV16/18 infection	Overall effectiveness of GSK Biologicals' HPV-16/18 vaccine against HPV-16/18 oropharyngeal infection in pooled Arms A and B versus Arm C, for birth cohorts 1994-1995, using stratified Mantel-Haenszel adjusted for clustering (Female study participants– 12 to 15 yoa,, Total enrolled cohort)	% (95% CI) over a median FU of 3–6 years	66.8% (95% CI: 19.8, 86.3) N=3192 Cases : 9	HepB : N=394 Cases : 4 NotVac : N=634 Cases : 8	Explo endpoint	HPV-040
Overall effectiveness in reducing prevalence of oropharyngeal infection with all oncogenic HPV types combined	overall effectiveness of GSK Biologicals' HPV-16/18 vaccine against oropharyngeal infection with specific HPV types in pooled Arms A and B versus Arm C, for birth cohorts 1994-1995, using stratified Mantel-Haenszel adjusted for clustering	% (95% CI) over a median FU of 3–6 years	24.8% (95% CI: -8.1, 47.7) N=3192 Cases : 136	HepB : N=394 Cases : 20 NotVac : N=634 Cases : 36	Exploratory endpoint	HPV-040
Supportive studies						
Community-based randomized study -Vaccine efficacy for the prevention of oral HPV infection	HPV-009 Costa-Rica Trial (N=2910:2924) VE against oral prevalent infection HPV-16/18 in women 18–25 yoa 4 years after Cervarix vaccination		N=2910 93.3% (95% CI: 62.5, 99.7) at 4 years after post-dose 3. VE type-specific : HPV-16 = 91.6% (95% CI: 51.7, 99.6) HPV-18 = 100% (95% CI: -12.0, 100.0) Any HPV type	N=2924	Exploratory endpoints pre-specified tertiary objective No baseline serology, limited analysis power	HPV-009 Herrero et al. PLoS ONE 2013;8:e 68329

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
			= 45.7% (95% CI: 6.9, 69.0)			
Effectiveness cross-sectional study in UK HPV oropharyngeal prevalence	Effectiveness cross-sectional study in UK HPV oropharyngeal prevalence (via HPV detection [DNA PCR] in different types of oral samples) collected in women 12-24 years of age undergoing tonsillectomy. HPV-16 in tonsils		0.5% vs 5.6%, (p=0.04) HPV-16/18 types : 1.1% versus 5.6% (p=0.07) Any HPV type : 19% versus 20% (p=0.76)		Cross-sectional epidemiological	Mehanna et al. cid 2019:69
Immunogenicity in males aged 10 to 18 years	Immunogenicity in males was assessed in 2 clinical trials HPV-011 (N=173) and HPV-040 (N=556). The data showed comparable immunogenicity in males and females. In study HPV-011, all subjects seroconverted to both HPV-16 and 18 and GMT levels were non inferior to those observed in females aged 15 to 25 years in study HPV-012.					HPV-040 HPV-011
Supportive study from Gardasil	Randomized, placebo-controlled study in US and Brazil included 575 HIV-infected adults ≥27 years of age who were randomized (1:1) to receive Gardasil or placebo (Wilkin, 2018) VE against persistent oral HPV infections in HIV-infected males and female (at 2 consecutive 6-month assessments) : 88% (95.1% CI: 2, 98, p=0.02) Systematic literature review of available evidence on the efficacy (incident and persistent HPV infections), effectiveness and safety of HPV vaccination in males of any age : Calculated VE against oral HPV-16/18 infection = 91% (95% CI: −59, 99.5) Cross-sectional study compared oral HPV prevalence in Gardasil versus unvaccinated male and female subjects (N = 2627) = 0.11% vs 1.61%, (p=0.008)					
Unfavourable Effects						
As demonstrated in previous safety studies of Cervarix, the most substantial risks of vaccination with Cervarix are associated with the inflammation produced at the injection site. Erythema, swelling, and pain are very common. However, the most injection site reactions are mild in severity, and they resolve relatively quickly and without sequelae. Syncope, allergic reactions and headache are the other most commonly reported adverse events.						

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

High effectiveness of Cervarix against prevalent HPV-16/18 oropharyngeal infection (based on assessment at a single timepoint) in young adult females up to 6 years after vaccination was observed (VE = 82.4% [95% CI: 47.3, 94.1]) in the main pivotal study HPV-040 in Finland. The type-specific vaccine effectiveness were 81.3% (95% CI: 25.8, 95.3), 78.9% (95% CI: 32.3, 93.4), 69.9% (95% CI: 29.6, 87.1) and 27.2% (95% CI: -2.2, 48.1) for respectively HPV-16, HPV-18, HPV-31/33/45 and any HPV type.

However, major uncertainties and limitations have been shown with the main clinical study (HPV-040) (such as prevention of persistence HPV-16/18 infection for at least 6 months not demonstrated, major statistical limitations – clinical study failed statistically, no data on oropharyngeal infection for men although up to 75% of the HNC burden occurs in men), and, therefore, the efficacy of Cervarix in the prevention of head and neck cancers is unknown.

5.7.2. Balance of benefits and risks

The Benefit / Risk profile for Cervarix is currently negative for the prevention of head and neck cancers causally related to certain oncogenic HPV types in males and females as of 9 years of age.

5.7.3. Additional considerations on the benefit-risk balance

5.8. Conclusions

Screening for HPV-related head and neck cancer is not feasible because precancerous lesions cannot be identified in routine medical practice. Precancerous-lesions will not be visible for oropharyngeal infections and therefore the proof of persistent infections will be important to claim for an indication of prevention for HNC. Favourable effects regarding prevention of persistent infections for at least 6 months for HPV-16/18 were not part of the data package presented in this application. This concern has already been stressed in the EMEA/H/C/721/II/0081 variation in 2017.

A Major Objection was proposed as the submitted data do not support any reliable conclusion on the efficacy of Cervarix in the prevention of head and neck cancers: the chosen surrogate endpoint is considered insufficient (as prevention of a persistent HPV infection for at least 6 months should have been considered) and the submitted study is considered to have failed statistically.

The submitted data and the rationales of the MAH regarding the MO still do not support any reliable conclusion on the efficacy of Cervarix in the prevention of head and neck cancers.

The Rapporteurs do consider that, based on the above discussions,

- protection against persistent oral HPV infection is the best valid and meaningful surrogate endpoint for the protection against head and neck cancers related to HPV;

- HPV-040 pivotal study has failed and no further indication can be derived; the currently data available documented in HPV-040 do not support an extension of the indication for Cervarix to prevent HPV-related HNC;

- supportive studies did not bring specifically compelling results;

- the rationale for not conducting a clinical trial to measure vaccine efficacy against oropharyngeal persistent HPV infection is not endorsed and a RCT is considered feasible and ethical;

- post-approval observational studies proposed cannot replace a RCT for approval of the extension of indication.

The data of a RCT is needed to conclude on the B/R for the new indication with oral persistent infection as surrogate endpoint for HPV-related HNC. The MAH is strongly recommended to seek for scientific advice regarding the design of the RCT.

The Major Objection is maintained for the intended extension of indication.

The Benefit / Risk profile for Cervarix for the prevention of head and neck cancers causally related to certain oncogenic HPV types in males and females as of 9 years of age and above is currently negative.

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7. Comments from Member States

Comments supporting a MO in relation to clinical efficacy were received from MS1, MS2, MS3 and MS4.

Responses to comments are given below. The MO was updated according to the different comments (Annex 1).

MS1:

Overall, data presented in the application suggest a possible benefit of Cervarix vaccination in preventing the oropharyngeal HPV-16/18 infections; however, it remains to be proved. It is noted that in the scientific communities, decrease in the prevalence of HPV-related oropharyngeal cancer is expected as a result of vaccination and also that it will take decades to confirm this https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6551449/. HPV-vaccination is recommended world-wide to prevent cervical and anal cancer. A placebo-controlled study is therefore not expected to be feasible and the request to provide long term follow-up data may not be possible to fulfil.

MS3:

The available data are cross-sectional and suggest there may be an effect on oropharyngeal HPV infection. What is missing but needed are data on the ability of vaccination to prevent persistent infection. The Rapporteur's MO on clinical efficacy is endorsed, however a more stringent wording is suggested:

"The Benefit/Risk profile for Cervarix for the prevention of head and neck cancers causally related to certain oncogenic HPV types in males and females as of 9 years of age and above remains unknown. ~~The MAH is requested to justify why the requested indication should be granted only based on prevalence (with all the shortcomings in the submitted data such as: unknown oropharyngeal baseline HPV infection status in the study participants prior to vaccination; only data in girls were generated and were post-hoc exploratory analysed with endpoints determined at one point in time; uncertainties remaining on potential type replacement of HPV epidemiology and also on the benefit to propose immunization to sexually active populations that are most probably not HPV naïve) without the submission of the relevant persistence data."~~ The efficacy of Cervarix in the prevention of head and neck cancers cannot be based on the prevalence of oropharyngeal infection measured at a single time

point. In order to correctly document vaccine efficacy against oropharyngeal persistent HPV infection, a long-term follow-up study with adequate serial oral sampling would need to be conducted.

Additional concern:

- If a long-term follow-up study will be conducted, it is suggested to also include male subjects as the majority of HPV-associated head and neck cancers occurs in men.

MS4:

We agree with Rapp and Co-Rapp that the presented data do not suffice for a new indication, prevention of Head and neck Cancers for Cervarix. Biologically it is likely that Cervarix protects against HPV persistent infection at oral sites, but it has to be confirmed with adequately designed RCT to ensure this indication. It is recommended that MAH to seeks Central SA.

Rapporteur response:

Although the decrease in the prevalence of HPV-related oropharyngeal cancer is expected as a result of vaccination in the following years (decades), the incidence of HPV-related oropharyngeal cancer has been increasing in the recent years, particularly in high-income countries (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6551449). The rapporteur agrees that a vaccine efficacy trial with a primary endpoint of established pre-malignant changes or of malignancy would not be feasible. However, a RCT with a primary endpoint of persistent oral HPV infection would be feasible in an acceptable timeframe. Such study might be conducted in countries were HPV vaccination in not yet part of the routine immunisation programme.

In light of these considerations, the Rapporteur agrees with the more stringent wording proposed by the MS3. This is also in line with MS4 comment suggesting the conduct of an adequately designed RCT in support to the intended indication. Since most of the OPC occur in males, the suggestion to mostly include males is supported and is included in the OC.

Annex 1: First Request for Supplementary Information

Major objections

Clinical efficacy aspects

1. The Benefit / Risk profile for Cervarix for the prevention of head and neck cancers causally related to certain oncogenic HPV types in males and females as of 9 years of age and above is currently negative. The submitted data do not support any reliable conclusion on the efficacy of Cervarix in the prevention of head and neck cancers:

   a) The pivotal study endpoint of prevention against HPV infection is a surrogate endpoint for the protection against head and neck cancers. To this end, HPV infection of study subjects has been monitored at one single time point at the age of 18.5 years. This is considered insufficient since it has been established that only the prevention of a persistent HPV infection for at least 6 months can be considered a valid and meaningful surrogate endpoint for the prevention of HPV related cancers (such as cervical and ano-genital).

   b) The statistical test for VE against oropharyngeal infections is not considered to be statistically significant. This endpoint was a key secondary endpoint which was part of a hierarchical approach to control for multiplicity. In this hierarchy, the first endpoint failed to show a statistically significant effect. Hence, all other endpoints are considered descriptive only. The study is therefore considered to have failed and no further indication can be derived.

   The Applicant is asked to discuss this negative study result in the light of the requested indication and Sec. 6.2 of the Draft Guideline on multiplicity issues in clinical trials (EMA/CHMP/44762/2017).

   c) The negative study result is further to be considered in the light of a single pivotal trial (please Cf. points to consider on Application with 1. Meta-Analyses; 2. One pivotal trial; CPMP/EWP/2330/99). These PtC further request specifically compelling results.

   The Applicant is asked to further discuss the formally negative study and the results in the light of these requirements.

   d) As discussed in the assessment on "Statistical methods" and the "Conduct of the study", it seems that only within the SAP a hierarchy of primary and key secondary analyses was defined, which included confirmatory testing for oropharyngeal infections. No multiplicity control over primary and key secondary endpoints was defined within the protocol. Given the very late change after study completion and after extensive interim analyses for immunogenicity and safety this should be considered as a post hoc choice and is hence not endorsed. Likewise, pooling of Arms A and B for the computation of VE against oropharyngeal infection was not defined in the protocol. Whether it was defined within the SAP or only in the CSR currently cannot be assessed due to the lack of the SAP. In contrary, in the protocol it was stated that "the statistical analysis of the second and third secondary endpoints will be done by evaluating the difference in HPV-16/18 and other oncogenic HPV types PCR prevalence rates in communities in different intervention arms A vs. C and B vs. C."

   The Applicant is asked to discuss the history of changes in the light of the accruing data and available information to rule out any perceived or real possibilities of data driven analyses. e) In order to correctly document vaccine efficacy against oropharyngeal persistent HPV infection, a long-term follow-up study with adequate serial oral sampling would need to be conducted.

The Applicant should clarify if an adequately powered clinical study has been initiated with the relevant primary endpoint for the protection against HNC with adequate serial oral sampling.

Other concerns

Clinical pharmacology aspects

2. The applicant shall justify why no neutralising antibody comparison has been performed in support of the claim of the current variation procedure. Neutralising titers are considered the more relevant parameter in terms of prevention of an HPV infection.
3. It is evident that the GMCs determined for female and male subjects in studies HPV-011 and HPV-012, respectively, are very different (i. e. much higher in males). Is there any explanation for this observation or are these differences due to different methodologies? In case of the latter, the GMC ratio analysis as conducted in table 7 of the "clinical overview addendum" is considered inappropriate. The applicant is requested to clarify these findings.

Clinical efficacy aspects

4. Testing algorithm may allow for infection endpoints to be used as primary endpoints in clinical studies of prophylactic HPV vaccines for HPV-associated cancers for which no other reliable surrogates exist, e.g., head and neck cancers. Meanwhile, the sensitivity and specificity values of both tests need to be documented. The Applicant should discuss the reliability of the results.
5. The Applicant is requested to clearly describe all steps of participant allocation and all randomization procedures (randomization of community, randomization of supplies, randomization of participants) including their purpose and technical details (including randomization ratios at all stages). For the minimization algorithm used for participant allocation, it needs to be clarified whether a random component exists.
6. The Applicant is requested to
   - provide all versions of the SAP including the final SAP used to analyse the data.
   - provide a detailed description of the computations for VE, including formulae if not included in the SAP. The applicant is asked to clarify on the underlying methods to adjust for clustering and provide the underlying references (e.g. Donner et al, 2000). Further, it should be clarified whether odds ratios or prevalence ratios were used.
   - discuss and explain possible changes in the computation of prevalence(s) from the Protocol to the SAP/CSR.
7. The Applicant is asked to clearly describe all applied methods for the extrapolation of seroprevalence status and provide a justification for the assumptions made. Stating that an assumption was reasonable without any justification is not endorsed.
8. The applicant is requested to explain the efficacy effect of Hepatitis B vaccination compared to non-vaccinated subjects to prevent prevalent infections demonstrated in Table 4.
9. The applicant should address, why so many subjects were not vaccinated.
10. If a long-term follow-up study will be conducted, it is suggested to also include male subjects as the majority of HPV-associated head and neck cancers occurs in men.

Risk Management Plan

RMP 1: In the paragraph on head and neck cancers (HNCs), the MAH comments that "*it is today well established that HPV is associated with head and neck cancers, and in particular with oropharyngeal cancer",* which is of course accurate. If available, figures should be provided on the proportion of HNC which are HPV-related.

RMP 2: The MAH should clarify whether oropharyngeal cancers will be included in the trends analysis to be conducted every 5 years from consulting 5 cancer registries. Similarly, the MAH should clarify whether head & neck cancers are considered of the feasibility of case-control studies. This should be clarified in the RMP, tables 7 and 8. Justifications should be provided in case HNC are not considered for those studies.

RMP 3: The PRAC Rapporteur is of opinion that 'Impact and effectiveness against anal lesions and cancer' should be removed from the table of safety concern. However, the category 3 studies addressing this concern should be maintained in the pharmacovigilance plan, tables 7 and 8. The MAH is invited to comment on this proposition. In case of disagreement, the MAH should discuss whether 'Impact and effectiveness against oropharyngeal cancers' should also be included as missing information in the table of safety concern. In this case, the pharmacovigilance plan should be adapted accordingly.

RMP 4: The PRAC Rapporteur disagrees that the results of the studies addressing 'Impact and effectiveness against anal lesions and cancer' are submitted through PBRER. This was already commented in the last PBRER report. First, it is preferable that study results are submitted through separate procedure. Second, in the last PBRER assessment, the PBRER frequency was changed from one year to three years, which will not be appropriate for the submission of quinquennial reports. The MAH is asked to correct the pharmacovigilance plan, tables 7 and 8, accordingly.

RMP 5: The RMP should be updated according to the conclusions of the CHMP on the extended indication.

Annex 2: Assessment of the responses to the First Request for Supplementary Information

Major objections

Clinical efficacy aspects

Question 1

The Benefit / Risk profile for Cervarix for the prevention of head and neck cancers causally related to certain oncogenic HPV types in males and females as of 9 years of age and above is currently negative. The submitted data do not support any reliable conclusion on the efficacy of Cervarix in the prevention of head and neck cancers:

Question 1a)

The pivotal study endpoint of prevention against HPV infection is a surrogate endpoint for the protection against head and neck cancers. To this end, HPV infection of study subjects has been monitored at one single time point at the age of 18.5 years. This is considered insufficient since it has been established that only the prevention of a persistent HPV infection for at least 6 months can be considered a valid and meaningful surrogate endpoint for the prevention of HPV related cancers (such as cervical and ano-genital).

Summary of MAH answer

The proposal to extend the indication of Cervarix for prevention of HPV-related head and neck cancers comes as a subsequent indication following an approval for use to prevent cervical/vulvar/vaginal cancers in women and ano-genital cancers in females and males. Prevention of those HPV-related cancers is a major driver for national HPV immunization programs that have been successfully implemented in many countries. In recent decades, there has been a significant increase in the incidence of head and neck cancers (HNC) worldwide. It is today well established that HPV is associated with a subset of head and neck cancers (oral cavity, oropharynx, larynx cancers), and that those HPV-related HNC differ substantially from HPV-unrelated ones (mainly caused by alcohol and tobacco) at the molecular, genetic, epidemiological and clinical level (Gillison, 2012). A review and meta-analysis revealed HPV DNA prevalence estimates by cancer site: 45.8% (95%CI: 38.9-52.9) for oropharynx, 22.1% (95%CI: 16.4-28.3) for larynx and 24.2% (95%CI: 18.7-30.2) for oral cavity (Ndiaye, 2014). Approximately 90% of malignant neoplasms of the head and neck (HN) are squamous cell carcinomas (SCCs), while around 5% are adenocarcinomas. The most prevalent types, among HNSCCs associated with HPV, are HPV-16 (approximately 87%) and HPV-18 (approximately 12%) (Götz, 2019).

HPV vaccines have been shown efficacious in prevention of anogenital pre-malignant lesions in women in both clinical trials as well as in post-marketing effectiveness and observational studies. Epidemiological and molecular associations between HPV and cervical and oropharyngeal cancers are quite similar (IARC Working Group, 2014). Moreover, given the association between sexual behaviours and oropharyngeal cancers, vaccination is likely to be the most protective prior the onset of sexual debut, as it is for the prevention of anogenital cancers (Gillison, 2012). Given the substantial burden associated with head and neck cancers, the rising public health focus on those cancers and the fact that screening of pre-cancerous lesions is not feasible, every effort should be made on prophylaxis

which represents so far, a valuable tool to tackle the disease. In line with the introduction of a gender-neutral HPV vaccination strategy, efforts to increase awareness of HPV and its association with non-cervical cancers should be envisaged. Therefore, considering the above, the benefit/risk profile should not be regarded solely for prevention of head and neck cancers causally related to certain oncogenic HPV types, like it would be the only indication, but should rather be treated holistically as continuum of HPV-related indications adding HPV-related cancers from other anatomical area.

The Company acknowledges that evidence generated in the pivotal study describes one single time point at age of 18.5 years i.e. 6.5 years after vaccination, and not persistent oral HPV-infection.

However, the endpoint has been considered to be appropriate as a surrogate endpoint for the protection against head and neck cancers, for the following reasons:

1. The histopathological progression of oral cavity squamous cell carcinomas is likely to be analogous to that for cervical cancers, notably because of similar genetic alterations. However, HPV oral infection has not been associated so far with abnormal cytology from individuals without detectable lesions. The multistep process of head and neck carcinogenesis being yet to be elucidated, there is no histological endpoint to be assessed in clinical trials (Fakhry, 2011; Berman, 2017) . Since there are no identified head and neck cancers precursor lesions, no effective screening program exists contrary to cervical cancer screening where mild morphological changes accompany early HPV infections (Berman, 2017). As a result, the relationship between oral HPV infection, as measured using current collection procedures (e.g. oral rinse and gargle for oropharyngeal cavity), and HPV-positive oropharyngeal cancer is not as tightly linked as that for anogenital infection and premalignant disease, for which initial abnormal findings by cytology or PCR are further investigated by localized sampling under visual control (e.g. cervical sampling using colposcopy) (Gillison, 2012). Given these facts and according to the IARC working group report from 2014, the best surrogate endpoint for risk of HPV-positive oropharyngeal cancer in a clinical trial would be prevention of incident **and persistent oral HPV-16 infection** (IARC Working Group, 2014). It is universally accepted that it is not possible for an individual to develop HPV positive oropharyngeal cancer in the absence of a preceding oral HPV-16 infection (Lowy, 2015). Moreover, incident infection is a precursor of persistent infection, thus prevention of incident infections implies reduction of persistent infections (IARC Working Group, 2014).
2. Anogenital and head and neck cancers share common carcinogenic pathways (chromosomal aberrations, gene expression, microRNA profiles). In early animal models, L1-based vaccine-like particles were shown to prevent canine oral papillomavirus-induced papillomas (Suzich, 1995). As a result, molecular mechanism underlying vaccine efficacy are thought similar in anogenital and head and neck cancers (IARC Working Group, 2014).
3. The observed vaccine efficacy (VE) against oral incident HPV-infection is in the same range as the demonstrated efficacy at other sites (cervical and anal sites). As a reference, efficacy against various endpoints from GSK and NCI studies are presented in Table 1 (CIN1, CIN2+, CIN3+, incident infection, 6- and 12-month persistent infection, anal and oral infection). Interestingly, VE against cervical incident infection (79.6%) is an underestimation of the VE against cervical disease and persistent infection endpoints, all above 90%. It can be assumed that the same trend may be observed for oral HPV-infection, with the observed VE against oral incident HPV-infection (82.4%)

being an underestimation of the VE against oral disease and persistence infection endpoints.

Table 1 Summary of Cervarix vaccine efficacy

Vaccine Efficacy GSK Sponsored study HPV-008 ATP cohort for Efficacy VE% (95% CI) – N=16114 – Month 48	
Associated with HPV-16/18	
Incident cervical infection	79.6% (76.7-82.1)
6-month cervical persistent infection	94.3% (92.0-96.1)
12-month cervical persistent infection	92.9% (89.4-95.4)
CIN1	92.8% (87.1-96.4)
CIN2+	94.9% (87.7-98.4)
CIN3+	91.7% (66.6-99.1)
Vaccine Efficacy NCI sponsored HPV-009 study Full analytical cohort VE% (95% CI) – N=5312 – Month 48	
Associated with HPV-16/18	
Incident cervical infection	76.4%* (66.9-83.4) 87.9%** (77.4-94.0)
Anal prevalent infection	62.1%* (47.3-73.1) and 83.6%** (66.7-2.8)
Oral infection at 4 years	93.3%* (62.5-99.7)
Vaccine Effectiveness GSK sponsored study HPV-040 Total Enrolled Cohort VE% (95% CI) – N=5899	
Associated with HPV-16/18	
Oropharyngeal infection at 6.5 years	82.4% (47.3-94.1)

Data source:
HPV-008 End of Study Clinical Study Report, NCI data: Herrero 2013, Kreimer 2011, *=full cohor t **=restricted cohort;
HPV-040 Study Report

4. The observed VE against oral prevalent HPV-infection 3.5 to 6.5 years after vaccination is more likely to be biased against the vaccine (since no baseline was available and the timepoint was much longer after vaccination than usual) than in favour of the vaccine.

Rapporteurs' Assessment

In the introducing sentences the applicant particularly argues with biological similarity between cervical malignancies and head and neck cancer. It should be noted that the entity of head and neck cancers is broad, and the natural history of infection at this non-genital site is less well understood than that of genital infection.

Molecular mechanisms share some similarities, but the head and neck cancers carcinogenic pathways are still not well understood. Persistent infection with high risk HPV type is necessary but not sufficient for the progression to HPV associated cancer (Moody, 2010). Natural history of oral HPV infection, encompassing establishment of infection and progression to cancer, remains poorly characterized and the histological and cellular differences of the oropharynx could play an important role in the progression to OPSCC which would not be comparable to anogenital sites.

The Applicant acknowledges that evidence generated in the pivotal study describes one single time point when subjects were 18.5 years of age (e.g. 3.5 to 6.5 years after vaccination), and not persistent oral HPV-infection. The Applicant still considers the endpoint to be appropriate as a surrogate endpoint for the protection against head and neck cancers, for different reasons that have been presented.

The Applicant refers to the report of the IARC working group mentioning that the best surrogate endpoint for risk of HPV-positive oropharyngeal cancer in a clinical trial would be prevention of incident **and persistent** oral HPV-16 infection (IARC Working Group, 2014). This was however not completely followed as only the incidence but not the persistence of HPV infection was assessed in study HPV-040 (and study HPV-009). For study HPV-040 (and study HPV-009), the oropharyngeal HPV infection status in study participants prior to vaccination was unknown. Detection of HPV-types in the samples collected 3.5 to 6.5 years later cannot be considered as representative for persistent infection.
In the absence of identifiable precancerous histological and clinical lesions suitable as clinical trial

endpoint, experts of IARC and the United States National Cancer Institute have agreed that HPV oral persistent infection could be considered the best appropriate endpoint as a surrogate for HPV-related head and neck cancer (Lowy 2015). Even if prevention of incident infections implies reduction of persistent infections (as incident infection is a precursor of persistent infection), it is recognized that persistence is required for progression to HPV pre-cancer and cancer (Gillison 2012). In addition, measuring incidental infections only is of limited value since most infections regress spontaneously and because technic of sample collection and assays vary in sensitivity and reliability. Of note, VE for the different anogenital indications of HPV vaccines were not approved on the basis of incident infection endpoints.

FDA agreed on oral HPV persistent infection as the primary endpoint in order to demonstrate vaccine efficacy against HPV related oropharyngeal cancer. The frequency of serial oral sampling has also been discussed. Please refer to Question 1e).

In summary, from the applicant's answer, and taking the FDA position into account the one single time point evaluation of oral infection cannot be supported. Therefore, the question should be further pursued in connection with question 1e, discussing the options for collection of additional clinical data supporting the indication. **Not solved.**

Question 1b)

The statistical test for VE against oropharyngeal infections is not considered to be statistically significant. This endpoint was a key secondary endpoint which was part of a hierarchical approach to control for multiplicity. In this hierarchy, the first endpoint failed to show a statistically significant effect. Hence, all other endpoints are considered descriptive only. The study is therefore considered to have failed and no further indication can be derived.

The Applicant is asked to discuss this negative study result in the light of the requested indication and Sec. 6.2 of the Draft Guideline on multiplicity issues in clinical trials (EMA/CHMP/44762/2017).

Summary of MAH answer

The Company acknowledges that, the first confirmatory objective in the hierarchy was not met and, consequently, only exploratory interpretation could be done for the subsequent confirmatory objectives (including efficacy against oropharyngeal infections). However, it is worth noting that the lower limit (47.3%) of the CI associated with the oropharyngeal infection objective (VE= 82.4% (95% CI: 47.3, 94.1) suggesting evidence of high effectiveness against oropharyngeal infection associated with HPV-16/18 and is similar to the vaccine efficacy against infection observed at other anatomical sites.

In the statistical procedure, the oropharyngeal and the cervical confirmatory endpoints are linked due to the hierarchical approach, however, from a physio-pathological perspective in an individual the two mucosal sites can be considered as unrelated, i.e. an effect at the oropharyngeal site may be observed independently from the outcome at the cervical site.

We acknowledge that the predefined analysis procedures would take preference over any post-hoc interpretations, however, it is also worth mentioning that, if a more conservative adjustment for multiplicity was applied to the four objectives of interest in the defined hierarchical procedure, the

observed p-value (0.002) for the efficacy against oropharyngeal infection associated with HPV-16/18 is less than the significance level of 0.0125 (Bonferroni adjustment of type I error).

As explained above and in the clinical overview submitted with this variation, the first confirmatory objective in the hierarchy was not met: the observed overall (total and indirect) effectiveness in Arm A against HPV-16/18 genital infection was 23.8% (95% CI: -19.0, 51.1); p-value = 0.232. The observed overall (total and indirect) effectiveness in Arm B against HPV-16/18 genital infection (second objective in the hierarchy) was 49.6% (95% CI: 20.1, 68.2), p-value= 0.004.

The overall effectiveness was expected to be higher for Arm A (female/male vaccination) as compared to Arm B (female vaccination) with efficient randomization at baseline, similar HPV vaccination coverage in females, and balanced behavioural characteristics during the follow-up years (Lehtinen, 2008). However, the data suggest that arm A seemed to have a higher transmission of HPV infection than the other two arms, indicating that the original randomization of the study communities using historical seroprevalence stratum may have failed to allocate comparable communities to each Arm. Therefore, a randomization bias may have been detrimental to comparisons between Arm A and Arm C leading to failure of the first objective in the hierarchy. It was noted that the area type (urban versus semi-urban) may have been a better prognostic variable for the HPV-16/18 infection rates. Therefore, a post-hoc analysis estimating the overall effectiveness stratified by the area type (urban, semi-urban) was performed.

- ☐ Arm A versus Arm C (Control): VE = 29.7% (95% CI: 0.0, 50.6), two-sided p-value = 0.05
- ☐ Arm B versus Arm C (Control): VE = 45.4% (95% CI: 11.8, 66.2), two-sided p-value <0.05

The post-hoc analysis shows improvement in the overall (total and indirect) effectiveness in Arm A against HPV-16/18 genital infection (first objective in the hierarchy). The results from primary and the post-hoc analysis estimating the overall (total and indirect) effectiveness in Arm B against HPV-16/18 genital infection (second objective in the hierarchy) were consistent. The results from the primary and post-hoc analysis showed no statistical evidence of difference in overall effectiveness between gender-neutral (arm A) and females-only (arm B) vaccination strategies.

In addition, a high total effectiveness against genital HPV-16/18 infection in Arm A versus Arm C, Arm B versus Arm C and pooled Arms A and B versus Arm C was observed (VE = 93.8% [95% CI: 84.1, 97.6]; 92.1% [95% CI: 80.0, 96.9]; 93.3% [95% CI: 87.7, 96.4], respectively), consistent with findings in global efficacy studies. The primary analysis for the overall (total and indirect) effectiveness in Arm A against HPV-16/18 genital infection (first objective in the hierarchy) was not met due to the limitations described above.

In addition, the efficacy data generated in the independent NCI study HPV-009 also suggested a very high and similar efficacy (VE = 93.3% (95% CI = 63% -100%)) of the vaccine against oropharyngeal infection associated with HPV-16/18.

As a conclusion, we were able to identify the failures in the study design of HPV-040, which led to an unmet first objective and we were able to compile evidence confirming that results of this study were consistent with global efficacy studies. We acknowledge the recommendations in the section 6.2 in the draft guidance on multiplicity issues in clinical trials (EMA/CHMP/44762/2017, EMA). However, as mentioned in section 6.3 of the draft guidance, if there is observed beneficial effect, but the study falls short of achieving its primary objective, information from further studies could be used to support the

observed beneficial effect. Taking into consideration the study results presented in the variation and the supportive data from the literature (see response to Question 1c), we believe this situation is applicable to our study and more generally to the context of our application.

Rapporteurs' Assessment

The relevance of the lower limit of the CI is acknowledged for vaccine efficacy in principle. However, the discussion of the lower CI limit for the prevention of oropharyngeal infection is not considered useful to resolve the raised issue about the lack of statistical significance due to a failed primary endpoint.

HPV-009 was submitted as supportive study in which VE against oral infections was studies as exploratory endpoint after 4 years. A supportive study, however, is not considered sufficient to rescue a failed study. Likewise, a retrospective meta-analysis with HPV-009 and HPV-040 would not be permissible in the given case with a failed study (see Points to consider on application with 1. Meta-analyses; 2. One pivotal study, Section II.1.3; CPMP/EWP/2330/99).

A randomisation issue regarding the stratification factor is discussed by the Applicant. It is stated that the "historical seroprevalence stratum may have failed to allocate comparable communities to each arm". This issue is considered by the Applicant as the main source of the failed study. No data other than a single post-hoc analysis using area type as stratum was provided to support the claim. Analyses adjusting for the observed historic seroprevalence rate per community rather than using a coarse cut-off might have helped as well. Further, if randomisation did not work as expected ("randomisation bias" occurred) and had such an impact on the analysis all other comparisons might be impacted as well and biased results cannot be excluded. To put it differently, if there was an imbalance in community types and this was indeed a confounder the results might be influenced (or driven) by this factor, which then could also affect all other analyses. **The Applicant is asked to adequately adjust the analysis of VE against oropharyngeal infections for community type. (OC)**

It is in principle understood that the hypotheses on vaccination strategies on the community level are not directly linked to the oropharyngeal hypothesis. Nevertheless, it was the Applicants choice to conduct the study in the way it was done. Alternative approaches for multiplicity control reflecting the different nature of hypotheses could have been pre-planned at the design stage or prior to unblinding of the Sponsor. This was not done. **Any post hoc definition is meaningless** as it is obviously made in the light of the results. It is hence also not agreed that a Bonferroni correction would be (always) more conservative than the hierarchical approach chosen by the Applicant. This can be easily seen in that case as a Bonferroni correction would have led to significant results, while the chosen approach did not. Consequently, there does not exist a uniformly most conservative approach which would justify a post hoc decision.

Taking Section 6.3 of the draft guidance on multiplicity issues in clinical trials (EMA/CHMP/44762/2017) into account is not considered appropriate, as this is not considered applicable here. Section 6.3 relates to a situation where an endpoint is clinically very important (mortality is given as an example) but defined as secondary endpoint only as the power for the endpoint was assumed to be too low at the planning stage. This is not the case in this trial. The study tried to answer two different (not directly related) questions at once (comparison of vaccine schedules and prevention of oropharyngeal infection) and failed. Of note, prevention of oropharyngeal infection is only a surrogate endpoint and hence its clinical relevance is limited. A situation which would resemble the situation discussed in Section 6.3 in the guideline would have been to use prevention of oropharyngeal infection as primary endpoint and prevention of oropharyngeal cancer as

secondary endpoint. When in that case a strong effect were to be observed in the latter endpoint, the primary endpoint would be somewhat irrelevant.

Overall, the issue around the lack of significance for the relevant endpoint is <u>not considered solved</u>. Additionally, an OC was raised on the suitability of the presented analyses.

Question 1c)

The negative study result is further to be considered in the light of a single pivotal trial (please Cf. points to consider on Application with 1. Meta-Analyses; 2. One pivotal trial; CPMP/EWP/2330/99). These PtC further request specifically compelling results.

The Applicant is asked to further discuss the formally negative study and the results in the light of these requirements.

Summary of MAH answer

The Company would like to reiterate that the Application does not only consist of one single pivotal trial. HPV-040 study was considered as the pivotal study used to support the indication and has been thoroughly described in the submission. However, additional evidence from another independent study (HPV-009) as well as from a cross-sectional study (Mehanna, 2019) were also included as supportive data to the pivotal study.

In addition, other researcher groups have provided evidence that routine vaccination against HPV, as part of a national immunization program, is associated with significant reduction in oropharyngeal HPV infections (Gillison, 2011; Grün, 2015; Kahn, 2015; Hirth, 2017; Chaturvedi, 2018; Chaturvedi, 2019). Among those studies, a herd effect has been reported in unvaccinated men in the US with a decline of 38% between 2009-2010 and 2015-2016 in vaccine-type oral HPV prevalence (Chaturvedi, 2019). In line with these results, a recent cross-sectional study conducted in Colombia also reported significant reduction of HPV-16 prevalence in the oral and oropharyngeal cavity of vaccinated high school students compared to unvaccinated counterparts (Castillo, 2019). Although these studies mainly assessed the effect of the quadrivalent HPV vaccine, they are consistent with the results presented in the Application. As a result, since all the available data from literature point to high efficacy, performing a meta-analysis would lead to similar efficacy estimates against oral infections caused by HPV-16/18, as observed in the studies HPV-040 and HPV-009 (as described in the Clinical overview addendum and Herrero 2013). In addition, and as mentioned by the Rapporteur in the PtC, the use of meta-analysis to support an indication is restricted to a number of circumstances and can't be considered as pivotal evidence.

Noteworthy, a recent registry-based US study has documented a reduced prevalence of oropharyngeal cancers (OPC) in the HPV-vaccinated group compared with the non-vaccinated group (Katz, 2020). Patients who were not vaccinated for HPV (9-valent HPV, quadrivalent HPV, or bivalent HPV vaccine) had a 19 times increased risk of developing OPC compared to those vaccinated (Relative risk (RR) = 19.37; 95%CI =[7.27: 51.62]; P-value = 0.0001). In this study where one third of vaccinated patients were males, they found that male patients who were not vaccinated had a 23 times (RR = 23.8; 95% CI = [3.36 -169.22]; P-value = 0.0015) increased risk of developing OPC while in non-vaccinated females, the risk was 9 times (RR=9.34; 95% CI = [3.01 -29.01]; P-value = 0.0001) higher. Based on these findings and on the fact that OPC affects more males than females, the authors hypothesized that HPV vaccination might be more effective for prevention of OPC especially in men (Katz, 2020). These data on the reduction of OPC incidence rates in HPV-vaccinated cohorts are among

the first ones to be reported and constitute first pieces of evidence on the effect of HPV vaccination on the occurrence of HPV-related OPC.

Available literature data do not point towards one single pivotal study but highlight substantial piece of evidence showing an effect of HPV vaccination on oral HPV infection. Accordingly, the Company believes that the currently data available supports an extension of the indication for Cervarix to prevent oral HPV infections and associated cancers.

Rapporteur Assessment

No discussion of pre-requisites for applications with a single pivotal trial were provided. Literature data and further supportive data do not cover up for replication in a pivotal trial but are always expected. No arguments to resolve the issues with a single pivotal trial were provided. The provided literature could be considered an informal / anecdotal literature based meta-analysis (mainly based on different vaccines) were further requirements would apply.

The cited paper on reduction of OPC in vaccinated individuals (Katz 2021) is not considered to "constitute (a) first pieces of evidence on the effect of HPV vaccination" as it is not scientifically sound. Age is a very strong confounder: As HPV vaccination was only recently introduced (starting 2006 in the first regions including USA) vaccination status is naturally correlated with age. Further, the risk of developing OPC strongly increases with age with a peak in the age group of 65-74 (see Katz 2021). Hence, unvaccinated individuals are naturally more likely to develop OPC (as they tend to be older). A suitable confounder-adjusted analysis (also considering other confounders) is lacking. The reported results hence do not support the claim that HPV vaccination reduces the risk of OPC by RR = 1/19.37 = 0.051 (which would be equivalent to a VE of 94.8%). Furthermore, the reported effects are not product specific and hence cannot be attributed to Cervarix.

Overall, the issue is not considered solved.

Question 1d)

As discussed in the assessment on "Statistical methods" and the "Conduct of the study", it seems that only within the SAP a hierarchy of primary and key secondary analyses was defined, which included confirmatory testing for oropharyngeal infections. No multiplicity control over primary and key secondary endpoints was defined within the protocol. Given the very late change after study completion and after extensive interim analyses for immunogenicity and safety this should be considered as a post hoc choice and is hence not endorsed. Likewise, pooling of Arms A and B for the computation of VE against oropharyngeal infection was not defined in the protocol. Whether it was defined within the SAP or only in the CSR currently cannot be assessed due to the lack of the SAP. In contrary, in the protocol it was stated that "the statistical analysis of the second and third secondary endpoints will be done by evaluating the difference in HPV-16/18 and other oncogenic HPV types PCR prevalence rates in communities in different intervention arms A vs. C and B vs. C."

The Applicant is asked to discuss the history of changes in the light of the accruing data and available information to rule out any perceived or real possibilities of data driven analyses.

Summary of MAH answer

The Company acknowledges that the hierarchy of primary and key secondary analysis was clarified in the study Statistical Analysis Plan (SAP) for study HPV-040 and no multiplicity control was defined in

the protocol. This change was proposed in the study SAP. The SAP was reviewed and approved by the study team (Clinical Research and Development Lead, Project Level Clinical Research and Development Lead, Lead Statistician, Scientific writers, Regulatory Affairs team representative, Safety Physician) according to the Company's Standard Operating Procedure (SOP) on 09 September 2015 before the randomisation codes and the laboratory data was unblinded to the Company's statistician. The access to the randomisation codes and the laboratory data was granted to the Company's statistician on 27 October 2015. The interim analysis of safety and immunogenicity was conducted in October 2012 in all male and female study participants from the 33 communities.

The interim analysis was initiated when the Month 12 telephone call had been completed for applicable subjects and conducted when Month 12 passive data for subjects enrolled by the end of 2009 were available. The immunogenicity assessment in the study was planned in a subset of subjects. The interim analysis was carried out by an external statistician, and blinding was maintained for all the applicable study personnel up to the end of the study. Individual listings and randomization list were not generated at the time of interim analysis.

The SAP for the final analysis of the study was approved on 9 September 2015. The access to the randomisation codes and the laboratory data was granted to the study statistician on 27 October 2015. The database archival for the final analysis was done on 11 November 2015. The SAP was finalised on 9 September 2015, before accessing the blinded data for the study. Hence, confirming that this was not a data driven analysis.

In addition, we would like to bring to your kind attention that an independent steering committee comprised of an independent group of experts was jointly established for this study to advise the investigating institutes (University of Tampere [UTA], University of Helsinki, National Institute for Health and Welfare [THL] and Finnish Family Federation) and GSK Biologicals. The roles and responsibilities of this Steering Committee are described in the Charter for the Steering Committee (provided in module 5.3.5.1 – charter for steering committee – HPV-040 study). The Steering Committee was responsible to provide recommendations for the conduct of the study and maintenance of study validity.

With regards to the analysis of oropharyngeal infection, the Company acknowledges that according to the protocol, the analysis of the secondary objective was planned by comparing the Arm A Vs Arm C and Arm B Vs Arm C. However, to note that this is the analysis of total effectiveness and is driven by the direct effect. Since HPV vaccine has shown high efficacy against HPV infection at other sites, it was reasonable to pool the arms A and B receiving HPV vaccine, to evaluate the total effectiveness against HPV- 16/18 oropharyngeal infection associated with HPV-16/18 to increase the power of the test. It should be noted that this decision was made in the SAP in consultation with the Steering Committee before accessing the blinded data.

The analysis is described in detail in the Statistical analysis Plan. The interim analysis SAP (dated 16 February) as well as the final analysis SAP (dated 9 September 2015) are provided in module 5.3.5.1 of this application.

Rapporteurs' Assessment

The Applicant reassures CHMP that all decisions were made without knowledge of individual group allocation and treatment. In principle this seems acceptable. However, it is noted once more that interim analyses for immunogenicity were conducted for (a subset) of study participants three years before the finalization of the final analysis SAP by external statisticians. Even if randomization codes of

individuals were not unblinded at that time to the company or any involved personnel, the summary level immunogenicity and safety data still might carry important information which might have influence the final SAP. The concern that choices for data analyses were made in the light of this data cannot be fully ruled out. In that case the changes would be ad hoc/post hoc data based changes of an ongoing study and hence might impact the credibility of results.

The Applicant provided the SAPs for interim and final analysis.

The final analysis SAP (Section 7.6 - Interpretation of analyses) defines the hierarchy of hypothesis, in line with the CSR, as follows:

All analyses will be descriptive/exploratory except the primary analysis associated to the following objectives:

1. To demonstrate the overall (direct and indirect) effectiveness of GSK Biologicals' HPV-16/18 vaccine in reducing the prevalence of HPV-16/18 genital infection in females approximately 18.5 years of age following community-based vaccination of 12 - 15 year old females only (Arm A versus Arm C).
2. To demonstrate the overall (direct and indirect) effectiveness of GSK Biologicals' HPV-16/18 vaccine in reducing the prevalence of HPV-16/18 genital infection in females approximately 18.5 years of age, following community-based vaccination of 12 - 15 year old females and males (Arm B versus Arm C).
3. To demonstrate the total effectiveness of GSK Biologicals' HPV-16/18 vaccine in reducing the prevalence of HPV-16/18 oropharyngeal infection in females approximately 18.5 years of age, following community-based HPV vaccination of 12 - 15 year old females or females and males versus control (pooled Arms A and B versus Arm C, birth cohort 1994 & 1995).
4. To demonstrate the indirect effectiveness of GSK Biologicals' HPV-16/18 vaccine in reducing the prevalence of HPV-16/18 genital infection in females approximately 18.5 years of age receiving control vaccine, following community-based vaccination of 12-15 year old females and males (Arm A versus Arm C).

To control the two-sided type I error below 5%, a hierarchical procedure, according to the order of the objective shown above, will be used for the multiple confirmatory objectives.

A justification for the pooling of Arms A and B was provided in the response, which is indeed reasonable. Nevertheless this was not pre-planned per protocol but only defined in the SAP.

The Applicant provided the SAP for the final analysis, which indeed defined the hierarchy and pooling of groups as stated in the CSR. This provides some reassurance. However, overall, the issue on data-driven choices cannot be fully ruled out, as summary level information was assumingly available at the time of finalization of the SAP. The issue remains as uncertainty but is **not further pursued**.

Question 1e)

In order to correctly document vaccine efficacy against oropharyngeal persistent HPV infection, a long-term follow-up study with adequate serial oral sampling would need to be conducted. The Applicant should clarify if an adequately powered clinical study has been initiated with the relevant primary endpoint for the protection against HNC with adequate serial oral sampling.

Summary of MAH answer

The Company's position is that the additional benefit of HPV vaccination against oral HPV infection and HPV-related head and neck cancers should be monitored as a post-authorisation activity and not as a placebo-controlled clinical trial. The rationale for not conducting a clinical trial to measure vaccine efficacy against oropharyngeal persistent HPV infection is based on the following:

☐ **Prophylactic HPV vaccines**:

☐ have demonstrated high efficacies against viral and histopathological endpoints at various anatomical sites (cervix, vulva, vagina, anus);

☐ are highly immunogenic in both genders;

☐ provide long-term protection against HPV infections;

☐ induce serum antibodies that are correlated with antibodies in oral cavity (Pinto, 2016; Parker, 2019);

☐ **Potential similarities between head and neck cancers and anogenital cancers:**

☐ in terms of HPV-induced cancer biology and risk factors (viral etiology, with HPV-16 and -18 strongly associated with both cancers, at-risk sexual behaviors, carcinogenic molecular biomarkers) (Berman, 2017; Näsman, 2020);

☐ in terms of association between infection at the cervix and oral cavity (degree of dependence of the oral site on the cervical site) (Frisch, 1999; Termine, 2011; Steinau, 2014);

☐ as HPV vaccines have shown to be effective against anogenital HPV infection and related precancerous lesions these may also prove effective against HPV-induced cancers occurring in the oral cavity

☐ **Points to consider for head and neck cancers:**

☐ No clear intraepithelial precursor lesion has been identified for head and neck cancers (no surrogate clinical endpoint to assess vaccine efficacy against head and neck cancers), the absence of subclinical HPV positive detectable cellular abnormalities precluding association of such lesions with persistent infection;

☐ Rates of persistence along with predictors of HPV oral cancer initiation are still poorly

understood, leading to uncertainties in the frequency of serial oral sampling;

☐ Evidence from database and surveillance studies has shown a reduction of oral HPV infection in HPV-vaccinated subjects (see references in response to Question 1c);

☐ **Ethical considerations** are that a placebo-controlled clinical study would not be acceptable in view of availability of HPV vaccines which are approved in more than 100 countries worldwide with proven efficacy and safety.

In view of the above and considering that a potential clinical trial should be performed in high risk populations in which the incidence of oral HPV infection may be sufficiently high to assess efficacy against oral persistent HPV infections, while there is no identified precursor intraepithelial lesion preceding the development of cancer in this anatomical site, the Company believes that nowadays conducting a placebo-controlled clinical trial would not be ethical and would provide little scientific insights. Therefore, the Company believes it would be appropriate to monitor the additional benefit of HPV vaccination against oral HPV infection and HPV-related head and neck cancers in a post-authorisation observational study.

Given all the evidences corroborating the mechanism of HPV infection in the induction of cancer in various anatomical sites, assessing the impact of the vaccine in a real-world setting on the ultimate clinical endpoint, i.e. cancer, seems a reasonable approach. However, it should be pointed out that given the time lag between vaccination and the development of cancer, an observational study design would likely bring information with regards to the effect of HPV vaccines on the incidence of head and neck HPV-related cancers although not within a short timeframe.

In this perspective, the Company has explored different options that would address such research question. The results of this evaluation along with specificities and assumptions are presented in the following sections.

1. Potential case-control study design

Monitoring trends of head and neck cancers to reveal the impact of vaccination can be challenging due to the need of robust baseline data before the implementation of vaccination, hurdles in the interpretation of year-to-year variations in natural trends and changes for reasons other than HPV vaccination. Moreover, a significantly high vaccine coverage might be needed to demonstrate the impact of the vaccine by ecological methods such as a trend analysis.

Therefore, the impact in the real world or effectiveness of the vaccine might be better assessed by the conduct of epidemiological studies such as case-control studies. Using a case-control design, vaccine effectiveness can be estimated comparing the proportion of vaccination exposure among head and neck cancer cases with the proportion of vaccinees among control patients who are free of an HPV-related cancer.

A case-control study represents a classical approach to determine vaccine effectiveness (in a real-world setting) and it also offers an opportunity to investigate other aspects such as assessing vaccine effectiveness in incomplete vaccination (i.e., not full vaccination schedule).

The Company has undertaken a preliminary assessment for the feasibility of such a case-control study

to evaluate Cervarix's effectiveness on head and neck cancers. The summary is presented below:

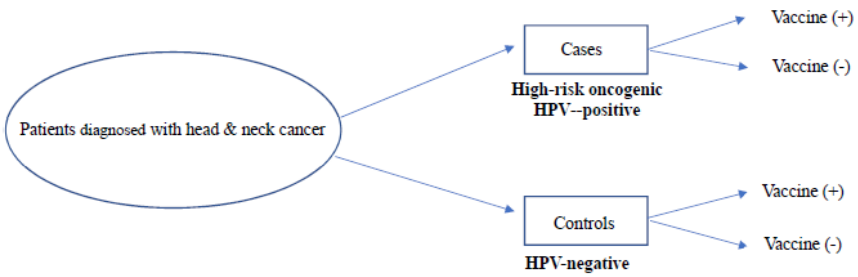
Study design

Two possible study designs are discussed below:

1. A prospective, multi-site, test-negative design (a modified case-control study) for the estimation of the vaccine effectiveness VE= (1-OR)*100.

In this type of study, cases are patients diagnosed with head and neck cancers caused by high-risk oncogenic HPV whereas controls are non-HPV-related head and neck cancer patients. Since vaccination for boys has only recently been introduced in some countries (see Table 5), the study population would be females eligible for Cervarix vaccination (birth cohorts from the first year of introduction of the vaccine in the NIP). Please see response to question 10 and section 1.3.4 in this document for inclusion of males in the study. See Figure 1 for an illustration of the study design.

Figure 1 Test-negative design to determine vaccine effectiveness



2. A retrospective database age-matched case-control study in any of the countries with linkage between the cancer registry and the vaccination registry.

The study population would be females eligible for Cervarix vaccination (birth cohorts from the first year of introduction of the vaccine in the NIP). Cases would be females in the registry with high-risk oncogenic HPV head and neck cancers whereas controls would be patients with non-HPV-related cancers (i.e., colon cancer). Controls would be sex- and age-matched and retrieved from the same registry.

In both cases, provisions would be made to adjust for confounders at the design and the analytical phases.

Evaluation of the countries

Five EU countries were identified to have cancer and vaccine registries that have implemented Cervarix in their National Immunization Programmes (NIPs) at some point in time. (See Table 5 for more information on vaccination schedules and vaccine coverage in the selected countries).

☐ Denmark: Implemented Cervarix in their NIP in February 2016. Both Cervarix and Gardasil

vaccines coexist although most of the females/girls have been vaccinated with Gardasil/Gardasil 9.

☐ Norway introduced Cervarix in their NIP in 2018.

☐ UK implemented HPV vaccination with Cervarix in 2008 and used it for 4 years (from 2008 to 2012). Further on, Cervarix was replaced by Gardasil, and Gardasil 9. Vaccine coverage was 60.4% for the combined first routine vaccinated cohort and catch-up cohorts (all 2008/2009 and 2009/2010 campaigns combined). Available data and services in the UK can be explored.

☐ Finland: Implemented Cervarix in their NIP in November 2013. Overall head and neck cancer incidence rates are lower compared to other countries. This might be a hurdle for the conduct of the case-control study and may delay the attainment of the adequate sample size within a reasonable timeline.

☐ The Netherlands is closely following the impact of Cervarix since its implementation in their NIP in 2010.

Simulations

This is a simulation of a case-control study in the Netherlands.

A few aspects must be considered: Since only girls aged 12 years old have been vaccinated via NIP in the Netherlands since 2010 the study population should be restricted to females. Therefore, the target population should be females born in 1998 or younger.

Case definition: Incident ICD-10 classification codes C00-C14, C30-C32 (histological verified diagnosis) and HPV-typed. Note: for this exercise we obtained data from the National Cancer Registry website. Therefore, for this exercise we have taken into account the exact figures reported on their website without considering which proportion would correspond to HPV types as this information is not provided.

For the sample size calculation: Two-sided confidence interval (1-alpha): 95%; power: 80%; ratio of controls to cases: 2. However, if a test-negative design is conducted, since cases and controls will not present sequentially in a real-world setting, it is likely that more than 2 controls per each case are recruited; hypothetical proportion of controls with exposure: Different scenarios of 80%, 70%, 60%, 50%, 40%, and 30% of vaccine coverage have been considered for the sample size calculation; least extreme Odds Ratio to be detected: 0.1, 0.2, 0.3, and 0.4. OR = (1-VE)/100 have been considered; allowance of 30% of cases/controls to be lost to follow-up.

Test-negative design

The sample size calculation for a test-negative design (unmatched case-control study where cases are high-risk oncogenic HPV -related head and neck cancer patients whereas controls would be non-HPV-

elated head and neck cancer patients) is presented in Table 1.

Table 1. Sample size calculation for an unmatched case-control study

Sample size for an unmatched case-control study: number of cases required to demonstrate vaccine effectiveness (VE), with 80% power using a two-sided test, alpha=0.05, with 2 controls per case and for given vaccine coverage in controls.								
		Vaccination coverage in controls						
		0.2	0.3	0.4	0.5	0.6	0.7	0.8
Detectable Odds Ratio (OR= (1-VE)/100)	0.1	48	31	23	18	15	13	13
	0.2	67	45	34	28	25	23	25
	0.3	96	65	51	43	39	39	44
	0.4	141	98	78	68	64	66	77

Fleiss (with continuity correction), Statistical Methods for Rates and Proportions
OpenEpi, Version 3, open source calculator—SSCC. Available here: https://www.openepi.com/SampleSize/SSCC.htm

Table 2. Estimation of the year in three European countries when a test-negative design study may be feasible

Country	Year Cervarix introduced	Starting point for a case-control study including cases aged 25 years	Average female birth cohort size[1] (x1000)	Estimated crude incidence[2] (cases per 100.000)				Calendar year for end of cases enrolment[3]					
								VE= 80%			VE= 90%		
				Age groups (years)				Vaccine exposure in controls			Vaccine exposure in controls		
				25-29	30-34	35-39	40-44	0.7	0.5	0.2	0.7	0.5	0.2
The Netherlands	2010	2023	86	0.9	1.24	2.05	4.3	2035	2034	2037	2033	2033	2035
United Kingdom	2008	2020	365	0.6	1.5	3.3	6.0	2027	2027	2029	2026	2026	2028
				20-29	30-39	40-49							
Finland	2013	2025	26	0.74	1.6	3.7		2045	2044	2046	2042	2041	2044

1. Rounded-up average from 2007 to the last available calendar year for each country from EUROSTAT https://ec.europa.eu/eurostat/databrowser/view/DEMO_FASEC__custom_607563/default/table?lang=en
2. Calculated as the average of the estimated crude incidence for every age group from 1983 to 2009 for the Netherlands, for 2017 for the United Kingdom and from 1953 to 2012 in Finland
3. Assuming that since the proportion of HPV-related cancer cases are around 33% of all HNC, the recruitment of the estimated number of controls needed (ratio case-control 1:2) would be reached before the end of the enrolment of cases

To estimate the incidence rate of head and neck cancer in the Netherlands, we calculated the average crude rate incidence (cases per 100.000 population) for every age group from 1983 to 2009 (last year before the implementation of HPV vaccination in the Netherlands). Cases are calculated by incrementing year and adjusting for the incidence rate in that age group (Table 2). For example, in 2023, there would be one birth cohort. In 2024, there would be two birth cohorts, in 2027 there would be five birth cohorts of ≤ 29 years of age. In 2028, there would be five birth cohorts of ≤29 years of age and 1 birth cohort of 30 years of age. Therefore, the incidence rate of every included age cohort is taken into account accordingly in computing the total number of cases and the cumulative number of

cases for every calendar year.

Discussion

The Company has preliminary evaluated the feasibility to conduct a case-control study using national cancer registry publicly available data to identify cases. For the Netherlands, a test-negative case-control study that would start in 2023, considering a vaccine coverage of 50% (similar to the vaccine coverage of 58% for 3-dose achieved for the first birth cohort) and VE of 80%, according to the estimated sample size in Table 1, would finish in 2034, when the estimated sample size would be achieved (including allowance for 30% of drop-outs). The assumptions for these calculations are that the study would start when the first vaccinated cohort would reach 25 years (vaccination started in 2010 in the Netherlands for the 12 years old female group). Therefore, 2034 would be the first year when the study could be completed (Table 2).

Additionally, a similar exercise has been conducted for the United Kingdom and Finland.

In the United Kingdom, the first vaccination cohort has reached 25 years in 2020 (Cervarix was implemented in 2008, see Table 5). We considered a vaccine coverage of 50% and VE of 80%. According to the estimated sample size in Table 1, the study would finish in 2027 (Table 2), when the estimated sample size would be achieved (including allowance for 30% of drop-outs). Data refer to ICD-10 classification codes C00-C14, C30-C32.

Note: Cervarix was introduced in the UK NIP in 2008 and was replaced by the quadrivalent-HPV vaccine in September 2012. For this exercise all birth cohorts have been considered and not only those birth cohorts eligible for universal vaccination with Cervarix (i.e., from 2008 through 2012).

In Finland, the first vaccinated cohort would reach 25 years in 2025 (Cervarix was implemented in 2013, see Table 5). We considered a vaccine coverage of 50% and VE of 80%. According to the estimated sample size in Table 1, the study would finish in 2044, when the estimated sample size would be achieved (including allowance for 30% of dropouts).

Matched case-control study

In the case of a retrospective database matched case-control study, the sample size calculation for the different vaccine coverage and vaccine effectiveness scenarios is showed in Table 3. Table 4 reflects the starting time point and the end time point of the study considering different vaccine coverage and

vaccine effectiveness scenarios.

Table 3. Sample size calculation for a matched case-control study

Sample size for a matched case-control study: number of cases required to demonstrate vaccine effectiveness (VE) , with 80% power using a two-sided test, alpha=0.05 , with 2 controls per case and for given vaccine coverage in controls.								
		Vaccination coverage in controls						
		0.2	0.3	0.4	0.5	0.6	0.7	0.8
Detectable Odds Ratio (OR= (1-VE)/100)	0.1	37	25	19	16	14	13	13
	0.2	57	40	31	27	24	24	27
	0.3	87	62	50	44	41	42	49
	0.4	136	97	80	71	69	72	86

PASS 2019; Tests for Two Correlated Proportions in a Matched Case-Control Design

Table 4. Estimation of the year when a matched case-control study is feasible in three European countries

Country	Year Cervarix introduced	Starting point for a case-control study including cases aged 25 years	Average female birth cohort size[1] (x1000)	Estimated crude incidence[2] (cases per 100.000)					Calendar year for end of cases enrolment[3]					
									VE= 80%			VE= 90%		
				Age groups (years)					Vaccine exposure in controls			Vaccine exposure in controls		
				25-29	30-34	35-39	40-44	45-49	0.7	0.5	0.2	0.7	0.5	0.2
The Netherlands	2010	2023	86	0.9	1.24	2.05	4.3	8.7	2035	2034	2036	2033	2032	2034
United Kingdom	2008	2020	365	0.6	1.5	3.3	6.0	8.3	2028	2027	2028	2026	2025	2027
				20-29	30-39	40-49								
Finland	2013	2025	26	0.74	1.6	3.7			2045	2044	2046	2040	2041	2044

1. Rounded-up average from 2007 to the last available calendar year for each country from EUROSTAT https://ec.europa.eu/eurostat/datsbrowser/view/DEMO_FASEC__custom_607563/default/table?lang=en
2. Calculated as the average of the estimated crude incidence for every age group from 1983 to 2009 for the Netherlands, for 2017 for the United Kingdom and from 1953 to 2012 in Finland
3. Controls in this study would be patients with a non-HPV related cancer with similar frequency (i.e., colon cancer)

In the case of a retrospective database age-matched case-control study, the study would end the recruitment of cases for a vaccine effectiveness of 80% and a vaccine coverage of 50% in 2034 in the Netherlands, in 2027 in the United Kingdom, and in 2044 in Finland.

Simulation of a retrospective database case-control study including catch-up vaccinated eligible female birth cohorts

Females vaccinated in catch-up campaigns have been considered (Table 5) for the total computation of the year when a retrospective database matched case-control study may be feasible in the three selected European countries.

In the Netherlands catch-up campaigns took place on 2009 for girls 13-16 years old (Table 5). If these birth cohorts are considered, the retrospective database study would consider 2019 as the starting time point and would reach the estimated sample size (including allowance for 30% of drop-outs) in 2031 for a vaccine effectiveness of 80% and a vaccine coverage of 50% of the eligible birth cohort.

In the United Kingdom the catch-up campaigns occurred in 2009/2010 for girls 14 to <18 years old (Table 5) , and with the same vaccine coverage and effectiveness parameters, the study would

consider data from 2015 and would attain the expected sample size by 2022.

Finland implemented catch-up vaccination campaigns in 2014 for 13-15 years old girls (Table 5). For a vaccine effectiveness of 80% and a vaccine coverage of 50% of the eligible birth cohort, the starting date for the study (including catch-up vaccinated female birth cohorts) would be 2022 and would reach the estimated sample size by 2041.

Simulation of a retrospective database case-control study including catch-up vaccinated eligible birth cohorts with a gender-neutral approach (females and males)

In this simulation, male vaccination has been factored into the equation when the first vaccinated male cohort will turn 25 years of age. Catch-up vaccinated birth cohorts have also been considered for the calculations, both for females and males for the three selected countries.

In the Netherlands, HPV vaccination for males will start with Cervarix in 2021. The first vaccinated female cohort would enter the study in 2019 and the first male cohort in 2030, and the estimated sample size could be reached in 2030 considering a vaccine coverage of 50% and a vaccine effectiveness of 80%.

Finland adopted a gender-neutral HPV vaccination policy in autumn 2020 (Table 5). Considering a vaccine coverage of 50% and a vaccine effectiveness of 80% and female and male cases (including catch-up campaigns), the study would start in 2022 for the first vaccinated female cohort and in 2030 for the first male cohort, attaining the estimated sample size in 2039.

This simulation exercise has not been conducted for the United Kingdom as the HPV vaccination for males (within the NIP indication) in this country have been done with the quadrivalent HPV vaccine.

Potential limitations to the case-control study

1. The Company relies on data linkage between cancer and vaccines registries. A more in-depth assessment of data linkage and database completeness for the registries in the considered countries is needed. At present, the Company is aware of this possibility for the selected countries but a thorough assessment and the possibility of data sharing and collaboration with the different registries and health authorities is required.

2. A further harmonisation of data might be needed (age adjustment of the incidence, same age groups, etc.) when understanding of the available data in each country is achieved.

3. Based on the estimated sample size calculation, further research is warranted to assess whether the adequate sample size (having into account the different scenarios) can be attained within reasonable timelines. All sample size calculations have been done with data publicly available on the respective national cancer registry websites where information on HPV type is not provided. Therefore, underestimation of the time to reach the estimated sample size may have occurred because oncogenic HPV-related head and neck cancer is a subset of the total head and neck cancer cases. The proportion of HPV-related head and neck cancer among all HNC has been estimated at 33% (Götz, 2019; Nidaye,

2014).

2. Annual monitoring and trend analysis

Yearly monitor the reporting of head and neck cancer cases by consulting five national cancer registries in the following countries: Denmark, Finland, Norway, Netherlands, and United Kingdom and a trend analysis could also provide information with regards to the effect of HPV vaccines on the incidence of head and neck HPV-related cancers All five countries have immunisation registries and potentially can be linked to the cancer registries (i.e., several additional databases can be linked to the National Cancer Registration and Analysis Services (NCRAS database) in the UK). Contact with the data owners and database curators will allow to determine the type of data available and depending on availability, a more in-depth analysis can be conducted achieving a finer granularity. A trend analysis would be performed every five years to monitor incidence of HNC and evolution, and over time, to assess the impact of vaccination. The first analysis would be run in 2026.

Type of data to be collected for the dataset

☐ Case definition: Ideally ICD-10 classification should be used (preferably ICD-10 codes C00-C14, C30-C32). Confirmation is needed of the use of ICD-10 classification or otherwise, request case definition for the country

☐ Histological classification (if available), i.e., ICD-O-3 or other

☐ HPV genotype. This might be difficult to obtain if only generic HPVpositive/ negative information is provided. At least, to obtain information whether the HNC case is HPV-related

☐ Number of cases (counts)

☐ Age-standardised yearly incidence. Preferably adjusted to the European standard population. If data are not available in this format in the registry, incidence as cases per 100.000 population can be used and standardised by the European standard population (EUROSTAT)

☐ By sex (male, female), by age group, or year by year and then grouped for the analysis and by calendar year

☐ Time periods:Pre-vaccine era: from 1997-2006 (before Cervarix commercialisation) From 2007 to the most recent and complete available calendar year in each registry.

☐ Vaccine coverage by year and age-group since the year of introduction (either at least 1-dose or vaccination completion as per label)

Statistical analysis

Trend analysis would be performed to determine the average annual percent change (AAPC) of the incidence between the inception and the final year of the data collection to evaluate trends by sex, histology, and age group, using joinpoint regression, linear regression, or any other statistical method considered adequate. Additionally, to assess the potential impact of vaccination, negative-binomial regression models may be fitted to compare trends in number of cases during the baseline (prevaccination) and post-vaccine introduction periods to determine observed vs. expected number of

cases, or any other relevant statistical methods may be used to assess potential differences over time comparing both periods.

Considerations and potential limitations to the trend analysis

a. The consulted national platforms analyse data from different periods of time, may use different populations for age adjustment and may apply a different or a more sensitive case definition (different ICD-10 classification codes or histological types of HNC). Therefore, direct comparison of incidence data is challenging. A further standardisation of the data provided might be needed.

b. All the countries identified to have cancer and vaccine registries have implemented Cervarix in their National Immunisation Programmes (NIP) at some point in time, albeit with different timelines and policies (see Table 5). In addition, in some countries the administration of the bivalent (Cervarix) and quadrivalent HPV (Gardasil) vaccines coexists (i.e., Denmark), or one has replaced the other (i.e, Norway, the UK) (Table 5). Hence, assessing the exclusive impact of Cervarix might not be possible and renders comparisons between countries cumbersome.

c. For the reasons stated above, vaccine coverage for Cervarix might be difficult to determine in some countries.

d. Changes in trends may occur over time for reasons other than HPV vaccination (i.e., changes in the surveillance and reporting system, increment of HNC diagnosis due to increased awareness among physicians, implementation of an HNC screening programme). In order to control for potential changes in the reporting of HNC over time, we propose to describe trends of another cancer that shares similar characteristics (similar incidence, similar mean age of diagnosis, absence of a screening programme) but not HPV-related.

3. Conclusion

To conclude and for the reasons mentioned in the first part of the response, the Company firmly believes that data from real-world settings and observational studies may provide sound information in support of the HNC indication in a more realistic manner compared to clinical studies. Based on the preliminary work and investigations provided above, the Company proposes to conduct similar post-marketing surveillance activities as those that are conducted to address the impact and effectiveness against anal lesions and cancer:

☐ The annual reporting of head and neck cancers would be monitored by consulting 5 national cancer registries (Finland, the Netherlands, the UK, Norway and Denmark) on a yearly basis.

☐ A trend analysis would be performed every 5 years, to allow to describe potential changes over time in the occurrence of head and neck cancers.

☐ A complete feasibility assessment for a case-control study would be performed every 5 years, starting in 2026 in order to ascertain the preliminary evaluation presented above.

The proposed surveillance activities have been reflected in the RMP (Impact and effectiveness against

head and neck cancers is a new missing information).

Rapporteurs' Assessment

The Applicant clarified that he does not intend to initiate an adequately powered clinical study with the relevant persistent infection primary endpoint for the protection against HNC with adequate serial oral sampling. Instead, the Company firmly believes that data from real-world settings and observational studies may provide sound information in support of the HNC indication in a more realistic manner compared to clinical studies.

The Applicant presented the rationale for not conducting a clinical trial to measure vaccine efficacy against oropharyngeal persistent HPV infection as well as the different options for post-approval studies.

1. Rationale for not conducting a clinical trial to measure vaccine efficacy against oropharyngeal persistent HPV infection are not agreed for the following reasons:

Regarding HPV vaccines:

Cervarix vaccine has demonstrated high efficacy against viral and histopathological endpoints at the cervix site. No efficacy studies against viral and histopathological endpoints at other anatomical sites (vulva, vagina, anus) have been conducted with Cervarix. There are no available data within or outside of a clinical trial on the ability of Cervarix to prevent persistent oropharyngeal infection.

It is not possible to necessarily assume that the ability of these vaccines to prevent persistent infections and their consequences in the anatomical anogenital sites can be extrapolated to the head and neck region. It is unknown whether sufficient vaccine-elicited immune responses will be effective in the oropharynx to prevent persistent infection and, hence, possible progression to pre-malignant changes. The detection of higher levels of anti-HPV antibody in oral fluids after vs. before vaccination does not confirm an expectation of efficacy as it is unknown what level of immunogenicity is sufficient for protection against oral HPV infection. Also, persistence of antibody in oral fluids may differ from that at other sites.

Regarding Potential similarities between head and neck cancers and anogenital cancers:

There are potential similarities in terms of HPV-induced cancer biology and risk factors. Nevertheless, there are also some differences between HPV-related OPSCC and uterine cervical cancer. HPV-related OPSCC and cervical cancer diverge in epidemiologic factors, molecular patterns, HPV type, mutational profile, cell-of-origin, treatment response, and clinical behaviour, suggesting that uterine cervical cancer and OPSCC are distinct (Pan, 2018). Natural history of oral HPV infection, encompassing establishment of infection, clearance and progression to cancer, remains poorly characterized. Also, the association between infection at the cervix and oral cavity has not been confirmed. Oral HPV infection occurs independently of cervical HPV infection and routes of transmission seem completely separate (Wierzbicka, 2021). Cervical lesions do not lead to HPV oropharyngeal infection; oral HPV infection may play an independent role in HPV transmission.

Regarding points to consider for HNC:

The IARC-WHO recommended protection against persistent infection for 6 months or longer with HPV 16 and 18 in the oral cavity as valid endpoints for prophylactic vaccine studies of oropharyngeal cancer. Rates of persistence along with predictors of HPV oral cancer initiation are still poorly understood, but incident infection cannot confirm any protection. Based on natural history of HPV infection, persistent infection is considered more relevant to progression to cancer than one-time

incident infection. Even though natural HPV infection was mostly studied for the cervix, it is generally accepted that findings with the cervix are applicable to other squamous epithelia susceptible to infection by high-risk HPV types and progression to cancer such as the vulva, vagina, and anal canal, as well as the oral cavity, pharynx and larynx (Gillison et al, 2012). Although there is no accepted definition of a threshold duration defining clinically important persistence, it is recognized that persistence is required for progression to HPV pre-cancer and cancer. The frequency of serial oral sampling has been discussed by FDA for the RCT Gardasil 9 (sBLA : STN 125508/868 - NCT04199689) : Oral HPV infection will be assessed by PCR of oral rinse and gargle samples collected at baseline, Month 7, Month 12 and every 6 months after for a total study duration up to 42 months.

Regarding the ethical considerations:

Adult male population is the most affected by OPSCC HPV-related in Europe compared to female adults. The indication of Cervarix in Europe is gender-neutral. Vaccine uptake is still especially low in boys and adolescents in most of the countries where the gender-neutral immunization program is applied. Not all the National Immunisation Programs (NIP) in EU have gender-neutral vaccination. Prevention and early detection through screening is not currently feasible due to lack of an identifiable HPV induced precancerous lesion, screening modalities, and risk-mitigation strategies.

Therefore, a RCT with persistent infection of the oropharynx (serial sampling) as primary endpoint could be conducted. To avoid ethical concerns with regarding a placebo-controlled trial, a trial with a non-HPV vaccine comparator might be an option.

This would be feasible (i) in countries where HPV NIP is not well/yet established, (ii) in countries with low HPV vaccination acceptance and coverage, (iii) in countries in male subjects where gender-neutral NIP is not established, or (iv) in subjects above the age recommended for HPV vaccination.

In summary, the ethical considerations of the Applicant to not accept RCT are not agreed and RCT could be still be ethical and feasible.

Of note, 2 studies with 9vHPV were initiated in early 2020 to assess the efficacy of the vaccine in preventing oral persistent infection. The first study will include 6000 males, 20–45 years old in the US, and the second study will include 500 cisgender men and transgender women, 20–50 years old in Brazil, living with HIV. These are the first large-scale studies with 9vHPV to evaluate efficacy using persistent infection as an endpoint (as a surrogate for prevention of HPV vaccine-type OPC). Results from both studies are expected in 2024.

2. Rationale for only conducting post-authorization observational studies to monitor the impact and effectiveness against HPV-related OPSCC to support the extension of indication for HNC prevention

The MAH believes that nowadays conducting a placebo-controlled clinical trial would not be ethical and would provide little scientific insights. Therefore, for the MAH, assessing the impact of the vaccine in a real-world setting on the ultimate clinical endpoint, i.e. cancer, seems a reasonable approach. However, it should be pointed out that given the time lag between vaccination and the development of cancer, an observational study design would likely bring information with regards to the effect of HPV vaccines on the incidence of head and neck HPV-related cancers although not within a short timeframe. In this perspective, the Company has explored different options that would address such research question. The MAH proposes to conduct similar post-marketing surveillance activities as those that are conducted to address the impact and effectiveness against anal lesions and cancer.

This rationale is not agreed for the following reasons:

Regarding Potential case-control study design:

Case–control studies are observational in nature and thus do not provide the same level of evidence as randomized controlled trials. The results may be confounded by other factors. It may also be more difficult to establish the timeline of exposure to disease outcome in the setting of a case–control study than within a prospective cohort study design where the exposure is ascertained prior to following the subjects over time in order to ascertain their outcome status. The most important drawback in case–control studies relates to the difficulty of obtaining reliable information about an individual's exposure status over time. Case–control studies are therefore placed low in the hierarchy of evidence.

Regarding annual monitoring and trend analysis:

Those observational studies have several important limitations and would take a considerable time.

In general, the post-authorisation observational studies proposed are supported provided that a clinical study is initiated to demonstrate the efficacy against persistent infection as discussed above in point 1. Reliable data on the ability to prevent persistent oropharyngeal infection could then also be collected e.g. during routine vaccination campaigns. This approach would require careful estimation of background rates and exclusion of bias.

3. Conclusion on the rationale for not conducting a clinical trial to measure vaccine efficacy against oropharyngeal persistent HPV infection

The Applicant clarified that he does not intend to initiate an adequately powered clinical study with the relevant persistent infection primary endpoint for the protection against HNC with adequate serial oral sampling. Instead, the Company firmly believes that data from real-world settings and observational studies may provide sound information in support of the HNC indication in a more realistic manner compared to clinical studies.

The reasons for this approach are not endorsed. On scientific and regulatory point of view, RCT is considered the appropriate approach to provide sound and robust data in support of the HNC indication for the following reasons:

- *Endpoints consideration:*

o Protection against incident oral HPV infection cannot be considered as a valid and meaningful surrogate endpoint for the protection against head and neck cancers related to HPV;

o Persistent viral infection is considered the most valid surrogate endpoint to demonstrate VE against HNC as there is no clear histopathological endpoints - intraepithelial precursor lesion – that has been identified for head and neck cancers;

o It is not possible to necessarily assume that the ability of the HPV vaccines to prevent persistent infections and their consequences in the anatomical anogenital sites can be extrapolated to the head and neck region.

- *Ethical consideration:*

o There is no proven preventive treatment for head and neck cancers and only observational data suggest that the licensed vaccines could confer some degree of protection against certain types of HPV-related squamous cell cancers. Therefore, a placebo or comparator-controlled efficacy trial with

persistent infection of the oropharynx as primary endpoint could be conducted in specific national context and be ethically acceptable.

- *Feasibility consideration:*

o It appears possible to conduct a RCT, which could potentially support an indication for prevention of cancer in the oropharynx provided that the SmPC explains that the primary endpoint was persistent infection. In a RCT sized with a case-driven approach and conducted in regions and/or populations expected to have high oropharyngeal infection rates, it should be possible to accrue sufficient cases of persistent infection in a timeframe that would make conduct of a prospective randomised trial feasible.

o In contrast, the post-approval observational studies proposed would take more time and have a number of important limitations. Epidemiological/Observational studies with HNC endpoint, as proposed by the Applicant, could be an additional approach to collect data to substantiate the findings of a randomized clinical trial with persistent oral infection as endpoint. Reliable data on the ability to prevent persistent oropharyngeal infection could then be collected e.g. during routine vaccination campaigns. This approach would require careful estimation of background rates and exclusion of bias.

In conclusion for MO1e), the rationale for not conducting a clinical trial to measure vaccine efficacy against oropharyngeal persistent HPV infection is not endorsed. The Rapporteurs consider that conducting a placebo or comparator-controlled clinical trial could be feasible on regulatory basis and would provide relevant scientific insights and the best possible estimates to confirm for protection for HPV-related HNC. Furthermore, the rationale for only conducting post-authorisation observational studies to monitor the impact and effectiveness against HPV-related OPSCC to support the extension of indication for HNC prevention is not endorsed. **Issue not resolved.**

OVERALL CONCLUSION ON THE MAJOR OBJECTION:

The Benefit / Risk profile for Cervarix for the prevention of head and neck cancers causally related to certain oncogenic HPV types in males and females as of 9 years of age and above is currently negative.

The submitted data and the rationales of the MAH regarding the MO do not support any reliable conclusion on the efficacy of Cervarix in the prevention of head and neck cancers.

The Rapporteurs do consider that, based on the above discussions,

- protection against persistent oral HPV infection is the best valid and meaningful surrogate endpoint for the protection against head and neck cancers related to HPV;
- HPV-040 pivotal study has failed and no further indication can be derived; the currently data available documented in HPV-040 does not support an extension of the indication for Cervarix to prevent HPV-related HNC;
- supportive studies did not bring specifically compelling results;
- the rationale for not conducting a clinical trial to measure vaccine efficacy against oropharyngeal persistent HPV infection is not endorsed and a RCT is considered feasible and ethical;
- post-approval observational studies proposed by the MAH cannot replace a RCT for approval of the extension of indication.

The Rapporteurs do not agree that the currently data available supports an extension of the indication for Cervarix to HPV-related HNC.

The Rapporteurs do not agree that the conduct of post-approval observational studies only is adequate to support a variation to extend Cervarix indication.

The data of a RCT is needed to conclude on the B/R for the new indication with oral persistent infection as surrogate endpoints for HPV-related HNC. The conduct of RCT is considered feasible and ethical. The MAH is strongly recommended to seek for scientific advice regarding the design of the RCT.

Based on the submitted package, the Major Objection is maintained for the intended extension of indication.

Other concerns

Clinical pharmacology aspects

Question 2

The applicant shall justify why no neutralising antibody comparison has been performed in support of the claim of the current variation procedure. Neutralising titers are considered the more relevant parameter in terms of prevention of an HPV infection.

Summary of MAH answer

The company understands the Co-Rapporteur's comment that neutralisation assays should be performed for measuring the antibody response elicited by HPV vaccination but that other types of assays that correlate with neutralization activity can be used as well. The pseudovirion-based neutralisation assay (PBNA) for HPV -16/18 was initially developed by the US NCI (Pastrana, 2004) and further adapted by GSK (Dessy, 2008). The assay uses pseudovirions that are independent of the virus-like proteins (VLPs) included in the vaccine, and thus constitutes an unbiased method for measuring HPV- vaccine induced serological response. As PBNA is labour intensive, technically complex and is not adequate for use in large-scale clinical trials (does not achieve a high throughput), GSK developed an enzyme- linked immunosorbent assay (ELISA) which uses Cervarix VLPs. This ELISA assay, which measures the total HPV-specific IgG response, both neutralizing and non-neutralizing antibodies, was shown to have a high degree of sensitivity and correlation with the PBNA in a study assessing data from two Cervarix trials, i.e. HPV-001 and HPV-007 (Dessy, 2008). The high degree of correlation between the ELISA and the PBNA was maintained up to 6 years after vaccination. Similar levels of correlation were also observed for different age groups. Therefore, the ELISA can be considered as a reliable surrogate for monitoring HPV-16 and HPV-18 neutralizing antibody responses in clinical trials (Dessy, 2008). When both assays were subsequently applied in a subset of Cervarix clinical trials, a high correlation was demonstrated as well (Leung, 2015; Puthanakit, 2016; Huang, 2017; Leung 2018). Lastly, similar dynamics of anti HPV-16 and anti HPV-18 geometric mean titres (GMTs) were noted at the different time points between the ELISA and the PBNA, reflecting a well-described pattern associated with HPV vaccination, i.e. peak at month 7 or month 13 (one month after last dose), gradual decline through month 24 and plateau until month 36. In line with WHO guidance for HPV vaccines " neutralizing assays are considered "the gold standard" for assessing the immune response induced by HPV vaccine" and the use of alternative assays, such as ELISA, can be considered based on a detailed analysis of the correlation between both assays (WHO 2007, WHO 2015, WHO 2017) . Of note, the assessment and registration of Cervarix has been conducted with both the ELISA and PBNA assays. Lastly, in line with WHO TRS 1004 Annex 9 (WHO 2017), antibody measurements in clinical trials (including HPV- 040 and HPV -009) are routinely performed using ELISA.

Assessor´s comments

In its response the applicant refers to published data, WHO guidance docs and the initial licensing procedure to justify its approach for applying an ELISA-based test for the characterization of the

serological immune response elicited by Cervarix. Although not all the mentioned details of this justification are supported the overall rationale of the applicant´s response is deemed appropriate and acceptable.

Conclusion: Issue resolved.

Question 3

It is evident that the GMCs determined for female and male subjects in studies HPV-011 and HPV-012, respectively, are very different (i. e. much higher in males). Is there any explanation for this observation or are these differences due to different methodologies? In case of the latter, the GMC ratio analysis as conducted in table 7 of the "clinical overview addendum" is considered inappropriate. The applicant is requested to clarify these findings.

Summary of MAH answer

First, we want to clarify that the same methodology has been applied for the assessment of immunogenicity in males and females in both trials. As mentioned in the clinical overview addendum, the antibody determinations in studies HPV-011 and HPV-040 were performed using Enzyme-Linked Immunosorbent Assay (ELISA). The results of the ELISA assay are expressed in ELISA units per milliliter (EL.U/mL). The cut-off for seropositivity for the method was 8 EL.U/mL and 7 EL.U/mL for HPV -16 and HPV -18, respectively, in study HPV- 011. The assay used to measure anti-HPV-16/-18 antibody concentrations at the designated laboratory was improved to increase the assay precision and the assay cut-off value changed from 8 EL.U/mL to 19 EL.U/mL for HPV-16 and from 7 EL.U/mL to 18 EL.U/mL for HPV-18. These new cut-off values have been applied in study HPV-040 for the testing of samples from Visit 5 (at 18.5 year of age) onwards. As a result, the cut-off considered for calculation of seropositivity rates in study HPV-040 for samples at Day 0 and Month 7 was different from the cut-off used for samples taken at Visit 5. A summarized description of the method is provided in the clinical study reports of each study. The validation of the improved assays was also previously submitted to EMA. In HPV-012 and HPV-011, the same ELISA assay was applied , but with using the initial cut-offs of 8 El.U/mL and 7 El.U/mL for HPV-16 and HPV-18 throughout the study, since these studies were carried out before the improvement of the assay and subsequent implementation in Cervarix- based trials .

Second, the higher immunogenicity of HPV vaccines in males vs. females has been observed for all available HPV vaccines, i.e. Cervarix , Gardasil and Gardasil 9, a difference that can go up to three-fold (Block, 2006; Petaja, 2009; Castellsagué , 2015).

Third, as described in women, HPV vaccines elicit higher antibody levels for both antigens in younger age groups (10 -14 years) compared to older age groups (15-25 years) (Pedersen, 2006). Therefore, the differences between genders are exacerbated when considering different age groups, which was the case for HPV-011 (males aged 10 -18 years) and HPV-012 (females aged 15- 25 years).

These gender differences in immunogenicity are less marked when performing the analysis in the same age group. In the same HPV-011 trial, the antibody levels at month 7 in the subset of boys aged 10 to 14 years were 27891.6 EL.U/mL [23975.6–32447.2] for HPV-16 and 10593.7 EL.U/mL [8875.8–12644.0]) for HPV-18. For girls of the same age in the study HPV-012, antibody levels were 17272.5 EL.U/mL [15117.9–19734.1] for HPV-16 and 6863.8 EL.U/mL [5976.3–7883.0]) [23] for HPV-18 (Petaja, 2009). Similar observation was made for Gardasil 9 . The GMT ratios for males/females were between 1.09 and 1.27 one month after completion of the vaccination schedule (Month 7), depending on the HPV type (Castellsagué, 2015). A noteworthy finding is that higher antibody levels have been observed in heterosexual men compared to men who have sex with men (Hillman, 2012; Castellsagué, 2015). Moreover, lower antibody levels to all 9 assessed HPV types were observed among men who have sex with men compared to women (Castellsagué, 2015). Likewise, racial differences have been highlighted with higher antibody titres at month 7 in black subjects compared to Caucasian and Asian subjects (Hillman, 2012). Overall, HPV vaccines being highly efficacious in all studied populations, these differences in immune response are unlikely to be of clinical relevance (Petersen, 2017).

Interestingly, a sex-difference in humoral response has been observed for many human vaccines (including influenza, hepatitis and pneumococcal polysaccharide vaccines) and would not depend

entirely on gonadal hormones but would rather reflect a gender-specific mechanism yet to be identified (Cook, 2008; Hillman, 2012). Hence the recommendation to include a representative sample of females and males in vaccine trials to be able to assess sex-differences that may translate into clinical implications.

As a conclusion, the Company does not consider these data as inappropriate or inaccurate and would like to re-emphasize the validity and reliability of the presented study results.

Assessor´s comments

The applicant has clarified that the same ELISA methodology (with only minor adjustments) has been used for immunogenicity assessment of serum samples from clinical trials. This suggests that the differences in titers observed are not due to different assay procedures.

Further, the applicant has elaborated on existing knowledge as regards the established age- and gender-specific differences in immunogenicity of the HPV vaccine. Considering this information, the observed GMC differences between males and females can be adequately explained.

Conclusion: Issue resolved.

Clinical efficacy aspects

Question 4

Testing algorithm may allow for infection endpoints to be used as primary endpoints in clinical studies of prophylactic HPV vaccines for HPV-associated cancers for which no other reliable surrogates exist, e.g., head and neck cancers. Meanwhile, the sensitivity and specificity values of both tests need to be documented. The Applicant should discussed the reliability of the results.

Summary of MAH answer

The HPV PCRs (SPF-10 DEIA [SPF-10 DEIA: Short PCR fragment -10, DNA Enzyme Immunoassay], LiPA [HPV genotyping Line Probe Assay] and MPTS1, 2 and 3 [Multiplex Type-Specific PCR 1, 2 and 3]) were validated using control samples and cervical specimens. Specificity and sensitivity of these assays were assessed and are documented in the following reports:
☐ The validation report for the SPF-10 DEIA and LiPA assays: HPVPCRPCV02 submitted to the EMA in 2006 (EMEA/H/C/000721);
☐ The validation report for the MPTS assays generated in 2010: HPV_multiplexing 123 PCR-Luminex_VR01 and is submitted together with the current response.

1. Specificity

The specificity of the different assays was assessed and confirmed theoretically (by comparison to sequence databases) and experimentally by:
☐ Testing plasmids containing the L1 gene (for SPF-10 DEIA and LiPA assays) or the E6 gene (for MPTS assays) from various HPV genotypes;
☐ Sequencing the amplicons generated from 166 and 85 HPV positive cervical specimens for the SPF10 and the MPTS amplifications, respectively;
☐ Sequencing of additional 859 amplicons generated from cervical specimens positive for SPF10 DEIA and negative for LiPA;
☐ Evaluating the performance of SPF10 PCR/DEIA and LiPA assays on non-HPV targets (i.e. cervical

specimens containing Herpes simplex virus 1 or bacteria such as *Chlamydia trachomatis* or *Neisseria gonorrhoeae*);
☐ Using a mixture of plasmids and WHO HPV International proficiency panel to evaluate the performance of SPF10 PCR/DEIA and LiPA primers and probes in case of mixed infection.

The theoretical and experimental specificity analyses showed that all the PCR assays unambiguously recognize HPV sequences and do not hybridize with non-HPV sequences. The specificity of these PCRs is mainly driven by the sequence of primers and probes and the composition of the PCR reagents. As these components are identical regardless the sample type, specificity results generated with controls and cervical samples are deemed adequate enough to confirm that PCR assays are also fit for purpose for oral rinse samples used in the head and neck cancers, excluding therefore the need to perform additional specificity experiments.

Specificity analyses are documented in detail in the validation reports: HPVPCRPCV02 (Specificity Section 6.3) and HPV_multiplexing 123 PCR-Luminex_VR01 (Section 5.4).

2. Sensitivity

2.1 Sensitivity assessed in the context of cervical samples

The sensitivity of the SPF-10 DEIA and LiPA assays was assessed using 10-fold serial dilutions of cells with HPV-integrated DNA: SiHa cells (i.e. cell line containing 10 HPV- 16 genome copies/cell) or HeLa cells (cell line containing 10 HPV-18 genome copies/cell). These cells were diluted in presence of various concentrations of HPVnegative cells (i.e. MOLT-4 [i.e. human T lymphoblast cells]) to normalize the total number of cells per sample at 106 cells/mL. The limit of detection (LOD) of the algorithm was established at 10 DNA copies/PCR for HPV-18 (corresponding to 50 cells/mL of sample) and 20 DNA copies/PCR for HPV-16 (corresponding to 100 cells/mL of sample).

The sensitivity of the MPTS assays was assessed using 10-fold serial dilutions of plasmid constructs containing E6 regions of the HPV genome in the presence of MOLT-4 genomic DNA at about 120 ng/PCR. The LODs of the MPTS PCRs were around 1 to 20 copies/ PCR for the HPV-6, -16, -18, -31, -33, -35, -35v, -45, -51, -52, -56, -58, -59, -66 and -68 and around 30 to 40 copies/PCR for the HPV-11 and -39.

Sensitivity assessments are documented in detail in the validation reports: HPVPCRPCV02 (Limit of detection Section 6.4) and HPV_multiplexing 123 PCRLuminex_ VR01 (Section 5.5). The outcome of these analyses confirmed that the sensitivity of the PCR amplification and of the HPV genotyping are sufficient to detect the presence of HPV in a lesion when present.

2.2 Selection of extraction method for oral rinse samples

Exploratory experiments were performed to optimize the nucleic acid extraction for oral rinse samples. The nucleic acid extraction method used for oral rinse samples (Amicon Ultrafiltration with easyMAG) was selected based on a limited set of experiments measuring:

i) the ability to detect the ribonuclease P (RNaseP) housekeeping gene present in clinical samples

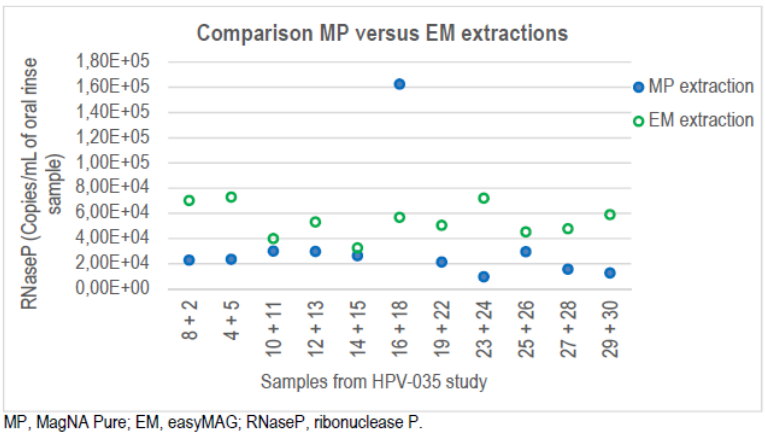
and

ii) the ability to detect the HPV-39 sequence from plasmid spiked in the same samples.

Ability to detect RNaseP housekeeping gene

Twenty-two samples originating from the HPV-035 study (Ngan HY et al., 2010), were pooled 2 by 2 to obtain volume large enough to evaluate the efficiency of the different nucleic acid extraction methods (i.e. MagNA Pure [MP] or easyMAG [EM]). For each pool, 4 mL aliquots of oral rinse were concentrated using the Amicon Ultrafiltration system and nucleic acids were extracted using either the MP or EM extraction systems. An indication of the efficiency of these DNA extraction methods was obtained by measuring the presence of the RNaseP housekeeping gene in clinical samples using a real-time PCR. RNaseP concentrations obtained with both extraction methods are presented in figure 1.

Figure 1 **RNaseP concentrations obtained from each pool with both extraction methods**



MP, MagNA Pure; EM, easyMAG; RNaseP, ribonuclease P.

As shown in Figure 1, for 10 pools out of 11, RNaseP concentrations were higher for the extraction using the EM method compared to the MP. Based on the RNaseP surrogate results, the EM method was therefore selected for the nucleic acid extraction.

Ability to detect HPV-39 plasmid in spiked samples

In total, 86000 copies of plasmid containing HPV-39 (L1 and E6 genes) were spiked in each of the pools described above before performing the nucleic acid extraction. A full HPV genotyping algorithm including the HPV SPF-10 DEIA, LiPA and MPTS qualitative assays, was applied. The equivalent of 8600 copies of plasmid was therefore used in the HPV SPF10 DEIA, LiPA assays and 25800 copies in the MPTS assay. The HPV-39 genotype was well detected with both EM and MP extraction methods.

Altogether, the experiments described in i) and ii) ensured to collect enough DNA from the oral rinse samples for use in the HPV PCRs and confirmed the ability of the HPV PCR/genotyping algorithm to detect the spiked HPV-39 plasmid. The nucleic acid extraction method (Amicon Ultrafiltration with easyMAG) was therefore used for oral rinse samples in the HPV-040 study.

Rapporteur Assessment

The HPV PCRs, LiPA and MPTS1, 2 and 3 are validated assays. Validation reports for the SPF-10 DEIA and LiPA assays were previously submitted to the EMA in 2006 (EMEA/H/C/000721). The validation

report for the MPTS assay generated in 2010 was submitted with the current response.

The sensitivity and specificity of the assays were assessed using control samples and cervical specimens. The Applicant summarized the outcomes of the validation and discussed the reliability of the results.

The MPTS123 PCR Luminex assays is considered adequately validated and suitable for HPV detection in cervical swabs samples. No PCR inhibition was encountered in the cervical swab samples tested with the MPTS123 PCR Luminex assays. This was not the case for the biopsy samples. This was expected and explained by the fact that the DNA of the cervical swab samples was extracted by MagnaPure system priori PCR amplified (purified DNA) which is not the case for the biopsy samples.
Overall, the testing of a panel of SPF-10 DEIA-positive cervical swab samples demonstrated good global agreement between SPF-10 DEIA LiPA and MPTS123 PCR Luminex assays.

The DNA extraction method that was selected for oral rinse samples was the easyMAG method that demonstrated to be more efficient than by the MagnaPure system. The easyMAG is an IVD-labeled automated system. It was demonstrated that HPV-39 genotype was well detected with the easyMAG extraction method (spike samples).

In conclusion, it is considered that the methods used to detect HPV DNA from oral rinse samples should be fit for purpose.

Issue resolved

Question 5

The Applicant is requested to clearly describe all steps of participant allocation and all randomization procedures (randomization of community, randomization of supplies, randomization of participants) including their purpose and technical details (including ramdomization ratios at all stages). For the minimization algorithm used for participant allocation, it needs to be clarified whether a random component exists.

Summary of MAH answer

The trial was a phase III/IV community-randomized, controlled trial with three arms. The trial was conducted in Finland in a total of 33 geographically distinct communities.

- Arm A included communities (N = 11) where 90% of male and female adolescents (birth cohorts 1992 - 1995) accepting study vaccination were to be vaccinated with the HPV- 16/18 L1 VLP AS04 vaccine (Cervarix) (vaccination strategy #1).
- Arm B included communities (N = 11) where 90% of the female adolescents (birth cohorts 1992 - 1995) accepting study vaccination were to be vaccinated with Cervarix (vaccination strategy #2).
- Arm C included communities (N = 11) where the adolescents (birth cohorts 1992 - 1995) were not vaccinated against HPV-16/18 (negative control). The adolescents accepting study vaccination received a Hepatitis B vaccine (HBV, Engerix-B) as negative control.

The trial was divided in two phases: the immunization phase (Day 0 to Month 12) and the effectiveness evaluation phase (Visit 5), during which the impact of the vaccine intervention was assessed in all female community residents born 1992-1995 (duration of follow-up approximately 3.5 to 6.5 years, which was the time needed to reach approximately 18.5 years of age).

The enrolment/randomization strategy aimed to achieve about 70% HPV vaccination coverage in the invited gender cohort in Arm A and B (Table 1).

Table 1 Immunization of study participants within communities

Arm	Allocation of study participants to receive HPV and HBV vaccines by intervention Arm				Target rate of HPV immunization within the communities (%)
	Males (%)		Females (%)		
A (M+F HPV vaccination)	HPV	90	HPV	90	70
	HBV	10	HBV	10	
B* (F HPV vaccination)	HPV	0	HPV	90	70*
	HBV	100	HBV	10	
C (HBV Control)	HPV	0	HPV	0	NA
	HBV	100	HBV	100	

* In this arm only female study participants were vaccinated with the HPV-16/18 L1 VLP AS04 vaccine.
M = Male study participants
F = Female study participants
NA = Not applicable
HPV = HPV-16/18 L1 VLP AS04 vaccine
HBV = Hepatitis B vaccine (Engerix-B)

Randomization of communities

The 33 geographically distinct communities were stratified by HPV16/18 seroprevalence into three strata based on HPV-16/18 seroprevalence rates in cohorts of women under the age of 23 years (50 per community) tested in 1983–2003 and 2006 (Kaasila, 2009; Lehtinen, 2006) using serum samples available at the population-based Finnish Maternity Cohort (Lehtinen, 2015).

The three HPV16/18 seroprevalence strata were the following:

- Level 1= Low (<20.5%)
- Level 2= Intermediate (20.5-24%)
- Level 3= High (>24%)

Within each seroprevalence stratum and before study start, communities were randomly assigned in equal numbers (1:1:1) to the three intervention arms using a random number generator. See Table 2, presented in the clinical study report as well, for details of the number of adolescents residing in each community.

This gave 12 communities in stratum 1, 9 communities in stratum 2 and 12 communities in stratum 3.

Table 2 List of communities and randomized allocation to Intervention Arms

Community	Number of females and males born in 1992, 1993, 1994, and 1995 (as per census*)			Stratification level	Seroprevalence rate used at randomization %	Intervention Arm
	Females	Males	Total			
Äänekoski	494	535	1029	1	12.96	B
Hämeenlinna	1145	1177	2322	1	20.37	C
Hyvinkää	1138	1236	2374	1	20.00	A
Iisalmi	525	518	1043	1	18.52	C
Jämsä	586	647	1233	2	22.00	C
Järvenpää	1067	1143	2210	2	22.22	A
Joensuu	1201	1295	2496	3	25.42	A
Jyväskylä	1657	1721	3378	1	17.54	A
Kajaani	959	987	1946	2	22.22	C
Kemi	762	649	1411	3	35.19	A
Kirkkonummi	1022	1085	2107	1	16.00	C
Kokkola	949	932	1881	1	11.32	A
Kotka	1213	1228	2441	2	22.64	A
Kouvola	672	657	1329	1	18.52	A
Kuopio	2038	2140	4178	3	31.48	C
Kuusamo	505	524	1029	1	18.03	B
Lahti	2183	2241	4424	3	25.93	A
Lappeenranta	1309	1368	2677	3	24.53	B
Lohja	977	1027	2004	2	20.83	C
Mikkeli	1130	1177	2307	3	25.93	B
Oulu	2922	2947	5869	1	7.41	C
Pori	1726	1713	3439	3	28.00	C
Porvoo	1358	1391	2749	3	24.53	A
Rauma	853	848	1701	3	24.53	C
Rovaniemi	1521	1577	3098	2	22.00	B
Salo	1092	1182	2274	1	17.02	B
Savonlinna	580	595	1175	2	21.15	B
Seinäjoki	899	821	1720	2	20.75	A
Tampere	4183	4294	8477	3	24.07	B
Turku	3156	3359	6515	1	14.58	B
Vaasa	1260	1347	2607	3	25.93	B
Vammala	719	795	1514	2	22.06	B
Varkaus	578	548	1126	3	26.00	C
Total	**42379**	**43704**	**86083**			

* From Population Register Centre (http://www.vaestorekisterikeskus.fi/default.aspx?site=3)

Randomization of supplies

A randomization list was generated at GSK Biologicals, Rixensart, using a standard SAS (Statistical Analysis System) program and was used to number the vaccines.

A randomization blocking scheme (9:1 ratio) was used to ensure that balance between treatments was maintained in all Arm A and female Arm B study participants: throughout the study, a single treatment number uniquely identified the vaccine doses to be administered to the same study participant. Arm C and male Arm B study participants received the control vaccine HBV (Engerix-B).

The vaccine doses were distributed to the study centre while respecting the randomization block size.

Randomization of study participants

The treatment allocation at the investigator site was performed using a central randomization system on Internet (SBIR).

For subjects accepting vaccination in Arm A (males and females), the randomization was stratified by community with a minimisation algorithm accounting for gender and birth year.

For subjects accepting vaccination in Arm B (females only), the randomization was stratified by community with a minimisation procedure accounting for birth year.

A 9:1 ratio was used to allocate study participants to HPV and HBV vaccines.

Male subjects in Arm B and all subjects in arm C communities were to receive HBV.

The person in charge of the vaccination accessed the randomization system on Internet. Upon providing a study participant number and identifying the gender and the age of the study participant, the randomization system used the minimization algorithm to determine the treatment number to be used for the study participant.

The minimization algorithm used in the randomisation system is based on the method suggested in Pocock, 1975. The determinism was set at 90% in the randomisation system for this study, thus indicating a randomness of 10%.

Assessor's comment

The Applicant clarified the randomization approach used in the study. There are two levels of randomization: 1) communities were randomized to intervention schemes (A, B and C) and 2) HPV-vaccination eligible participants (m + f in Arm A, f in Arm B and nobody in arm C) within these communities were randomized in a 9:1 ratio to either HPV or HBV vaccination. Randomization of supplies is only used to label supplies. This is now understood and considered acceptable.

The patient level randomization was achieved using a minimization algorithm (as described in Pocock S, Simon R. Sequential Treatment Assignment with Balancing for Prognostic Factors in the Controlled Clinical Trial. Biometrics 1975; Vol. 31, No. 1.) stratified for community with only 10% randomness. Minimization accounted for age and (in Arm A also gender). This has some consequences: 1) It shows that the trial was primarily planned to compare communities rather than individuals. 2) Statistical theory for hypothesis tests might not hold. Permutation tests might be more reliable here. 3) Minimization factors age (and gender) were not used in the primary analysis model, while it is expected to be the case.

The Applicant is requested to provide adequate analyses for both primary endpoints and the key secondary endpoint adjusting for the minimization factors age and gender and to use permutation tests for the key secondary endpoint. **(OC)**

The issue is <u>partially solved</u>. Relevant steps of the randomization procedure have been clarified but gave rise to new questions.

Question 6

The Applicant is requested to

- **provide all versions of the SAP including the final SAP used to analyse the data.**
- **provide a detailed description of the computations for VE, including formulae if not included in the SAP. The applicant is asked to clarify on the underlying methods to adjust for clustering and provide the underlying references (e.g. Donner et al, 2000). Further, it should be clarified whether odds ratios or prevalence ratios were used.**
- **discuss and explain possible changes in the computation of prevalence(s) from the Protocol to the SAP/CSR.**

Summary of MAH answer
The interim analysis of safety and immunogenicity is described in the Statistical Analysis Plan dated 03 May 2012. The final analysis is described in the Statistical Analysis Plan dated 09 September 2015. The documents are provided in module 5.3.5.1.

The true vaccine effectiveness was computed as 1 minus the odd ratio of true prevalence rate between the investigated arm and the control arm.

The estimate of overall and total effectiveness was done primarily using the Mantel Haenszel method, adjusted for clustering and stratified by the historical seroprevalence used in the randomization (historical seroprevalence under 20.5%, between 20.5-24% and over 24%). The 95% CI on effectiveness and 2-sided p-value for the null hypothesis of no effectiveness was computed using the general inverse variance approach.

The method described in Darlington GA 2007 was used as main reference for this analysis (Darlington, 2007). The method required adaptation for avoiding the bias in the overall effectiveness favouring the direct effect. The adaptation was developed in collaboration with Allan Donner who was part of the Steering Committee for this study. Please refer to the answer to question 7 for further details.

The detailed explanation of the computation of the effectiveness including methods to adjust for clustering are also provided in the "Section 7.5, Analysis of Effectiveness" and "Appendix B Statistical Method" of the Statistical Analysis Plan provided in module 5.3.5.1.

All changes from the planned analysis in the protocol are summarised in the "Section 10, Changes from planned analysis" in SAP.

The only change from the protocol related to computations of prevalence rate is the use of weights for estimating the overall effectiveness. Using this weight allowed restoring the proportion of non-vaccinated subjects among evaluable subjects and hence better reflected the estimate for overall effectiveness. Please refer to the response to question 7 for more details.

Assessor's comment

The Applicant provided two SAPs, one for the interim analysis of immunogenicity and safety and one for the final analysis. Both are labelled as "Version 1". It is hence assumed that no other SAPs exist.

VE was estimated as 1 – OR where the OR was estimated using a Mantel-Hasenszel estimate stratified for historical seroprevalence (as used for the stratified allocation of communities to arms) and accounting for clustering. The latter was done using a modified version of an approach of Donner (Darlington 2007). Details were provided with the SAP. However, formulae in the SAP are not readable. It is *assumed* that the GIV approach was used.
The Applicant is requested to provide the SAP in a version where all formulae are readable. Furthermore, the Applicant is requested to explain which of the four methods discussed in Darlington (2007) was used for the estimation of treatment effects. The Applicant is further invited to discuss why the original and most powerful approach, the corrected MH (CMH) approach was not used given the availability of raw data and to provide results based on this approach for a sensitivity check. **(OC)**

The prevalence odds ratio was not further explained but is understood as OR based on prevalence data (i.e. infected) rather than incidence data (i.e. newly infected) as it would usually be the case for VE.

The list of changes in the SAP (see Section 10) is by no means exhaustive. This listing does not even mention the central changes of adding a hierarchical testing sequence and changing the endpoints (e.g. pooled vs. separate analysis of oropharyngeal infections). However, the applicant explained that the only change to the computation of prevalence (and hence VE) was the use of weights as discussed in question 7.

The issue is considered <u>partially solved</u>. Further information is requested.

Question 7

The Applicant is asked to clearly describe all applied methods for the extrapolation of seroprevalence status and provide a justification for the assumptions made. Stating that an assumption was reasonable without any justification is not endorsed.

Summary of MAH answer

The Company would like to clarify that extrapolation for seroprevalence status at baseline was not performed. The estimate of overall and total effectiveness was done primarily using the Mantel Haenszel method adjusted for clustering and stratified by the *historical seroprevalence factor* used in the randomization (*historical seroprevalence under 20.5%, between 20.5-24% and over 24%*).

The company acknowledges that "seroprevalence" was mentioned in the section 4.1.3.3 of the Clinical Overview submitted with the variation:

*"Since **HPV seroprevalence status** was measured in a subset and not in all invited subjects, this had to be inferred from the prevalence observed among the subset of subjects with measurable prevalence. When the subset of subjects with measurable HPV seroprevalence was representative..."*

However, this was an error in the Clinical Overview. This section is indeed related to analysis of overall effectiveness in reducing the prevalence of HPV-16/18 infection and is referring to the prevalence status of HPV infection and not to the seroprevalence used for the randomization. The correct sentence is:

*"Since **HPV prevalence status** was measured in a subset and not in all invited subjects, this had to be inferred from the prevalence observed among the subset of subjects with measurable prevalence. When the subset of subjects with measurable HPV prevalence was representative..."*

The true vaccine effectiveness of interest was computed as 1 minus the odd ratio of true prevalence rate between the investigated arm and the control arm. 'True' is used to differentiate a parameter one wants to estimate from an estimate based on observation. The definition of overall effectiveness, indirect effectiveness and total effectiveness are summarized in Table 1.

Table 1 **True prevalence rate in the investigated arm and the control arm used for defining overall effectiveness, indirect effectiveness and total effectiveness**

Type of Effectiveness	Prevalence rate in the investigated arm	Prevalence rate in the control arm C
Overall	prevalence rate in all subjects from the investigated arm*	prevalence rate in all subjects from arm C*
Indirect	prevalence rate in all subjects which are not HPV vaccinated from the investigated arm	prevalence rate in all subjects from arm C
Total	prevalence rate in HPV vaccinated subjects from the investigated arm	prevalence rate in all subjects from arm C

*Note that this rate can also be expressed as (coverage * the prevalence rate in vaccinated subjects) + (1-coverage) * the prevalence rate in unvaccinated subjects

According to the study protocol, the vaccine effectiveness was to be evaluated by comparing the HPV PCR prevalence rates in communities in different interventional arms.

For the overall effectiveness, the estimated HPV prevalence status should represent the prevalence one would have measured for all invited subjects (i.e. HPV DNA PCR testing/cervical swabbing was not performed in all subjects) using the prevalence observed among the subset of subjects with measurable prevalence (i.e. subjects who allowed for cervical swabbing and results were available).

If the subset of subjects with measurable prevalence (i.e., those with HPV DNA PCR testing/cervical swabbing done) is representative from the invited subjects, the prevalence rate observed in subjects with measurable prevalence can be used to estimate the prevalence rate in all invited subjects.

Since in the investigated arm, the proportion of HPV vaccinated subjects among evaluable subjects is larger than the proportion of HPV vaccinated subjects among invited subjects, an estimate of

prevalence using weighted observation from unvaccinated subjects was used for the analysis of overall effectiveness (for details, refer to Appendix B in the final SAP of the study provided in module 5). The weight is the ratio between the rate of evaluable subjects in vaccinated subjects over the rate of evaluable subjects in non-vaccinated subjects, from pooled Arms A, B and C. Using this weight allows restoring the proportion of non-vaccinated subjects among evaluable subjects. The weighted approach for estimating of the prevalence rates was necessary to overcome the biased estimate of overall effectiveness favouring the direct effect.

This method was applied in the study following the expert advice from Allan Donner, the independent statistician in the Steering Committee for the study HPV-040. Allan Donner is Professor Emeritus at the Department of Epidemiology and Biostatistics, The University of Western Ontario, London, Ontario, N6A 5C1, Canada. Please refer to the Steering Committee charter (provided in module 5) for the role and responsibility of the independent statistician in the steering committee.

Table 2 and Table 3 provide the weights computed for the genital infection and oropharyngeal infection. The tables also provide the information on the proportion of evaluable subjects in the vaccinated and not vaccinated group.

Table 2 **Weight used in the computation of overall effectiveness of GSK Biologicals' HPV-16/18 vaccine against genital infection (Female study participants, Total invited cohort)**

	Arm A				Arm B				Arm C		Pooled Arms A, B and C			
Parameters	HPV	HepB	Pooled HPV and HepB	Invited not vac	HPV	HepB	Pooled HPV and HepB	Invited not vac	HepB	Invited not vac	HPV	HepB	Pooled HPV and HepB	Invited not vac
N	5799	669	6468	5775	6601	766	7367	7203	6684	5923	12400	8119	20519	18901
n	2784	346	3130	499	3069	369	3438	591	2711	457	5853	3426	9279	1547
%	48.0	51.7	48.4	8.6	46.5	48.2	46.7	8.2	40.6	7.7	47.2	42.2	45.2	8.2
Weight	5.6				5.7				5.3		5.5			

HPV = HPV-16/18 L1 VLP AS04 vaccine
HepB = Hepatitis B vaccine
Invited not vac = enrolled control without vaccination or invited but not enrolled
Arm A = 90% of vaccinated males and females were randomized to HPV
Arm B = 90% of vaccinated females were randomized to HPV
Arm C = 0% of vaccinated subjects were randomized to HPV
N = number of subjects invited and included in the specified Arm and Vaccine group
n = number of subjects with HPV DNA PCR result available for the cervical sample taken at the time of effectiveness phase
% = n/N
Weight = % in pooled HPV and HepB group / % in not vaccinated group

Table 3 **Weight used in the computation of overall effectiveness of GSK Biologicals' HPV-16/18 vaccine against oropharyngeal infection for birth cohorts 1994-1995 (Female study participants, Total invited cohort)**

	Arm A				Arm B				Arm C		Pooled Arms A, B and C			
Parameters	HPV	HepB	Pooled HPV and HepB	Invited not vac	HPV	HepB	Pooled HPV and HepB	Invited not vac	HepB	Invited not vac	HPV	HepB	Pooled HPV and HepB	Invited not vac
N	2964	338	3302	2607	3207	370	3577	3403	3378	2689	6171	4086	10257	8699
n	1606	203	1809	290	1586	191	1777	344	1446	233	3192	1840	5032	867
%	54.2	60.1	54.8	11.1	49.5	51.6	49.7	10.1	42.8	8.7	51.7	45.0	49.1	10.0
Weight	4.9				4.9				4.9		4.9			

HPV = HPV-16/18 L1 VLP AS04 vaccine
HepB = Hepatitis B vaccine
Invited not vac = enrolled control without vaccination or invited but not enrolled
Arm A = 90% of vaccinated males and females were randomized to HPV
Arm B = 90% of vaccinated females were randomized to HPV
Arm C = 0% of vaccinated subjects were randomized to HPV
N = number of subjects invited and included in the specified Arm and Vaccine group
n = number of subjects with HPV DNA PCR result available for the oropharyngeal sample taken at the time of effectiveness phase
% = n/N
Weight = % in pooled HPV and HepB group / % in not vaccinated group

As mentioned above, please note that the weighted approach was used only for the analysis of the overall effectiveness and not for the analysis of the indirect and the total effectiveness.

Accordingly, the analysis from the clinical study report is provided below in Table 4 to explain analysis of overall effectiveness and in Table 6 to explain analysis of total effectiveness.

Table 4 provides the results for the overall effectiveness against the genital infection. The analysis uses the weights for the estimation of true prevalence rates.

Table 4 **Confirmatory objectives - overall effectiveness of GSK Biologicals' HPV-16/18 vaccine against HPV-16/18 genital infection in Arm A versus Arm C and Arm B versus Arm C, using stratified Mantel-Haenszel adjusted for clustering (Female study participants, Total enrolled cohort)**

								VE			
									95%CI		
HPV Type	Arm	N invited	Group	N	n+	n	%	%	LL	UL	P-value
16/18	A	12243	HPV	2784	9	18	0.6	23.8	-19.0	51.1	0.232
			HepB	346	11	46	13.3				
			Not vaccinated	499	10	75	15.0				
			Total	3629	11	139	8.1				
	B	14570	HPV	3069	8	27	0.9	49.6	20.1	68.2	0.004
			HepB	369	9	31	8.4				
			Not vaccinated	591	10	59	10.0				
			Total	4029	11	117	5.7				
	C	12607	HepB	2711	11	276	10.2	-	-	-	-
			Not vaccinated	457	9	53	11.6				
			Total	3168	11	329	10.9				

HPV = HPV-16/18 L1 VLP AS04 vaccine
HepB = Hepatitis B vaccine
Not vaccinated = enrolled control without vaccination
Arm A = 90% of vaccinated males and females were randomized to HPV
Arm B = 90% of vaccinated females were randomized to HPV
Arm C = 0% of vaccinated subjects were randomized to HPV
N invited = number of subjects invited to participate in the study
N = number of subjects with available results
n+ = number of communities with at least one event
n = number of subjects reporting an event
% = n/N except for the Total where %=(n(HPV)+n(HepB)+w*n(Not vaccinated))/(N(HPV)+N(HepB)+w*N(Not vaccinated))
w = 5.5 (% of evaluable subjects among vaccinated subjects (HPV and HepB)/% of evaluable subjects among subjects invited to participate in the trial and not vaccinated, from pooled Arms A, B and C)
VE (%) = vaccine effectiveness (1-OR)
OR = odd ratio
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
P-value = two-sided p-value for H0: Arm A/B is equal to Arm C, based on Mantel-Haenszel adjusted for clustering and stratified by the historical HPV-16/18 seroprevalence used in the randomization

For illustrative purpose, Table 5 below provides the analysis of overall effectiveness without the weighted approach. As shown in the table, the estimate of prevalence rate in group "Total" is 3.8% and it leads to a vaccine effectiveness of 64.7% in arm A as compared to a prevalence rate of 8.9% and vaccine effectiveness of 23.8% in the table above using weighted approach. Hence, if the weighted approach was not used, it would have led to biased estimate of overall effectiveness favouring the direct effect. We therefore considered that this weighted approach was methodologically correct.

Table 5 Overall effectiveness of GSK's HPV-16/18 vaccine against HPV-16/18 genital infection in Arm A versus Arm C and Arm B versus Arm C, using stratified Mantel-Haenszel adjusted for clustering (Female study participants, Total enrolled cohort)

								VE		
									95%CI	
HPV Type	Arm	N invited	Group	N	n+	n	%	%	LL	UL
16/18	A	12243	HPV	2784	9	18	0.6	**64.7**	**47.4**	**76.3**
			HepB	346	11	46	13.3			
			Not vaccinated	499	10	75	15.0			
			Total	3629	11	139	**3.8**			
	B	14570	HPV	3069	8	27	0.9	**75.0**	**59.4**	**84.6**
			HepB	369	9	31	8.4			
			Not vaccinated	591	10	59	10.0			
			Total	4029	11	117	**2.9**			
	C	12607	HepB	2711	11	276	10.2	-	-	-
			Not vaccinated	457	9	53	11.6			
			Total	3168	11	329	10.4			

HPV = HPV-16/18 L1 VLP AS04 vaccine
HepB = Hepatitis B vaccine
Not vaccinated = enrolled control without vaccination
Arm A = 90% of vaccinated males and females were randomized to HPV
Arm B = 90% of vaccinated females were randomized to HPV
Arm C = 0% of vaccinated subjects were randomized to HPV
N invited = number of subjects invited to participate in the study
N = number of subjects with available results
n+ = number of communities with at least one event
n = number of subjects reporting an event
% = n/N
VE (%) = vaccine effectiveness (1-OR)
OR = odd ratio
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
P-value = two-sided p-value for H0: Arm A/B is equal to Arm C, based on Mantel-Haenszel adjusted for clustering and stratified by the historical HPV-16/18 seroprevalence used in the randomization

Table 6 provides the results for the total effectiveness against the oropharyngeal infection. This analysis uses the observed prevalence rates for estimating the effectiveness. Table 7 provides the results for the overall effectiveness against the oropharyngeal infection. The analysis uses the weights as computed in Table 3 for the estimation of true prevalence rates and overall effectiveness.

In conclusion, the weighted approach was only used for the analysis of the overall effectiveness to overcome the bias in favour of the direct effect. The analysis of the indirect and the total effectiveness were performed based on the observed prevalence rate.

Table 6 **Confirmatory objectives - total effectiveness of GSK Biologicals' HPV-16/18 vaccine against HPV-16/18 oropharyngeal infection in pooled Arms A and B versus Arm C, for birth cohorts 1994-1995, using stratified Mantel-Haenszel adjusted for clustering (Female study participants, Total enrolled cohort)**

									VE			
										95%CI		
HPV Type	Birth cohort	Arm	N invited	Group	N	n+	n	%	%	LL	UL	P-value
16/18	1994-1995	Pooled A and B	12889	HPV	3192	5	9	0.3	82.4	47.3	94.1	0.002
		C	6067	HepB	1446	9	18	1.2	-	-	-	-
				Not vaccinated	233	5	9	3.9				
				Total	1679	10	27	1.6				

HPV = HPV-16/18 L1 VLP AS04 vaccine
HepB = Hepatitis B vaccine
Not vaccinated = enrolled control without vaccination
Arm A = 90% of vaccinated males and females were randomized to HPV
Arm B = 90% of vaccinated females were randomized to HPV
Arm C = 0% of vaccinated subjects were randomized to HPV
N invited = number of subjects invited to participate in the study
N = number of subjects with available results
n+ = number of communities with at least one event
n = number of subjects reporting an event
% = n/N
VE (%) = vaccine effectiveness (1-OR)
OR = odd ratio
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
P-value = two-sided p-value for H0: pooled Arms A and B is equal to Arm C, based on Mantel-Haenszel adjusted for clustering and stratified by the historical HPV-16/18 seroprevalence used in the randomization

Table 7 **Exploratory objectives - overall effectiveness of GSK Biologicals' HPV-16/18 vaccine against HPV-16/18 oropharyngeal infection in pooled Arms A and B versus Arm C, for birth cohorts 1994-1995, using stratified Mantel-Haenszel adjusted for clustering (Female study participants, Total enrolled cohort)**

									VE			
										95%CI		
HPV Type	Birth cohort	Arm	N invited	Group	N	n+	n	%	%	LL	UL	P-value
16/18	1994-1995	Pooled A and B	12889	HPV	3192	5	9	0.3	66.8	19.8	86.3	0.014
				HepB	394	3	4	1.0				
				Not vaccinated	634	7	8	1.3				
				Total	4220	10	21	0.8				
		C	6067	HepB	1446	9	18	1.2	-	-	-	-
				Not vaccinated	233	5	9	3.9				
				Total	1679	10	27	2.4				

HPV = HPV-16/18 L1 VLP AS04 vaccine
HepB = Hepatitis B vaccine
Not vaccinated = enrolled control without vaccination
Arm A = 90% of vaccinated males and females were randomized to HPV
Arm B = 90% of vaccinated females were randomized to HPV
Arm C = 0% of vaccinated subjects were randomized to HPV
N invited = number of subjects invited to participate in the study
N = number of subjects with available results
n+ = number of communities with at least one event
n = number of subjects reporting an event
% = n/N except for the Total where %=(n(HPV)+n(HepB)+w*n(Not vaccinated))/(N(HPV)+N(HepB)+w*N(Not vaccinated))
w = 4.9 (% of evaluable subjects among vaccinated subjects (HPV and HepB)/% of evaluable subjects among subjects invited to participate in the trial and not vaccinated, from pooled Arms A, B and C)
VE (%) = vaccine effectiveness (1-OR)
OR = odd ratio
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
P-value = exploratory two-sided p-value not adjusted for the number of endpoints, for H0: pooled Arms A and B is equal to Arm C, based on Mantel-Haenszel adjusted for clustering and stratified by the historical HPV-16/18 seroprevalence used in the randomization

Assessor's comment

The weighting approach was explained in detail. The reason for the weighting was explained with very different response rates among subjects invited for testing which would then no longer

represent the overall composition of vaccinated vs unvaccinated subjects in the community. This would then distort the estimated *overall* (i.e. community wide) effectiveness in the prevention of infection. Only about 7.7% to 8.6% of unvaccinated subjects who were invited accepted to be tested for genital infection (compared to 40.6% to 48.4% in vaccinated subjects). Similar but slightly higher response rates were seen for tests for oropharyngeal infections. This is understood and the correction endorsed.

It is not fully understood, though, if the chosen weights are the ***best*** choice to fully reduce imbalances in the ratio of subjects who accepted to be tested for infections in vaccinated (both HPV or HepB) and unvaccinated subjects (i.e. those who refused to participate in the vaccine campaign or were deliberately not vaccinated). Nevertheless, it is agreed that the choice seems at least reasonable.

A further issue is that the resulting weights make only sense if the number of invitations sent out reflects the true proportion of the groups (HPV-vaccinated, HepB-vaccinated and not-vaccinated). While this is not fully clear to the Rapporteur, it seems to be at least (much) closer to the true ratios than the observed ratios amongst tested subjects.

As the weights were only used in the computation of overall effectiveness and were not necessary for total and indirect effectiveness, they were only relevant for the two co-primary hypothesis on the prevention of genital HPV infection in females (Arm A vs C and Arm B vs C). The hypothesis of primary interest here, prevention of oropharyngeal infections, was only to be confirmed via the *total* (i.e., amongst vaccinated) effectiveness. Hence, it could have only affected the gate-keeping process. The Applicant showed that the unweighted estimates of overall effectiveness against genital HPV infections were severely biased upwards and lower confidence limits would have both exceeded 0, indicating a significant effect. Hence, the introduced weights led to a better estimate and a more conservative analysis. While the chosen weights used in the overall effectiveness computations are in principle understood, they rely on the untestable assumption that the observed participants are a random sample of the unobserved participants. This is, however, not considered relevant for this procedure as it would only impact the estimates of overall VE regarding the different vaccination schemes.

In the protocol it was stated that the primary analysis cohort was the Total Cohort, which was to include all study participants from all communities for whom HPV DNA PCR data was collected. As can be seen from Table 3 in response to Q7 only around 50% of HPV vaccinated subjects from Arms A and B, and around 40% of HepB vaccinated and 10% of unvaccinated subjects from Arm C provided oropharyngeal samples and hence contributed to the analysis of VE against oropharyngeal infections. This very high amount of missing data and differential pattern of missingness between study arms makes the derived VE against oropharyngeal infections highly questionable. The Applicant is requested to discuss this issue. Furthermore, an analysis of VE in the total invited cohort with sensible imputation methods for missing oropharyngeal samples (with sound justification) should be conducted to further supplement the primary estimate; a tipping point analysis is requested. **(OC)**

Overall, the Applicant explained the weighting approach and showed that it only affected the co-primary analyses in a conservative manner (a significant result in the unadjusted analysis was no longer significant) and did not affect the estimated total effectiveness against oropharyngeal infections. The issue is considered solved.

Question 8

The applicant is requested to explain the efficacy effect of Hepatitis B vaccination compared to non-vaccinated subjects to prevent prevalent infections demonstrated in Table 4.

Summary of MAH answer

To our knowledge, there is no biological plausibility that the recombinant Hepatitis B (HepB) vaccine may have any efficacy against HPV infections. The HBs antigen used in the HepB vaccine has no relationship to the L1 and L2 proteins that are components of the HPV capsid or the vaccine VLPs (L1 only). Any efficacy of the Hepatitis B vaccine against HPV infection is therefore not anticipated. Knowing this, hepatitis vaccines (Hepatitis A or Hepatitis B) have been commonly used as comparator vaccines in clinical trials assessing Cervarix.

The observation for oral infections Rapporteur alluded is probably reference to relatively low rate of HPV-16/18 infections (1.2%) observed in HepB arm compared to 3.9% in non-vaccinated subjects (Table 1), which is likely to have occurred by chance. Moreover, this difference in infection rate between hepatitis B-vaccinated and unvaccinated subjects was not observed for genital infections (Table 2: see birth cohorts of 1994-1995, same as those for assessment of VE against oral HPV infection). Of note, when evaluating the vaccine effectiveness of Cervarix excluding the 223 non-vaccinated subjects from Arm C, the vaccine effectiveness remains very close at 77% ((1- ((9(n in HPV group)/3192 (N in HPV group))/(18(n in HepB group)/1446(N in HepB group))*100) = 77.3%), attesting of the robustness of the analysis.

As a conclusion, the Company does consider these data as appropriate and accurate and would like to re-emphasize the validity and reliability of the presented study results.

Table 1 Total effectiveness against HPV-16/18 and HPV-16 oropharyngeal infection in pooled Arms A and B for birth cohorts 1994-1995 (Female study participants, Total enrolled cohort)

						VE			
							95%CI		
HPV Type	Arm	Group	N	n	%	%	LL	UL	P-value
HPV-16/18	Pooled A and B	HPV	3192	9	0.3	82.4	47.3	94.1	0.002
	C	**HepB**	**1446**	**18**	**1.2**	-	-	-	
		Not vaccinated	**233**	**9**	**3.9**				
		Total	1679	27	1.6				
HPV-16	Pooled A and B	HPV	3192	6	0.2	81.3	25.8	95.3	0.017
	C	HepB	**1446**	**13**	**0.9**	-	-	-	
		Not vaccinated	**233**	**6**	**2.6**				
		Total	1679	19	1.1				
HPV-18	Pooled A and B	HPV	3192	4	0.1	78.9	32.3	93.4	0.009
	C	HepB	**1446**	**7**	**0.5**	-	-	-	
		Not vaccinated	**233**	**3**	**1.3**				
		Total	1679	10	0.6				

HPV = *Cervarix*; HepB = *Engerix-B*; Not vaccinated = enrolled control without vaccination
Arm A = 90% of vaccinated males and females were randomized to HPV; Arm B = 90% of vaccinated females were randomized to HPV; Arm C = 0% of vaccinated subjects were randomized to HPV
N = number of subjects with available results; n = number of subjects reporting an event
% = n/N; VE (%) = vaccine effectiveness (1-OR); OR = odd ratio
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
P-value = two-sided p-value for H0: pooled Arms A and B is equal to Arm C, based on Mantel-Haenszel adjusted for clustering and stratified by the historical HPV-16/18 seroprevalence used in the randomization
Data source: HPV-040 PRI (106636) Report (13-Apr-2016), adapted from Table 30 and Table 110.

Table 2 Sub-group exploratory analysis - overall effectiveness of GSK Biologicals' HPV-16/18 vaccine against HPV-16/18 genital infection in Arm A versus Arm C and Arm B versus Arm C, by birth cohort, using stratified Mantel-Haenszel adjusted for clustering (Female study participants, Total enrolled cohort)

									VE			
										95%CI		
HPV Type	Birth cohort	Arm	N invited	Group	N	n+	n	%	%	LL	UL	P-value
16/18	1992	A	3143	HPV	729	7	9	1.2	12.5	-47.4	48.1	0.615
				HepB	101	6	12	11.9				
				Not vaccinated	115	7	19	16.5				
				Total	945	10	40	8.6				
		B	3844	HPV	811	4	7	0.9	55.1	7.5	78.2	0.030
				HepB	100	5	7	7.0				
				Not vaccinated	125	5	9	7.2				
				Total	1036	9	23	4.0				
		C	3398	HepB	769	11	75	9.8	-	-	-	-
				Not vaccinated	111	6	12	10.8				
				Total	880	11	87	10.2				
	1993	A	3191	HPV	735	4	4	0.5	19.1	-30.7	49.9	0.387
				HepB	85	6	9	10.6				
				Not vaccinated	113	10	23	20.4				
				Total	933	10	36	9.7				
		B	3746	HPV	800	2	4	0.5	42.4	0.7	66.6	0.047
				HepB	98	5	9	9.2				
				Not vaccinated	136	7	21	15.4				
				Total	1034	8	34	7.8				
		C	3142	HepB	645	11	70	10.9	-	-	-	-
				Not vaccinated	110	7	15	13.6				
				Total	755	11	85	12.2				
	1994	A	3063	HPV	730	2	4	0.5	39.8	-31.1	72.4	0.201
				HepB	90	8	16	17.8				
				Not vaccinated	167	7	19	11.4				
				Total	987	10	39	7.2				
		B	3572	HPV	778	6	7	0.9	55.8	2.8	79.9	0.042
				HepB	94	4	6	6.4				
				Not vaccinated	184	8	16	8.7				
				Total	1056	11	29	5.4				
		C	3040	HepB	709	11	81	11.4	-	-	-	-
				Not vaccinated	128	5	16	12.5				
				Total	837	11	97	12.0				
	1995	A	2846	HPV	590	1	1	0.2	20.9	-59.5	60.8	0.512
				HepB	70	7	9	12.9				
				Not vaccinated	104	7	14	13.5				
				Total	764	8	24	7.1				
		B	3408	HPV	680	6	9	1.3	40.9	-35.1	74.1	0.213
				HepB	77	5	9	11.7				
				Not vaccinated	146	4	13	8.9				
				Total	903	7	31	5.7				
		C	3027	HepB	588	11	50	8.5	-	-	-	-
				Not vaccinated	108	6	10	9.3				
				Total	696	11	60	8.9				

HPV = HPV-16/18 L1 VLP AS04 vaccine

HepB = Hepatitis B vaccine
Not vaccinated = enrolled control without vaccination
Arm A = 90% of vaccinated males and females were randomized to HPV
Arm B = 90% of vaccinated females were randomized to HPV
Arm C = 0% of vaccinated subjects were randomized to HPV
N invited = number of subjects invited to participate in the study
N = number of subjects with available results
n+ = number of communities with at least one event
n = number of subjects reporting an event
% = n/N except for the Total where %=(n(HPV)+n(HepB)+w*n(Not vaccinated))/(N(HPV)+N(HepB)+w*N(Not vaccinated))
w = 5.5 (% of evaluable subjects among vaccinated subjects (HPV and HepB)/% of evaluable subjects among subjects invited to participate in the trial and not vaccinated, from pooled Arms A, B and C)
VE (%) = vaccine effectiveness (1-OR)
OR = odd ratio
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
P-value = exploratory two-sided p-value not adjusted for the number of endpoints, for H0: Arm A/B is equal to Arm C, based on Mantel-Haenszel adjusted for clustering and stratified by the historical HPV-16/18 seroprevalence used in the randomization

Assessor's comment

The data provided by the applicant in Table 1 and 2 are accurate for the studies. Therefore, the efficacy effect of Hepatitis B vaccination is questioned and just by mischance in the groups to understand.
Issue is **solved**.

Question 9

The applicant should address, why so many subjects were not vaccinated.

Summary of MAH answer

Enrolment in the study happened between 2007 and 2009. Invitation letters were sent to the parents of 39,420 girls and 40,852 boys in Finland. Out of these 39,420 girls, 26,813 were invited in Arms A and B, and 12,400 received HPV vaccine, leading to a vaccine coverage of 46.2%. Out of the 40,852 invited boys, 12,463 were invited in Arm A and 2436 received HPV vaccine, leading to a vaccine coverage of 19.5% (Table 1). Oral presentations were given at schools and at parent's evenings to inform parents and children and to recruit subjects. At the time of enrolment in the study, HPV vaccines were recently licensed (2006 for Gardasil and 2007 for Cervarix) in Europe, which could explain the relative high rate of unvaccinated subjects in the study. With that respect, a survey conducted in Finland on acceptance of HPV vaccination by adolescents and their parents during the years preceding the study start showed an acceptance rate of 83% and 86%, respectively. Lack of knowledge and awareness on sexually transmitted diseases and HPV were suggested to be key factors on resistance to HPV vaccination (Woodhall SC, 2007).

Table 1 Number of subjects enrolled into the study, by Arm group, gender and Vaccine group, at subject level (Total enrolled cohort)

	Female						Male					
	Arm A N = 7064		Arm B N = 8099		Arm C N = 7281		Arm A N = 2808		Arm B N = 5011		Arm C N = 4149	
Vaccine group	n	%	n	%	n	%	n	%	n	%	n	%
HPV	5799	82.1	6601	81.5	0	0.0	2436	86.8	2	0.0	0	0.0
HepB	669	9.5	766	9.5	6684	91.8	299	10.6	4880	97.4	4040	97.4
Not vaccinated	596	8.4	732	9.0	597	8.2	73	2.6	129	2.6	109	2.6

Arm A = 90% of vaccinated males and females were randomized to HPV
Arm B = 90% of vaccinated females were randomized to HPV
Arm C = 0% of vaccinated subjects were randomized to HPV
HPV = HPV-16/18 L1 VLP AS04 vaccine
HepB = Hepatitis B vaccine
Not vaccinated = enrolled control without vaccination
N = number of subjects
n = number of subjects included in each Vaccine group, for a given Arm, by gender
% = n / N x 100

References:

Woodhall SC, Lehtinen M, Verho T, Huhtala H, Hokkanen M, Kosunen E. Anticipated acceptance of HPV vaccination at the baseline of implementation: a survey of parental and adolescent knowledge and attitudes in Finland. J Adolesc Health 2007 May;40(5):466-9.

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Assessor's comment

The survey conducted in Finland on acceptance of HPV vaccination by adolescents and their parents during the years preceding the study start showed an acceptance rate of 83% and 86%, respectively explains the low enrollment rate.
Issue **solved**.

Question 10

If a long-term follow-up study will be conducted, it is suggested to also include male subjects as the majority of HPV-associated head and neck cancers occurs in men.

Summary of MAH answer

As stated in the response to Question 1e), the Company proposes to do a feasibility assessment for a case-control study. The study would estimate vaccine effectiveness in women comparing the proportion of vaccination exposure among HPV-related head and neck cancer cases with the proportion of vaccinees among control patients who are free of any HPV-related head and neck cancer.

Vaccination in boys has only recently been introduced in the selected countries (see Table 1). The earliest introduction was in 2018 in Norway and 2019 in the UK. It is therefore too soon to assess the direct impact or vaccine effectiveness on head and neck cancers in men through such a case-control

design. In addition, due to the natural history of head and neck cancers evolution, it may take many years since a person is infected until cancer develops (no pre-cancerous lesions in HPV-related HNC). Moreover, vaccine coverage among men might take time before reaching similar levels as those in females. However, given the higher incidence of head and neck cancers in males, it is likely that the effect of vaccination on the prevention of those cancers will be visible after less years of vaccine implementation compared to females.

Table 1. Vaccination schedules and vaccine coverage in the selected 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 girls (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	2010	Bivalent HPV (Cervarix)	0m, 1m, 6m	12 yo girls	13-16 yo girls (2009/2010)	58% 3-dose (birth cohort 1998)	January 2014 *Announced 2021*	Cervarix (0m, 6m) girls *Cervarix (0m, 6m) girls and boys 12 yo*
Norway	August 2009	Quadrivalent HPV (Gardasil)	0m, 2m, 6m	12 yo girls (born 1997) (school-based)	Girls born in 1991 or later (2016-2018)	Birth cohort 1997 -65% 3-dose in 2011 Birth cohort 2004- 83% 3-dose in 2016/2017 school year	September 2018	Cervarix (0m, 6m) girls and boys 12 yo
United Kingdom	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

In conclusion and similarly to the assessment conducted in females, the Company will investigate the possibility of a study on HPV-related head and neck cancer in men once gender-neutral Cervarix vaccination programmes have been implemented for a longer time period. As mentioned, it is likely that the results of such evaluation will lead to a more realistic timeline provided that a sufficient vaccine coverage is reached in the coming years in male population.

Rapporteur Assessment –

It is acknowledged that the MAH will investigate the possibility of a study on HPV-related head and neck cancer in men once gender-neutral Cervarix vaccination programmes have been implemented for a longer time period.
Please also refer to the discussion Question 1e.
Issue not pursued

RMP

Question RMP 1.

In the paragraph on head and neck cancers (HNCs), the MAH comments that "it is today well established that HPV is associated with head and neck cancers, and in particular with oropharyngeal cancer", which is of course accurate. If available, figures should be provided

on the proportion of HNC which are HPV-related.

MAH answer

Head and neck cancers (HNCs) include all malignant tumours from the border of the lip to the beginning of the esophagus. In the US, cancers of the oral cavity and pharynx account for 3% of all diagnosed cancers every year (Ellington, 2020) and up to 2% of all diagnosed cancers worldwide in 2018 (Bray, 2018). Around 90% of malignant neoplasms of the head and neck are squamous cell carcinomas (SCCs), while around 5% are adenocarcinomas (Götz, 2019). A rapid increase of the incidence rate of oropharyngeal cancers, particularly
cancers of the tonsils and base of the tongue has been observed during the last 20 years in different regions of the world, and has been associated with high-risk human papillomavirus (HPV) (Ellington, 2020;(Gillison, 2015; Haeggblom, 2019). In the recent meta-analysis by Götz et al, the prevalence among HPV-associated HNSCC cases was 87.32% for HPV-16 and 11.65% for HPV-18 (Götz, 2019). Proportion of HPV types in HNC per anatomical site may vary, for example, HPV-16 was more common in oropharyngeal SCC than in oral SCC (90.6 vs. 69.7%), and HPV-18 was more often detected in oral SCC than in oropharyngeal SCC (26.0 vs. 8.1%) (Götz, 2019; Kreimer,
2005). HPV-associated oropharyngeal SCCs partially share the same risk factors with cervical cancer: high number of sexual partners and younger age at sexual onset (Syrjänen, 2019).

The HPV Information Centre has determined global estimates for age-standardised incidence rates (World standard) of HNCs attributable to HPV. The incidence rate reported per 100,000 per year for men is 3.7 in Oceania, 3.6 in Europe, 3.0 in the Americas and 1.2 in Asia while for women this is 0.9 in Europe, 0.7 in Oceania, 0.6 in the Americas and 0.2 in Asia (Bruni, 2019).

Based on the most recent global cancer statistics, a conservative estimate of the prevalence of HPV-related HNCs would be approximately 0.8% of all diagnosed cancers every year globally, and this figure is only expected to increase following current trends (Bray, 2018; Götz, 2019). In 2012, a global conservative estimate of the total number of incident cases per year of head and neck cancer was established at 38.000 cases (de Martel, 2012).

In a systematic review and meta-analysis, Ndiaye et al included 148 studies containing data from 12163 cases of head and neck SCCs (oral cavity, oropharynx, larynx, -including hypopharynx-) from 44 countries. They found that the prevalence of HPV DNA among oropharyngeal HNSCCs was 45.8% whereas the overall HPV DNA prevalence among all HNSCC cases was 29.5% (Ndiaye, 2014). Considering that the prevalence of SCCs among
all HNCs has been determined at around 90% (Götz, 2019; Tumban, 2019), and extrapolating the findings from the study of Ndiaye et al (Ndiaye, 2014), the overall prevalence of HPV-related HNCs could be established at around 33%.

New molecular techniques and combination of methods are being developed for the diagnosis of HPV-related HNCs and this may reveal a higher burden of HPV-related HNCs in the near future.

The section 'SI.1 Indication' of the RMP has been updated accordingly.

PRAC Rapporteur's updated Assessment

The MAH has included an estimation of the proportion of HNCs which are HPV-related, and global estimates for incidence rates of HNCs attributable to HPV in section SI.1 of the RMP. This is acknowledged. ***Issue resolved****.*

Question RMP 2.

The MAH should clarify whether oropharyngeal cancers will be included in the trends analysis to be conducted every 5 years from consulting 5 cancer registries. Similarly, the MAH should clarify whether head & neck cancers are considered of the feasibility of case-control studies. This should be clarified in the RMP, tables 7 and 8. Justifications should be

provided in case HNC are not considered for those studies.

MAH answer

The Company proposes to perform a trend analysis every 5 years, by consulting 5 national cancer registries (Finland, the Netherlands, the UK, Norway and Denmark) on a yearly basis to allow to describe potential changes over time in the occurrence of head and neck cancers.

In addition, a feasibility assessment to perform a case-control study to assess the effectiveness and /or impact of HPV vaccination programmes using Cervarix will be performed every 5 years.

The pharmacovigilance plan in the RMP, including tables 7 and 8, has been updated accordingly.

Please refer also to the response to question 1e for more details.

PRAC Rapporteur's updated Assessment

The MAH proposes to conduct similar post-marketing surveillance activities for head and neck cancer as those that are conducted to address the impact and effectiveness against anal lesions and cancer, namely a trend analysis every 5 years and a feasibility assessment for a case-control study every 5 years. These pharmacovigilance activities have been added in tables 7 and 8 of the RMP. This is acknowledged. ***Issue resolved.***

Question RMP 3

The PRAC Rapporteur is of opinion that 'Impact and effectiveness against anal lesions and cancer' should be removed from the table of safety concern. However, the category 3 studies addressing this concern should be maintained in the pharmacovigilance plan, tables 7 and 8. The MAH is invited to comment on this proposition. In case of disagreement, the MAH should discuss whether 'Impact and effectiveness against oropharyngeal cancers' should also be included as missing information in the table of safety concern. In this case, the pharmacovigilance plan should be adapted accordingly.

MAH answer

The PRAC Rapporteur is of opinion that 'Impact and effectiveness against anal lesions and cancer' should be removed from the table of safety concerns. However, the category 3 studies addressing this safety concern should be maintained in the pharmacovigilance plan (tables 7 and 8). The MAH recognizes that this concern is indeed more related to efficacy than to safety. However, the MAH prefers not to remove this as a safety concern in the RMP to keep alignment between the table of safety concerns and the pharmacovigilance plan as per GVP module V (EMA/838713/2011 Rev 2, 28 March 2017 https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-goodpharmacovigilance-practices-module-v-risk-management-systems-rev-2_en.pdf).

In line with the risk management strategy related to anal lesions and cancer, the MAH has added 'Impact and effectiveness against head and neck cancers' as missing information in the RMP.

To address this safety concern, the MAH has included the following post-marketing surveillance activities in the pharmacovigilance plan in the RMP:

- Monitoring of annual reporting of head and neck cancers by consulting 5 national cancer registries (Finland, The Netherlands, UK, Norway and Denmark). Monitor data for the quinquennial trend analysis of the occurrence of head and neck cancer and other HPV-related cancers. Data monitoring through consultation of the registries will start in 2021 and will be conducted yearly to prepare the quinquennial trend analysis described below.
- Trend analysis of HPV-related head and neck cancers every 5 years. Describe the potential changes over time in the occurrence of head and neck cancers in countries where Cervarix is used. The first trend analysis will be performed in 2026.
- Feasibility assessment to perform a case-control study to assess the effectiveness and/or impact of HPV vaccination programmes using Cervarix. This feasibility assessment will be

performed every 5 years. The first feasibility assessment will be performed in 2026.

These post-marketing surveillance activities will allow the MAH to identify the potential changes over time in the occurrence of head and neck cancers in countries where Cervarix is used.

PRAC Rapporteur's updated Assessment

*The MAH prefers to keep 'Impact and effectiveness against anal lesions and cancer' as missing information in the table of safety concerns and also added 'Impact and effectiveness against head and neck cancers' as missing information. This is acceptable****. Issue resolved****.*

Question RMP 4.

The PRAC Rapporteur disagrees that the results of the studies addressing 'Impact and effectiveness against anal lesions and cancer' are submitted through PBRER. This was already commented in the last PBRER report. First, it is preferable that study results are submitted through separate procedure. Second, in the last PBRER assessment, the PBRER frequency was changed from one year to three years, which will not be appropriate for the submission of quinquennial reports. The MAH is asked to correct the pharmacovigilance plan, tables 7 and 8, accordingly.

MAH answer

The Company acknowledges the Rapporteur's request to identify a more appropriate pathway for submission of the quinquennial reports resulting from the anal lesions and cancer post marketing surveillance activities. This was already commented by the PRAC last year, during the request for supplementary information for the update of the Cervarix SmPC with HPV-019 and HPV-073 study results (procedure EMEA/H/C/000721/II/0106). At that time, the Company had proposed to not update the submission pathway in the RMP, as the discussion of the results of those activities falls under the scope of the PBRER. This was agreed by the Rapporteur in the Assessment report EMA/CHMP/PRAC/20445/2020. However, since at a later stage, the Cervarix PBRER frequency was changed from one year to three years, the Company understands that submission of the quinquennial reports through the PBRER would lead to a delay in the provision of the data and that a more appropriate procedure should be identified.

The activities "*Trend analysis of HPV-related cancer every 5 years" and "Feasibility assessment to perform a case-control study to assess the effectiveness and /or impact of HPV vaccination programmes using Cervarix" that will be performed to address the missing information "Impact and effectiveness against anal lesions and cancer*" were
classified as category 3 (MEA) additional pharmacovigilance activities in the RMP. As explained in the response to the question RMP 3 of the present application, the Company considers that the activities should be maintained in the list of category 3 activities as well as in the pharmacovigilance plan.

Based on the above, the Company proposes to keep the activities as MEAs in the RMP, and to remove the wording "submitted with the next cyclical PBRER". The results of the activities will be submitted according to the procedures under which category 3 study results should be submitted.

The RMP has been updated accordingly.

PRAC Rapporteur's updated Assessment

The MAH confirmed that the results of the studies addressing 'Impact and effectiveness against anal lesions and cancer' will be submitted according to the applicable procedures for submission of category 3 study results. The submission procedure for the results of these studies ("submitted with the next cyclical PBRER") has been removed in the pharmacovigilance plan (tables 7 and 8). This is acknowledged. ***Issue resolved.***

Question RMP 5.

The RMP should be updated according to the conclusions of the CHMP on the extended

indication.

MAH answer

As requested, the Company has updated the RMP according to the conclusions of the CHMP on the extended indication. Please refer to the RMP v24 in the present submission.

PRAC Rapporteur's updated Assessment

The CHMP rapporteur still has major objections to the extension of the indication for Cervarix to prevent oral HPV infections and associated cancers. The RMP should be updated according to the final decision of the CHMP on this extension of indication.

Annex 3: Second Request for Supplementary Information to be addressed in an oral explanation and/or in writing

Major Objection

1. The Rapporteurs consider that the submitted data and discussions of the MAH on the major objection do not support any reliable conclusion on the benefit/risk of Cervarix in the prevention of head and neck cancers.

   The data of a RCT is needed to conclude on the B/R for the new indication with oral persistent infection as surrogate endpoint for HPV-related HNC.

   The MAH is strongly recommended to seek for a scientific advice regarding the design of the RCT.

Other concerns

2. Regarding HPV-040, the Applicant is asked to adequately adjust the analysis of VE against oropharyngeal infections for community type if community type is assumed to be such a strong confounder. The results of this analysis shall be discussed as necessary.
3. The Applicant is requested to provide adequate analyses for both primary endpoints and the key secondary endpoint adjusting for the minimization factors age and gender and to use a permutation test for the key secondary endpoint.
4. The Applicant is requested to provide the SAP in a version where all formulae are readable. Furthermore, the Applicant is requested to explain which of the four methods discussed in Darlington (2007) was used for the estimation of treatment effects. The Applicant is further invited to discuss why the original and most powerful approach, the corrected MH (CMH) approach was not used given the availability of raw data and to provide results based on this approach for a sensitivity check.
5. As can be seen from Table 3 in response to Q7 only around 50% of HPV vaccinated subjects from Arms A and B, and around 40% of HepB vaccinated and 10% of unvaccinated subjects from Arm C provided oropharyngeal samples and hence contributed to the analysis of VE against oropharyngeal infections. This very high amount of missing data and differential pattern of missingness between study arms makes the derived VE against oropharyngeal infections highly questionable. The Applicant is requested to discuss this issue. Furthermore, an analysis of VE in the total invited cohort with sensible imputation methods for missing oropharyngeal samples (with sound justification) should be conducted to further supplement the primary estimate; a tipping point analysis is requested.